# MAIN THEME: PSYCHOIMMUNOLOGY

## Introduction into modern immunology – relevance for neuropsychiatry

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Vertebrates are equipped with two complementary immune systems, the innate and the adaptive. The adaptive immune system is mediated by the highly sophisticated and recently evolved B and T cells, which specifically target the invader, and provide a memory response to prevent a repeat of the infection. The innate immune system, which is evolutionarily more ancient than adaptive immunity, represent the first line of immunity and must rapidly detect any infectious agent, and categorize the type of it – as virus, bacteria, fungus or parasite. (1) The inter- and intracellular communication between innate and adaptive immune cells is mostly mediated by cytokines. These peptides contribute to a chemical signaling language that regulates development, tissue repair, haemopoiesis, inflammation and the specific and nonspecific immune responses. (2) Potent cytokine polypeptides (such as interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor (TNF)-a) have pleiotropic activities and functional redundancy; in fact, they act in a complex, intermingled network where one cytokine can influence the production of, and response to, many other cytokines. Many cytokines that regulate the immune system are also involved into regulation of development, migration, cell proliferation, hormone secretion and feedback control of nerve cells and nerve tissue. Therefore it is not surprisingly that cytokine production by immune system, (e.g. during infection), influence the nervous system and vice versa. (3)

The second important set of inflamation – induced signalling molecules, chemokines, constitute a superfamily of small proteins (8–14 kDa) that are instrumental for the trafficking of leukocytes in normal immunosurveillance as well as the coordination of infiltration of inflammatory cells under pathological conditions. (4) Chemokines and their receptors form an elaborate signalling system. Numerous detailed studies demonstraded, that the endogenous cells of the CNS synthesise distinct chemokines and might respond to chemokine stimulation by chemokine receptor expression. Several lines of evidence indicate that all types of endogenous cells of the CNS (astrocytes, oligodendrocytes, microglia and neurones) express functional chemokine receptors. In the brain, chemokines mediate local immune responses and also attract leukocytes, which are believed to migrate along a concentration gradient of chemokines across the blood–brain barrier to their target. (5) It has been suggested that chemokine receptor expression on neurones plays a role in the developmental organisation of the brain by regulating the migration of neuronal progenitors. The inflammatory process with chemokine production may therefore be very disturbing particullary in the developing brain by interferring normal nerve cell migration. A lot of experimental evedence also indicate that glial-derived chemokines may have a significant impact on the survival of neurones during injury and underline the function of chemokines in the communication between glial cells and neurones.

Communication between immune and nerve systems is clearly bidirectional — we are learning that the immune system is capable of producing hormones and neuropeptides as if it were a neuroendocrine organ in its own right. Its cytokines and chemokines can profoundly affect central nervous system (CNS) function; correspondingly, cells of the CNS are found to express a range of appropriate specific receptors. These cytokines and chemokines regulate various acute-phase CNS activities such as growth promotion, fever induction, sleep, appetite, pain, and activation of the hypothalamic-pituitary- adrenocortical axis. In turn, cells of the nervous system are capable of synthesising cytokines cytokines and chemokines that were initially classified within the domain of the immune system and we are learning that immune cells carry an array of receptors for the classical transmitters of the CNS. (3)

In particular, during pathological conditions driven by chronic infection, autoimmunity, hypersensitivity, trauma or chronic stress, a chain reaction of pathophysiologic events may lead to developement of pathological process both in immune system as well as in nerves tissue. (6) As the neuroendocrine and immune systems communicate bidirectionally, many pathological conditions in nerves tissue may be connected to immunological reactions and vice versa: e.g. the pathophysiology of inflammatory hyperalgesia, infection and autoimmune and malignant diseases, as well as multiple sclerosis, paraneoplastic neurological autoimmunity, Guillain-Barré syndrome, schizophrenia, depression, bipolar disorder and cognitive impairment due to infection and/or inflammation. (7–9) In addition, many transmitter molecules important in nerve tissue communications are produced by activated lymphocytes, e.g. opioid peptides, adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH). Hence it was proposed that the term 'immuno-transmitter' be used to describe molecules that are produced predominantly by cells that comprise the immune system but that transmit specific signals and information to neurons and other cell types.

Also the mechanisms, from both the neural and immunological perspective, involved in stress-induced alteration of immune function are being extensively studied. The immune system is regulated in part by the central nervous system (CNS), acting principally via the hypothalamic–pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS). In recent years, our understanding of the interactions between the HPA axis and immune-mediated inflammatory reactions has expanded enormously. (7) It should be outlined that the HPA axis and immune-mediated inflammatory reactions exert the influences on each other and many mechanisms whereby these interactions are mediated, are described. We should also stress the importance od HPA interactions and oxidative stress molecules, which regulates a plethora of cellular functions including proinflammatory-mediated processes, important in pathophysiology of many developmental and inflammatory diseases of CNS. (10)

**References:**

1. Janeway C.A. Jr. How the immune system works to protect the host from infection: a personal view. Proc Natl Acad Sci USA 2001;**98**:7461–7468.
2. Sansonetti P.J. The innate signaling of dangers and the dangers of innate signaling. Nat Immunol 2006;**7**:1237–1242.
3. Szelényi J, Vizi ES. The catecholamine cytokine balance: interaction between the brain and the immune system. Ann N Y Acad Sci 2007;**1113**:311–324.
4. Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. Immunity 2000;**2**:121–127.
5. Murphy PM, Baggiolini M, Charo IF, Hebert CA, Horuk R, Matsushima K, Miller LH, Oppenheim JJ, Power CA. International Union of Pharmacology. XXII. Nomenclature for chemokine receptors. Pharmacol Rev 2000;**52**:145–176.




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6. Li W, Galey D, Mattson MP, Nath A. Molecular and cellular mechanisms of neuronal cell death in HIV dementia. Neurotox Res 2005;**8**:119–34.
7. Lozovaya N, Miller AD. Chemical neuroimmunology: health in a nutshell bidirectional communication between immune and stress limbic-hypothalamic-pituitary-adrenal systems. Chembiochem 2003;**4**:466–84.
8. Tonelli LH, Holmes A, Postolache TT. Intranasal immune challenge induces sex-dependent depressive-like behavior and cytokine expression in the brain. Neuropsychopharmacology 2008;**33**:1038–48.
9. Li W, Galey D, Mattson MP, Nath A. Molecular and cellular mechanisms of neuronal cell death in HIV dementia. Neurotox Res 2005;**8**:119–34.
10. Banno M, Mizuno T, Kato H, Zhang G, Kawanokuchi J, Wang J, Kuno R, Jin S, Takeuchi H, Suzumura A. The radical scavenger edaravone prevents oxidative neurotoxicity induced by peroxynitrite and activated microglia. Neuropharmacology 2005 Feb;**48**:283–90.

## LATE BREAKING LECTURES – PSYCHOIMMUNOLOGY

### Psychoimmunology

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Interest in the relationship between psychiatric symptoms and immune function has been a consistent theme since the beginning of modern medicine. By the beginning of the 20th century the term 'homeostasis' was introduced and it represented the need for mental and physical balance of the whole organism. Although research on that subject continued and yielded some very interesting findings it was in 1964 that George F. Solomon and associates forged the term 'psychoimmunology'. Following on that, in 1975, Robert Ader and Nicholas Cohen coined another term – 'psychoneuroimmunology' and with it laid out the underlying premise that the brain and immune system represent a single, integrated system of defense. Contemporary advances in psychiatry, immunology, neurology and other integrated disciplines of medicine has fostered enormous growth for psychoneuroimmunology, an area of medicine that has evolved to study the relationship between immunity, endocrine system, and the central and peripheral nervous systems. Nowadays, there is sufficient data to conclude that immune modulation by psychosocial stressors and/or interventions can lead to actual health changes. Although that might be the case, researchers still need to reveal the vast number of ways in which different behaviors and health are inter-related, with focus on the immunological mechanisms that underlie these interactions. These mechanisms likely have clinical and therapeutic implications that will not be fully appreciated until more is known about the extent of these interrelationships in normal and pathophysiological states.

### Neuropathology of schizophrenia and depression - with a focus on inflammatory aspects

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Numerous structural imaging studies by computed tomography or magnetic resonance imaging reported a broad variety of subtle structural alterations of in brains of schizophrenics (1, 7, 8, 10). The most consistent findings are: lateral ventricular enlargement (by about 20%), enlargement of frontal, temporal and parietal sulci, smaller volume of hippocampus and parahippocampal gyrus (by about 10%), decreased thickness of frontal, temporal and parietal association cortex (by 5%), reduced asymmetry between right and left hemisphere.

Post mortem studies found changes also at the microscopical level (8, 9): these are: cellular disarray and abnormally positioned neurons in entorhinal cortex, hippocampus and prefrontal brain indicating a prenatal disorder of neurodevelopment, reduced neuropil and synaptic markers, while the number of nerve cells is unchanged, alterations in myelin and oligodendroglia components, reduction of inhibitory interneuron terminals.

While cellular disarray in limbic mesiotemporal structures and frontal cortex as well as reduced cortical asymmetry are a strong argument for a prenatal developmental disorder, several MRI-studies could demonstrate a progressive loss of cortical tissue in the first years after the onset of clinical symptoms. This points to an additional degenerative component that adds to a primary neurodevelopmental disorder.

Neuroimaging studies in affective disorder are much more inconsistent (1). CT and MRI studies did not show major changes at the macroscopical level with the exception of subtle hippocampal atrophy in depression. Postmortem studies could demonstrate reduced volumes of some basal ganglia and hypothalamic regions (6) as well as subtle histopathological alterations in serotonergic and noradrenergic brain stem neurons and hypothalamic cell groups (2, 3, 4, 5).

Immune mechanisms have been discussed in the (co)etiology of schizophrenia and affective disorder during the past few decades. Historical indications of a possible significance of neuroinflammatory processes (infectious or autoimmune) in schizophrenia were provided by Wagner v. Jauregg (1887) demonstrating the positive effects of fever therapy (with attenuated strains of *Salmonella typhii*, *Plasmodium malariae* or *Mycobacterium tuberculosis*) and a lower incidence of rheumatoid arthritis in schizophrenia. The onset of schizophrenia in early adulthood, with progressive as well as benign courses, exacerbations and remissions, shows similarities to autoimmune disorders (e.g., multiple sclerosis, psoriasis) and may lead to the speculation of similar pathogenetic components. However, altered immunological parameters have been investigated mainly in peripheral blood and cerebrospinal fluid and less frequently in the brains of patients with schizophrenia or affective disorder.

Some postmortem studies have suggested microglial activation in the context of schizophrenia (13, 14), whereas others provided evidence against this notion (15, 16). Several microglial markers have been investigated in these studies, including MHC-II, CD40, CD68 and the peripheral-type benzodiazepine receptor. In particular, the induction of major histocompatibility complex class II (MHC-II, e.g. HLA-DR) in microglial cells is a well-known, sensitive marker of neuroinflammatory and neurodegenerative processes in histological studies. The role of microglia in affective disorder has been investigated only qualitatively in a small number of cases (13). HLA-DR immunostaining was observed in one of six patients with affective disorder, while five cases did not show any microglial immunolabelling.

Our recent postmortem study (17) revealed increased microglial densities in two schizophrenic patients who had committed suicide. Therefore, the hypothesis of microglial activation during acute psychosis was proposed. Alternatively, 'suicide' could be a diagnosis-independent factor leading to microgliosis.

We therefore analyzed microglial HLA-DR expression by immunohistochemistry in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), mediodorsal thalamus (MD) and hippocampus of 16 schizophrenics, 14 depressed patients with affective disorder and 10 matched controls. A subgroup of 6 schizophrenics and seven patients with affective disorder who committed suicide was included. We observed no effect of Axis-I diagnosis on microglial density. However, significant microgliosis was observed in the DLPFC ($P = 0.004$), ACC ($P = 0.012$) and MD ($P = 0.004$) of suicide patients. A similar trend was seen in the hippocampus ($P = 0.057$).




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In conclusion, immunological factors may play a hitherto underestimated role in suicide. First, microglial activation might be interpreted as a consequence of presuicidal stress. Second, one might speculate a causal link between microglial activation and suicidal behaviour, such as neuroendocrine factors, cytokines, and nitric oxide, which are released from microglial cells and are known to modulate noradrenergic or serotonergic neurotransmission and thus may trigger suicidality.

S100B is a protein which has also been linked to microglia and inflammatory processes. Several studies have revealed increased S100B levels in peripheral blood and cerebrospinal fluid (CSF) of patients with schizophrenia. In this context, it was postulated that elevated levels of S100B may indicate changes of pathophysiological significance to brain tissue in general and astrocytes in particular. We therefore analysed the cell density of S100B-immunopositive glia in the anterior cingulate, dorsolateral prefrontal (DLPF), orbitofrontal, and superior temporal cortices/adjacent white matter, pyramidal layer and alveus of the hippocampus, and the mediodorsal thalamic nucleus of 18 patients with schizophrenia and 16 matched control subjects (11). Cortical brain regions contained more S100B-immunopositive glia in the schizophrenia group relative to controls ($P = 0.046$). This effect was caused by the paranoid schizophrenia subgroup ($P = 0.018$). Separate analysis of white matter revealed no diagnostic main group effect ($P = 0.846$). However, the white matter of patients with paranoid schizophrenia contained more (mainly oligodendrocytic) S100B-positive glia as compared to residual schizophrenia ($P = 0.021$). These effects were particularly pronounced in the DLPF brain area. Our study reveals distinct histological patterns of S100B immunoreactive glia in two schizophrenia subtypes. This may be indicative of a heterogenic pathophysiology or distinct compensatory abilities: Astro-/oligodendroglial activation may result in increased cellular S100B in paranoid schizophrenia. On the contrary, residual schizophrenia may be caused by white matter oligodendroglial damage or dysfunction, associated with a release of S100B into body fluids.

**References:**


1. Baumann B, Bogerts B. The pathomorphology of schizophrenia and mood disorders: similarities and differences. Schizophr Res 1999;**39**:141–147.
2. Baumann B, Danos P, Diekmann S, Krell D, Bielau H, Wurthmann C, Bernstein HG, Bogerts B. Tyrosine hydroxylase immunoreactivity in the locus coeruleus is reduced in depressed non-suicidal patients but normal in depressed suicide patients. Eur Arch Psychiatry Clin Neurosci 1999;**249**:212–219.
3. Baumann B, Bielau H, Krell D, Agelink MW, Diekmann S, Wurthmann C, Trübner K, Bernstein H-G, Danos P, Bogerts B. Circumscribed numerical deficit of dorsal raphe neurons in mood disorders. Psychol Med 2002;**32**:93–103.
4. Bernstein H-G, Krell D, Emrich H, Baumann B, Danos P, Diekmann S, Keilhoff G, Bogerts B. Fewer beta-endorphin expressing arcuate nucleus neurons and reduced beta-endorphinergic innervation of paraventricular neurons in schizophrenics and patients with depression. Cell Mol Biol 2002; 48:OL 259–265.
5. Bernstein H-G, Heinemann A, Krell D, Mawrin C, Bielau H, Danos P, Diekmann S, Keilhoff G, Bogerts B, Baumann B. Further immunohistochemical evidence for impaired NO signaling in the hypothalamus of depressed patients. Ann N Y Acad Sci 2002;**973**:91–93.
6. Bielau H, Trübner K, krell D, Agelink MW, Bernstein H-G, Stauch R, Mawrin C, Danos P, Gerhard L, Bogerts B, Baumann B. Volume deficits of subcortical nuclei in mood disorders. A post-mortem study. Eur Arch Clin Neurosci 2005;**255**:401–412.
7. Bogerts B. The neuropathology of schizophrenic diseases: historical aspects and present knowledge. Eur Arch Psychiatry Clin Neurosci 1999;**249** Suppl:2–13.
8. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 2005;**10**: 40–68.
9. Lewis DA, Hashimoto T, Volk, DW. Cortical inhibitory neurons and schizophrenia. Nature Reviews 2005;**6**:312–324.
10. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia. Systematic review and meta-analysis of magnetic resonance imaging studies. Brit J Psychiat 2006;**188**:510–518.
11. Steiner J, Bernstein HG, Bielau H, Farkas N, Winter J, Dobrowolny H, Brisch R, Gos T, Mawrin C, Myint AM, Bogerts B. S100B-immunopositive glia is elevated in paranoid as compared to residual schizophrenia: A morphometric study. J Psychiatr Res: online [doi:10.1016/j.jpsychires.2007.10.001] 2007.
12. Wagner-Jauregg, J. Über die Einwirkung fieberhafter Erkrankungen auf Psychosen. Allgemeine Zeitschrift für Psychiatrie 1887;**27**:93–131.
13. Bayer TA, Buslei R, Havas L, Falkai P. Evidence for activation of microglia in patients with psychiatric illnesses. Neurosci Lett 1999;**271**:126–128.
14. Radewicz K, Garey, LJ, Gentleman SM, Reynolds, R. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. J Neuropathol Exp Neurol 2000;**59**:137–150.
15. Arnold SE, Trojanowski JQ, Gur RE, Blackwell P, Han LY, Choi C. Absence of neurodegeneration and neural injury in the cerebral cortex in a sample of elderly patients with schizophrenia. Arch Gen Psychiatry 1998;**55**:225–232.
16. Falke E, Han LY, Arnold SE. Absence of neurodegeneration in the thalamus and caudate of elderly patients with schizophrenia. Psychiatry Res 2000;**93**:103–110.
17. Steiner J, Mawrin C, Ziegeler A, Bielau H, Ullrich O, Bernstein HG, Bogerts B. Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization. Acta Neuropathol (Berl) 2006;**112**:305–16.


## Psychoneuroimmunology of schizophrenia


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This overview presents a hypothesis to bridge the gap between psychoneuroimmunological findings and recent results from pharmacological, neurochemical and genetic studies in schizophrenia. In schizophrenia, a glutamatergic hypofunction is discussed to be crucially involved in dopaminergic dysfunction. This view is supported by findings of the neuregulin- and dysbindin genes, which have functional impact on the glutamatergic system. Glutamatergic hypofunction is mediated by NMDA (N-methyl-D-aspartate) receptor antagonism. The only endogenous NMDA receptor antagonist identified up to now is kynurenic acid (KYN-A). KYN-A also blocks the nicotinergic acetycholine receptor, i.e. increased KYN-A levels can explain psychotic symptoms and cognitive deterioration. KYN-A levels are described to be higher in the CSF and in critical CNS regions of schizophrenics.

Another line of evidence suggests that of the immune system in schizophrenic patients is characterized by an imbalance between the type-1 and the type-2 immune responses with a partial inhibition of the type-1 response, while the type-2 response is relatively over-activated. This immune constellation is associated with the inhibition of the enzyme indoleamine 2,3-dioxygenase (IDO), because type-2 cytokines are potent inhibitors of IDO. Due to the inhibition of IDO, tryptophan is predominantly metabolized by tryptophan 2,3-dioxygenase (TDO), which is located in astrocytes, but not in microglia cells. As indicated by increased levels of S100B, astrocytes are activated in schizophrenia. On the other hand, the kynurenine metabolism in astrocytes is restricted to the dead-end arm of KYN-A production. Accordingly, an increased TDO activity and an accumulation of KYN-A in the CNS of schizophrenics have been described. Thus, the immune-mediated glutamatergic-dopaminergic dysregulation may lead to the clinical symptoms of schizophrenia. Therapeutic consequences, e.g. the use of anti-inflammatory cyclooxygenase-2 inhibitors, which also are able to directly decrease KYN-A, are discussed.

## Psychoimmunology of depression

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Depression has a huge impact on individuals and society. With a lifetime prevalence of over 15%, depression will be the second leading illness in the world by 2020 as projected by the World Health Organization. In addition to the emotional consequences of depression, this disorder is increasingly implicated in a wide range of medical conditions. As recently described in a comprehensive meta-analysis of over 180 studies with more than 40 immune measures, many immunological changes reliably occur in patients with major depressive disorder (1), and studies began to consider the behavioral correlates and biological mechanisms that might be involved. Evidence has also emerged that depression is associated with activation of the innate inflammatory immune response including alterations in the ability of immune cells to express proinflammatory cytokines (2). Interactions between the serotonergic and immune systems gain increasing interest within the research community (3).

Recent research has focused on the influence of peripheral immune signals which can lead to an exacerbation of sickness and the development of symptoms of depression in vulnerable individuals (4). This illustrates that inflammation is an important biological event that might increase the risk of major depression. On the other hand, brain cells such as microglia and astroglia, are not only target but also source of immune modulators such as cytokines (5). This report focuses on the role of immunocompetent brain cells for the development of depression.

Morphological studies demonstrate abnormalities in the brains of individuals with major depression (6). A brain volume reduction in limbic and cortical regions has repeatedly been reported. Most of the imaging studies focusing on the right hippocampus found a significant volume reduction in depressed patients (7). Longer duration of illness appears to be associated with a decrease of gray matter volume (8). The volume loss is predominantly due to a loss of glial cells leading to an increase of neuronal density. In addition, neuronal cells are smaller in depressed individuals than in healthy controls (9).

The relevance of these findings for the etiopathogenesis of depression is supported by the facts that antidepressants are capable to influence morphological changes. It has been shown that antidepressants prevent stress induced hippocampal atrophy in an experimental condition. Furthermore, they increase local concentrations of the neuronal growth factors BDNF and Neurotrophin 3, and support hippocampal neurogenesis (10).

Astrocytes and microglia cells are the major immunocompetent cells within the brain. An activation of these cells directs toward inflammation and immune reactions indicated by the release of modulators such as cytokines. S100B, an astrocyte derived protein, is such a modulator pointing toward an activation of astrocytes evolving autocrine and paracrine effects. It is involved in the regulation of the balance between proliferation and differentiation of cells. It influences the energy metabolism by stimulation of fructose-1,6-bisphosphate aldolase phosphoglucomutase and gyanylatecyclase in a calcium dependent manner. Furthermore, S100B modifies the cytoskeleton by inhibition of microtubule assembly and type III intermediate filaments leading to a sequestration of intermediate filament subunits. Consequently, S100B can display trophic effects by promotion of neuronal survival, neurite outgrowth and synapse formation. Pathologically high concentration, however, are toxic leading to neuronal dysfunction of death by e.g. increasing the release of inflammatory cytokine and nitric oxide (11).

In clinical studies S100B has been found to be significantly increased in acute major depression directing towards astrocyte activation (12, 13). Obviously, this phenomenon is limited to the more biologically determined types of depression such as the melancholic subtype (14). In these patients a moderately elevated S100B concentration seems to be beneficial since patients with higher S100B showed better response and remission rates (15). Antidepressant treatment appears to normalize S100B concentrations (16).

On a functional level it could be shown that depressed patients with increased S100B experience a better normalization of initially pathological evoked potential (ERP) patterns (P3-latency) than patients with unchanged S100B (16). Even three months after psychopathological remission only those patients with primarily higher S100B showed normal ERP patterns while in patients with initially normal S100B the pathological patterns remained (17).

These findings suggest that the activation of astrocytes is an important pathogenic factor for the development of depression. Astrocytic activation is associated with course of disease, treatment response, and functional parameters such as evoked potentials. This exemplarily illustrates the importance of immunological mechanisms in the etiopathogenesis of major depression. Central as well as peripheral processes are relevant at various pathogenic levels.

**References:**

1. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seliman DA, Schmidt K. The relationship of depression and stressors to immunological assays: A meta-analytic review. Brain Behav Immunity 2001;**15**:199–226.
2. Schiepers OJG, Wichers MC, Maes M. Cytokines and major depression. Prog Neuro Psychopharmacol Biol Psychiatry 2005;**29**:201–217.
3. Müller N, Schwarz MJ. Immunologische Aspekte bei depressiven Störungen. Nervenarzt 2007;**78**:1261–1273.
4. Dantzer R, O'Connor JC, Freund GC, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;**9**:46–57.
5. Miller DB, O'Callaghan JP. Depression, cytokines, and glial function. Metabolism 2005;**54**:33–38.
6. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nat Med 2001;**7**:541–547.
7. Videbech P, Ravnkilde B. Hippocampal volume and depression: A meta-analysis of MRI studies. Am J Psychiatry 2004;**161**:1957–1966.
8. Lampe IK, Hulshoff Pol HE, Janssen J, Schnack HG, Kahn RS, Heeren TJ. Association of depression duration with reduction of global cerebral gray matter volume in female patients with recurrent major depressive disorder. Am J Psychiatry 2003;**160**:2052–2054.
9. Cotter D, Mackay D, Landau S, Kerwin R, Everall I. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. Arch Gen Psychiatry 2001;**58**:545–553.
10. D'Sa C, Duman RS. Antidepressants and neuroplasticity. Bipolar Disord 2002;**4**:183–194.
11. Rothermundt M, Peters M, Prehn JHM, Arolt V. S100B in brain damage and neurodegeneration. Microscopy Res Tech 2003;**60**:614–632.
12. Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Ceresér KM, Santin A, Gottfried C, Salvador M, Kapczinski F, Gonçalves CA. Serum S100B and antioxidant enzymes in bipolar patients. J Psychiat Res 2007;**41**:523–529.
13. Schroeter ML, Abdul-Khaliq H, Diefenbacher A, Blasig IE. S100B is increased in mood disorders and may be reduced by antidepressive treatment. Neuroreport 2002;**13**:1675–1678.
14. Rothermundt M, Arolt V, Wiesmann M, Missler U, Peters M, Rudolf S, Kirchner H. S-100B is increased in melancholic but not in non-melancholic major depression. J Affect Disord 2001;**66**:89–93.
15. Arolt V, Peters M, Erfurth A, Wiesmann M, Missler U, Rudolf S, Kirchner H, Rothermundt M. S100B and response to treatment in major depression: A pilot study. Eur Neuropsychopharmacol 2003;**13**:235–239.
16. Hetzel G, Moeller O, Evers S, Erfurth A, Ponath G, Arolt V, Rothermundt M. The astroglial protein S100B and visually-evoked event-related potentials before and after antidepressant treatment. Psychopharmacol 2005;**178**:161–166.




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17. Dietrich DE, Hauser U, Peters M, Zhang Y, Wiesmann M, Hasselmann M, Rudolf S, Jüngling O, Kirchner H, Münte TF, Arolt V, Emrich HM, Johannes S, Rothermundt M. S100B serum levels correlate with target evaluation processing in remitted major depression. Neurosci lett 2004;**354**:69–73.

## Tryptophan and phenylalanine in systemic and CNS inflammatory disorders

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Patients suffering from inflammatory conditions like infections or cancer are at an increased risk to develop neuropsychiatric deviations such as fatigue and depression. Usually this is believed to relate to the disease burden and/or to the negative future expectation, to which e.g. cancer patients are exposed. However, similar clinical observations can develop as side effects of treatment with pro-inflammatory cytokines such as interleukins, interferons or tumor necrosis factor-$\alpha$. It seems that the immune response, which is triggered during cytokine administration might play a role in the precipitation of these symptoms. Accordingly, innate and adaptive immune mechanisms, which involve the production of pro-inflammatory cytokines, may directly or indirectly cause mood disturbances and sickness behaviour in above-mentioned diseases and during cytokine treatment (1–3).

In past recent years, tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) was recognized to be stimulated during immune response *in vitro* and *in vivo* (4, 5). IDO is strongly induced by Th1-type cytokine interferon-$\gamma$ (IFN-$\gamma$), and tryptophan degradation in patients is detectable by low tryptophan concentration and an increased kynurenine to tryptophan ratio (kyn/trp). When kyn/trp correlates with concentrations of immune activation markers like neopterin or soluble cytokine receptors such as serum soluble interleukin-2 receptor or 75 kD tumor necrosis factor-$\alpha$ receptor, the tryptophan metabolic changes are very likely to be caused by an increased IDO activity (5, 6). Accelerated tryptophan degradation has been confirmed in cytokine-treated peripheral blood mononuclear cells *in vitro* (4) and *in vivo* during virus infections, e.g. HIV-1 infection (6), autoimmune syndromes (7) and malignant diseases (5, 8) as well as during pregnancy (9). In patients with cancer, higher kyn/trp was found to correlate with more progressed disease and weight loss and to predict prognosis in, e.g., colorectal cancer or malignant melanoma (8, 10, 11).

Due to the close relationship between tryptophan availability and biosynthesis of serotonin (5-hydroxytryptamine, 5HT), tryptophan depletion during chronic diseases could relate to serotonin deficiency and an increased susceptibility for neuropsychiatric deviations in such patients (1, 12). Likewise in patients with major depression, accelerated tryptophan degradation together with immune activation phenomena has been described (13), and associations were described between quality of life, development of depression and tryptophan catabolism in patients with cancer and, e.g., during IFN-$\gamma$ therapy of malignant melanoma (14-16). Notably, accelerated tryptophan degradation has been also reported in the blood of patients with cardiovascular disease (17) as well as within normal aging (18), in patients with progressed stages of Alzheimer's disease and of other forms of dementia and in Parkinson's disease (19, 20). Thus, activation of IDO could underlie the reduced quality of life, mood changes, the increased risk for developing depression and cognitive impairment in such patients. In agreement, in a murine model system, lipopolysaccharide-induced depressive-like behaviour was confirmed to be mediated via activation of IDO (21).

Beside their effect on IDO, immunological stimuli can disturb neuronal circuits and neurotransmitters of the serotonergic as well as the adrenergic system also by some other means. The same pro-inflammatory stimuli, which are known to trigger IDO also stimulate the biosynthesis of 5,6,7,8-tetrahydrobiopterin (BH4), a cofactor of several aromatic amino acid monooxygenases (4, 22), and the high output of reactive oxygen species. Again Th1-type cytokine IFN-$\gamma$ is the most important stimulus, and the overproduction of reactive oxygen species not only can wipe out antioxidant systems but also destroys oxidation-labile compounds such as BH4. As a consequence, the activity of BH4-dependent hydroxylases and thus also the conversion of phenylalanine to tyrosine by phenylalanine 4-hydroxylase (PAH) is hampered, as is the biosynthesis of DOPA and of catecholamines dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline). Moderate hyperphenylalaninaemia is common in patients with consuming diseases such as HIV infection or cancer (23, 24), and just recently a correlation between higher blood phenylalanine concentrations and phenylalanine to tyrosine ratios (phe/tyr, a measure of PAH activity) and increased neopterin concentrations has been observed in patients post trauma and in cancer (25, 26). While during states of acute inflammatory responses, BH4-dependent enzymes and thus formation of catecholamines dopamine, epinephrine and norepinephrine and also of serotonin can be stimulated via up-regulation of BH4 production, their biosynthesis may be diminished due to the oxidative loss of BH4, when an inflammatory process has become chronic.

In summary, immune system activation and inflammation can substantially influence monoamine metabolism. The influence of activated IDO on depletion of tryptophan is more profound than any changes of phenylalanine and tyrosine concentrations. However, not only a decline of serotonin production due to the accelerated tryptophan degradation by IDO, but also (or in addition) deviations of phenylalanine and tyrosine and their neuroendocrine products are affected by inflammatory and immune activation processes and can influence brain function. Effects can differ between acute and chronic immunpathologies: in acute inflammatory responses, biosynthesis of several neurotransmitters can be stimulated by the up-regulation of BH4 production. By contrast, when an inflammatory process has become chronic, the oxidative loss of BH4 can diminish the biosynthesis of catecholamines dopamine, epinephrine and norepinephrine. The coincident measurement of phe/tyr and kyn/trp may allow a dissection, whether serotonergic or adrenergic treatment is more adequate for the individual patient. In any case, it should also be possible to improve these abnormalities to a certain extent, when inflammation and oxidative stress is attenuated by administration of anti-inflammatory drugs or by increasing the dietary intake of nutrients rich in natural antioxidant compounds (27).

**References:**

1. Widner B, Laich A, Sperner-Unterweger B, Ledochowski M, Fuchs D. Neopterin production, tryptophan degradation, and mental depression–what is the link? Brain Behav Immun 2002;**16**:590–595.
2. Dantzer R. Cytokine, sickness behavior, and depression. Neurol Clin 2006;**24**:441–460.
3. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;**9**:46–56.
4. Werner ER, Werner-Felmayer G, Fuchs D, Hausen A, Reibnegger G, Wachter H. Parallel induction of tetrahydrobiopterin biosynthesis and indoleamine 2,3-dioxygenase activity in human cells and cell lines by IFN-gamma. Biochem J 1989;**262**:861–866.
5. Wirleitner B, Neurauter G, Schroecksnadel K, Frick B, Fuchs D. Interferon-gamma-induced conversion of tryptophan: immunologic and neuropsychiatric aspects. Curr Med Chem 2003;**10**:1581–1591.
6. Fuchs D, Möller AA, Reibnegger G, Stöckle E, Werner ER, Wachter H. Decreased serum tryptophan in patients with HIV-1 infection correlates with increased serum neopterin and with neurologic/psychiatric symptoms. J Aquir Immune Defic Syndr 1990;**3**:873–876.

7. Widner B, Sepp N, Kowald E et al. Enhanced tryptophan degradation in systemic lupus erythematosus. Immunobiology 2000;**201**:621–630.
8. Denz H, Orth B, Weiss G et al. Weight loss in patients with hematological neoplasias is associated with immune system stimulation. Clin Investigator 1993;**71**:37–41.
9. Schröcksnadel H, Baier-Bitterlich G, Dapunt O, Wachter H, Fuchs D. Decreased plasma tryptophan in pregnancy. Obstet Gynecol 1996;**88**: 47–50.
10. Brandacher G, Perathoner A, Ladurner R et al. Prognostic value of indoleamine 2,3- dioxygenase expression in colorectal cancer: impact on tumor-infiltrating T-cells. Clin Cancer Res 2006;**12**:1144–1151.
11. Weinlich G, Murr C, Richardsen L, Winkler C, Fuchs D. Decreased serum tryptophan concentration predicts poor prognosis in malignant melanoma patients. Dermatology 2007;**14**:8–14.
12. Fuchs D, Werner ER, Dierich MP, Wachter H. Cellular immune activation in the brain and human immunodeficiency virus infection. Ann Neurol 1988;**24**:289.
13. Maes M, Scharpe S, Meltzer HY et al. Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: further evidence for an immune response. Psychiatry Res 1994;**54**:143–60.
14. Huang A, Fuchs D, Widner B, Glover C, Henderson DC, Allen-Mersh TG. Serum tryptophan decrease correlates with immune activation and impaired quality of life in colorectal cancer. Brit J Cancer 2002;**86**:1691–1696.
15. Capuron L, Neurauter G, Musselman DL et al. Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. Biol Psychiatry 2003;**54**:906–14.
16. Schroecksnadel K, Fiegl M, Winkler C, Denz HA, Fuchs D. Diminished quality of life in patients with cancer correlates with tryptophan degradation. J Cancer Res Clin Oncol 2007;**133**:477–485.
17. Wirleitner B, Rudzite V, Neurauter G et al. Immune activation and degradation of tryptophan in coronary heart disease. Eur J Clin Invest 2003;**33**:550–554.
18. Frick B, Schroecksnadel K, Neurauter G, Leblhuber F, Fuchs D. Increasing production of homocysteine and neopterin and degradation of tryptophan with older age. Clin Biochem 2004;**37**:684–687.
19. Widner B, Leblhuber F, Walli J, Tilz GP, Demel U, Fuchs D. Tryptophan degradation and immune activation in Alzheimer's disease. J Neural Transmission 2000;**107**:343–353.
20. Widner B, Leblhuber F, Fuchs D. Increased neopterin production and tryptophan degradation in advanced Parkinson's disease. J Neural Transm 2002;**109**:181–189.
21. O'Connor JC, Lawson MA, André C et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry (in press).
22. Widner B, Fuchs D, Leblhuber F, Sperner-Unterweger B. Does disturbed homocysteine and folate metabolism in depression result from enhanced oxidative stress? J Neurol Neurosurg Psych 2001;**70**:419.
23. Ollenschläger G, Jansen S, Schindler J, Rasokat H, Schrappe-Bächer M, Roth E. Plasma amino acid pattern of patients with HIV infection. Clin Chem 1988;**34**:1787–1789.
24. Roth E, Zöch G, Schulz F et al. Amino acid concentrations in plasma and skeletal muscle of patients with acute hemorrhagic necrotizing pancreatitis. Clin Chem 1985;**31**:1305–9.
25. Ploder M, Neurauter G, Spittler A, Schroecksnadel K, Roth E, Fuchs D. Serum phenylalanine in patients post trauma and with sepsis correlate to neopterin concentrations. Amino Acids (in press).
26. Sperner-Unterweger B, Grahmann AV et al. Serum phenylalanine, tyrosine, neopterin and isoprostane in patients with ovarian carcinoma. Pteridines 2007;**18**:62–63.
27. Schroecksnadel K, Winkler C, Fischer B, Schennach H, Weiss G, Fuchs D. Antioxidants down-regulate Th1-type immune response in vitro. Drug Metabol Lett 2007;**1**:166–171.

## The role of infectious agents on cognitive impairment in bipolar disorder

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**Background:** There is growing evidence of an association of infectious agents including herpes simplex virus type 1 and 2 (HSV-1 and -2), cytomegalovirus (CMV), toxoplasma gondii and influenza viruses with psychiatric disorders. HSV-1 was previously found to be correlated with cognitive deficits in bipolar and in schizophrenic patients (1, 2).

Regarding gene-environmental interactions and its meaning for the pathophysiology of severe psychiatric diseases it has been shown that alterated genes coding for the catechol-O-methyltransferase (COMT) are associated with frontal lobe dysfunction and impaired cognitive function in schizophrenic patients. In bipolar disorder, polymorphisms of COMT have been linked to HSV-1 infections in bipolar patients (3, 4). Further gene-environment relationships reflect the fact that herpesviridae including HSV-1 and apolipoprotein E genes are associated to cognitive impairment (5).

The aim of this study was to examine the prevalence of serum antibodies to different infectious agents in bipolar patients and to compare it with a control group. Cognitive and clinical outcome were recorded separately.

**Methods:** Thirty bipolar patients and 20 healthy volunteers took part in this study. Clinical severity was assessed by structured interviews (HRSD-21, YMRS, PANSS). Cognitive outcome was tested with the Repeatable Battery for the Assessment of Neuropsychological Status, the Trail Making Test A&B, as well as with two verbal subtests from the WAIS III - the Letter Number Sequencing Task and the subtest on information. Antibody prevalence was analyzed in cooperation with the Johns Hopkins University, Stanley Division of Developmental Neurovirology, Baltimore, USA. Medication was tested for effects on cognition.

**Results:** A significant association of HSV-1 antibodies with cognitive impairment in bipolar patients was found. Although prevalence rates of HSV-1 did not differ significantly in both groups, a significant cognitive impairment of bipolar patients was found strongly correlated with the prevalence of HSV-1. This impairment included verbal subscores, attention and immediate memory. The association proved to be independent of clinical and demographical parameters that might affect the neuropsychological outcome (like current manic, depressive or psychotic symptoms as well as medication, age of onset and duration of illness, or education). For antibodies to CMV, HHV-6, HSV-2, Influenza B and toxoplasma gondii, only weak correlations with cognitive function were found.

The prevalence of antibodies to HSV-1, HSV-2, CMV, HHV-6, influenca-B and toxoplasma gondii in our study population was comparable to a normally distributed population in Europe and Northern America (6–8). The findings to neuropsychological impairment correspond to previous results in euthymic bipolar patients (9). Martinez-Arán et al. described a selective decrease of verbal memory and of frontal executive tasks as a residuum in bipolar disorder, while an overall impairment of cognitive function seemed to be associated with acute manic or depressive episodes (10). However, in our study, all patients where euthymic while have been tested.

Furthermore, cognitive decline of patients who recovered from herpes simplex encephalitis was similar to the deficits found in our bipolar group (11).




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**Conclusion:** The results of our study indicate a higher vulnerability of bipolar patients for viruses affecting the central nervous system that subsequently impairs cognitive functioning. This might be triggered by gene-environmental interactions. Previous infections with HSV-1 might have an influence on the functional outcome of bipolar disorder.

In conclusion, cognitive functioning in bipolar disorder might be improved by reducing infection rates of HSV-1, e.g. by vaccination or antiviral medication. Thus, larger prospective randomized clinical studies are needed.

**References:**


1. Dickerson FB, Boronow JJ, Stallings C, Origoni A, Ruslanova I, Yolken RH. Association of serum antibodies to herpes simplex type 1 with cognitive deficits in individuals with schizophrenia. Arch Gen Psychiatry 2003a May;**60**:466–472.
2. Dickerson F, Boronow JJ, Stallings C, Origoni A, Cole S, Krivogorsky B and Yolken RH. Infection with herpes simlex virus type 1 is associated with cognitive deficits in bipolar disorder. Biol Psychiatry 2004;**55**:588–593.
3. Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Cole S, Leister F, Krivogorsky B and Yolken RH. The catechol O-methyltransferase Val158Met polymorphism and herpes simplex virus type 1 infection are risk factors for cognitive impairment in bipolar disorder: additive gene-environmental effects in a complex human psychiatric disorder. Bipolar Disord. 2006 Apr;**82**:124–132.
4. Egan MF, Goldberg TE, Kolachana BS, Callicot JH, Mazzanti CM, Straub RE, et al. Effect of COMT Vall 08/158 Met Genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A 2001;**98**:6917–6922.
5. Strandberg TE, Pitkala K, Erola J, Tilvis R, Tiennari PJ. Interaction of herpesviridae, APOE gene, and education in cognitive impairment. Neurobiol Aging 2005;**26**:1001–100.
6. Kayser FH, Bienz AZ, Eckert J, Zinkernagel RM. Medizinische Mikrobiologie. Georg Thieme Verlag Stuttgart. New York 1998.
7. Xu F, Sternberg MR, Kottiri BJ, McQuillan GM, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006 Aug 23;**296**(8):964–73.
8. Pebody RG, Andrews N, Brown D et al. The seroepidemiology of herpes simplex virus type 1 and 2 in Europe. Sex Transm Infect. 2004 Jun;**80**(3):185–91.
9. Glahn DC, Bearden CE, Niendam TA, Escamilla MA. The feasability of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. Bipolar Disord 2004;**6**:171–182.
10. Martinez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M. Cognitive function across manic or hypomanic, depressed, and euthymic state in bipolar disorder. Am J Psychiatry 2004;**161**:262–270.
11. Caparros-Lefebvre D, Girard-Buttaz I, Reboul S, Lebert F, Cabaret M, Verier A, Steinling M, Pruvo JP, Petit H. Cognitive and psychiatric impairment in herpes simplex virus encephalitis suggest involvement of the amygdalo-frontal pathways. J Neurol 1996 Mar;**243**(3):248–256.




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# MAIN THEME: NEUROIMMUNOLOGY

## Basic cerebrospinal fluid – diagnostic in neuroimmunological diseases

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Quantitative protein analysis is the core of the cerebrospinal fluid (CSF) analysis for diagnosis of neurological diseases providing the recognition of disease-related, typical immunoglobulin class patterns and most sensitive quantitation of intrathecal specific antibody response. A CSF data report resembles all protein data of a single patient together with complementary data like cell count, oligoclonal IgG and lactate or glucose eventually together with surrogate marker proteins for tumors and noninflammatory degenerative processes in the brain. The interpretation of the compiled data takes advantage of recent knowledge about blood CSF barrier function and the particular immune response in brain.

**Knowledge base:** The target of CSF protein analysis is to discriminate between a blood- and brain-derived fraction and their disease-related changes (1–4). An increased protein concentration in CSF can be due to a blood CSF barrier dysfunction with an increased blood-derived fraction or/and an increased intrathecal synthesis of a brain-derived fraction.

Blood-CSF barrier function. The increase of the albumin CSF/serum concentration quotient, $Q_{Alb}$, indicates the change of the blood derived fraction, as albumin represents an exclusively blood derived protein in CSF. The blood CSF barrier dysfunction is due to a decreasing CSF flow rate. It is not a morphological leakage - still a widespread misunderstanding. The terms 'barrier leakage' or 'barrier impairment' got a new meaning: Reduced CSF flow rate, biophysically coupled with a subsequently increased molecular flux of proteins across the capillary walls can explain quantitatively the nonlinear increase of blood-derived proteins in CSF without any damage of the morphological structures (3). This view is directly confirmed by imaging techniques and different pathophysiological processes known to occur in neurological diseases.

Intrathecal immune response. The reference of immunoglobulin CSF/serum concentration quotients, $Q_{Ig}$, to the albumin quotient allow the discrimination of the brain-derived from a blood-derived Immunoglobulin fraction (1,2). The nonlinear relation, a hyperbolic function, between the CSF/serum-quotients of different proteins became the base of the actual quotient diagrams also used in many commercial evaluation programs (6). The hyperbolic reference range is theoretically founded and empirically fitted with data from 4300 patients (3).

Immunoglobulin patterns. The well known IgM to IgG isotype switch in blood does not occur in brain. This is the base for a disease-related (typical) immunoglobulin response pattern in CSF(1), which vary in different neurological diseases depending on causative microorganism, course and location of the immunological process (Figs.1,2).

The linear IgG Index with QIgG/QAlb represents the oldest still frequently used evaluation concept, but leads to many false positive interpretations (1).

The qualitative detection of oligoclonal IgG as a very sensitive method to detect intrathecal IgG synthesis is proposed as the complementary method of choice in case of chronic inflammatory diseases like multiple sclerosis, but in general it can not replace the quantitative protein analysis including IgA and IgM analysis for differential diagnosis of neurological diseases.

**Applications:** The immune response patterns of several viral diseases (Fig.1) and bacterial diseases (Fig.2) of the CNS are shown in the double logarithmic diagrams with hyperbolic functions (Qlim) for discrimination between the blood-derived and brain-derived IgG, IgA and IgM fractions (Reibergrams). The dynamics of a change in the blood-derived vs. a pure change of brain-derived fractions can be recognized at one glance.

The data of a patient with a facial nerve palsy are represented in Fig.1a with a normal CSF protein pattern. With the suggested diagnosis this pattern leads to the further analysis of varicella zoster antibodies (5) by which a VZV caused disease was confirmed. The patient was cured by an antiviral treatment. In another case of facial nerve palsy with a dominant intrathecal IgM synthesis (e.g. like in Fig 2d) the analysis of borrelia-specific antibodies would have been performed instead with the guess to detect a Neuroborreliosis which would need a different therapy. There is no other way to discriminate the causes of this disease to allow a correct treatment of the patients.

The treatment of a viral encephalitis (Fig.1b) or a bacterial meningitis (Fig 2a) needs a fast decision of the medical doctor, based on cell count, total protein and lactate or glucose. The immunoglobulin analysis may be not helpful in these cases in the early course of the disease, where the intrathecal immunoglobulin synthesis has not yet started (e.g. in HSV encephalitis in Fig.1b, at time of first, diagnostic puncture). For early diagnosis of an HSV encephalitis PCR analysis is the analysis of choice. The later antibody detection is only of confirmative relevance. In immune suppressed or HIV patients (Fig.1c) only the CSF data pattern can give the clear indication for an opportunistic infection by detection of the three class immune response with or without a barrier dysfunction. On the base of this pattern the search for the causative antigen can use PCR or intrathecal antibody synthesis, successful in cases of toxoplasmosis or CMV infections. In this case an isolated intrathecal IgM synthesis can point to a lymphoma in the CNS (Fig.1d).

In case of a bacterial meningitis with an immediate, successful treatment (Fig 2a) the initially increased albumin quotient might be normalized in a few days without any intrathecal immunoglobulin synthesis, but in case of complications e.g. by a life threatening abscess, the detection of an intrathecal IgA synthesis might be a very important diagnostic help.

The case of a dominant IgA synthesis in Fig.2b with an increased lactate concentration in CSF together with a pleocytosis suggest a tuberculous meningitis. In this case the very typical data pattern leads the clinical chemist to perform a possibly confirmative PCR analysis. In contrast an intrathecal IgA synthesis is mostly missing in cases of neurosyphilis. The corresponding examples in Fig.2c show that also different localizations with a different course of the disease might be reflected by the diagrams.

An expanding field of knowledge in CSF diagnosis comes from research in tropical neurological diseases, like in sleeping sickness in Africa (7). The analysis of brain-derived surrogate marker proteins in CSF for diagnosis of brain tumours (Carcinoembryonic antigen), dementia (Tau protein and Beta amyloid 1-42), hypoxia (Neuronspecific enolase) has found particular awareness. Also the detection of CSF contamination in nasal secretions by analysis of Beta trace protein gained increasing relevance. It was of theoretical and practical interest to recognize that the dynamics of the brain proteins in CSF (4) fit into a general theory developed to explain the dynamics of blood derived proteins (3).




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A convenient tool for CSF analysis is offered by a new software (6) which allows to calculate statistics in quotient diagrams for comparison of patient groups in clinical studies or allows to follow the course of a disease in a single patient.

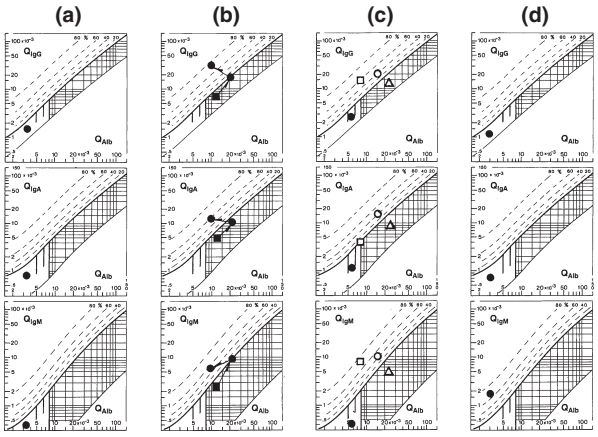


Fig. 1. Viral Infections of the CNS in Reibergrams.
The upper hyperbolic curves thick lines of the reference range represent the discrimination lines $Q_{Lim}$ (Lim from limit) between brain-derived and blood-derived immunoglobulin fractions in CSF. Values above $Q_{Lim}$ represent intrathecal fractions (IF) in percent of total CSF concentration as $IgG_{IF}$, $IgA_{IF}$, or $IgM_{IF}$. These intrathecal fractions can be conveniently and directly read from the quotient diagrams with lines for 20, 40, 60 and 80% intrathecal synthesis with reference to the upper discrimination line ($Q_{Lim}$) as 0% synthesis.
The limit of the reference range for $Q_{Alb}$ between normal and increased CSF protein concentration (blood-CSF barrier dysfunction) is age-dependent with a general formula for the age groups above 5 years: $Q_{Alb} = (4 + age(y.)/15)\cdot 10^{-3}$ (e.g. vertical line at $Q_{Alb} = 8 \cdot 10^{-3}$ for patients up to 60 years).
(a) Zoster Ganglionitis
Data of a patient with a facial nerve palsy. Only the VZV-Antibody-Index was increased (VZV-AI = 2.4; HSV-AI = 1.0), oligoklonal IgG was not detectable. The cell count was normal.
(b) Herpes simplex encephalitis
(■, •). The patient was punctured at days 1, 7 and 30 after admission to the hospital. 1st day without a humoral immune response, cell count 57/$\mu$L, no oligoclonal IgG in CNS but identical olicoclonal bands in CSF and serum. HSV-AI = 0.7; VZV-AI = 1.0; HSV-PCR positive. Second puncture after 7 days: cell count 280/$\mu$L, oligoclonal IgG in CSF in addition to identical bands in CSF and serum. HSV-AI = 10.5; VZV-AI = 1.6; HSV-PCR positive. 3rd puncture at day 30 after admission: Three class immune response ($IgG_{IF}$, $IgA_{IF}$, $IgM_{IF}$ >0), oligoclonal IgG. HSV-AI = 97; VZV-AI = 65; cell count 30/$\mu$L.
(c)HIV-Infection and opportunistic Toxoplasmosis
Case 1 (•) 30 year old patient with HIV Encephalopathy in an early phase, 22 cells/$\mu$L, no oligoclonal IgG, HIV-AI = 1.9 und Toxoplasma-AI = 0.9.
Case 2 (○) HIV Encephalitis with an opportunistic toxoplasmosis, increased albumin quotient and humoral three class immune reaction, cell count 140/$\mu$L, Toxoplasma-AI = 9.2; HIV-AI = 5.7; CMV-AI = 1.0. The other cases also had an opportunistic toxoplasmosis with blood CSF barrier dysfunction and an opportunistic toxoplasmosis with a two class immune response (□) d) Intrathecal lymphoma of a patient with AIDS, late stage. Cell count 18/$\mu$L, no oligoclonal IgG, HIV-AI = 4.5; $IgM_{IF}$ = 65%.

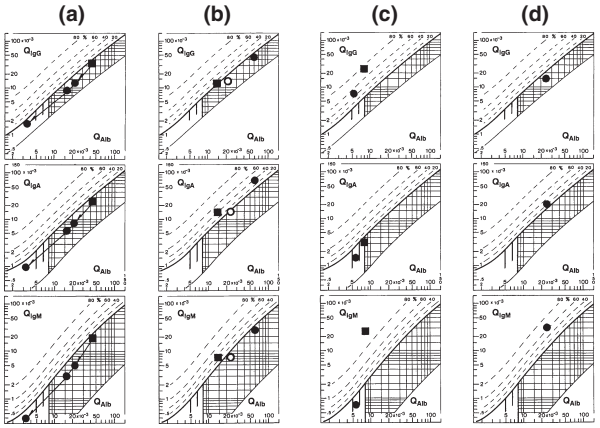


Fig. 2. Bacterial infections of the CNS in Reibergrams (explanation in legend of Fig.1)
(a) Meningococcus-Meningitis
The patient was punctured at the days 1 (■), 3, 6 and 13. Cell counts were 7250/$\mu$L; 2730/$\mu$L; 213/$\mu$L and 2/$\mu$L, correspondingly. (■) represents the diagnostically relevant first lumbar puncture. The therapy was started immediately at the first day and the course was without complications.
(b) Tuberculous meningitis. Patient1 (•) with a predominant intrathecal IgA-fraction IgAIF = 35%. Patient 2 (□) with an IgA quotient below the discrimination line, the intrathecal IgA synthesis was detectable due to the relation QIgA > QIgG (QIgG = $13.9 \bullet 10^{-3}$, QIgA = $17.1 \bullet 10^{-3}$). Patient 3 (■) with a late CSF puncture has an IgA and an additional IgM synthesis, frequently seen after start of therapy.
(c) Neurosyphilis. Patients with a meningovascular course of the disease (•) with an IgG synthesis (IgGIF = 30%) or a parenchymatous course of the disease (■) (progressive paralysis) with a predominant IgM-synthesis (IgMIF > 80%) besides an intense IgG synthesis (IgGIF = 80%). In both cases an intrathecal IgA-synthesis was absent.
(d) Neuroborreliosis. Predominant IgM class reaction, blood CSF barrier dysfunction, increased cell count (336/$\mu$L) and normal lactate concentration (< 2.1 mmol/L). This pattern has a clinical sensitivity of 70% and specificity of 96% (already before analysis of a specific intrathecal borrelia antibody synthesis).

**References: (for download see www.horeiber.de)**


1. Reiber H and Peter JB. Cerebrospinal fluid analysis – disease-related data patterns and evaluation programs. J Neurol Sci 2001;**184**:101–122.
2. Wildemann B. Oschmann P, Reiber H (eds) (2006) Neurologische Labordiagnostik. Thieme-Verlag, Stuttgart.
3. Reiber H. Flow rate of cerebrospinal fluid (CSF) a concept common to normal blood-CSF barrier function and to dysfunction in neurological diseases. J Neurol Sci 1994;**122**:189–203.
4. Reiber H. Dynamics of brain-derived proteins in cerebrospinal fluid. Clin Chim Acta 2001;**310**:173–186.
5. Reiber H and Lange P. Quantification of Virus-Specific Antibodies in Cerebrospinal Fluid and Serum: Sensitive and Specific Detection of Antibody Synthesis in Brain. Clin Chem 1991;**37**:1153–1160.
6. Reiber H. and Albaum W. Statistical evaluation of intrathecal protein synthesis in CSF/Serum quotient diagrams. ACN 2008; 20: 48–49.
7. Lejon V, Reiber H, Legros D, Djé N, Magnus E, Wouters I, Sindic CJM, Büscher Ph. Intrathecal immune response pattern for improved diagnosis of central nervous system involvement in trypanosomiasis. J Infect Dis 2003;**187**:1475–1483.




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## Primary angiitis of the central nervous system

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**Introduction:** Many forms of vasculitis may involve the central nervous system (CNS), including Behcet's disease, polyarteritis nodosa, vasculitis associated with connective tissue diseases such as lupus (systemic lupus erythematosus; SLE), Wegener granulomatosis, Churg-Strauss syndrome etc. Cerebral vasculitis is a rare disease characterized noninfectious granulomatous angiitis of the nervous system affecting small and medium arteries in the brain and rarely in the spinal cord (1).

The first description of granulomatous angiitis of the nervous system appeared in 1959 (2). Between 1959 and 1986, only 46 cases of central nervous system angiitis had been described in the literature, most of these diagnosed at post-mortem (3). In 1991, Crane and Kerr illustrated 11 cases from the preceding decade (4) and more recently a six-patient series had magnetic resonance (MR) and angiographic findings were described (5). Clinical experience suggest more patients suffering PACNS are now being recognized, but there are no data to evaluate whether this represents a true increase in incidence, or if it reflects the availability of advanced neuroimaging techniques that enables the diagnosis to be made during life allowing treatment to begin (6).

**Terminology:** Central nervous system vasculitis has been called by other names including isolated angiitis of the CNS (IACNS), emphasizing the confinement of the disease process to the brain and the spinal cord. Another name for this disorder has been granulomatous angiitis of the nervous system (GANS), a name that draws attention to a pathological feature of the disease seen in most cases. More recently, the preferred name for this form of vasculitis has been primary angiitis of the central nervous system (PACNS), and benign angiopathy of the CNS (BACNS) for the milder form of the disease (1, 6, 7).

**Etiology:** The exact cause of PACNS is not known, although reports suggest a possible viral infections as a cause, most often the herpes zoster infection (8–15). However, in most of these patients there is also a history of malignancy, especially lymphoma. Histopathologically these patients have granulomatous vasculitis identical to that of PACNS (11, 12). On the other hand, high level of anti-varicella virus antibodies have been isolated from cerebrospinal fluid of patient with PACNS (13), and electron microscopy identified herpes-like intranuclear particles in another patient with PACNS (16). Granulomatous angiitis has also been described in a patient having human immunodeficiency virus isolated from brain and cerebrospinal fluid (17), and electron microscopy demonstrated mycoplasma-like structures in wall and within granulomatous reaction of the patient with PACNS (18). It is possible that viral infections initiate the autoimmune inflammatory process. Some case series associate BACNS with heavy nicotine or caffeine use as well as with oral contraceptive and cold remedy use, the true associations between these exposures and the development of BACNS remain uncertain.

It seems that genetic does not appear to play a clinically significant role in pathogenesis, and it is extraordinarily rare for PACNS to occur in two people in the same family.

Primary angiitis of the central nervous system ia s rare disorder of unknown etiology almost exclusively confined to CNS – is usually involes the brain, less commonly the spinal cord (19). It is a serious disease, potentially causing 3–5% of cerebrovascular accidents in patients younger than 50 years (20).

**Pathology:** The angiitic process is focal and segmental in distribution, with a predilection for small arteries, particularly in the leptomeninges. Inflammation and associated mural damage are often multifocal, producing a series of 'skip lesions' along an affected blood vessel, with multiple associated foci of infarction or haemorrhage. At each point, the disease process may be circumferential or only segmental, and the inflammation may be granulomatous, necrotizing, lymphocytic or mixed in character. Most authorities now recognize the non-specificity of the angiographic changes and believe that a certain diagnosis depends on a positive biopsy (21).

The distribution of PACNS has a slight male predominance (4 : 3). The mean age of people affected by the disease is approximately 42 years, most of the patients get a disease in their 40s or 50s, with mean age of people affected by the disease of approximately 42 years, but the range is very wide - the disease has been detected in children as young as 3, and and adults as old as 78 (3, 22). On the contrary, patients with BACNS tend to be young women, often those with previous histories of headaches, most often migraine. These patients often have histories of heavy nicotine or caffeine use, over–the–counter cold remedy use, and oral contraceptive or estrogen replacement therapy, but whether the relationship between these exposures and the development of BACNS exist is stil unclear (23).

**Clinical picture:** Clinical picture is highly variable, but the triad of headache, organic brain syndrome, and multifocal neurologic deficits is most suggestive (3,4).

There are two main differences in the clinical presentations of PACNS and BACNS. First, patients with PACNS are more likely to develop symptoms subacutely and remain undiagnosed for months, while patents with BACNS are more likely to have relatively acute presentations and be diagnosed within weeks of onset. Second, without treatment, patients with PACNS tend to have steadily progressively course of disease that often leads to death (23, 27). On the contrast, BACNS patients may require less aggressive treatment than PACNS. The clinical manifestations of PACNS and BACNS may be identical, and include many neurologic symptoms and signs: headache, focal weakness, seizures, bleeding within the CNS, confusion, disorders of memory, and altered consciousness (3, 7, 23). It seems that PACNS could have diffuse (headache, concentration difficulties, mood and personality changes, seizures) as well as focal neurological symptoms (Hemiparesis, apasia), resulting from affecting predominantly small-sized vessels disease or middle-sized vessels (6, 7).

**Diagnosis:** Most affected patients do not have systemic symptoms, signs, or abnormal routine blood tests, including ESR. Diagnosis of PACNS is confirmed by either an angiogram or biopsy of the brain. Magnetic resonance imaging and angiography (MRI, MRA) as well as CT scanning and angiography (CTA) have been more and more often replacing angiography. Angiography has a sensitivity of 80% and specifitiy of 30% (24). It was suggested that angiography in a patient with possible cerebral vessel inflammation is unsafe, and may result in complications, but a study of 125 cerebral angiograms, found no greater risk of complications in patients with proven vasculitis than in controls. Lumbar puncture is also helpful in the diagnostic work–up of a patient with suspected PACNS. Cerebrospinal fluid shows pleocytosis with an elevated protein level (3). MRI is the most sensitive, being abnormal in more than 80% of patients. The diagnosis is very rare when both the cerebrospinal fluid cells and protein level as well as the MRI are normal.

The characteristic angiographic features of cerebral vasculitis consist of vascular narrowings and focal dilatations. When the vascular narrowings alternate with the focal dilatations, theme is a 'string-of-beads' appearance. The vascular narrowings in cerebral angiitis may be due to spasm, edema, cellular infiltration or proliferation of the vessel wall, or compression by surrounding thickened meninges from exudate or fibrosis. Similarly, focal dilatations may result from weakening of a damaged vessel wall or




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vasoparalysis secondary to an adjacent inflammatory process. The angiographic findings of cerebral vascubitis are nonspecific and can be seen in a variety of noninflammatory and inflammatory disorders (1, 26). Since the diagnosis cannot always be proven by angiography, consideration is often given to performing a brain biopsy. Brain biopsy has sensitivity of 53% and specificity of 87% (24). In the absence of positive results on biopsy specimen analysis, the diagnosis of PACNS should be doubted.

Calabrese and coworkers suggested definitive criteria for the diagnosis of isolated angiitis of the central nervous system:

i). an acquired neurological deficit that remained unexplained after complete evaluation

ii). a diagnostic cerebral angiogram that included diffuse areas of symmetric narrowing of vessels with areas of dilation and/or beaded vessel appearance, displacement of vessels or vessel occluded

iii). no evidence of systemic vasculitis or any other condition that could mimic the angiogram findings (3, 27, 28).

Differential diagnosis of PACNS includes systemic vasculitis, central nervous system infection (e.g. human immunodeficiency virus, syphilis), lymphoma, demyelinating disease, strokes caused by atherosclerosis, tumors, tuberculosis, severe migraine headaches, drug use (e.g. cocaine or amphetamine), sarcoidosis, and rare vasculopathies such as fibromuscular dysplasia, moyamoya disease and CADASIL (2, 22, 25).

**Treatment and prognosis:** Primary angiitis of the central nervous system was a fatal condition in most patients, with death occuring in a mean of 45 days after diagnosis, but immunosuppressive therapy has significantly improved the prognosis. However, no therapeutic regimen for PACNS has been the subject of a controlled trial to assess comparative efficacies of drugs. Therefore the treatment uses drugs known to sustain remission in the more common systemic vasculitides involving similar vessel types outside of the central nervous system (6, 7). Some patients with PACNS respond well to treatment with high doses of corticosteroids, while others require the addition of cyclophosphamide or azathiprine to corticosteroids (6). In most cases the disease is treated with high doses of corticosteroids for one month, adding cyclophosphamide only if corticosteroid therapy fails or if patients develop unacceptable side–effects of corticosteroid treatment. Treatment for patients with PACNS is usually long lasting (6, 7). In children with PACNS authors described two types of PACNS: progressive and nonprogressive. Predictors of progressive disease include neurocognitive dysfunction, multifocal parenchymal lesions on MRI, ad bilateral or distal vessel stenosis on angiography at initial presentation (7). In another study, authors differentiate patients with small-sized vessel disease that had relapses in 30% cases in the first two years. All relapses were successfully re-introduced into clinical remissions, but all patients had further neurological deficit clinically and radiologically. Patients with middle-sized vessel disease were relapse free during 6 years follow-up and all had discontinued therapy (6).

Patients who fit the typical patient profile of BACNS and who have clinical presentations compatible with that diagnosis may be candidates for less intensive treatment regimens. Patients believed to have BACNS may be treated with calcium–channel blockers for a few weeks, along with a comparatively short course of corticosteroids (23). However, no firm guidelines exist regarding the length of therapy, and decisions about the length of treatment must be made on a case–by–case basis.

Other treatment options such as anticoagulant and/or antithrombotic therapy, must be considered in each particular patient according to the clinical condition and the progression of each patient (6, 7).

Although progress has been slow in the understanding and treatment of PACNS, the prognosis for patients with PACNS is significantly better than it was two or three decades ago because imaging techniques permit earlier diagnosis and starting of treatment.

**References:**


1. Greenan TJ, Grossman RI, Goldberg HI. Cerebral vasculitis: MR Imaging and Angiographic Correlation. Radiology 1992;**182**:65–72.
2. Cravioto H, Feigin I. Noninfectious granulomatous angiitis with the predilection for the nervous system. Neurology 1959;**9**:599–609.
3. Calabrese LH, Mallek JA. Primary angiitis of the CNS: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine 1988;**67**:20–37.
4. Crane R, Dublin Kerr L. Spiera H. Clinical analysis of isolated angiitis of the central nervous system. Arch Int Med 1991;**151**:2290–2295.
5. Wasserman BA, Stone JH, Hellmann DB, Pomper MG. Reliability of normal findings on MR imaging for excluding the diagnosis of vasculitis of the central nervous system. Am J Roentgeno 2001;**177**:455–459.
6. Maclaren K, Gillespie J, Shrestha S, Neary D, Ballardie FW. Primary angiitis of the central nervous system: emerging variants. Q J Med 2005;**98**:643–654.
7. Benseler SM, Silverman E, Aviv RI, Schneider R, Armstrong D, Tyrrell PN, deVeber G. Primary Central Nervous System Vasculitis in Children. Arthritis Rheum 2006;**54**:1291–1297.
8. Gilbert GJ. Herpes zoster ophthalmicus and delayed contralateral hemiparesis. JAMA 1974;**229**:302–304.
9. Mackenzie PA, Forbes GS, Karnes WE. Angiographic findings in herpes zoster arteritis. Ann Neurol 1981;**10**:458–464.
10. Walker RJ III, el-Gammal T, Allen MB Jr. Cranial arteritis associated with herpes zoster: case report with angiographic findings. Radiology 1973;**107**:109–110.
11. Rosenblum WI, Hadfield MG. Granulomatous angiitis of the nervous system in cases of herpes zoster and lymphosarcoma. Neurology 1972;**22**:348–354.
12. Kolodny EH, Rebeiz JJ, Caviness VS, Richardson EP. Granulomatous angiitis of the central nervous system. Arch Neurol 1968;**19**:510–524.
13. Vilchez-Padilla JJ, Redon J, Ruiz A, Lopez-Aldeguer J. CNS varicella-zoster vasculitis (letter). Arch Neurol 1982;**39**:785.
14. Blue MC, Rosenblum WI. Granulomatous angiitis of the brain with herpes zoster and varicella encephalitis. Arch Pathol Lab Med 1983;**107**:126–128.
15. Rosenblum WI, Hadfield MG, Young HF. Granulomatous angiitis with preceding varicella zoster. Ann Neurol 1978;**3**:374–375.
16. Reyes MG, Fresco R, Chokroverty 5, Salud EQ. Virus-like particles in granulomatous angiitis of the central nervous system. Neurology 1976;**26**:797–799.
17. Yankner BA, Skolnik PR, Shoukimas GM, Gabuzda DH, Sobel RA, Ho D. Cerebral granulomatous angiitis associated with isolation of human T-lymphotropic virus type III from the central nervous system. Ann Neurol 1986;**20**:362–364.
18. Arthur G, Margolis G. Mycoplasma-like structures in granulomatous angiitis of the central nervous system. Arch Pathol Lab Med 1977;**101**:385–387.
19. Scolding NJ, Jayne DR, Zajicek JP, Meyer PAR, Wraight EP, Lockwood CM. The syndrome of cerebral vasculitis: recognition, diagnosis and management. Q J Med 1997;**90**:61–73.
20. Ferro JM. Vasculitis of the Central Nervous System. J Neurology 1998; **245**:766–776.
21. Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, Ellison D, Hilton DA, Williams TL, MacKenzie JM, Xuereb JH, Love S. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. Brain. 2005;**128**:500–515.
22. Lie JT. Primary (granulomatous) angiitis of the central nervous system: a clinicopathologic analysis of 15 new cases and a review of the literature. Hum Pathol 1992;**23**:164–171.
23. Hajj-Ali RA, Furlan A, Abou-Chebel A, Calabrese LH. Benign angiopathy of the central nervous system: cohort of 16 patients with clinical course and long-term follow-up. Arthritis Rheum 2002;**47**:662–669.
24. Duna GF, Calabrese LH. Limitations of invasive modalities in the diagnosis of primary angiitis of the central nervous system. J Rheumatol. 1995;**22**:662–667.
25. Engelter ST, Rueegg S, Kirsch EC, Fluri F, Probst A, Steck AJ, Lyrer PA. CADASIL mimicking primary angiitis of the central nervous system. Arch Neurol 2002;**59**:1480–1483.

26. Ferris EJ, Levine HL. Cerebral arteritis: classification. Radiology 1973;**109**:327–341.
27. Calabrese LH, Duna GF, Lie JT. Vasculitis in the Central Nervous System. Arthritis Rheum 1997;**40**:1189–1201.
28. Calabrese LH. Vasculitis of the central nervous system. Rheum Dis Clin North Am 1995;**21**:1059–1076.

## Vasculitic neuropathies

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Vasculitic neuropathies are immune mediated diseases of the peripheral nervous system, in which inflammation of the blood vessels causes damage to the nerves. We distinguish neuropathies associated with primary and secondary systemic vasculitis, with rheumatic diseases, with malignant disorders, drug-induced vasculitis and the non-systemic vasculitic neuropathies (NSVN). The typical clinical picture consists in an asymmetric or multifocal, painful sensorimotor neuropathy with an acute, subacute or chronic course and acute relapses. Neurophysiology reveals an active, asymmetric, axonal sensorimotor neuropathy. The disorders usually respond to immunosuppressive treatment. A diagnosis of definite vasculitis can be made with evidence of vasculitis in a biopsy specimen. The absence of positive morphological evidence, however, does not exclude the diagnosis. There is no single laboratory test that can prove or exclude vasculitis, in NSVN even an elaborate panel of blood tests can show normal findings. Systemic vasculitis has an incidence of 4/100 000 per year and, untreated, has a poor prognosis, which is greatly improved by the use of immunosuppressive treatment. The prognosis of NSVN is generally better, although many patients need long term immunosuppression. Current treatment recommendations for vasculitic neuropathies are presented.

## Neuromuscular junction disorders

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**Introduction:** A neuromuscular junction (NMJ) is the synapse junction of the axon terminal of a motoneuorn with the motor end plate, the highly-excitable region of muscle fiber plasma membrane responsible for initiation of action potentials across the muscle's surface, ultimately causing the muscle to contract. In vertebrates, the signal passes through the NMJ via the neurotransmitter acetylcholine (ACh). In the terminal bout on the motor nerve, structures known as presynaptic active zones accumulate synaptic vesicles filled with the ACh, which diffuses across the synaptic cleft and binds to the nicotinic acetylcholine receptors (AChR) that dot the motor end plate. The action of ACh is terminated when the enzyme acetylcholinesterase degrades the neurotransmitter and the unhydrolysed neurotransmitter diffuses away (1).

The formation of the NMJ during embryonic development is well understood. Namely, during development, the growing end of motor neuron axons secretes a protein known as agrin. This protein binds to several receptors on the surface of skeletal muscle. The receptor which seems to be required for formation of the NMJ is called the muscle specific kinase protein (MuSK protein) (2). MuSK is a receptor tyrosine kinase - meaning that it induces cellular signaling by causing the release of phosphate molecules to particular tyrosines on itself, and on proteins which bind the cytoplasmic domain of the receptor (3). Upon activation by its ligand agrin, MuSK signals via two proteins called 'Dok-7' and 'rapsyn', to induce 'clustering' of AChR. In addition to the AChR and MuSK, other proteins are then gathered, to form the endplate to the NMJ (4).

**Neuromuscular Junction Disorders:** Disorders in which the NMJ malfunctions (neuromuscular transmission/NMT disorders) include myasthenia gravis, an acquired autoimmune disease in which the AChRs on the postsynaptic membrane are destroyed, the myasthenic syndromes, heterogeneous group comprising the congenital myasthenic syndromes, botulism, Eaton-Lambert myasthenic syndrome, neuromyotonia (Syndrome of continuous muscle fiber activity; Isaacs syndrome), drug-induced myasthenias (including very high doses of some antibiotics), organophosphate poisoning (certain insecticides), some types of paralysis caused by snake venom (bungarotoxins) or by curare (an extract from plants formerly placed on the tip of some poison darts and used to paralyze and kill), and some types of nerve gases (5,6).

Research advances over the last 30 years have shown that key transmembrane proteins at the NMJ are vulnerable to antibody-mediated autoimmune attack. These targets are AChRs and muscle specific kinase (MuSK) in myasthenia gravis, voltage-gated calcium channels (VGCCs) in the Lambert-Eaton myasthenic syndrome (LEMS), and voltage-gated potassium channels (VGKCs) in neuromyotonia. In parallel with these immunological advances, mutations identified in genes encoding pre-synaptic, synaptic and postsynaptic proteins that are crucial to NMT have revealed a similar diversity of congenital myasthenic syndromes (CMS). These discoveries have had a major impact on diagnosis and management (7).

**Myasthenia gravis:** Myasthenia gravis (MG) is an autoimmune disease of the NMJ usually mediated by antibodies to AChR, which are present in 75–94% of patients with generalized MG (seropositive) (8,9,10,11,12). Patients without anti-AChR antibody have been referred to as 'seronegative'. Several lines of evidence indicate differences between seronegative and seropositive MG, for example, thymoma is rarely found in seronegative patients (13, 14). It is now known that up to 70% of seronegative MG patients have antibodies against the muscle specific receptor tyrosine kinase (MuSK), which is responsible for agrin induced AChR clustering at the postsynaptic membrane (15). A. Moreover, antibodies to other possible muscle antigens, such as titin and ryanodine receptor (RyR), are detected in some MG patients and could have an effect on muscle function, although they have so far only been reported in patients who are seropositive (16).

Myasthenia gravis encompasses all of the immunologically-mediated disorders affecting the endplate region of the postsynaptic NMJ. Nearly all of these disorders involve a loss of immunological self-tolerance, though transitory neonatal MG is self-limited disorder that follows passive transfer of maternal antibodies to the fetus. CMS stem from genetic mutations that result in abnormal NMT. MG is termed ocular MG when weakness is exclusive to the eyelids and extraocular muscles (about 15% of patients), and generalized MG when weakness extends beyond these ocular muscles (85% of patients). Seropositive MG defines disease with circulating antibodies to the AChR, while seronegative patients lack these antibodies (14).

Myasthenia gravis is a rare disorder: Contemporary prevalence rates approach 1/5 000. The disease presents with painless, fluctuating, fatigable weakness involving specific muscle groups. The main clinical feature is changeable pathologic fatigability and weakness of one or more skeletal muscles and variable distribution of affected muscles. Ocular weakness with asymmetric ptosis and binocular diplopia is the most typical initial presentation, while early or isolated oropharyngeal or limb weakness is less common. The course is variable, and most patients with initial ocular weakness develop bulbar or limb weakness within three years of initial symptom onset. MG results from antibody-mediated, T-cell-dependent immunologic attack on the endplate region of the postsynaptic membrane. In patients with fatigable muscle weak-




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ness, the diagnosis of MG is supported by: i) pharmacologic testing with edrophonium chloride that elicits unequivocal improvement in strength; ii) electrophysiological testing with repetitive nerve stimulation studies and/or single-fiber electromyography that demonstrates a primary postsynaptic neuromuscular junctional disorder; and iii) serologic demonstration of AChR or MuSK antibodies. Differential diagnosis includes CMSs, LEMS, botulism, and organophosphate intoxication, mitochondrial disorders involving progressive external ophthalmoplegia, acute inflammatory demyelinating polyradiculoneuropathy, motor neuron disease, and brainstem ischemia. Treatment must be individualized, and may include symptomatic treatment with cholinesterase inhibitors and immune modulation with corticosteroids, azathioprine, cyclosporine, and mycophenolate mofetil. Rapid, temporary improvement may be achieved for myasthenic crises and exacerbations with plasma exchange (PEX) or intravenous immunoglobulin (IVIg). Owing to improved diagnostic testing, immunotherapy, and intensive care, the contemporary prognosis is favorable with less than five percent mortality and nearly normal life expectancy (13). Recently (5) it was published 'Guidelines for the treatment of autoimmune neuromuscular transmission disorders' which was agreed upon by the European Federation of Neurological Societies (EFNS) Task Force. In case of MG it is as follows: i) Anticholinesetarse drugs should be the first drug to be given in the management of MG (good practice point); ii) Plasma exchange is recommended as a short-term treatment, especially in severe cases to induce remission and in preparation for surgery (level B recommendation); iii) Intravenous immunoglobulin and plasma exchange are equally effective for the treatment of MG exacerbations (level A recommendation); iv) For patients with non-thymomatous autoimmune MG, thymectomy is recommended as an option to increase the probability of remission or improvement (level B recommendation); v) Once thymoma is diagnosed thymectomy is indicated irrespective of the severity of MG (level A recommendation); vi) Oral corticosteroids is a first choice drug when immunosuppressive drugs are necessary (good practice point); vii) In patients where long-term immunosuppression is necessary, azathioprine is recommended together with steroids to allow tapering the steroids to the lowest possible dose whilst maintaining azathioprine (level A recommendation).

**Congenital myasthenic syndromes:** Congenital myasthenic syndromes are a heterogeneous group of genetically determined non-autoimmune disorders affecting NMT, with an estimated prevalence of less than 1/500 000 (17). All of the ones that have been described to date are transmitted in an autosomal recessive inheritance pattern, with the exception of the autosomal dominant slow channel syndrome. The defective components of NMT in a particular syndrome are frequently presynaptic involving the ACR, but can be postsynaptic, or both (17, 18). The presynaptic defects involve the synthesis, packing, and release of acetylcholine quanta. The combined presynaptic and postsynaptic defects involve a deficiency of acetylcholinesterase, and the postsynaptic defects involve kinetic abnormalities of the ACRs (6). The understanding of the molecular basis of the different types of CMSs has evolved rapidly in recent years. Mutations were first identified in the subunits of the nicotinic AChR, but now mutations in ten different genes – encoding post-, pre- or synaptic proteins – are known to cause CMSs. Pathogenic mechanisms leading to an impaired NMT modify ACRs or endplate structure or lead to decreased Ach synthesis and release. However, the genetic background of many CMS forms is still unresolved (18). CMSs should be considered in the differential diagnosis of seronegative MG and other neuromuscular disorders. They are present at birth but may not manifest until childhood or adult life (19). Strategies for therapy are based on whether a given CMS decreases or increases the synaptic response to acetylcholine (ACh). Cholinesterase inhibitors that increase the synaptic response to ACh and 3, 4-diaminopyridine, which increases ACh release, are useful when the synaptic response to ACh is attenuated. Long-lived open-channel blockers of the AChR, guanidine, and fluoxetine, are useful when the synaptic response is increased by abnormally prolonged opening episodes of the AChR channel. Ephedrine has beneficial effects in some CMSs but its mechanism of action is not understood (20). Slow channel syndrome usually does not become apparent till adolescence, sometimes only in early adulthood. It is due to an excessively prolonged opening time of the cation channels of the AChR. Unlike in MG, muscle atrophy is present. The treatments that are beneficial in MG, for example anticholinesterase drug, have no effect, but fluoxetine can be very effective (21).

**Lambert-Eaton myasthenic syndrome:** Lambert-Eaton myasthenic syndrome is a rare disorder of the neuromuscular junction causing muscle weakness (most commonly in the upper arms and legs). It is an autoimmune disease in which the body's own antibodies prevent the release of the chemical acetylcholine. This interferes with transmission of nerve impulses to the muscles. LEMS usually precedes, occurs with, or develops after certain cancers, especially lung cancer. Eaton-Lambert syndrome causes muscle weakness, but persistent use of a muscle causes an increase rather than a decrease in strength (as occurs in MG). People also tire easily. The mouth is dry, the eyelid droops, and the upper arms and thighs are painful. Men may have erectile dysfunction. Symptoms suggest the diagnosis, but electromyography is needed to confirm the diagnosis. Treating cancer, if present, sometimes relieves symptoms due to LEMS. Guanidine, a drug that increases the release of ACh, often lessens symptoms but may inhibit the bone marrow's production of blood cells and impair liver function. Corticosteroids and plasmapheresis help some people (22). According to EFNS Task Force Guidelines 3, 4-diaminopyridine is recommended as symptomatic treatment and intravenous immunoglobulin has a positive short-term effect in LEMS (good practice point), and for immunosuppressive treatment of LEMS it is reasonable to adapt treatment procedures by analog with MG (good practice point) (5).

**Botulism:** Botulism is caused by a neurotoxin produced from the anaerobic, spore forming bacteria–clostridium botulinum. The disease is usually caused by toxins type A, B and E. Since the disease was first recognized in the beginning of the nineteenth century as food poisoning, different forms of intoxication were described. Infantile botulism, wound botulism, infectious botulism and inadvertent botulism are all clinical syndromes caused by the same toxin. Botulism is characterized by its classic triad: i) symmetric descending flaccid paralysis with prominent bulbar palsies ii) afebrile patient iii) clear sensorium. The paralysis usually begins in the cranial nerves where blurred vision, dysarthia and dysphagia are the initial complaints. Diagnosis is based on clinical findings, history of suspicious exposure and supportive ancillary testing to rule out other causes of neurologic dysfunction that mimic botulism such as the Guillain-Barre syndrome, MG or cerebrovascular stroke. Laboratory confirmation of suspected cases is usually delayed and treatment should begin before confirmation is completed. The treatment includes supportive care, and the administration of antitoxin which reduces mortality if given early. Laboratory proof of botulism is established with the detection of toxin in the patient's serum, stool, or wound. The detection of Clostridium botulinum bacteria in the stool or wound should also be considered evidence of clinical botulism. Electrophysiological studies can provide presumptive of botulism in patients with the clinical signs of botulism. Electrophysiological testing can be especially helpful when bioassay studies are negative. The most consistent electrophysiological abnormality is a small evoked muscle action potential in response to a single supramaximal nerve stimulus in a clinically affected muscle. Posttetanic facilitation can be found in some affected muscles.



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Single-fiber electromyographic (EMG) studies typically reveal increased jitter and blocking, which become less marked following activation. The major treatment for severe botulism is advance medical and nursing supportive care with special attention to respiratory status (23, 24).

**Neuromyotonia:** Neuromyotonia (Syndrome of continuous muscle fiber activity; Isaacs syndrome), disease first described by Isaacs in 1961 (25), is characterized by muscle rigidity, spontaneous fine wave-like contraction in muscle (myokymia), and continuous spontaneous muscle fiber activity on EMG studies, recently identified as an immune-mediated channelopathy (6, 26, 27). Cases of neuromyotonia are usually sporadic and only rarely familial. The disease can appear relatively suddenly at any age. All neuromyotonia patients should be treated symptomatically with an anti-epileptic drug that reduces peripheral nerve hyperexcitability (5, 28, 29, 30).

**References:**


1. Kandel ER, Schwartz JH, Jessell TM. Priciples of Neural Science, 4th ed., New York: McGraw-Hill, 2000
2. DeChiara T, Bowen D, Valenzuela D, Simmons M, Poueymirou W, Thomas S, Kinetz E, Compton D, Rojas E, Park J, Smith C, DiStefano P, Glass D, Burden S, Yancopoulos G. ''The receptor tyrosine kinase MuSK is required for neuromuscular junction formation in vivo''. Cell 1996;**85**(4):501–512.
3. Valenzuela D, Stitt T, DiStefano P, Rojas E, Mattsson K, Compton D, Nuñez L, Park J, Stark J, Gies D. ''Receptor tyrosine sinase specific for the skeletal muscle lineage: expression in embryonic muscle, at the neuromuscular junction, and after injury''. Neuron 1995;**15**(3):573–584.
4. Glass D, Bowen D, Stitt T, Radziejewski C, Bruno J, Ryan T, Gies D, Shah S, Mattsson K, Burden S, DiStefano P, Valenzuela D, DeChiara T, Yancopoulos G. ''Agrin acts via a MuSK receptor complex''. Cell 1996;**85**(4):513–523.
5. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Hart IK, Harms L, Hilton-Jones D, Melms A, Verschuuren J, Horge HW. Guidelines for the treatment of auotoimmune neuromuscular transmission disorders. Europ J Neurol 2006;**13**(7):691–699.
6. Mumenthaler M, Mattle H. Neurology. 4th edition. George Thieme Verlag; New York, 2004.
7. Newsom/Davis J. The emerging diversity of neuromusuclar junction disorders. Acta Myol 2007;**26**(1):5–10.
8. Sinanović O, Zonic L, Pejanovic Škobic N, Salihovic D, Piric N. Myasthenia gravis: some clinical data of 58 patients. Acta Myologica 2007;**25**(3):142.
9. Sanders DB, Andrewa PI, Howard JF Jr. Seronegative myasthenia gravis. Neurology 1997;**48**(Suppl 5):S40–S45.
10. Nemoto Y, Kuwabara S, Misawa S, Kawaguchi N, Hattori T, Takamori M, Vincent A. Patterns and severity of neuromuscular transmission failure in seronegative myasthenia gravis. J Neurol Neurosurg Psychiatry 2005;**75**:714–718.
11. Lavrnic D, Losen M, Vujic A, De Baets M, Hajdukovic LJ, Stojanovic V, Trikic R, Djukic P, Apostolski S. The features of myasthenia gravis with autoantibodies to MuSK. J Neurol Neurosurg Psychiatry 2005;**76**:10099–1102.
12. Sinanović O, Karamehić J, Dizdarević Z. Imunološki aspekti neuroloških bolesti. U: Karamehić J, Dizdarević Z i saradnici. Klinička imunologija. Sarajevo: Svjetlost, 2007:513–542.
13. Verma OK, Oger JJ. Seronegative generalized myasthenia gravis: low frequency of thymic pathology. Neurology 1992; 42:586–589.
14. Juel VC, Massey JM. Myasthenia gravis. Orphanet J Rare Dis 2007;**2**:44.
15. Hoch W, Mcconville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med 2001;**7**:365–368.
16. Skeie GO, Lunde PK, Sejersted OM, Mygland A, Aarli JA, Gilhus NE. Autoimmunity against the ryanodine receptor in myasthenia gravis. Acta Physiol Scand 2001;**171**(3):379–384.
17. Middleton LT. Congenital Myasthenic Syndromes. In: Emery AEH ed. Neuromusuclar Disorders: Clinical and Molecular Genetics. John Wiley and Sons: Chichester 1999:469–485.
18. Muller JS, Mihaylova V, Abicht A, Lochmuller H. Congenital myasthenic syndromes. Spotling on genetic defects of neuromuscular transmission. Expert Rev Mol Med 2007;**9**(22):1–20.
19. Harper CM. Congenital myasthenic syndromes. Semin Neurol 2004;**24**(81):111–123.
20. Engel AG. The therpy of congenital myasthenic syndromes. Neurotherapeutics 2007;**42**:252–257.
21. Colomer J, Müller JS, Vernet A, Nascimento A, Pons M, Gonzalez V, Abicht A, Lochmüller H. Long-term improvement of slow-channel congenital myasthenic syndrome with fluoxetine. Neuromuscul Disord 2006;**16**(5):329–333.
22. Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome. Cochrane Database Syst Rev 2005;(2):CD003279.
23. Cherington M. Clinical spectrum of botulism. Muscle Nerve 1998;**21**6:701–710.
24. Cherington M. Botulism: update and review. Semin Neurol 2002;**24**(29):155–163.
25. Isaacs H. Syndrome of continuous muscle-fibre activity. J Neurol Neurosurg Psychiatry 1961;**30**:319–325.
26. Gonzalez G, Barros G, Russi ME, Nunez A, Scavone C. Acquierd neuromyotonia in childhood: a case report and review. Pediatr Neurol 2008;**38**1:61–63.
27. Sinanović O, Jušić A. Neuromiotonija kod dvanaestogodišnje djevojčice. U: Jušić A (urednik). Novosti u neuromuskularnim bolestima i elektromioneurografiji. Školska knjiga; Zagreb, 1989:270–274.
28. Sinanović O, Burina A, Tupković E. The drug treatment of myotonic muscle stiffness. Acta Cardiomiol 1991;**2**:215–220.
29. Sinanović O. Neuromyotonia. In: Ratner AY (ed). Children's Neurology Problems. Kasan, 1991:141–142.
30. Sinanović O. Myotonic disorders. Neurol Croat 2007;**56** Suppl 1:125–132.


## Polymyositis, dermatomyositis and inclusion-body myositis


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**Introduction:** The inflammatory myopathies or myositis are a group of diseases that involve chronic muscle inflammation, accompanied by muscle weakness. The inflammatory process leads to destruction of muscle tissue, and is accompanied by weakness and sometimes pain. Over time, atrophy occurs. In most cases, the cause of an inflammatory myopathy is unclear. For some reason, the body's immune system turns against its own muscles and damages muscle tissue in an autoimmune response. The condition is rare and illness can affect the skin and muscles, and frequently other parts of the body including joints, lungs, gut and blood vessels.

Diagnosis is based on the patient's medical history, results of a physical exam and tests of muscle strength, and blood samples that show elevated levels of various muscle enzymes and autoantibodies.

There are three main types of inflammatory myopathy:

*polymyositis*, a disease that affects skeletal muscles;

*dermatomyositis*, a disease that affects skeletal muscles and skin;

*inclusion-body myositis*, a disease of older people, partly inflammatory and partly a degenerative muscle disease.

Clinical features, characteristic muscle biopsy findings, immune markers, and histopathologic findings differentiate these illnesses.

In both PM and DM, immune-mediated muscle inflammation and vascular damage occur. In PM, the immune system is primed to act against previously unrecognized muscle antigens. In DM, complement-mediated damage to endomysial vessels and microvasculature of the dermis occurs.

In 1975, Bohan and Peter first suggested a set of criteria to aid in the diagnosis and classification of dermatomyositis and polymyositis. Four of the 5 criteria are related to the muscle disease, as follows: progressive proximal symmetrical weakness, elevated




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muscle enzymes, an abnormal finding on electromyogram, and an abnormal finding on the muscle biopsy sample. The fifth criterion was compatible cutaneous disease. PM and DM have many shared clinical features. Both are inflammatory myopathies that present as symmetric muscle weakness that develops over weeks to months. Both conditions may be associated with malignancies. Despite these similarities, muscle biopsy findings and characteristic skin findings of DM reveal each as a distinct clinical entity. Both PM and DM are more common in females, while IBM occurs more frequently in men.

**Polymyositis (PM)** PM is a disease of adults. It is rarely seen in persons under age 18; most cases are in adults between the ages of 31 and 60. Slow, but progressive muscle weakness starts in the proximal muscles. The incidence has been estimated at 3.9–4.1 cases per million people. People with PM may also experience difficulty swallowing, but muscles are usually painless. Presence of malignancy has been reported in 10–15% of patients, and 50% in patients older than 65 years.

**Dermatomyositis (DM)** The diseases can affect people of any age. A female preponderance has been reported. The incidence has been estimated at 4.9–5.5 cases per million people fror adult, and at 1.9–3.2 for juvenile form of disease. Cardinal symptom of DM is a skin rash that precedes or accompanies progressive muscle weakness. The rash looks patchy, with red discolorations, and characteristically develops on the eyelids and on knuckles, elbows, heels and toes. Adults with dermatomyositis may experience low-grade fever and be sensitive to light. Muscle involvement is manifested by proximal muscle weakness. Children and adults with dermatomyositis may develop calcium deposits, which appear as hard bumps under the skin or in the muscle (called calcinosis). Calcinosis most often occurs 1–3 years after the disease begins. These deposits are seen more often in children with dermatomyositis than in adults. Dysphagia occures in 1/3 patients, and 50% of children and 25% of adults experience muscle pain. Dermatomyositis may be associated with collagen-vascular or autoimmune diseases. Malignancy is possible in 10–15% of patients, but it occurs more frequently in adults older than 50 years.

**Inclusion body myositis (IBM)** IBM is rare disease. Sporadic inclusion body myositis (s-IBM) and hereditary inclusion body myopathies (h-IBM) encompass a group of disorders sharing the common pathological finding of vacuoles and filamentous inclusions. According to population-based studies, a prevalence of 5–7.9 per million was reported. The onset of muscle weakness in IBM is generally gradual (over months or years) and affects both proximal and distal muscles. Muscle weakness may affect only one side of the body. Symptoms of the disease usually begin after the age of 50, although the disease can occur earlier. IBM occurs more frequently in men than in women. Clinical suspicion for s-IBM should be very high when the pattern of weakness affects (1) the finger/wrist flexors out of proportion to the finger/wrist extensors and shoulder abductors or (2) knee extensors disproportionate to the hip flexors. Dysphagia is common, occurring in 50% of patients. Muscle biopsy is the criterion standard for ascertaining the diagnosis of s-IBM.

**Rare forms of myositis** Eosinophilic myositis (EM) is a rare entity characterized by eosinophilic infiltration of skeletal muscles, usually associated with parasite infections, inflammatory systemic disorders, or the intake of drugs. Mutations in CAPN3 (gene encoding calpain-3) can cause EM. Thus, a subset of idiopathic EM is genetically determined, with an autosomal recessive mode of inheritance. Patients presented with a triad that appears to be indicative of CAPN3 mutations: EM in the first decade, elevated serum creatine phosphokinase levels (isolated or with little corresponding weakness), and inconstant peripheral hypereosinophilia.

Amyopathic dermatomyositis is a variant of dermatomyositis that is characterized by the typical skin rash but without the muscle abnormalities. Interstitial lung disease is frequent in amyopathic dermatomyositis.

Orbital myositis is a relatively rare ocular inflammatory disease. It is currently classified as an idiopathic orbital inflammatory disease, but has been associated with ocular and systemic disorders, including scleritis, rheumatoid arthritis, Crohn's disease, and systemic lupus erythematosis. Orbital myositis has also been associated with infectious disease such as streptococcal pharyngitis, viral upper respiratory infection, and Borrelia burgdorferi infection.

**Pathologic findings** Polymyositis biopsy shows endomysial inflammation with invasion of fibers by lymphocites, but unlike s-IBM, rimmed vacuoles and ragged red fibers are infrequent and amyloid deposits and tubulofilaments not seen.

Characteristic biopsy findings FOR DM are perifascular atrophy, muscle infarcts, microvascular macrophage deposits in the endomysium, focal capillary depletion, and conspicuous alterations in endothelial cells of endomysial microvasculature.

In IBM muscle biopsy sample shows myopathic changes with varying degrees of inflammation, predominantly within the endomysium. The biopsy sample is unique because of its *inclusion bodies*, for which the disease is named. These "bodies" which don't appear in normal cells, contain clumps of discarded cellular material. Inflammatory cells can be seen invading muscle tissue. Intracellular amyloid deposits tend to occur adjacent to vacuoles and are wispy or plaquelike in appearance.

**Autoantibodies** An autoimmune response to nuclear and cytoplasmic autoantigens is detected in patients with PM and DM. Some serum autoantibodies are shared with other autoimmune diseases (ie, myositis-associated antibodies: MAA), and some are unique to myositis (myositis-specific antibodies: MSA). The MSA are found in approximately 50% of patients with PM and in only 10% of children patients. The MSA were discoverd 20 years ago. As many as 6 of 20 aminoacyl-tRNA synthetases have been described, but anti-histidyl-tRNA synthetase (Jo-1) is most common (20–30%). Autoantibodies directed toward the other synthetases specific for alanine (anti-PL12), glycine (anti-EJ), isoleucine (anti-OJ), threonine (anti-PL7), and asparagine (anti-KS). Anti-Jo-1 autoantibodies were originally described as precipitating autoantibodies in sera of patients with PM. Anti-Mi-2 antibodies recognize a major protein of a nuclear complex formed by at least 7 proteins that is involved in the transcription process. Autoantibodies recognizing Mi-2 are considered specific serologic markers of DM. The MAA are found in the sera of 20–50% of patients and are commonly encountered in other connective tissue diseases. The most important antigenic targets of the MAA are the PM/Scl nucleolar antigen, the nuclear Ku antigen, the small nuclear ribonucleoproteins (snRNP), and the cytoplasmic ribonucleoproteins (RoRNP). Recently, novel MSA was identified in clinically amyopathic dermatomyositis (anti-CADM-140 antibody) and malignancy-associated myositis (anti-p155 and anti-p155/p140 antibodies). Recent findings suggest cytokines as important key molecules in the pathogenic mechanisms of idiopathic inflammatory myopathies.

**Therapy** The standard treatment for PM and DM is a corticosteroid drug. Immunosuppressant drugs, such as azathioprine and methotrexate, may reduce inflammation in people who do not respond well to prednisone. Periodic treatment using intravenous immunoglobulin can also improve recovery. Other immunosuppressive agents used to treat the inflammation associated with polymyositis include cyclosporine A, cyclophosphamide, and Infiximab. No definitive treatment has been proven effective for IBM, since it is resistant to corticosteroids and immunosuppressive drugs.

Physical therapy is usually recommended to prevent muscle atrophy and to regain muscle strength and range of motion.



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# MAIN THEME: VERTIGO

## Vertigo – clinical picture and classification

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Body position in space is controlled by ocular, vestibular and somatosensory system. Somatosensory system provides information from skin, muscles and joints, most important being proprioceptive system located in the neck muscles and joints. Information from these three systems are processed in the brain stem, and finally integrated into the cortical perception system enabling postural reflexes that maintenance of body position in space, and conscious perception of spatial orientation (1).

Mismatch of this sensory information causes vertigo. Vertigo is defined as a hallucination of movement or erroneous perception of self or object motion. It is usually unpleasant sensation due to distortion of the static gravitational orientation perceived by the cortical spatial perceptional system, associated with difficulties in balance and gait. This erroneous perception of motion of person or environment may be linear or angular (rotatory). Central compensatory mechanisms enable deficiencies in one area to be overcome by other intact sensory systems (1,2).

Vertigo is a symptom that is perceived at higher cortical levels. Vertigo may be due to excessive physiological stimulation or pathological dysfunction. Symptoms that most often accompany vertigo include nausea, vomiting, nystagmus, and imbalance in standing and walking. Patients with vertigo may also complain of dizziness, lightheadedness, unsteadiness, imbalance, spinning, floating, and swaying. Gait imbalance or ataxia result from inappropriate or abnormal signals from the vestibulospinal system. Nausea and vomiting may occur from activation of the chemoreceptor trigger zone in the medullar vomiting center. Nystagmus may be observed as a result from dysfunction of the vestibulo-ocular system (1,2,3).

Vertigo is among the most common symptoms causing patients to visit a physician, almost as common as back pain and headache. The overall incidence of vertigo is 20–30% (4), reaching 50% in older patients and it is the most frequent symptom in patients older than 75 years (5). Vertigo was a cause for 2% of consultations in general practice in United Kingdom (6).

Vertigo can be caused by an inner ear disturbance – peripheral vertigo, by a central (brain) disturbance – central vertigo, by systemic diseases, or it can be psychogenic. Most authors take vestibular nuclei in brainstem as a point differencing peripheral (before vestibular nuclei) and central vertigo (after vestibular nuclei). As a result central compensatory mechanisms, symptoms of peripheral labyrinth dysfunction will eventually recover. Symptoms of central nervous dysfunction, although usually milder, tend to persist over time (1,2,7).

The most common causes of peripheral vertigo include benign paroxysmal positional vertigo (BPPV), vestibular neuronitis and Méniére's disease. The most common cause of central dizziness is migraine, frequently referred to as vestibular migraine or migraine-associated dizziness, while other central causes include vertebrobasilar insufficiency, cerebellar and brainstem lesions, acoustic tumors, and demyelination (2, 9).

Vertigo could be produced by physiological and pathological causes. In physiological vertigo the sense of disequilibrium is due to physiological excess of visual, vestibular, or somatosensory signals which cannot be compensated by the other systems. In pathological vertigo there is an abnormal sensory signal (from the sensors) or abnormal signal processing (by the central nervous system) (10,11).

**Physiological vertigo:** Physiological vertigo occurs in normal individuals when the brain is confronted with a mismatch among the three stabilizing sensory systems when the vestibular system is subjected to unfamiliar head movements to which it is un-adapted, such as in seasickness; unusual head/neck positions, such as the extreme head extension (e.g. painting a ceiling); or following a spin. Intersensory mismatch also explains carsickness, height vertigo, and the visual vertigo most commonly experienced with inadequate during motion picture chase scenes where the visual sensation of environmental movement is unaccompanied by concomitant vestibular and somatosensory movement information, or when inadequate spectacles are worn. Space sickness, a frequent transient effect of active head movement in the weightless zero-gravity environment, is another example of physiological vertigo (1,3,9,11,12).

**Pathological vertigo:** Pathological vertigo results from lesions of the visual, somatosensory, or vestibular systems. Visual pathological vertigo occurs or by the sudden onset of an extra-ocular muscle paresis usually accompanied with diplopia. Somatosensory vertigo, rare in isolation, is usually due to a peripheral neuropathy or myelopathy especially of dorsal columns that reduces the sensory input necessary for central compensation when there is dysfunction of the vestibular or visual systems. In the past the most often cause was tabes dorsalis (2,3,10).

However, the most common cause of pathological vertigo is vestibular dysfunction. Pathological vestibular vertigo can be due to either peripheral labyrinth dysfunction, systemic derangement (such as metabolic, endocrine, or circulatory abnormalities), or central vestibular dysfunction. This vertigo is frequently accompanied by nausea, nystagmus, postural unsteadiness, and gait ataxia. Psychogenical vertigo results from hyperventilation in a patient with known psychiatric disease who can complain of severe vertigo without associated nystagmus or other physical findings. Severely incapacitating vertigo may be seen in anxiety attacks (2,5,9).

Sudden onset and vivid memory of vertiginous episodes are often due to inner-ear disease, especially if hearing loss, ear pressure, or tinnitus is also present. Gradual and ill-defined symptoms are most common in central nervous system (CNS), cardiac, and systemic diseases. The time course of vertigo is also important. Episodic true vertigo that lasts for seconds and is associated with head or body position changes is probably due to BPPV. Vertigo that lasts for hours or days is probably caused by Méniére's disease or vestibular neuronitis. Patients with peripheral vertigo can usually ambulate during episodes and are consciously aware of their environment (3,5,7,8,13).

Vertigo of sudden onset that lasts for minutes can be due to brain or vascular disease, especially if cerebrovascular risk factors are present. Central vertigo secondary to brainstem or cerebellar ischemia is often associated with other brainstem characteristics, including diplopia, autonomic symptoms, nausea, dysarthria, dysphagia, or focal weakness. Patients with cerebellar disease are frequently unable to ambulate during acute episodes of vertigo. Dysdiadochokinesis and gait ataxia during episodes are more likely due to cerebellar diseases, especially in the elderly population. Sensory and motor symptoms and signs are usually associated with CNS diseases (10,11,13,11,14,15).




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**Causes of vertigo:** The most common systemic causes of vertigo include cardiac disease, arterial hypertension and hypotension, hematological diseases (e.g. anemia, leukemia, lymphomas, polycytemia), hypoglycemia, hypoadrenalism, Cogan's syndrome (interstitial keratitis with vestibular symptoms) and cervical vertigo.

Psychogenic vertigo results most often from hyperventilation in a patient with known psychiatric disease. A patient with psychogenic vertigo may have a subjective complaint of severe vertigo without associated nystagmus or other physical findings. Severely incapacitating vertigo may be seen in anxiety attacks or in severe height vertigo (acrophobia). Psychogenic vertigo would be treated based on the underlying psychiatric diagnosis. Psychotherapy and desensitization procedures are often useful. A diagnosis of psychogenic vertigo presumes that no physical findings substantiate an organic cause for the vertigo symptoms (18).

**The most common causes of peripheral vertigo:** One of the most common peripheral vestibular syndromes is benign paroxysmal positional vertigo (BPPV), which may occur at any age. The characteristic history is of brief episodes of positionally induced vertigo, particularly with rapid changes in position such as getting out of bed. The true vertigo or rotational sensation usually lasts less than 1 min; however, a non-specific dizziness often described as a swimming sensation or disequilibrium, may last hours to days. BPPV has often been described as 'self-limiting' because symptoms often subside or disappear within 6 months of onset. Although BPPV usually remits spontaneously, one third of patients have recurrent symptoms for more than 1 year (19,20).

Acute unilateral labyrinth dysfunction (vestibular neuritis or neuronitis) presents with the acute onset of severe vertigo with associated positional imbalance, nausea, and nystagmus. This syndrome is different from benign paroxysmal vertigo because it has a much more prolonged course, is usually more severe, and is not positionally induced. Vestibular neuronitis often has viral etiology. In vestibular neuronitis, due to the reduced signal from the affected side, the nystagmus fast phase is directed away from the affected side 3 to 5 days after the onset of acute vertigo the patient will probably have spontaneous resolution of nausea and be able to partially suppress nystagmus by fixation. Generally, within 2 to 3 weeks vertigo ceases (21,22).

Méniére's disease (endolymphatic hydrops) is a common cause of recurrent vertigo and auditory symptoms. Méniére's disease is characterized by fluctuating hearing loss in the low frequencies, a sensation of ear fullness or pressure and tinnitus, and prolonged vertigo reaching its maximum over minutes and resolving over hours with associated postural imbalance and nausea. There is often a low tolerance for loud noises. During the vertigo attack, which usually lasts 30 to 60 min, a characteristic nystagmus is seen, with the fast phase away from the affected ear (23).

Toxic substances known to cause vertigo and auditory symptoms include alcohol intake, heavy metal exposure and drugs. Aminoglycoside antibiotics such as streptomycin and gentamicin are known vestibular toxins, while neomycin and kanamycin are ototoxic. Other vestibulotoxic and ototoxic drugs include acetylsalycilic acid intoxication, chloroquine, furosemide, quinidine and quinine (24).

**Central vertigo:** Central causes of vertigo are less common than peripheral. Causes of vestibular vertigo include migraine, cerebrovascular diseases of the posterior cerebral circulation including transient ischemia attack (TIA) (vertebrobasilar insufficiency), epilepsy, demyelinating disease of the posterior fossa, congenital malformations such as Arnold-Chiari malformation, subdural hematoma, fractures, cysts, arachnoiditis, syringobulbia, platibasia, neoplastic diseases, degenerative diseases of the posterior fossa, infectious diseases, toxic lesions, lesions of temporal lobe, and supratentorial lesions compressing brainstem (1,2,14,15).

Lesions of the vestibular nuclei and the vestibular portion of the cerebellum may cause vertigo, nystagmus, disequilibrium, and nausea, there are usually other signs of central nervous system dysfunction. Symptoms result from involvement of brain stem structures responsible for eye movement, speech, sensation of the face, extremities, and trunk, and motor control of the facial muscles and extremities. The presence of other neurological signs helps distinguish central from peripheral vertigo. Central vertigo tends to be less severe with fewer autonomic symptoms such as nausea and vomiting. Central vertigo tends to persist over longer periods of time and tends to occur in less sudden or severe attacks, except in the case of migraine or vascular disease (1,2,15,25).

Due to the dysfunction of brain stem compensating structures in central vertigo syndromes, vertigo, as well as nystagmus, may persist over considerable periods of time. Central nystagmus looks more severe than the patient's corresponding symptoms of vertigo or nausea. Postural changes tend to stimulate peripheral vertigo more than central one. Peripheral vertigo tends to be reduced with fixation with the eyes open. Central vertigo tends to be worse with the eyes open, because of the conflict of visual and vestibular information. With the eyes closed, the visual information is reduced, which reduces the visual vestibular conflict and reduces the sense of vertigo. Peripheral vertigo tends to fatigue with repeated head movements because of intact brainstem compensation mechanisms. In central vertigo the vertigo does not fatigue or habituate with repeated movements, however it may vary on a day to day basis (2,25,26,27).

**Cerebrovascular diseases:** Vertebrobasilar insufficiency (TIA of the posterior cerebral circulation) denotes reversible episode of focal ischemic neurological deficit that most often last 2–15 min causing transient neurological symptoms. Vertebral-artery disease can cause transient attacks of vertigo that are usually accompanied by other brain-stem or cerebellar symptoms (25).

The most common causes of vertebrobasilar ischemia are embolism, large-artery atherosclerosis causing arterial stenosis and occlusion, penetrating small-artery disease, artery dissection and subclavian steal syndrome (narrowing of subclavian artery proximally to the vertebral artery origin when blood flows around through left and right vertebral artery, and posterior parts of brain receives insufficient blood supply causing neurological symptoms). Stenosis and occlusion most often occur at or near the origin of vertebral artery (26,27).

Posterior-circulation ischemia rarely causes only one symptom but rather produces a collection of symptoms and signs. Symptoms and signs depend on the affected part of brain: brain stem (medulla, pons, midbrain), cerebellum, and posterior parts of brain (26).

Dizziness, vertigo, headache, vomiting, double vision, loss and blurring of vision, ataxia, numbness and/or weakness, gait and limb ataxia, oculomotor palsies, and oropharyngeal dysfunction are frequent symptoms in patients with vertebrobasilar artery disease (25,26,27).

TIA can occur after a patient has been standing or in situations that reduce blood pressure or blood flow. These symptoms are related to ischemia of vestibulocerebellar structures in the medulla and cerebellum, most often consisting of dizziness, difficulty focusing visually, vertigo, loss of balance, and spells of decreased vision and ataxia (25,26,27).

Patients with cerebellar infarcts often report dizziness, occasionally in conjunction with frank vertigo, blurred vision, difficult in walking, and vomiting. They often veer to one side and cannot sit upright or maintain an erect posture without support. Patients may have hypotonia of the arm on the side of the infarct.

Ischemic infarcts can involve one posterior cerebral artery, which most often leads to a hemianopia of the contralateral visual field. Hemisensory symptoms may be present on the same side of the body and face as the hemianopia. Difficulty reading and naming colors often accompanies large infarcts of the left posterior cerebral



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artery, whereas neglect of the left visual field and disorientation to place may accompany infarcts of the right posterior cerebral artery (25,26,27).

Stenosis and occlusion of the basilar artery usually cause bilateral symptoms or crossed findings: ipsilateral symptoms of cranial nerves and contraleral symptoms of the trunk and limbs. Embolic infarction of the rostral midbrain and thalamus leads to a top-of-the-basilar syndrome characterized by somnolence and sometimes, stupor; inability to make new memories; small, poorly reactive pupils and defective vertical gaze, and when severe, can cause the locked-in syndrome (25,27,28).

Wallenberg, or lateral medullary, syndrome occlusion of vertebral or posterior cerebellar artery causing vertigo, nausea, vomiting, facial pain, ataxia, nystagmus, diplopiae, ipsilateral decreased pain and temperature in face, Horner's syndrome, limb ataxia, laryngeal and pharyngeal paralysis causing hoarseness, dysphagia and contralateral decreased pain and temperature sensations in trunk and limbs (1,2,3,25).

Occlusion of superior cerebellar artery causes vertigo, ipsilateral deafness, facial paresis and ispilateral ataxia. Occlusion of labyrinth artery causes infarction of labyrint with vertigo, deafness and nystagmus. (1,2,25).

**Vertebral artery dissection:** Vertebral artery dissection may be caused by trauma of cervical spine such as whiplash injury, fierce rotational movements of head, manipulative therapy of the neck, by hiperextension of the neck, and by degenerative spondylotic changes of cervical spine, by hereditary connective tissue disorders and genetic disorders, migraine, high serum homocysteine level, infection, and use of oral contraceptives. The vertebral artery is most mobile and thus most vulnerable to mechanical injury at C1 to C2 as it leaves the transverse foramen of the axis vertebra and suddenly turns to enter the intracranial cavity. Women are 2.5 times more frequently affected by the extracranial vertebral dissections. Intracranial vertebral artery dissections are more common in men (25,28).

The cardinal symptom in patients with vertebral artery dissections is pain, most often in the posterior part of the neck or occiput, spreading into the shoulder. Diffuse, mostly occipital, headache, dizziness, diplopia, also occurs. Intracranial vertebral artery dissections cause medullary, cerebellar, and pontine ischemia and can cause subarachnoidal hemorrhage (28,29,30).

**Tumors of pontocerebellar angle:** Tumors of pontocerebellar angle are most often benign. In younger patients the most frequent is acoustic neuroma, while in older patients meningeoma is more common.

Earliest symptoms of tumors of pontocerebellar angle include unilateral sensorineural hearing loss/deafness, disturbed sense of balance and altered gait, vertigo with associated nausea and vomiting, and pressure in the ear, all of which can be attributed to the disruption of normal vestibulocochlear nerve function. Additionally most patients have reported tinnitus (most often a unilateral high-pitched ringing, sometimes a machinery-like roaring or hissing sound, like a steam kettle). Large tumors of pontocerebellar angle may affect other local cranial nerves. Involvement of the facial nerve may lead to facial weakness, and impairment of glandular secretions; involvement of the trigeminal nerve may lead to loss of taste and loss of sensation in the face and mouth, involvement of the glossopharyngeal and vagal nerves may lead to altered gag or swallowing reflexes. Even larger tumors may compress the adjacent brainstem and lead to increased intracranial pressure, with its associated symptoms such as headache, vomiting, and altered consciousness (31,32).

**Migraine and vertigo:** Many patients with migraine have vertigo, between 26.5–42% of migraine patients experience vertigo. Almost one third of them have vertigo even without headache, while others experience vertigo during and after headache episode. Patients having migraine with aura have vertigo more often, probably because they can experience vertigo during aura (33,34,35). On the other hand, 16–32% patients with vertigo have migraine (36,37). These data suggest some connection between migraine and vertigo. Half patients with BPPV younger than 50 years fulfill diagnostic criteria for migraine (38,39). Migraine is threefold more common in patients with BPPV than in control group (40). Therefore BPPV could be a form of migraine without headache, or migraine aura that does not evolve in migraine headache attack. The other hypothesis suggests that inner ear could be damaged with migraine associated vasospasm leading to symptoms of BPPV (40).

In basilar migraine vertigo is one of the symptoms lasting from 5 min to 1 h, accompanied with tinnitus, hearing loss, ataxia, dysarthria, visual symptoms, diplopia, paresthesias, paresis, and consciousness disorders followed by migraine headache. Most patients with basilar migraine have positive family history (41).

**Cervical vertigo:** Proprioceptive information from neck muscles and joints assist in coordination of eyes, head and body. Therefore disorders of this proprioceptive information could cause vertigo named cervical vertigo. Symptoms accompanying cervical vertigo include disorientation, instability, gait ataxia, and gaze abnormalities that tend to worsen with head movements. Cervical vertigo is more common in elderly patients probably due to degenerative changes of cervical spine and atherosclerosis (42,43). However, some authors do not consider cervical vertigo as distinct form of vertigo because mechanisms of cervical vertigo are not fully understood, and in differential diagnosis it is difficult to exclude other forms of vertigo (44).

**References:**


1. Victor M,Ropper AH. Adams and Victor's principles of neurology. 7th ed. McGraw-Hill: New York, 2001;301–328.
2. Storper IS. Dizziness and hearing loss. In: Rowland LP (ed.). Meritt's Neurology. 11th Ed. Lippincott, Williams & Wilkins: Philadelphia, 2005;32–38.
3. Hain TC, Mico AG. Cranial nerve VIII: Vestibular System. In: Goetz CG (ed.): Textbook of clinical neurology. 2nd Ed. Saunders: Philadelphia, 2003;195–210.
4. Yardley L, Owen N, Nazareth I, Luxon L. Prevalence and presentation of dizziness in a general practice community sample of working age people. Br J Gen Pract 1998;**48**:1131–1135.
5. Byrne M. Assessment of the dizzy patient. Aust Fam Physician 2002;**31**:722–727.
6. Bird JC, Beynon GJ, Prevost AT, Baguley DM. An analysis of referral patterns for dizziness in the primary care setting. Br J Gen Pract 1998;**48**:1828–1832.
7. Greenberg DA, Aminoff MJ, Simon RP. Disorders of equilibrium. In: Greenberg DA, Aminoff MJ, Simon RP. (eds) Clinical Neurology. 5th Ed. New York: McGraw-Hill, 2002; 95–126.
8. American Academy of Otolaryngology-Head and Neck Surgery: Contemporary vestibular assessment. Otolaryngol Head Neck Surg 2000;**8**:391–397.
9. Brandt T, Daroff RB. The multisensory physiological and pathological vertigo syndromes. Ann Neurol 1980;**7**:195–203.
10. Drachman DA, Hart CW. An approach to the dizzy patient. Neurology 1972;**22**:323–334.
11. Baloh RW. Honrubia V, Jacobson K. Benign positional vertigo, clinical and oculographic features in 240 cases. Neurology 1987;**37**:371–78.
12. Cawthorne T: Positional nystagmus. Ann Otol Rhinol Laryngol 1954;**63**:481–490.
13. Halmagyi GM, Gresty MA. Clinical signs of visual-vestibular interaction. J Neurol, Neurosurg, Psychiatry 1979;**42**:934–939.
14. Troost BT: Dizziness and vertigo in vertebrobasilar disease. Part I. Peripheral and systemic causes. Curr Cone Cerebrovasc Dis 1979;**14**:21–24.
15. Troost BT: Dizziness and vertigo in vertebrobasilar disease. Part II. Central causes and vertebrobasilar disease. Stroke 1980;**11**:413–415.
16. Hall SF, Ruby RR, McClure JA: The mechanics of benign paroxysmal vertigo. J Otolaryngol 1979;**8**:151–158.
17. Brandt T, Daroff RB. Physical therapy for benign paroxysmal positional vertigo. Arch Otolaryngol 1980;**106**:484–485.
18. Tiwari S, Bakris GL. Psychogenic vertigo: a review. Postgrad Med. 1981;**70**:69–71.






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19. Froehling DA, Silverstein MD, Mohr DN, Beatty CW, Offord KP, Ballard DJ. Benign positional vertigo: incidence and prognosis in a population-based study in Olmsted County, Minnesota. Mayo Clin Proc 1991;**66**:596–601.
20. Lanska DJ, Remler B. Benign paroxysmal positioning vertigo: classic descriptions, origins of the provocative positioning technique, and conceptual developments. Neurology 1997;**48**:1167–1177.
21. Baloh RW. Clinical practice. Vestibular neuritis. N Engl J Med 2003;**348**:1027–1032.
22. Strupp M, Brandt T. Vestibular neuritis. Adv Otorhinolaryngol 1999;**55**:111–136.
23. Wittner S. Diagnosis and treatment Meniere's disease. JAAPA. 2006;**19**:34–39.
24. Lheureux P, Penaloza A. Ototoxicity-related vertigo. Rev Med Brux 2002;**23**:A356–362.
25. Savitz SI, Caplan LR. Current concepts - Vertebrobasilar Disease. N Engl J Med 2005;**352**:2618–2626.
26. Caplan LR. Posterior circulation ischemia: then, now, and tomorrow - the Thomas Willis Lecture-2000. Stroke 2000;**31**:2011–2023.
27. Millikan CH, Siekert RG. Studies in cerebrovascular disease: the syndrome of intermittent insufficiency of the basilar arterial system. Mayo Clin Proc 1955;**30**:61–68.
28. Rubinstein SM, Peerdeman SM, van Tulder MW, Riphagen I, Haldeman S. A systematic review of the risk factors for cervical artery dissection. Stroke 2005;**36**;1575–80.
29. Wityk RJ, Chang HM, Rosengart A, Han WC, DeWitt LD, Pessin MS, Caplan LR. Proximal extracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. Arch Neurol 1998;**55**:470–478.
30. Caplan LR, Baquis GD, Pessin MS, D'Alton J, Adelman LS, DeWitt LD, Ho K, Izukawa D, Kwan ES. Dissection of the intracranial vertebral artery. Neurology 1988;**38**:868–877.
31. Yoshimoto Y. Systematic review of the natural history of vestibular schwannoma. J Neurosurg 2005;**103**:59–63.
32. Ho SY, Kveton JF. Acoustic neuroma. Assessment and management. Otolaryngol Clin North Am 2002;**35**:393–404.
33. Kayan A, Hood JD. Neuro-otological manifestations of migraine. Brain 1984;**107** (Pt 4):1123–1242.
34. Selby G, Lance JW. Observations on 500 cases of migraine and allied vascular headache. J Neurol Neurosurg Psych 1960;**23**:23–32.
35. Kuritzky A, Ziegler DK, Hassanein R. Vertigo, motion sickness and migraine. Headache 1981;**21**:227–31.
36. Stewart WF, Shechter A, Rasmussen BK. Migraine prevalence. A review of population-based studies. Neurology. 1994;**44**(Suppl 4):S17–23.
37. Stewart WF, Shechter A, Lipton RB. Migraine heterogeneity. Disability, pain intensity, and attack frequency and duration. Neurology 1994;**44**(Suppl 4):S24–39.
38. Hain TC, Squires TM, Stone HA. Clinical implications of a mathematical model of benign paroxysmal positional vertigo. Ann N Y Acad Sci. 2005;**1039**:384–394.
39. Uneri A. Migraine and benign paroxysmal positional vertigo: an outcome study of 476 patients. Ear Nose Throat J. 2004;**83**:814–815.
40. Ishiyama A, Jacobson KM, Baloh RW. Migraine and benign positional vertigo. Ann Otol Rhinol Laryngol. 2000;**109**:377–380.
41. Bickerstaff ER. Impairment of consciousness in migraine. Lancet 1961;**2**:1057–1059.
42. Brandt T, Bronstein AM. Cervical vertigo. J Neurol Neurosurg Psychiatry 2001;**71**:8–12.
43. Bolton PS. Assessment of cervicogenic vertigo. J Manipulative Physiol Ther 1991;**14**:487–488.
44. Brandt T. Cervical vertigo-reality or fiction? Audiol Neurootol 1996;**1**:187–196.

## Dizziness and unsteadiness as leading symptoms of patient's illness

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Patients with sudden onset of the vestibular (lateral semicircular canal) damage, experience vertigo i.e. the virtual impression that the surrounding is moving in front of them. Some patients complain only of dizziness, flightiness, they explain that they had 'unclear', or they have a constant feeling that they are going to faint away. Sometimes they complain only of certain unsteadiness. All those complaints are 'not typical' symptoms of vestibular damage. We analyzed the neurootological findings of a group of 35 patients with 'non-typical' symptoms of vestibular disease. In all of them the general neurological examination and the cardiologic examination were normal. Seven (20%) of those patients had a normal functioning of the periferal and central vestibular pathways. Further two (5%) had a normal finding as well, but they were diagnosed as phobic disorder. In seventy and 5%, spontaneous square wave jerks, horizontal or vertical gaze-evoked nystagmus, dysfunction of the flocculo-vestibular connections, other central vestibular disorders or unilateral vestibular hypotonia were revealed. Patients who complain of flightiness, 'unclear' had or feeling that they are going to faint away must undergo the neurootological examination. In a high percentage of those patients a peripheral or central vestibular disorder can be revealed.

## Pharmacotherapy of vertigo

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Dizziness is a general term that may encompass symptoms from differente causes. We will be using the term vertigo referring to a common subtype of dizziness that is characterized by the illusion of rotational motion. Most vertigo is due to otologic alterations and caused by dysfunction of the rotational velocity sensors of the inner ear, the semicircular canals. Almost one century has passed since the first description of the clinical presentation of the most frequent vertigo syndromes such as benign paroxysmal positional vertigo (BPPV), Ménière's disease, and vestibular neuronitis.

BPPV is by far the most common vertigo syndrome. It is characterized by sudden violent spells of vertigo triggered by a change in position such as turning over in bed or extending the head back to look up. It is caused by the deposition of debris in the cupola of the posterior semicircular canal. Most cases of BPPV can be cured with a simple manoeuvre that rotates the patient around the plane of the posterior semicircular canal with the head back, an action called particle repositioning manoeuvre (PRM). Although the majority of patients are cured after a single PRM, the cure rate is improved by repeating the procedure until no vertigo or nystagmus occurs in any position.

The classic symptom triad of Ménière's disease is vertigo, hearing loss, and tinnitus. The vertigo occurs in recurrent attacks typically lasting several hours, but may vary from minutes to days. During an attack, the patient will have nystagmus and be off-balance when standing. Typically there is associated nausea and vomiting. The hearing loss begins in the low frequencies and fluctuates. Ménière's disease resulted from an accumulation of fluid in the inner ear and the treatment of choice is diuretics and salt restriction diet.

Vestibular neuritis is as a single severe attack of vertigo with subsequent permanent unilateral deficit on caloric testing. Unlike attacks with Ménière's disease, the vertigo with vestibular neuritis is prolonged. Assuming that vestibular neuritis is the result of a viral inflammation of the vestibular nerve, treatment should be aimed at stopping the inflammation with an antiviral agent. Unfortunately, so far there have been only a few randomized, placebo controlled studies and each has important limitations. A brief course of high dose steroids seems to improve the outcome compared to placebo but it is unclear whether the risk of steroids is worth the improved outcome.

Regardless the aetiology of the disease, vestibular suppressant and antiemetic drugs are the mainstay of vertigo treatment. Vestibular

suppressants are drugs that reduce nystagmus evoked by a vestibular imbalance or reduce motion sickness. Conventional vestibular suppressants consist of three major drug groups: anticholinergics, antihistamines, and benzodiazepines. The choice of anti-emetics agent depends on considerations of the route of administration and the side-effects.

## Clinical neurophysiological investigations of vertigo

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Vertigo and dizziness belong to the frequent symptoms in outpatient clinics of general practitioners, ENT specialists, ophthalmologists, neurologists and psychiatrists. In spite of many advances both in basic neurosciences and in the recent possibilities of their functional diagnostic elaboration: ENG and oculographic analyses, computerized electronic recordings and analyses of equilibrium (posturography), vertigo still need in practice expert evaluation. Among many reasons for this difficulty the complex mutual influences between the peripheral and central vestibular mechanisms and the interference between vestibular, optomotor and proprioceptive neural structures (1). It is necessary to know the central regulatory mechanisms of nystagmus (habituation, compensation, central suppression, directional 'preponderance', 'recovery' nystagmus, etc). They are present in both physiological and pathological situations in the maintenance of equilibrium.

A primary function of the vestibular system is the automatic control of ocular and body movements in order to stabilize central vision and posture and to secure the equilibrium, enabling adequate positioning of the head and body, especially in our erect position. It is specialized for motor adaptations to gravity and to linear and angular acceleration in the changing relations between the body and the environment.

Phylogenetically, it is an old acquisition of the nervous system, modified in its connections to the younger neural structures, performing its functions in the integration with the proprioceptive and visual systems. Through the processes of encephalization the vestibular system has achieved a very specific role in the orientation in the world in which we live, but also in the maintenance of alertness, awareness and consciousness. Therefore, it may get significant psychological consequences in patients with primary mental disturbances in their sensation of stability, leading to subjective sense of insecurity and dizziness.

Symptoms of vertigo: a hallucinatory sensation of rotation, lifting up, falling down or to the side, or of dizziness-disturbed feeling of stability with less defined characteristics of hallucinatory movements may be the consequence of peripheral vestibular disturbances (Ménière's disease, vestibular neuronitis, traumatic and other causes of peripheral vertigo), central dysfunctions (epilepsies, cerebral tumors, circulatory, metabolic, toxic, infectious causes), or optomotor disturbances.

'Vestibular system' is very complex organization of peripheral receptor organs and various parts of the central nervous system. In spite of intensive investigations, both anatomic and physiologic, in experimental animals and in humans, the vestibular connections and their functions cannot be sharply delineated as an autonomous and separate, precisely defined, system. This holds true especially regarding its higher connections and specific cortical representation areas. Most of the authors stress the perplexity of its phylogenetic connections to the two other functionally related systems, proprioceptive and visual, with their mutual interactions in their common paths, what seems quite logical in their common functions of maintaining the equilibrium of the individuals. In a monograph entitled 'Neurotology' (2) a broad field of problems connected with peripheral and central clinical vestibular disorders is covered: chapters are included giving the descriptions of the anatomy (3) and physiology of the vestibular system (4). In line with the important earlier investigations (5), in the book are summarized the relevant publications in the field, presenting a basis for clinical approach to these problems.

For a long time vestibular system, mainly concerned with oculomotor and postural adjustments, with nystagmus, its clinically most manifest parameter was mostly analyzed by ENT specialists. Although still Gowers pointed to neurological significance of vertigo (6), until recently the vestibular disturbances, and so nystagmus, stayed for neurologists a field of relatively low understanding for its diagnostic functional, localizatory and etiologic significance (except in cerebellar dysfunctions or multiple sclerosis). In the preelectroencephalographic era the Gowers' and Marie's observations, like Stauder's investigations, have shown, that caloric or rotatory vestibular stimulation might induce epileptic attacks (7,8). It must be kept in mind the then nonexistent satisfactory entiepileptic medication. For the same reason the then investigators using EEG machines could describe relatively frequent appearance of epileptic EEG patterns after vestibular stimulation, sometimes accompanied by clinical attacks: the new term 'vestibulogenic seizures' (Behrman, Wyke) was coined (9). The question was raised by various investigators (9,10), what mechanisms and which cortical foci could be responsible in humans for vertiginous manifestations after the vestibular, caloric or rotatory stimulations.

Controversial results of clinical studies, particularly a clinically stimulant study by Molnár, Kekesi and Gosztonyi (11), led us to the conclusion that the appropriate methodology should be found in order to answer to many questions posed by earlier data, correlated with relevant basic neurophysiological studies. The appropriate occasion has been shown, when the author received the offer to study these problems, posed in his already commenced Doctoral dissertation, in the optimal conditions at the Neurophysiology Department, University Hospital in Uppsala (Sweden). The first report on these studies was published in 1965 (12). The complete analysis of the mentioned investigations, studied by the new methods, was published in 1967 (13). In the paper on 'vestibulogenic' seizures were summarized two conclusions: i) Different abnormal EEG patterns, focal or generalized, besides temporal foci, may be found in connection with vertiginous and other epileptic manifestations of vestibular dysfunction. ii) In the observed cases with vertiginous and gyratory epileptic attacks no other EEG responses to the stimulation of the horizontal semicircular canals were seen, than otherwise occasionally observed in patients with epilepsy. The term 'vestibulogenic seizures' should be used with caution only in the sense of a reflex induction of an epileptic phenomenon' (14). The studies were continued at Zagreb Neurologic University Department as a NIH (Bethesda, USA) project (15).

In the explanation of vestibular dysfunctions the important role belongs to the relevant history and character of vertiginous disturbances and the related neurological data. Clinical neurophysiological investigations are a contemporary complementary tool to neurology, sometimes neglected, or, when used, sometimes inappropriately programmed or insufficiently performed. When investigating the vestibular problems, parallel with recording the EEG, the parameters of vestibular activation must be appropriately registered, for special purposes possibly also correlated with parameters of other body systems (electrocardiogram, pulse, blood pressure, respiration).

As a neurophysiological parameter of vestibular function must be registered nystagmus by ENG. In neurophysiological studies the speed of the slow phase of the nystagmus, indicative of the activation of the vestibular system, must be recorded: for the ENG





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registration the systems with long *time constant* (tc) must be used, (16): our nystagmograms were recorded on the channel with a long time constant (3 sec). Simultaneous registration of EEG and ENG curves, mostly neglected in the earlier studies, enabled us to study the mutual relations between vestibular and cortical neurophysiologic parameters. Due to technical reasons, like the majority of other authors, we limited ourselves to the investigation of vestibular mechanisms connected with the stimulation of horizontal semicircular canals.

To solve the controversies from previous studies, we considered as inevitable to introduce studies with the simultaneous registration of the ENG as an indicator of the activation of the vestibular system, and the EEG as a parameter of the electrocortical activities. In the ENG the slow phase of nystagmus, as a specific parameter of the activation of the vestibular system, was analyzed.

In order to compare different kinds of vestibular stimulation, we introduced two methods of A) caloric stimulation: monaural and binaural, and of B) rotatory stimulation; pendular and linear with a sudden stop. For caloric stimulation we used the modification of Fitzgerlad–Hallpike's method, 30 sec for monaural and 20 sec for binaural activation, with the application of a specially constructed electronically controlled caloric stimulator, which enables the exact temperature and duration of stimulation. For rotatory stimulation we used Tonnies' rotatory chair, which can be electronically programmed. We introduced a continuous analysis of the ENG and EEG curves. *In the ENG* response we analyzed the intensity (slow phase) and the central qualities (quick phase) of the induced nystagmus:

a) Direction of nystagmus (quick phase),
b) Duration of nystagmic response (directional preponderance, after-nystagmus),
c) Sequential intensity of nystagmus (changes in the slow phase speed, possible suppressions)
d) Regularity and rhythms of nystagmus.

In the EEG activities must be taken into account:

a) Background EEG activity (amplitude and frequency),
b) Episodic slow waves,
c) Paroxysmal discharges (focal or generalized),
d) Possible asymmetries of the basic and/or paroxysmal activities, correlating them with the changes in the ENG parameters.

Such analysis of the ENG and EEG parameters is time-consuming and has to be done in a very meticulous and careful way, because the characteristic phenomena are practically never observed during the whole period of nystagmic response. They appear repeatedly, sometimes appear in the 'waxing and waning type' but may be regarded as specific when they appear correlated to one direction of nystagmus, without respect whether it was introduced by caloric or rotatory stimulation.

Early in the course of our investigations we concluded that there is a systemic influence of the vestibular system on the EEG activities, depending on the direction of the nystagmus, regardless of the way in which it has been provoked, with the tendency of the occurrence of the hypersynchronized activities in the hemisphere towards which the nystagmus is beating, and the desynchronized activities in the opposite hemisphere.

We also noticed that the episodic activities which can be seen in the EEG (focal and/or generalized episodic or paroxysmal discharges) can disturb the intensity and rhythm of the nystagmus, or even to cause its suppression. However, in accordance with observations of some earlier authors, some central factors which cannot be seen in the EEG, can also cause disturbances of the nystagmic response (respiration, blood pressure).

In order to explain possible mechanisms of the observed phenomena, we compared the results of vestibular with the intermittent light stimulation (ILS) in the same subjects (17,18,19). These correlations showed the probability that the occurrence of synchronized rhythms resp. 'hypersynchronized' discharges could be the result of the involvement of the identical 'non-specific' thalamocortical structures, well known through their recruiting capabilities.

The investigations carried out on the character of vestibular influences on the electroencephalogram, proved that vestibular activation of the EEG has specific characteristics, asymmetrical EEG responses to vestibular stimulation in regard to changes in normal activities, as well as in pathologic EEG patterns:

A. Tendency to synchronized or hypersynchronized activities in the hemisphere towards which the nystagmus is beating (quick phase):
a) enhancement of alpha spindles,
b) appearance of episodic slow waves,
c) activation of focal paroxysmal discharges, which can be generalized, as usual.

B. Tendency to desynchronized activities in the opposite hemisphere:
a) asymmetric blocking of the alpha rhythms,
b) decreased episodes of theta waves,
c) suppression of paroxysmal discharges in the opposite hemisphere.

Partly were described such changes earlier, by several authors independently, although not interpreted. Detailed analysis was published in Barac (20).

The asymmetric influences of vestibular activation on the normal and pathological EEG elements we correlated with the experimental investigations of Moruzzi (21,22), Cordeau and Mancia (23) and Rossi et al.(24), explaining them by the influences of the mechanisms of the tonic, direction-specific vestibular activation upon the antagonistic, inhibiting or activating structures in the brainstem reticular formation, with their ascending influences through the non-specific thalamic structures (25,26). We applied the results of these investigations in solving some clinical problems in the investigations of cerebrovascular diseases, epilepsy, posttraumatic conditions (concussion, contusion) (27,28).

Of great relevance for the studies of vestibular influences upon electrocortical activities is the experimental work of Gerebtzoff (29,30). Two-phase acceleratory-deceleratory rotation in the 'encephale-isolé' cat preparations was used: the responses which he schematically described as 'an acceleration and augmentation of the amplitude in the same time as the regularization of spontaneous waves' were seen on the homolateral cortex at the start of ampullopetal or at the end of ampullofugal rotation. The changes were observed in all parts of the cortex, however mostly pronounced in the posterior part of the suprasylvian gyrus. These findings, perfectly consistent with our investigations, clearly implicate the asymmetrical cortical responses.

On the other hand, the divergence of the two kinds findings in previous investigations could be explained: while the authors, who used evoked potentials techniques, found that the vestibulocortical pathway is mainly crossed (31,32,33), the authors who used physiological (rotatory) (34,29,30) or more natural way of stimulation, like calorization, found changes which were either generalized or present in one of either hemispheres - sometimes homolateral, sometimes contralateral, dependent on 'synchronisation' or 'desynchronisation' type of reactions described. It seems plausible that the 'unspecific' projection systems are at least partly responsible for the tendency of reciprocal electrocortical modifications of the EEG in the two hemispheres after physiologic vestibular stimulation. Gernandt and Thulin (35) presented electrophysiological evidence for rich vestibuloreticular connections. We related the observed phenomena of this tendency to the asymmetrical changes of synchronization, resp. desynchronization after vestibular stimulation in human subjects, with the mechanisms responsible for the electrocortical synchronising mechanisms. They were mainly studied in connection with sleep mechanisms (36,37) and the role of the reticular brainstem structures upon the appearance of cortical asymmetries in the electrocortical synchronization processes in the natural or pharmacologically induced sleep (38,36). So they found



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that the rostropontine hemitransection induces the increased synchronization on the ipsilateral cortex, while the middlepontine hemitransection produces permanent desynchronization on the ipsilateral cortex.

Taking into account the specific character of the vestibular system (its tonic, direction-specific properties), we put forward a hypothesis that the tonic direction-specific vestibular stimulation of the semicircular canals through the natural, physiological way of stimulation induces the sudden and strong activation of one half of the pontine reticular system, while on the opposite side the sudden decrease of usual afferent impulses would lead to a kind of functional hemi-deafferentation' in the sense of Moruzzi (21,22) and so permit the antagonistic system with a synchronizing influence upon the ipsilateral cerebral cortex to be dominant.

The mutual influences of the lower brainstem vestibular mechanisms regulating the automatic optomotor and vestibulomotor reactions and of their higher vestibular connections, including cortical vestibular representations, are still incompletely known in their functions of maintaining equilibrium and conscious perception of balance and orientation in space. The interaction of proprioceptive, vestibular and visual structures are involved in these functions are important in normal and pathologic circumstances. The diagnosis of vertigo, however, may still be a complicated task for neurologist. Understanding the mutually interwoven mechanisms is a prerequisite for both the clinical practice and further research.

Clinical neurophysiologic investigations are a powerful tool in the follow-up of the dynamics in these processes, specifically of mechanisms of central compensation. Unspecific reticular structures are playing here an important role. They may be regarded as mediators for the observed influences of the vestibular system on electrocortical activities and vice-versa. Further studies with clinical neurophysiological methods, appropriately programmed, may be of great practical and theoretical use.

**References:**


1. Barac B. On the nystagmus from the neurologic aspect (in Croatian, Summary in English) Neuropsihijatrija (Zagreb) 1963 **9**:327–332.
2. Jackier RK, Brackmann DE (eds.). Neurotology. St Louis, Mosby: 1994.
3. Gacek RR. Anatomy of the central vestibular system. In: Jackier RK and Brackmann DE (eds). Neurotology. St Louis, Mosby: 1994. 41–58.
4. Schwarz DWF, Tomlinson RD. Physiology of the vestibular system. In: Jackier RK and Brackmann DE (eds.) Neurotology. St Louis, Mosby: 1994. 59–98.
5. Brodal A, Pompeiano O, Walberg F. The vestibular nuclei and their connections. Anatomy and functional correlations. Edinburgh & London. Oliver & Boyd, 1962.
6. Gowers W R. Borderlands of Epilepsy. Churchill, London, 1907.
7. Marie P et Pierre JR. Étude sur la variabilité des réactions vestibulaires des épileptiques étudiées par la méthode de Bárány. Rev neurol 1922;**38**:86–92.
8. Stauder KH. Epilepsie und Vestibularapparat. Arch Psychiat Nervenkr 1934;**101**:739–761.
9. Behrman S, Wyke BD. Vestibulogenic seizures. A consideration of vertiginous seizures, with particular reference to convulsions produced by stimulations of labyrinthine receptors. Brain 1958;**81**:529–541.
10. Karbovski K. Á propos de l'utilité de la stimulation labyrinthique calorique, en tant que méthode d' activation en électroencéphalographie. Confin neurol (Basel) 1965;**25**:210–214.
11. Molnár L, Kekesi F, Gosztonyi G. Die Wirkung der Labyrinthreizung auf das normale und patholo-gische Elektroencephalogramm beim Menschen. Arch Psychiatr Nervenkr 1959;**199**:152–171
12. Barac B. Correlation between EEG and ENG responses. 8th Scandinavian EEG meeting, Uppsala.Electroenceph Clin Neurophysiol 1965;**19**:616.
13. Barac B. Vestibular influences upon the EEG of epileptics. Electroenceph Clin Neurophysiol 1967;**22**:245–252.
14. Barac B. Vertiginous epileptic attacks and so-called 'vestibulogenic seizures'. Epilepsia 1968;**9**:137–144.
15. Barac B. Vestibular influences on cerebral activity. Final Report. Research grant PL 480, NIH, DHEW, Zagreb, 1983.
16. Aschan G, Bergstedt M, Stahle J. Nystagmography. Recording of nystagmus in clinical neurologic examinations. Ada Otolaryng (Stockh) 1956;**129** (Suppl.): 1–103.
17. Barac B. The clinical value of vestibular activation of EEG. Electroenceph Clin Neurophysiol 1977;**43**:514.
18. Brinar V, Barac B. Correlation of influence of intermittent light stimulation (ILS) and vestibular caloric stimulation in focal EEG abnormalities. Electroenceph Clin Neurophysiol 1977;**43**:515.
19. Brinar V. Comparative analysis of intermittent photostimulation and caloric vestibular activation of the electroencephalogram. Master's degree thesis in Croatian. Center for postgraduate training, University of Zagreb, 1978.
20. Barac A. Bosko. Neurological approach to vertigo and vestibular dysfunctions. In: Sinha KK and Chandra P (eds.) Advances in Clinical Neurosciences, vol. 5, Ranchi, India: 1995. 429–444.
21. Moruzzi G. EEG activating influences in the 'cerveau isolé' preparation. In: CF Cori, et al. Eds. Perspectives in Biology. Amsterdam; Elsevier, 1963:434–438.
22. Moruzzi G. Active processes in the brainstem during sleep. The Harvey lectures series. New York and London Academic Press, 1963;**58**:233–297.
23. Cordeau SP, Mancia M. Evidence for the existence of an electroencephalographic synchronization mechanisms originating in the lower brainstem. Electroenceph Clin Neurophysiol 1959;**11**:551–564
24. Rossi GF, Minobe K, Candia O. An experimental study of the hypnogenic mechanisms of the brainstem. Arch Ital Biol 1963;**101**:70–492.
25. Barac B. On the mechanisms of vestibular activation of electroencephalogram, (in Croatian. Summary in German and English). Neuropsihijatrija (Zagreb) 1967;**15**:87–96.
26. Barac B. Some problems of clinical neurophysiology in the investigations of the vestibular system (in Croatian, summary in English). Acta Med Iug 1969;**23**:11–30.
27. Barac B, Brinar V. Clinical neurophysiological methods in the diagnosis of the post-traumatic syndrome. Neurologija (Zagreb) 1983;**31(1–2)**:11–24.
28. Barac B. Vertigo as a driving license problem. In Croatian, summary in English. Psihomedicina saobraćaja (Osijek). 1971;**3**:11–15.
29. Gerebtzoff MA. Recherches sur la projéction corticale du labyrinths. 1. Des effets de la stimulation labyrinthique sur l'activitéé électrique de l'écorce cerebral. Arc Int Physiol 1940;**50**:59–99.
30. Gerebtzoff MA. Le foyer véstibulaire cérébrale. Ada otolaryngol belg 1950;**4**:259–304.
31. Andersson S, Gernandt BE. Cortical projection of vestibular nerve in cat. Acta otolaryng Stockh 1954;**116** (Suppl.):10–18.
32. Mickle WA, Ades HW. A composite sensory projection area in the cerebral cortex of the cat. AmerJ Physiol 1952; **170**:682–689.
33. Spiegel E, Szekely EG, Gildenberg PL. Vestibular responses in midbrain, thalamus and basal ganglia. Arch Neurol (Chic) 1965;**12**:258–269
34. Makarjan SS, Koreskov AA. The changes in bioelectrical activity of cerebral cortex dependent on the degree of stimulation of the vestibular analyzer in Russian. Vestn Oto-rino-laring 1961;**23(2)**:97.
35. Gernandt BE, Thulin CA. Vestibular connection of the brainstem. AmJPhysial 1952; **171**:121-127.
36. Moruzzi G. EEG activating influences in the cerveau isolé preparation. In: CF Cori, et al. Eds. Perspectives in Biology. Amsterdam; Elsevier, 1963:434–438.
37. Rossi GF, Minobe K, Candia O. An experimental study of the hypnogenic mechanisms of the brainstem. Arch Ital Biol 1963;**101**:70–492.
38. Cordeau SP, Mancia M. Evidence for the existence of electroencephalographic synchronization mechanisms originating in the lower brainstem. Electroenceph Clin Neurophysiol 1959;**11**:551–564.


## Neurosurgical approach to patients with vertigo


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**Classification and Clinical Symptoms:** Vertigo can be caused by either peripheral or central vestibular disorders. In a peripheral lesion, vertigo of any significance is accompanied by nystagmus





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and the two are usually directly proportional. Also the presence of concomitant auditory symptoms suggests a peripheral lesion. In central lesions, the vertigo and nystagmus are not usually proportional. Because of the location and progression of most central lesions that cause vertigo, usually other symptoms and signs are associated.

**Etiology** Common peripheral causes of vertigo are benign paroxysmal positional vertigo, Menierés disease, vestibular neuritis, post-traumatic cause such as temporal bone fracture(3), and drug induced toxicity (e.g. Phenytoin, Gentamycin, Streptomycin). Common central causes of vertigo are brainstem lesions (arteriovenous malformation, tumor, trauma), posterior fossa lesions (e.g. vestibular schwannoma, meningeoma, metastatic tumor), vascular diseases (e.g. acute infarction or hemorrhage of the brainstem or cerebellum), demyelinating diseases (e.g. encephalitis disseminata), and congenital anomalities, such as Arnold–Chiari malformation.

A. Central Causes of Vertigo

1. *Arnold–Chiari Malformation*: The type I Arnold - Chiari malformation consists of a caudal descent of the cerebellar tonsils through the foramen magnus towards the spinal cervical channel. The usual clinical presentation are occipital headache and cervical pain as well as common dizziness and crisis of central positional vertigo in which down beating nystagmus can be observed (1,23). Due to the coexistence of hydrocephalus and syringomyelia, surgery is indicated.

2. *Brainstem Lesions*: Primary brainstem tumors, such as gliomas, are usually characterized by slowly progression and infiltration of the brainstem nuclei and fiber tracts, producing multiple signs and symptoms. In adults they constitute approximately 1% and in children 5–10% of intracranial tumors. Vestibular and cochlear signs occur in 50% of the patients (17).

3. *Tumors of the Posterior Cranial Fossa*: Tumors adjacent to the fourth ventricle can produce symptoms by compressing the vestibular nuclei. These tumors include medulloblastoma, ependymoma, papilloma, teratoma and epidermoid cyst. Vestibular schwannomas (acoustic neuromas), which are by far the most common neoplasms of the posterior fossa, are composed of Schwann cells and typically involve the vestibular rather than the acoustic division of the 8th cranial nerve. These tumors cause the four major clinical complaints: unilateral hearing loss, tinnitus, vertigo and unsteadiness. It should be noted, that vestibular schwannomas result in vertigo in fewer than 20% of patients, although as many as 50% of patients experience imbalance. Recent studies indicate, however, that vertigo is a powerful predictor for health-related quality of life, whereas unilateral hearing loss and tinnitus have less impact on quality of life patients with vestibular schwannoma (18,19). In many cases the tumor may remain unchanged for many years following diagnosis. Treatment for vestibular schwannoma must be individualized and requires an experienced, well-integrated, multidisciplinary team approach. Microsurgery remains the treatment of choice, including routine intraoperative monitoring of the facial nerve. In the majority of cases, however, the tumor is small, leaving the clinician and patient with the option of either control serial scanning by MRI or active treatment by LINAC- or gamma knife radiosurgery or microsurgery (2,5,12,14,24). If vertigo could be relieved by treatment, the symptom should be a primary focus when discussing treatment options in small to medium-sized vestibular schwannoma. Research is needed on the relative benefits and risks of all management options, including pharmaceutical and other alternative medical treatments such as tumor suppressing agents.

4. *Vascular Diseases*: Vertigo can be the initial symptom of spontaneous cerebellar hemorrhage or infarction. Cerebellar hemorrhage results from the same causes as other intracerebral hemorrhages. Approximately two thirds of cerebellar hemorrhages are hypertensive hemorrhages, other causes are anticoagulant use, aneurysm or arteriovenous malformation rupture or hemorrhage into tumor. Long-standing hypertension with degenerative changes in the vessel walls and subsequent rupture is believed to be the most common cause of a typical cerebellar hemorrhage. An estimated 10% of intracerebral hemorrhages are believed to be cerebellar in location, and an estimated 1–2% of strokes are cerebellar hemorrhages. Cerebellar hemorrhages may occur at any age, depending on the etiology. Generally, incidence increases with age; most hypertensive hemorrhages occur in patients older than 50 years. Rupture of a vascular malformation may be the most common cause in children. The onset of symptoms is generally abrupt. Clinical symptoms vary greatly depending on the size and location of the hemorrhage. Some patients are alert with headache of sudden onset, dizziness and vertigo, nausea and vomiting; others may be unresponsive with impaired or absent brainstem reflexes. Surgical care has been the mainstay of therapy for cerebellar hemorrhage, although some patients with small hematomas may be treated successfully without surgery. Indications for surgery are controversial (21,22). Ventricular drainage is indicated in patients with hemorrhage and hydrocephalus, suboccipital craniotomy with clot evacuation is indicated in patients with altered level of consciousness and the large clot (diameter over 30 mm). Patients with a large central clot and absent brainstem reflexes have a poor prognosis. In these cases, some advocate supportive therapy only (11). Vascular occlusion of the vertebral artery may result in a lateral medullary infarction (Wallenberģs syndrome). Major symptoms include vertigo, nausea, vomiting, intractable hiccupping, ipsilateral facial pain, diplopia, dysphagia and dysphonia. The lesion occurs caudal to the cochlear nuclei and cochlear nerve entry zone, and, therefore hearing preserves. Patients with Wallenberģs syndrome experience a prominent motor disturbance characterized by their body and extremities strongly deviating towered the side of the lesion. Vascular occlusion of the anterior inferior cerebellar artery (AICA) usually results in an infarction of the dorsolateral pontomedullary region and the inferiorlateral cerebellum. In 80–90% of patients the labyrinthine artery supplying the cochlear arises from the AICA, and, therefore infarction of the membranous labyrinth is common. Major symptoms include severe vertigo, nausea and vomiting (20,21). Vascular occlusion of the vertebral artery, the posterior inferior cerebellar artery (PICA), results in cerebellar infarction without brain stem involvement. The initial symptoms are severe vertigo, vomiting and ataxia, brain stem signs are absent. The presence of cerebellar symptoms is the unique differentiating feature of a peripheral vestibular disorder.

B. Peripheral Cause - Menierés Disease

As above mentioned there are many peripheral causes for vertigo, one of the most common peripheral cause is the Menierés disease. The cardinal symptoms in Menierés disease are fluctuating sensorineural hearing loss and episodes of vertigo, which have a usual duration of one to several hours. Tinnitus consistently accompanies the hearing loss and may be a major complaint of the patient. The disorder is usually limited to one ear (85%), but can be bilateral in approximately 15–20%. The disease characteristically affects young and middle-aged adults, although occasionally the disorder is seen in the second decade of life. The histopathologic correlate of Menierés disease is endolymphatic hydrops, which is manifested as distention of the endolymphatic compartment of the pars inferior (cochlear and saccule).

**Surgical Treatment of Vertigo.** Surgical management is recommended when the degree of disability prevents acceptable social or work life because of the frequency and the severity of vestibular symptoms. Based on the clinical diagnosis, hearing levels, and age of the patient, traditional procedures include repair of perilymphatic fistula, endolymphatic sac operations, labyrinthectomy, selective vestibular nerve transsection and microvascular decompression. The repair of perilymphatic fistula,



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endolymphatic sac operations and labyrinthectomy are neurootological operations.

1. *Selective Vestibular Nerve Transsection*: This ablative procedure is indicated in those patients with intractable severe vertigo caused by unilateral pathologic involvement of the labyrinth whose hearing function is at a useful level. Selective transsection of the vestibular nerve can be accomplished at two levels: the internal auditory canal and the cerebellopontine angle. The middle cranial fossa approach to the vestibular nerve in the internal auditory canal was published by Fisch and by Glasscock and Miller (6,7). This approach is used to selectively transsect the vestibular nerve with preservation of the cochlear and facial nerves after they are exposed in the internal auditory canal. Auditory function is maintained by avoiding surgical exposure of the labyrinth and preserving the cochlear division of the 8th nerve. Since the vestibular and cochlear nerves are separated in the distal end of the internal auditory canal, the vestibular nerve branches can be isolated from cochlear nerve fibers. Transsection of the distal and proximal ends of the superior and inferior division of the vestibular neurons within the internal auditory canal permits resection of the vestibular ganglion. Excision of this segment reduces the possibility of regeneration of vestibular nerve fibers. Selective transsection of the vestibular nerve in the cerebellopontine angle can also be approached by a lateral suboccipital craniotomy. The advantages of this approach, which allows a wide exposure of the seventh and eighth nerves are, that the exposure is technically easier than the middle fossa approach and the incidence of facial paralysis is less since surgical exposure of the facial nerve is not used to locate the internal auditory canal.

Indications for this procedure are patients with unilateral peripheral labyrinthine disease, usually Menierés disease or vestibular neuritis with an excellent hearing level in the affected ear (4). The hearing level should not exceed a threshold elevation of 20–30 dB and discrimination scores should not be less than 80%. Patients with threshold elevations between 30 and 50 dB and with word discrimination scores between 50 and 80% can be considered on a case-by- case basis. Patients selected for this procedure should be favourable medical risks for the procedure and they should not be greater than 70 years of age and in good medical health. Contraindications are poor hearing in the involved ear or intractable vertigo and excellent hearing in an only hearing ear. The former group of patients require labyrinthectomy while the latter are best treated by medical ablation of the vestibular system. The results in the control of vertigo, providing the superior and inferior division nerve branches have been transsected and excised, is approximately 98–100%. The incidence of sensorineural hearing loss is below 10% and temporary facial paralysis may occur in approximately 25% of patients. While the short term results for relieve of vertigo and hearing preservation are equal by both approaches to selective vestibular nerve transsection, significant differences may become apparent over long-term evaluation. The loss of a small portion of auditory neurons would not affect hearing function while a patient is young, but when the neural loss caused by the aging process appears, a significant hearing loss become more apparent. Furthermore, since the vestibular ganglions cells remain viable in the internal auditory canal after transsection of axons, the potential for neuroma formation by regenerating axons exists in the cerebellopontine angle.

2. *Neuromicrovascular Decompression*: In some patients with disabling positional vertigo a vascular cross-compression at the root entry zone of the cochlear-vestibular nerve complex is detected in the MR-angiography. This entity is distinct from Menierés disease, vestibular neuritis, and benign positional vertigo. Vascular cross-compression of the appropriate part of the auditory nerve (cochlear, vestibular or both) may result in pure vestibular or combined cochlear-vestibular hyperactive dysfunction or in pure cochlear symptoms. In these cases a neurovascular decompression at the root entry zone of the appropriate part of the eighth nerve is recommended (8,9,10,15,16). The postoperative results show a marked improvement of vertigo in 80%, the recurrence rate after more than 1 year of symptom-free follow up is 10%. The blood vessels that cause eighth nerve dysfunction are the most subtile and the most difficult to decompress because of the threat of injury to the nerve. The use of brainstem auditory evoked potential monitoring had made these procedures safer. The incidence of hearing loss after microvascular decompression is 1%. This outcome compares very favorably with the results of destructive procedures involving the eighth nerve, which may result in hearing loss. Although vascular compression itself eventually results in progressive hearing loss if it is unrelieved, this does not occur after microvascular decompression.

3. *Ventriculo-peritoneal Shunt*: Ventriculo-peritoneal shunt insertion for refractory perilymphatic fistula: recent data suggest that some patients with disabling vertigo, tinnitus and headache due to perilymphatic fistula, whose conventional medical and surgical therapies are failed to produce a cure, benefit from ventriculo-peritoneal shunt implantation (13). It is hypothesized that ventriculo-peritoneal shunt placement blunts intracranial pressure increases, which would cause secondary elevations in perilymphatic fluid pressure. Shunt implantation reduces leakage into the middle ear and may permit closure of the fistula.

**References:**


1. Albers FW, Ingels KJ. Otoneurological manifestations in chiari-I malformation. J Laryngol Otol 1993;**107**:441–3.
2. Andrews JC, Wackym PA, Canalis RF. Translabyrinthine approach to the cerebellopontine angle and internal auditory canal. In Samii M, Cheatham M, Becker DP. eds. Atlas of Cranial Base Surgery, Philadelphia, WB Saunders., 1995:18–23.
3. Cannon CR, Jahrsdoerfer RA. Temporal bone fractures. Review of 90 cases. Arch Otolaryngol 1983;**109**:285–8.
4. Dandy WE. Treatment of Menierés disease by section of only the vestibular portion of the acoustic nerve. Bull. Johns Hopkins Hosp 1933;**53**:52–55.
5. Flickinger JC, Kondziolka D, Pollock B, Lunsford LD. Improved results for vestibular schwannoma radiosurgery. J Rad Oncolog Biolog Physics 1995;**32**:146.
6. Garcia-Ibanez E, Garcia-Ibanez JL. Middle fossa vestibular neurectomy. A report of 373 cases. Otolaryngol Head Neck Surg 1980;**88**:486–490.
7. Glasscock ME, Miller GW. Middle fossa vestibular nerve section in the management of Menierés disease. Laryngoscope 1977;**87**:529–541.
8. Horrii A, Okumura K, Kitahara T, Kubo T. Intracranial vertebral artery dissection mimicking acute peripheral vertigo. Acta Otolaryngol 2006;**126**:170–173.
9. Jannetta PJ. Moller MB, Moller AR. Disabling positional vertigo. N Engl J Med 1984;**310**:1700–1705.
10. Jannetta PJ. Neurovascular cross-compression in patients with hyperactive dysfunction symptoms of the eighth cranial nerve.Surg Forum 1975;**26**:467–468.
11. Jensen MB, St Louis EK. Management of acute cerebellar stroke. Arch Neurol 2005;**62**:537–544
12. Likhterov I, Allbright RM, Selesnickck SH. Linac radiosurgery and radiotherapy treatment of acoustic neuromas. Otolaryngol Clin North Am 2007;**40**:541–570.
13. Lollis SS, Wieder DJ, Phillips JM, Roberts DW. Ventriculo-peritoneal shunt insertion for the treatment of refractory perilymphatic fistula. J Neurosurg 2006;**105**:1–5.
14. Matthies C, Samii M. Management of 1000 vestibular schwannomas (acoustic neuromas): clinical presentation. Neurosurg 1997;**40**:1–9.
15. Moller MB, Moller AR, Jannetta PJ, et al. Diagnosis and surgical treatment of disabling positional vertigo. J Neurosurg 1986;**64**:21–28.
16. Moller MB, Moller AR, Jannetta PJ, et al. Microvascular decompression of the eighth nerve in patients with disabling positional vertigo: selection criteria and operative results in 207 patients. Acta Neurochir 1993;**125**:75–82.
17. Musiek F. ABR in eighth-nerve and brainstem disorders. Am Otol J 1982;**3**:243
18. Myrseth E, Moller P, Wentzel-Larsen T, Goplen F, Lund-Johansen M. Untreatd vestibular schwannomas: vertigo is a powerful predictor for health-related quality of life. Neurosurg 2006;**59**:67–76.






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19. Myrseth E, Pedersen PH, Moller P, Lund-Johansen M. Treatment of vestibular schwannomas. Why, when and how? Acta Neurochir 2007;**149**:647–660.
20. Oas JG, Baloh RW. Vertigo and the anterior inferior cerebellar artery syndrome. Neurolog 1992;**42**:2274.
21. Sivenius J, Riekkinen PJ, Smets P, et al. The European Stroke Prevention Study (ESPS). Results by arterial distribution. Ann Neurol 1991;**29**:596.
22. Uno M. Surgical treatment for spontaneous cerebellar hemorrhage. Nippon Rinsho 2006;**28**:485–491.
23. Weber PC, Cass SP. Neurotologic manifestations of Chiari 1 malformation. Otolaryngol Head Neck Surg 1993;**109**:853–860.
24. William A, Friedman MD, Kelly D, Foote MD. Linear accelerator-based radiosurgery for vestibular schwannoma. Neurosurg Focus 2003;**14**: Article 2.

## Psychogenic vertigo

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Some of mental disorders have vertigo (psychogenic) as a symptom, which is manifested by the sensation of instability, dizziness, and less frequent appearance of nausea and vomiting. In the English literature (neurology, psychiatry, otology etc), for vertigo are frequently used synonyms (very often in wrong way): dizziness, imbalance, disequilibrium, giddiness, lightheadedness, etc. Of course, the synonyms for vertigo exist in other languages, too, but they always mean individual sensation of moving around in space or having objects move around the person. According to the some of authors, dizziness has very broad concept that includes vertigo, lightheadedness, presyncope and disequilibrium (Kroenke K et al.1992). Vertigo in neurology is non-specific symptom, which is diagnosed in cases with a disorder of vestibular function. This disorder may be found in the area of peripheral or central vestibular system, i.e. labyrinth, vestibular nerve, brain stem, cerebellum, cortex. Peripheral or central vestibular syndromes are mainly manifested in combination of vertigo, nystagmus, imbalance, and nausea. It is considered that vertigo comes up as a result of disorder of cortical-spatial orientation (Brandt TH, 1999).

The causes of vertigo are various, and they belong to organic (family, infective, neoplastic, metabolic, toxic, vascular, autoimmune, traumatic) and psychogenic factors. It is necessary to identify, the cause of vertigo. If it is certainly proved that it is organic etiological factor of vertigo - its location and characteristics should be defined as soon as possible. Because, vertigo, in some cases may be a sign of serious brain disease that requires prompt neurosurgical intervention. Mutual, mental disorders and vertigo, in dizzy patients can be in specific roles. They may be both a cause and a consequence of dizziness (Staab JP, Ruckenstein MJ, 2003). Two kinds of connection between vertigo and mental disorders may be distinguished, where vertigo could be:

1. Symptom of mental disorder (psychogenic vertigo), and
2. Symptom of mental disorders in dizzy patients.

*Ad.1.* Psychogenic vertigo as a symptom of mental disorders is mainly manifested within anxious, depressive, somatic disturbances consists of a sensation of motion (spinning, rocking, etc). This group of patients involves 15% of patients with vertigo, in which in clinical (otological, neurological) and laboratory examinations any abnormalities cannot be found. Generally, it is caused by the stress and manifested continuously during some period of time (several weeks) indicating the psychogenic cause of vertigo (Hain, TC, 2007). Vertigo in depressive and anxious disorders show tendency to be chronic, and patients may have rocking or/and floating sensations. This type of vertigo can be provoked by eye movements when the head is still.

In everyday practice vertigo is mostly occurring in panic disorder. Panic disorder's characteristics are: the attacks of short-term dizziness combined with sensation of strong anxiety, difficult respiration and asphyxia, chest pain, patient's sensation that is going crazy that will fall on the ground, get a myocardial infarct, stroke, with symptoms of disturbed VNS (tachycardia, perspiring, nausea, etc.). Panic attacks are frequent, come up almost daily, go on usually for few minutes, and sometimes are related to specific situations, for example car drive and/or driving in public transport. Panic attacks may also happen in other places and situations such as workplace, during relaxation or sleeping time. In that case, we speak about spontaneous attacks. Vertigo associated with panic attacks can sometimes be elicited by hyperventilation in the patient. Incidence of panic disorders is 0.7% in men, and 1% in women. They usually start in the early adulthood, and the onset is related to some stressful event. More than 80% of patients with diagnosis of anxious disorders have, also, the panic attacks (GAD, neurasthenia, and other anxiety disorders).

Somatization disorders have chronic course and frequently include, besides other symptoms, the vertigo, too. Basic characteristic of somatization disorders is the onset of recurrent, multiple, clinically significant discomforts, mostly in persons under 25 years, in which organic pathological values cannot be found in laboratory testing. Among various symptoms that may be found in somatization disorder, there are those that suggest the presence of an neurological disorder, such as paralysis, double vision, blindness, deafness, and, of course, vertigo. Life prevalence of somatization disorder in women is from 0.2% to 2%, and in men up to 0.2%. Bad mood in depressive disorder may be united with, so-called, somatic symptoms, as well as with panic attacks. In these cases, vertigo is present, too.

*Ad.2.* Psychological abnormalities are very frequent in persons suffering from dizziness. It is best showed in the results from the study of Garcia et al. in Portugal, 2003. They found in dizzy patients: somatization 41.9%, hostility 20.9%, interpersonal sensitivity 18.6%, anxiety 23.3%, phobic anxiety 20.9% , OCD (obsessive compulsive disorder) 53.5%, depression 30.2%, paranoid traits 11.6%, and psychotic traits 2.3%. In this study is applied SCL-90 test, and results demonstrated that large number of persons suffering of dizziness has OCD and somatization features. The other studies found that most individuals suffering of organic vertigo had reactive anxious and depressive disorders (Hain TC, 2007). Finally, it can be concluded that vertigo, although only a symptom, is a significant tool for making diagnosis, and defining adequate therapy in neurology and psychiatry.

Key words: vertigo, psychogenic vertigo, panic attacks, somatization, depression

**References:**

1. Brandt TH. Vertigo: its multisensory syndromes. 2nd edn.Springer, London, 1999
2. Garcia FV et al. Psychological manifestations of vertigo: a pilot prospective observational study in a Portuguese population. Int. Tinnitus J 2003;**9**:42.
3. Hain TC. Vertigo and psychological disturbances, http://www.dizziness-and-balance.com/disorders/psych/psych.htm, Page last modified: December 26, 2007.
4. Kroenke K. et al. Causes of persistent dizziness. A prospective study of 100 patients in ambulatory care. Ann. Int.med.11711 898, 1992
5. Staab JP, Ruckenstein MJ. Which comes first? Psychogenic dizziness vs. Otogenic anxiety. Laryngoscope 2003;**113**:1714.

## Neurosonology methods in diagnosis of vertigo

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***Vertigo*** is a subjective or objective illusion of motion, either rotation or spinning. It is a symptom of dysfunction of the peripheral or central vestibulo-cerebellar system. Isolated vertigo can not be considered as a definite symptom of brainstem ischemia

because the same sensation can occur in labyrinthine disorders such as benign positional vertigo.

***Vertigo*** should be distinguished by ***Dizziness*** which is a sensation of imbalance when standing or walking due to impairment of vestibular, sensory, cerebellar, visual or motor function and consequently it may be due to lesions in many parts of the nervous system.

***Unsteadiness*** is a common neurological symptom, but unless it is associated with clearly focal signs of weakness or ataxia it may be difficult to decide whether the patient complains of weakness, incoordination, vertigo, presyncope or anxiety.

Many patients complain of vertigo or dizziness either around the onset of s stroke or at different times, but this term alone is too imprecise to be of localizing value even between carotid and vertebrobasilar territories, although it is more frequent in the latter. The tendency to label any episode of vertigo, especially in elderly people, as vertebrobasilar ischemia or vertebrobasilar insufficiency should be strongly avoided.

Trapping of the vertebral arteries by cervical spondilosys is frequently supposed as a cause of vertigo, but in reality vertigo and X-ray documented cervical spondilosys are frequent in elderly people and rarely there is a convincing cause and effect relationship.

***Vertigo*** as an isolated symptom, particularly when it is induced by head movements, is almost always an expression of a peripheral rather than of a central dysfunction. However some cerebellar strokes and lesions of more central vestibulo-cerebellar pathways may also mimic peripheral symptoms. Moreover acute cerebellar syndromes that can mimic strokes may be caused by drug toxicity. Most of the central vestibular syndromes and some of the peripheral vestibulary syndromes may have vascular causes. Ischemia will sometimes produce a combination of central and peripheral symptoms, as in the anterior inferior cerebellar artery (AICA) infarction, the territory of which encompasses the labyrinth, pontine and cerebellar structures.

The vertigo, which is often abrupt in onset and sometimes transient in vertebrobasilar ischemia, should be differentiated from the episodic vertigo commonly seen in other conditions such as Meniere disease and basilar migraine.

The literature indicate that twenty percent of the ischemic events damage the brain tissue supplied by the vertebrobasilar circulation, so that the sudden involvement of the vertebrobasilar arteries can be devastating, and some forms have high rates of death.

During the recent years, information provided by detailed clinical studies and brain imaging has modified our understanding of the clinical aspects, causes, mechanisms, treatments, and prognosis of posterior-circulation ischemia.

Doppler Sonography of the vertebrobasilar system has in the past been playing a limited role in the evaluation of the posterior circulation. This limitation has been related to the difficulties in vessel identification and to the partial role of surgery in the correction of stenoses in this vascular territory.

The introduction of transcranial Doppler sonography (TCD) and transcranial imaging techniques by ultrasound (TCCS) has opened the door to the intracranial segments of the vertebro-basilar system. The transtemporal window allows the evaluation of the posterior cerebral arteries, the posterior communicating arteries and the top of the basilar artery while the suboccipital window allow the evaluation of both vertebral arteries and of the origin of the basilar artery.

Extracranial evaluation of the vertebral arteries is obtained through an angulation of the transducer parallel to the carotid artery, laterally and inferiorly and then looking for the vertebral bodies. From this side the vertebral arteries lie perpendicularly to the vertebral bodies.

The vertebral and the basilar arteries have normally a low resistance flow patterns with high diastolic velocity.

The so-called '***subclavian steal syndrome***' or '***subclavian steal phenomenon***' may cause symptoms and signs of vertebrobasilar ischemia. Depending on the degree of the subclavian artery stenosis there is a reduced velocity, an alternating or a reversed flow in the ipsilateral vertebral artery. An accelerated flow velocity in the contralateral vertebral artery, consequent to a greater blood volume required for the brain and arm supply is often observed.

Symptoms of vertebrobasilar ischemia including vertigo may be caused by a stenosis at the origin of the vertebral arteries with intracranial embolization. In this case ultrasound studies allows the direct visualization of the stenotic plaque with an increased flow velocity. Indirect signs show a poststenotic turbulent flow with decreased systolic and diastolic flow velocities. A high resistance flow patterns with low diastolic velocity and a normal calibre is suggestive of an intracranial stenosis of the vertebral artery.

An acute vertigo with symptoms and signs of the lateral medullary syndrome may result from vertebral artery dissection with impairment of blood flow in the territory of the posterior inferior cerebellar artery (PICA). Spontaneous dissection of the vertebral arteries can affect all segments of the VA. Color Doppler imaging may detect wall abnormalities in the V0 – V1 – V3 segments.

Imaging abnormalities in patients with vertebral artery dissection may reveal an irregular stenosis, a thickened hypoechogenic vessel wall, a dissecting membrane with a true or a false lumen, a pseudoaneurysm or a vertebral stenosis with a distal occlusion. Pathologic ultrasound hemodynamic patterns in young patients with an acute vertigo in the absence of atherosclerotic vessels suggest that a vertebral dissection could be the underlying cause of the neurological symptoms. A combination of local increase in vessel diameter with hemodynamic signs of stenosis or occlusion at the same level and a decreased pulsatility index with presence of intravascular echoes in the enlarged vessel has been considered a typical sign of dissection (1).

The dynamic aspect of transcranial Doppler sonography and transcranial Doppler ultrasound imaging of the posterior circulation seems very helpful in the diagnosis of patients with signs and symptoms of vertebrobasilar ischemia. Ultrasound examination of the extracranial and intracranial vertebral arteries and of the basilar artery yields important informations on the hemodynamics of the vertebrobasilar system. However some difficulties in interpretation of the results still exists (2).

It is important to apply strictly the hemodynamic rules and consider the results of the ultrasound investigation in the light of the clinical signs and symptoms in order to obtain an accurate interpretation of the data provided by the extracranial and intracranial investigation of the posterior circulation(3).

**References:**


1. Caplan LR, Baquis GD, Pessin MS. Dissection of the intracranial vertebral artery. Neurology 1988;**38**:868–877.
2. Lee H, Cho YW. Auditory disturbance as a prodrome of anterior inferior cerebellar artery infarction. J Neurol Neurosurg Psychiatry 2003;**74**: 1644–1648.
3. Savitz SI, Caplan LR. Vertebrobasilar disease. N Engl J Med 2005;**352**:2618–2626.






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# ACADEMIC LECTURE

## The relevance of the psychopathology of Kurt Schneider for today's psychiatry

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**Introduction:** The phenomenological psychopathology, termed also introspective, descriptive or understanding psychopathology, has been advanced by K. Jaspers and continued and modified in the European psychiatric tradition by K. Schneider. Phenomenological psychopathology has to be differentiated from the phenomenological-anthropological approach taken by Husserl and Binswanger. For several decades the opinion has been widespread that in phenomenological psychopathology new findings scarcely are to be expected. In our opinion the comment of K. Schneider of 1946 is still today valid: Doubtless, the task of psychopathology has not yet come to an end; rather it has a great field of work before it (49,57). When we speak of psychopathology (PP) in the following, we mean phenomenological psychopathology (PhPP) in the direction of K. Jaspers and K. Schneider, who created a basic psychopathological framework for clinical and scientific psychiatry which still today seems practically useful and heuristically fruitful. The Jaspersian-Schneiderian approach leaves room for new developments that may correct and change many aspects of traditional and contemporary psychiatric views.

The well known classics of the phenomenological-descriptive PP are the General Psychopathology by Jaspers (88) which first appeared in 1913 and has remained unchanged since the 4th edition in 1946; further Schneider's monograph The Psychopathic Personalities (105) that appeared first in 1923, his Abnormal Psychological Reactions (1927) and the Clinical Psychopathology (109), the book, K. Schneider said about, it would include all that he had to say the psychiatry, based on his own results as far as they were still valid for him. It was republished with a commentary by us in the 13th (1987), 14th (1992) and the 15th edition in 2007 (109).

**Main features and aims of phenomenological psychopathology:** For the representatives of the old Heidelberg school, the authors of the handbook Schizophrenia (1932), PhPP was fundamental to clinical psychiatry (100). Clinical psychiatry originated with Kraepelin, but its pronounced psychopathological orientation was established by Jaspers and K. Schneider. The psychiatry of Kraepelin has been completed by PhPP, which aims at the elucidation of the patient's own inner experiences, the inner world of mental illness [Kaplan 1964 (89)], comprehensible primarily through the self-reports of the patients and only secondarily through the observation of behaviour and expression. Not until Jaspers' book General Psychopathology, a scientifically satisfying PP, particularly concerning the methods of the from within descriptive phenomenology and the genetic understanding, the differentiation between understandable and causal connections, between developments of a personality and cerebral-organic processes has been provided. With Jaspers (88: p 507; 110) and the medical-scientific definition of disease by K. Schneider the provisional, didactic-classifying Triadic System of psychiatric disorders has been introduced, and since that time PP has been the via regia of psychiatric diagnostics. Moreover, since the elaboration of this psychopathological basic frame-work, psychiatry has been seen to be founded on two pillars, i.e. on PP and on somatology (108,109). There is no doubt, as we have shown in earlier essays (16), that PhPP represents also today an indispensable foundation for psychiatry. Jaspers' book in its 4th edition of 1946, written together with K. Schneider, is the starting point of all later developments of clinical PP and psychiatry. The too objectifying psychiatry of Kraepelin, being based mainly on behaviour and expression, has been overcome by the PhPP of Jaspers and K. Schneider, aiming at experience and modes of experience (Erleben und Erlebnisweisen), elicited by self-reports of the patients. The connection of the descriptive-phenomenological with the method of genetic understanding had been characteristic from the very outset for this PP. The differentiation of static and genetic understanding can be considered as the basis of an attitude of the psychiatrist, similar that termed by Sullivan as participating observation. This means that both, the ability of communication and the ability of the investigator to place him- or herself at a distance, should be combined and reconciled in the person of the psychiatrist and psychotherapist. JASPERS recognized that this phenomenological attitude [phänomenologische Einstellung 88: p (48)], requested by him, is not at all self-evident, but has to be acquired by critical work always anew overcoming prejudices. This Jaspersian-Schneiderian PP is open and does not constitute a self-contained theory, but only an order, based on methodological reflexion that should show ways for the clinical research. Therefore, the PhPP takes the lead of all sciences, relevant for psychiatry and ensures that single methods of consideration and the aspects and partial cognitions, gained by them, cannot be taken absolutely as a model of universal validity.

**Jaspers' General Psychopathology and its bearing on the psychiatry of K. Schneider:** JASPERS was working in the Psychiatric University Hospital at Heidelberg, before he moved away from medicine towards psychology and philosophy. Yet, he continued to retain his interest in PP, expanding and revising the General Psychopathology until the 4th edition, which has been realized in yearlong close co-operation and with the critical support by Kurt Schneider. Jaspers' concepts influenced Kurt Schneider's thinking, whose psychiatric orientation and teaching is summarized mainly in his books Clinical Psychopathology and Psychopathic Personalities (105,109). We outline some tenets of K. Schneider's scientific approach.

**Tenets and Positions of the Clinical Psychopathology:** (1) There is a lack of specificity of psychopathological phenomena, symptoms and syndromes. Hence, the fundamental rule of psychiatric diagnostics is that diagnosis in psychiatry is not possible without a complete somatic and neurological investigations (72: pp 15,21; 75,91). (2) The form and theme of psychotic experiences have to be differentiated: The diagnosis considers the form, the how, and not the theme, the contents. (3) The notions schizophrenia and cyclothymia, i.e., affective psychoses, are defined as only psychopathological state-course-units. A diagnosis in the strict sense, as in somatically definable psychoses, i.e. brain diseases, is not possible as long as characteristic, pathognomonic somatic findings are lacking: Schizophrenias, cylothymias, and other types of endogenous psychoses, often mistaken for nosological entities, are only provisional diagnostic conventions (9,22,23,59). If we stay with the disease hypothesis, we do not expect that a somatic disease discovered some day, will correspond to a psychopathologically and by the long-term course definable type of an endogenous psychosis. Real disease entities cannot be found by the Kraepelin–Kahlbaum method, not even with comprehensive observation of the whole syndrome and course. The efforts to single out certain schizophrenic, schizoaffective and affective psychoses as independent nosological units, are »chasing after a phantom (63,65). Proceeding from this view, only a differential typology is




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possible, and not a differential diagnosis within the field of idiopathic (schizophrenic, schizoaffective and affective) psychoses (109: pp 7, 66, 86f.). There are transitions and intermediate states (Zwischen–Fälle - K. Schneider) between schizophrenia and cyclothymia (see below). (4) PhPP attends to the psychologically abnormal with regard to clinical units; thus, it becomes a doctrine of symptoms and diagnostics and loses its nosological neutrality. Beginning with Jaspers (88: pp 507f.), PhPP distinguished between psychic abnormalities as consequences of diseases in the medical–scientific sense (known somatic diseases with their psychic effects) and variations of psychic being, e.g. psychopathic personality disorders and abnormal psychic reactions and developments including neuroses (109). To the consequences of illness belong first the psychoses that are somatically definable on the basis of known brain diseases, and, secondly, the so-called endogenous psychoses, the somatically not yet definable schizophrenic and affective psychoses. This Triadic System of clinical psychiatry (72: p 25; 88, 109: p 120) must have, at the present state of our knowledge, a provisional character. Only with the somatically definable psychoses the diagnostics is two-tracked: The notions and terms are partly somatological, partly psychopathological. Distinct from the notion psychosis the terms abnormal, abnormality and psychopathological are nosologically neutral and are used both for the variations and the psychoses (63). (5) Using the patient's introspection and the static empathy and genetic comprehending of the investigator, the aim of PhPP is to elicit the movement, connection and continuity of the psychic life, not only in neurotic–psychopathic developments, but also, as far as possible, in psychoses. One essence of the Jaspersian-Schneiderian approach consists of the attempt to get an understanding of the patient's own experiences and to formulate these experiences as precisely and unequivocally as the limitations to transfer experiences in language allow. Due to the close connection of phenomenology with genetic understanding, the psychiatrist is at the same time a participating physician and one, who observes and states signs and symptoms while using himself as an instrument to explore.

In the epoch after Kraepelin the psychiatrist's interest increasingly turned to the development of personality, the whole life situation and to the subjective experiences of the patient (49,53,57). The restriction of genetic understanding, remaining in the scope of conscious and preconscious experiences, must not impede exploration of the patient's biography and the communication with him or her. The objection, that PhPP could disturb this communication, rather refers to the psychiatry of Kraepelin and even more to the modern operationalized diagnostics (see 24). (6) The psychopathologist tries to grasp first the subjective experience of the patient, the process of experiencing itself, and not only its result. The PP since Jaspers has taken the step from the apparent objective, the expression and behaviour, to the subjective, the individual, inner experiences of the patient. Phenomenology in a stricter sense, i.e., the realization and description of the modes of experiences, of psychic states and qualities, by means of self-reports as well as of the expression of the patient, works hand in hand with the genetic understanding, feeling into how experiences develop from other experiences with evidence [Jaspers (88)]. At the beginning is the description of what the patient communicates. The definition of and the assignment to certain notions and terms and their fixing by conventions should be, as Schneider emphasized, the second step (109).

The subjectivity of the method of genetic understanding, its dependence on the capability of the investigator to understand, of his or her norms determined by different social and cultural factors has frequently been critized. Nevertheless, genetic understanding remains an important and indispensable aspect of clinical PP and cannot be replaced by other modes of comprehending, e.g. by psychoanalytic and other hermeneutic methods of as-if-understanding (88). It is a tenet of the PhPP that there exists for many psychiatric symptoms and syndromes of psychoses a point and a limit beyond which the psychological analysis cannot go. Yet, also in the field of psychoses much can be comprehended with Jaspers' method of genetic understanding. The themes of the psychoses are determined by biographic experiences and largely understandable. Every psychosis has its psychological-reactive traits (49,57,109). Psychological reactions to the psychotic and other psychopathological experiences and disturbances are much more common; freedom, insight, and responsibility are available to a much greater extent than is conceded by the classical psychiatry, but also by anthropological phenomenology, which claimed as a rule a total and specific change of personality, a principal, insurmountable heterogeneity of the schizophrenic human being (58,60,74).

K. Schneider was rather a pragmatic clinician and teacher than a theorist, building a system of psychiatry. His work built much more on Jaspers than on Kraepelin. Nevertheless, Schneider appreciated thoroughly the great achievement of Kraepelin. In his speech to celebrate the centenary of Kraepelin's birthday (106) Schneider discussing the manifold post-Kraepelinian schools sums up: Everywhere the Kraepelinian clinical entities remain fundamental and the Kraepelinian epoch is far from over«. Schneider did also Jaspers work not leave as he found it: Jaspers phenomenology was not taken over by Schneider without far-reaching changes. The Clinical Psychopathology (109) was in perpetual growth with vast and profound modifications in each subsequent edition, until his last, 8th edition of 1967. Schneider intended to apply Jaspers methodology to the need of the clinician. The concern with clinical application, his meticulous and methodical shifting to add precision to diagnostic work, gave his book its special quality and value, scarcely achieved by other authors.

The basic positions of the Schneiderian PP form a fundamental frame-work for the clinic and could unfold an internal power, clearing, founding and establishing concepts (71,117). The approach is undogmatic and means no final conclusion and codification, the later editions of the Clinical Psychopathology brought a further development of the starting points with improvements and changes, incessantly correcting earlier views according to the own daily clinical experience. For Schneider the psychiatry remained an unfinished building, whose future shape could not be recognized. The Jaspersian-Schneiderian PP seems to be also today the most reliable fundament for the clinical psychiatry. In spite of possible objections to some positions, e.g. to the notions of disease, norm and understanding, it can be called a concept of the present. It is everything but rigid though it could and can, as each doctrine, be misused against the intention of its creators. Anyone who is concerned with psychiatry cannot do so without arguing in consent with or contradiction against positions of this PP, even if he or she then follows his or her own ways (57).

Many contributions in the last decades were concerned with the work of Jaspers and Schneider. The various trials and discussions led to uneven and also conflicting results and the value of the PhPP for the psychiatry has been put in question. Some European and Anglophone authors as Hoenig (s. in 109: pp 119ff.) have shown that much of the dilemma stems from misunderstanding of or unfamiliarity with the context of their work. With Kraepelin, K. Schneider and Jaspers certainly are, as Hoenig wrote, the European psychiatrists most frequently cited in the anglophone literature, but, without reaching a deeper understanding of their general approach to psychiatry that could only provide the presuppositions of a fruitful and constructive-critical discussion of their concepts of phenomenological and clinical PP.

**Older and Newer Results Acquired by Means of PhPP:** In the following we present some concepts, findings and results, obtained with the Jaspersian-Schneiderian approach, demonstrating its use and relevance for the past and present clinical psychiatry: (1) The concept of personality disorders; (2) the schizophrenia concept;




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(3) the Basic Symptom Concept (BSC) with the Basic Symptom oriented Early Recognition Study and (4) the Bonn Schizophrenia Long-term Study with (5) the precursor stages of schizophrenia.

**(1) Personality disorders**

The contributions on personality disorders and the functional, so-called endogenous (idiopathic) psychoses, the cyclothymia (affective psychoses), and schizophrenia, come essentially from K. Schneider. In his book The psychopathic personalities (105), an area which Kraepelin never succeeded in delineating clearly, K. Schneider describes a number of abnormal personality types, encountered in clinical practice. The description is based on psychopathological criteria and partly also on deviations in social adjustment that are mainly expressions of different psychological characteristics. One merit of Schneider's work lies in the clear conceptual demarcation of these disorders from psychotic illnesses, i.e. the organic psychosyndromes, and the schizophrenic and affective psychoses (111). Schneider's humanity led him to avoid as much as possible value judgements: The psychopathic personality is simply such a person, suffering from him- or herself, except some types of psychopathics under whom the society suffers. For the term psychopathic personality and the overlapping generic term abnormal personality, the average-norm and not the value-norm is decisive. The abnormal and the psychopathic personalities pass on without sharp border to the personalities, who are to be termed as normal (109: p 9): Both types, the people, who suffer from the abnormality, or whose abnormality makes the society suffer, overlap. Abnormal and psychopathic personalities are extreme variations of a certain personality trait, an extreme prominence of distinct traits of personality, representing excesses or deficiencies in a statistical sense. The abnormality depends on the distinctness and dominance of a certain personality trait that *per se* can be more or less present in every human being.

The most comprehensive criticism of his concept of psychopathic personalities came from Schneider himself (107; 109: pp 15ff., 90f.). He warns of the danger of a labelling, the tendency to regard on the field of psychopathic and also psychogenic personality developments psychological descriptions as diagnosis, to designate and classify personalities and emotional reactions of personality like illnesses or psychic consequences of illnesses, because this would be a unjustified analogy. Then, the typological designation never can grasp the whole of the personality. Schneider objected to the until today usual tendency, to record and classify the immense field of variations of psychic life, of personalities and reactions to life events, according to the medical model of diseases, and to label the individual patient with terms, looking like diagnoses. Because in the variations it is, unlike to the psychosis, a question of the contents, every description instantly becomes an individual portrait, going beyond the type. To delineate such portraits of personalities only succeeds according to K. Schneider great poets, as e.g. Shakespeare and Dostojewski, Jens Peter Jacobson, Rilke or Hermann Hesse (107,108,109: pp 9f.).

Furthermore, the relativity of the permanent, habitual character of the personality disorders is emphasized: Certainly, they would arise on the basis of a largely inborn constitution; but they are nevertheless changeable by development, by fluctuations of the unexperienced underground (104,109) or by the effects of life events and personal experiences in the widest sense, what K. Schneider is at pains to point out. Especially certain personality traits can be formed and intensified or weakened and reduced by environmental factors, while other traits are not or less susceptible to social surroundings and thus also to psychotherapy. We must not ignore the biographical factors and motives of fluctuations and the possibility of psychotherapeutic influences; but, neither the constitutional pecularities, points of risk and Achilles heels. K. Schneider means by constitution a disposition or diathesis (Anlage), a potential for the development and realization of a personality. Also, if it remains a stumbling block, there are dispositions of personality that must be accepted as such and taken into consideration. These dispositions appear early in the course of the individual development as consequence more of constitutional than of social factors. Schneider's concept of psychopathy stands in contrast to the view of psychoanalysis, for which the character neurosis is resolved in terms of faulty infantile development and also to views that locate normality, psychopathy and psychosis as points on a continuum (98).

With regard to the modern designation personality disorder we can scarcely see a true progress and profit, at least not for each type of them: E.g., a depressive or sensitive personality may be rather an expression of the conditio humana than a disorder. This is according to Schneider also valid regarding emotional psychic reactions (Erlebnisreaktionen). The so-called abnormal, psychic-reactive, neurotic as well as personality developments, are in essence not separable from 'normal' psychic reactions and personalities. This position of K. Schneider agrees with Kretschmer's view that the psychology of neuroses is the very psychology of the human mind. Also critics of Schneider's unsystematic typology with the description of the hyperthymic, depressive, insecure (with sensitive and anancastic subtypes), fanatic, attention seeking, mood-labile, explosive, affectionless, weak-willed and asthenic personalities, acknowledge that there is a high degree of internal consistency in these accounts and that the issues, presented in it, are still and until today the major ones in the field of personality disorders [Standage (111)]. Further, that K. Schneider set out to replace Kraepelin's socially valuing descriptions with a typology, that was non-evaluating, psychopathological and clinically relevant (see 105,111).

**(2) The concept of schizophrenia - first, second and third rank symptoms**

With the PhPP the diagnostic criteria and the classification of schizophrenia and of affective illnesses or cyclothymias, as Schneider called them, have been improved and clarified. Schneider's schizophrenia concept has received the most attention in the anglophone literature. Within Schneider's provisional Triadic System of clinical psychiatry, schizophrenia and cyclothymia are defined as small disease units, i.e. purely psychopathological state-course-entities. Also the schizophrenia concept relies preferentially on abnormal modes of experiences and, unlike to the Neo-Kraepelinian anglophone schools, less on observable behaviour. Among the abnormal modes of experience some were set off as first rank symptoms (FRS). Three are auditory hallucinations: Hearing one's own thoughts aloud; hearing voices, conversing with one another or maintaining a running commentary on the patient's behaviour. Somatic hallucinations (somatic passivity) are experiences of being bodily influenced by some external agency. Disorders of ego experience are thought broadcasting, thought withdrawal, thought insertion and made volitional acts (Willensbeeinflussung). The ninth FRS is delusional perception, the experience that some real percepts have an abnormal meaning, specifically directed to the patient. Probably, delusional perceptions are based on basic deficiencies of visual or auditory perception (74,90). Mellor (101) has added two further ego-boundary disturbances, made feelings and made impulses (drives), we imperative voices (72). K. Schneider stated: When FRS undeniably are present and no underlying somatic illness can be



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found, we speak clinically in all modesty of schizophrenia (109: pp 62f.). All other abnormal modes of experience are termed as second rank symptoms, among them other hallucinations (auditory hallucinations, that are not FRS, visual, olfactory and gustatory hallucinations), delusional notions (Wahneinfall), depressed and elated moods, experienced impoverishment of feeling (erlebte Gefühlsverarmung) and some other. FRS do not always have to be present, the diagnosis has to be made often in their absence. We often have to base the diagnosis on second rank and expression symptoms, exceptionally even merely on expression symptoms alone, provided, they are adequately distinct and present in large numbers. To the expression (behavioural) symptoms (Ausdrucks-symptome) belong thought and affective, catatonic and expression symptoms strictly speaking, e.g. stiffness, affectation, mannerism, grimacing and oddity. According to Schneider these expression phenomena are, unless they are strongly marked, very uncertain symptoms and therefore only third rank symptoms with a lower diagnostic weight than second and still more FRS.

There are no specific schizophrenic symptoms (see above): All, also FRS, can be observed also in brain diseases. This means that there are cases of symptomatic schizophrenia, psychopathologically not distinguishable from idiopathic schizophrenias (25, 46, 61, 72). Further aspects of Schneider's concept are the differentiation of delusional perception from delusional notion and of schizophrenic disorders of ego-experience against depersonalization; then the priority of diagnostics according to the state against diagnostics according to the course, correctly: The outcome. Yet, the state-diagnosis also includes the course before and after the current inquiry as sequence and development of stages. The point is that for the diagnosis the favourable or unfavourable outcome is not decisive. The rule of Kraepelin: Schizophrenias correspond with a bad, manic-depressive (affective) psychoses with a good outcome, has many exceptions (4, 26, 47, 72, 83).

K. Schneider emphasized that in the psychopathological picture (but not in the substrate) are seen transitions between psychopathic personalities and psychoses (109: pp 17,40,68). The illness, working with pre- and extrapsychotic material, transposes biographical desires and conflicts into psychotic experiences. In inactive periods the disease can work with biographical contents to such a degree, that the cross-section syndrome cannot be differentiated from neurotic and personality developments: There exists a partial phenomenological overlap between psychotic and psychogenic disorders with states that have been called e.g. pseudoneurotic, pseudopsychopathic or larvate schizophrenia (see 72). The Schneiderian concepts of schizophrenia and cyclothymia rely on the careful description of the phenomena: Phenomenology stands before genesis as Schneider said. If this axiom would not have been considered, the most relevant findings of clinical psychiatry had not been made. Between schizophrenias and affective psychoses are intermediary cases [Zwischen–Fälle (109)], separated by other schools e.g. as schizophreniform, reactive, psychogenic, schizoaffective or cycloid psychosis (2,33,63,65,70,99). There exists only a differential typology, not a differential diagnosis between schizophrenic and affective psychoses. All pecularities, used for dividing up the intermediary cases, e.g. syntonic premorbid personality, acute onset, psycho-reactive releasing, depressive features do not allow a differentiation against Schneiderian schizophrenias. The claimed criteria fail, when the long-term courses with their enormous variety and changeableness are considered (70,83,86). The criteria, used for differentiation of the various types of intermediary psychoses, coincide with the prognostically favourable outcome criteria of the Bonn-Schizophrenia-Study (63, 65, 86).

As to the frequency of FRS, the considerably different proportion of patients, showing these symptoms with a range from 33% to 80% (96) has been criticized. But, by this has been disregarded the duration of observation. E.g., in the Bonn-Study FRS occurred in the first 6 months after onset in 52%, in the whole course in 78%. Then it must be considered that since the beginning of the psychopharmacological era, the FRS were seen less frequently than before as a consequence of a decrease of the productive-psychotic, positive symptoms in favour of more or less uncharacteristic symptoms and residues. This has been shown by the comparison of samples of the years 1949 to 1954 and of 1960 to 1964. FRS was found in the older sample in 72%, in the patients of the 60s only in 42%.

The PhPP following Schneider and Jaspers stresses the importance of a synoptic consideration of the total clinical picture, including anamnesis, biography and personality, making a diagnosis of schizophrenia. It is, as Schneider said, not possible, to practice PP on the razors edge (109). This seems to be, in view of the reductionistic character of operationalized diagnostics, today still more important than earlier (22,72: pp 28f; 84). According to Schneider every concept of schizophrenia in the present state of our knowledge can not be more than a provisional convention (9,22,23,49). The question which concept is right? is unanswerable, until pathognomonic somatic findings are available. Today we can possibly ask which concept is best? and answer: This concept which can predict the outcome best (54: pp 147,157). But this would be only pertinent, if schizophrenia would be an always progressive disorder with regularly unfavourable outcome, a doctrine, definitively disproved by the European long-term studies (83). By the Bonn- and the Zürich-Study has also been demonstrated that the Schneiderian or Bleulerian schizophrenia concept cannot predict the outcome (4,83). Some of FRS are good predictors and others are not (13). E.g. first rank auditory hallucinations are correlated with a bad outcome, delusional perception with a favourable one (13,83,86). Yet, not only the Schneiderian or Bleulerian, but all concepts and even very restrictive concepts as DSM-III or Feighner criteria, cannot predict the outcome [see Kendell 1985 in: (54)].

**(3) The basic symptom concept and the basic symptoms oriented early recognition study of schizophrenia**

The basic symptom concept (BSC), gradually developed since the 50s (80; review: 116), originated with the first description of the cenesthetic type of schizophrenia (42,67) and the pure defect (41,43,45). The pure defect (see also 83) represents a non-psychotic residual type of schizophrenia, determined by manifold basic symptoms (BS), which are in detail defined in the Bonn scale for the Assessment of Basic Symptoms [BSABS (35,39)]. The patients perceive and report the BS as complaints and disturbances and are able to develop self-help strategies and coping behaviour, attempts of defending, avoiding and compensating. The pure defect, later called pure dynamic-cognitive deficiency syndrome, develops mainly already in the first years after the first psychotic episode. Patients with the component of pure defect – but not all schizophrenias – were found to have slight enlargements of the 3rd and the lateral ventricles (31,41,43,44,78). Already these findings led to a revision of the doctrine that residues of schizophrenia are psychopathologically always typical schizophrenic and quite different from organic psychosyndromes (50,82,83). Thus, the first observation of the BS research has been the discovery that many schizophrenics in the course look no longer specific schizophrenic, but reveal non-psychotic psychosyndromes, not recognizable with regard to their schizophrenic provenance. Already since the 50s has been described that distinct, rather characteristic, mainly cognitive level-2-BS are the starting point for the development for distinct FRS, e.g. cenesthesias for bodily hallucinations, or perception disorders for delusional perceptions (41,74).

The second observation the BSC proceeded from has been the first description of a subclinical, i.e. as to the diagnosis subthreshold type of the disorder, the cenesthetic schizophrenia (41,42,67). These were patients, who complained on various bodily sensations (table 1).




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Table 1: Different types of cenesthesias (41,42) of the 4th main category of the BSABS (35,39,72)

| BSABS – Item | |
|---|---|
| D.1 | Sensations of numbness and stiffness |
| D.1.1 | Somatopsychic depersonalization |
| D.2 | Sensations of motor weakness |
| D.3 | Circumscribed sensations of pain |
| D.4 | Migrating sensations |
| D.5 | Electrifying sensations |
| D.6 | Thermic sensations (heat or coldness) |
| D.7 | Sensations of movements, pulling and pressure, of crawling, itching, touching inside the body or on its surface |
| D.8 | Sensations of abnormal heaviness, lightness or emptiness, of falling, sinking, levitation or elevation |
| D.9 | Sensations of diminution, shrinking or constriction, of enlargement or extension |
| D.10 | Kinesthetic sensations |
| D.11 | Pseudovestibular sensations. Qualitatively peculiar disturbances of balance and space sense |
| D.12 | Sensually, tactually, emotionally released dysesthesias |
| D.13 | Not classifiable cenesthesias |
| D.14 | Dysesthetic crises |
| D.15 | Paroxysmal (endogenous) anxiety states without cenesthesias |

By follow-up these pseudohypochondriac patients for years, a schizophrenic psychosis occurred, even if, as a rule, only in brief acute exacerbations. The usually present prodromes of the type had duration of 7 years on average and the outcome after 20 years has been mainly (66%) a pure defect syndrome. That such yearlong prodromes occur also in the other subtypes of schizophrenias has been shown in 1969 by G. Gross by the first systematic study on precursor stages on the basis of a sample of 290 patients (6). Already at that time a nosological congruity and unity of the typical psychotic episodes on the one side and the uncharacteristic pre- and postpsychotic basic stages, i.e. of the prodromes and pure defect syndromes on the other side, was evident. The findings of the 50s and the early 60s have been replicated and specified by the Bonn Schizophrenia Study by means of personal inquiry of 502 patients, admitted between 1945 and 1959 in the Bonn University Clinic (see below). After two decades were found, besides 22% with full remission and 35% with typical defect psychoses, 40% with pure residues, constituted by BS (83).

Thus, the concept of BS and basic stages led to a new doctrine of hitherto neglected symptoms of schizophrenia, the dynamic and cognitive BS (table 2) that are not considered in the international literature (14,55,56,64,76,92,95,116). There are until the late 80s only a few notable exceptions, f.i. the contributions of J. Chapman (5), of Herz (40) and of Böker and Brenner (112).

Table 2: Five main categories and additional category of the Bonn Scale (35,39)

| BSABS (Bonn Scale for the Assessment of Basic Symptoms) Five main categories, 163 items |
|---|
| A. Dynamic deficiencies with direct and indirect minus symptoms<br>Increased impressionability; obsessional-compulsive, phobic, depersonalization phenomena |
| B. Cognitive thought, perception and action (movement) disturbances |
| C. Cenesthesias and dysesthetic crises |
| D. Central-vegetative disturbances |
| E. Additional category: |
| F. Coping strategies |

**(4) The Bonn Schizophrenia Long-term Study**

Also some of the most important findings of the Heidelberg, Wiesloch (41,43) and Bonn (83,86) Long-term Studies on schizophrenic and related disorders could only be gained, using the phenomenological-psychopathological approach. The Bonn-Study agrees with the Zürich-Study of Bleuler (3), that a reliable prediction of outcome is not possible at the onset, that 20–30 years after onset nearly a quarter of patients show full psychopathological and about a half social remissions, and that course and outcome of schizophrenias are extremely different (70,83, s. below).

Table 3: Remission types in 502 schizophrenic patients of the Bonn-Long-term-Study (83) after on average 22.4 years of course [taken from (72,86)].

| Types of Remission | N % | Groups of Remission Types |
|---|---|---|
| Complete remission | 111 (22.1) | Complete remissions 22.1% |
| Minimal residual types | 55 (11.0) | Uncharacteristic residues 43.2% |
| Slight pure residues | 118 (23.5) | |
| Severe pure residues | 29 (5.8) | |
| Structural deformations without psychosis | 16 (3.0) | |
| Mixed residues | 83 (16.5) | Characteristic deficiency syndromes 34.7% |
| Typical schizophrenic defect psychoses | 54 (10.8) | |
| Chronic pure psychoses | 21 (4.2) | |
| Structural deformation with psychosis | 16 (3.2) | |

The global term of the schizophrenic defect or residual state had been psychopathologically differentiated in the Heidelberg and Wiesloch follow-up studies (41,43,45) in full remissions, the uncharacteristic pure defect syndromes (see above) and typical schizophrenic defect psychoses (s. table 3). As to social remission 56% were socially recovered (fully employed), but only 38% at their premorbid professional level, yet 18% below it. Social and psychopathological outcome revealed a high positive correlation: 60% of the pure residues, but only 25% of the typical schizophrenic residues were socially cured (83).

Table 4: Frequency and rate of social remission in 12 different course types ($n$ = 502) of the Bonn-Study (83)

| Types of Course | Frequency N (%) | Social Remission N (%) | Course Type Groups |
|---|---|---|---|
| I. Monophasic | 50 (10.0) | 50 (100) | Favourable |
| II. Polyphasic | 61 (12.1) | 59 (96.7) | |
| III. Chronic pure psychoses | 21 (4.2) | 19 (90.5) | |
| IV. One manifestation to pure residues | 31 (6.2) | 25 (80.6) | Relatively favourable |
| V. Phasic/shift-like to pure residues | 50 (10.0) | 35 (70.0) | |
| VI. In shifts with 2nd positive bend to Pure residues | 29 (5.8) | 19 (65.5) | |
| VII. In shifts or simple to structural deformations | 31 (6.2) | 16 (51.6) | Relatively unfavourable |
| VIII. Simple to pure residues | 27 (5.4) | 13 (48.1) | |
| IX. In shifts to pure residues | 65 (12.9) | 29 (44.6) | |
| X. In shifts to mixed residues | 48 (9.6) | 12 (25.9) | Unfavourable |
| XI. Simple to mixed residues | 36 (7.2) | 3 (8.3) | |
| XII. In shifts or simple to typical schizophrenic defect psychoses | 53 (10.5) | 1 (1.9) | |



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We distinguished phasic (22%), shift-like (48%) and simple straight-line progressing (30%) courses. Combining the kind of course with the type of psychopathological outcome ensued 12 course types, ranked according to their social remission (table 4). While the mono- and polyphasic course types I and II show a complete recovery after one or on average five episodes, in the course types X–XII the social remission rate drops from 25% in type X to 1.9% in type XII, which includes the »schizophrenic catastrophes. Their rate in the Bonn-Study is with 4% lower than that found by BLEULER in 1941 [5–18% – (3,4,86)]. On the whole, there are four groups of course types (see table 4): The prognostically favourable, relatively favourable, relatively unfavourable and unfavourable, each accounting for one quarter of all patients with extremely different social remission rates from nearly 100% in types I and II dropping off until 2% in type XII.

The following findings of the Bonn-Study speak for the continuum hypothesis of idiopathic psychosyndromes: In the course of schizophrenias occurred endogenomorphic-depressive phases in 18.7% of the 502 patients (10,17); schizoaffective psychoses show pure residues as frequently as schizophrenias (26,32,33,34); the prognostically favourable factors of Schneiderian schizophrenias are identical with the criteria, used to define schizoaffective, schizophreniform, cycloid, atypical or reactive psychoses, i.e. syntonic premorbid personality, precipitating life events, peracute onset and endogenomorphic-depressive symptoms (12,65,66,83). In the Bonn-Study revealed the subsample ($n$ = 113) meeting the criteria for schizoaffective or cycloid psychoses (according to Kasanin, RDC, Angst or Leonhard and Perris), a highly significantly more favourable long-term prognosis than the whole sample of Schneiderian schizophrenias (2,32).

The findings of the Bonn-Study and the Bonn-Cologne basic symptom oriented early recognition study have led to a revision of two doctrines of traditional psychiatry: (1) The dogma of an always present fundamental psychopathological heterogeneity and numinous singularity of schizophrenias compared with organic brain diseases and (2) the dogma of an incessant progression of the disorder (50,68,83,116,119).

The Bonn-Study provided also hints on a favourable influence of somatic therapy on outcome. The patients ($n$ = 273) treated in the first year of disease, including the prodromes, revealed a significantly more favourable outcome, than the patients treated later or never (see table 5). The longer untreated prodromes last, the rarer are full remissions (15,83). The results of the Long-term Studies have, as Zubin said, revolutionized our knowledge about schizophrenias and emanzipated the illness from the yoke of inevitable chronicity (118).

Table 5: Early treatment (within 1 year after onset of the disease including prodromes) of the 1st psychotic episode vs late or no treatment and long-term prognosis in schizophrenic patients ($n$ = 491) of the Bonn-Study. Chi- sqare 16.4 (2df), $p < 0.1$

| Treatment | Complete Remissions n % | Uncharacteristic Residues n % | Characteristic Residues n % | N % |
|---|---|---|---|---|
| Early treated | 76 (27.8) | 117 (42.9) | 80 (29.3) | 273 (55.6) |
| Late or not treated | 30 (13.8) | 98 (45.0) | 90 (41.3) | 218 (44.4) |

The following results of the Long-term Studies seem to be unambiguously verified (s. also 26).

(1) The illness shows no progressive deterioration. Nearly a quarter shows complete remission; more than the half (56%) shows social remission on the premorbid (38%) or below the premorbid level (18%). Even after decades improvement in the sense of a second, now positive bend with remission on pure residues is possible. (2) The long-term prognosis is extremely different; there are 4 course type groups, each accounting for one quarter of all patients, from a quite favourable to a quite unfavourable outcome. (3) The outcome has improved in the last decades, probably mainly due to psychopharmacological treatment. The long-term prognosis is significantly more favourable, if the patients are treated as early as possible after the onset of the disease, i.e. of the prodromes, preceding the first psychotic episode. (4) The true onset is in the majority of patients not marked by the first psychotic episode, but by precursor stages, i.e. prodromes and/or outpost syndromes. These findings have shown a way towards early basic symptom oriented recognition and intervention in the prodromes with the chance to inhibit the outbreak of the psychosis (19,37,80,94).

(5) Precursor stages of schizophrenia

We summarize some points of the issue. (1) Precursor stages, i.e. prodromes and/or oupost syndromes before the first psychotic episode are determined by BS, recognizable by self-reports, assessed with the BSABS. BS are likely to precede rather regularly the first psychotic episode as prodromes and/or as outpost syndromes. Only 11% of schizophrenic patients are primary negative anosognosia schizophrenias (59,60,62,63), commencing with true negative symptoms. (2) Prodromes pass over after an average duration of course of 3.3 years (range: 2 months until 35 years) continuously into the first psychotic episode. Prodromes are determined by uncharacteristic level-1-BS and - mostly later in the course - rather characteristic, mainly cognitive level-2-BS. The frequently observed deficits of social competence and emotional stability before the first psychotic manifestation are predominantly not traits of the premorbid personality, but already the consequences of the initial prodromal stages of the disorder. (3) Outpost syndromes are full remitting phases, lasting 5 months on average, preceding the first psychotic episode 10 years on average (range: 1 year until 37 years). The symptomatology of prodromes and outpost syndromes, i.e. of the pre- and post-psychotic (reversible or irreversible) basic stages is psychopathologically largely identical. Therefore, the BS both of the prepsychotic and the postpsychotic basic stages can be examined with the BSABS or the Francfort Complaint Questionnaire (35,39,113,114,115,116).

Table 6: Ten BSABS prodromal symptoms with a very good predictive power (ppp > 0.70), being present in at least one quarter of the patients developing positive symptomatology (72,73,94).

| BSABS Item | |
|---|---|
| C.1.1 | Thought interference |
| C.1.2 | Obsessive-like perseveration of thoughts (often past events) |
| C.1.3 | Pressure of thoughts |
| C.1.4 | Blocking of thoughts, |
| C.1.6 | Disturbances of receptive speech |
| C.1.15 | Disturbances to discriminate between imaginations or perceptions, fantasy and memory contents |
| C.1.17 | Immediately corrected tendency to self-reference, subject centrism |
| C.2.1/C.2.3 | Optic perception disturbances |
| C.2.4/C.2.5 | Acoustic perception disturbances |
| C.2.9 | Captivation by details of perception |
| C.2.11 | Derealization |

(4) Distinct cognitive level-2-BS of the prodromes, i.e. cognitive thought, perception and action BS and cenesthesias, are initial experiences for the development of distinct positive first rank symptoms, as has been shown in the Bonn–Cologne prospective early recognition study (19,37,94) and in the transition sequences study of Klosterkötter (90). Some of these transition-relevant mainly cognitive thought, perception and action BS (s. table 6) could be proved to be the best psychopathological predictors of the schizophrenic psychosis (8,18,19,20,21,38,69,94). (5) The Bonn-




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Cologne prospective basic symptom oriented early recognition study (19,37,38,72: pp 408–422; 80,94) has revealed, that many seemingly neurotic and personality disorders are prepsychotic basic stages of schizophrenia and that there exists a fluent transition from minus to positive schizophrenias and vice versa. The transition of minus to positive symptoms represents the development of distinct positive schizophrenic first rank symptoms out of distinct BS, that are already quasi microproductive, i.e. positive symptoms in statu nascendi. BS develop mostly in a distinct chronological sequence: First dynamic and cognitive BS as the first manifestations of the disorder, out of which arise positive symptoms and only later negative symptoms, except the mentioned small subgroup of primary negative anosognosia schizophrenias. (6) Early treatment within 1 year after the true onset, i.e. after the beginning of the prodrome, improves the long-term prognosis (19,72,79,81,83). Full remissions are the more rarely, the longer the prodromes persist untreated (15,37). (7) Early intervention in the prodromes, guided by the BS, can inhibit the development of the psychosis. The modern diagnostic systems do not define the prodromal (and residual) BS adequately. The in DSM-III-R listed Prodromal and Residual Symptoms (PRS (1), s. table 7) are not experiential in kind, but abnormal behaviour and negative symptoms, by which the prodromes and the true onset of schizophrenia cannot be identified. This is possible by means of the BS, accessible by the self-reports of the patients, and not by observation of behaviour and expression. The patients in the prodromes of schizophrenia are aware of the BS as deficiencies and able to develop coping strategies against the complaints, unlike patients with negative and behavioural symptoms, who, as a rule, do not perceive their deficit symptoms in the same manner as patients with prodromal BS and are not able to develop self-help strategies against them.

Table 7: Prodromal and residual symptoms as diagnostic criteria according to DSM-III-R

| |
|---|
| (1) Marked social isolation or withdrawal |
| (2) Marked impairment in role functioning |
| (3) Marked peculiar behaviour (e.g. collecting garbage etc.) |
| (4) Marked impairment in personal hygiene and grooming |
| (5) Blunted or inappropriate affect |
| (6) Digressive, vague, overelaborate or circumstantial speech, poverty of speech or its contents |
| (7) Odd beliefs or magical thinking, ideas of reference |
| (8) Unusual perceptual experiences, e.g. recurrent illusions, sensing the presence of a force or person, not actually present |
| (9) Marked lack of initiative, interests or energy |

(8) Already today a primary BS oriented prevention of the schizophrenic psychosis in the precursor stages is justified and necessary (s. 72: pp 408–422).

The BS, constituting in the long-term courses of schizophrenia both the prepsychotic prodromal and the postpsychotic basic stages, have been ascertained, as the other cited findings of the BS research, of the Bonn Schizophrenia Long-term and the Bonn–Cologne Early Recognition Study, essentially by means of the PhPP in the direction of Schneider.

**Biological-psychiatric Research and Psychopharmacological Therapy:** PhPP is relevant also for biological-psychiatric research above all in order to detect correlations between clinical syndromes and functional or structural brain deviations. K. Schneider has time and again also in the Clinical Psychopathology referred to the meaning of such correlation studies, and on generally, on the importance of biological-somatic research for the psychiatry (s. 109: p 5; s. also 60,75,87,91,92,94). Inconsistencies of findings of biological-psychiatric research in psychoses and in schizophrenia result frequently from lacking consideration of the clinical PP and the criteria of the BS- and process activity concept (11,69,77,78,84,85). Opposed to a select by diagnosis strategy, a strategy differentiating process active and inactive stages is suitable to correlate dynamic-functional, f.i. electroencephalographic or neurochemical parameters with the clinical syndrome (73,77,82,85,103). Another strategy has to be used to correlate morphological changes in schizophrenia with the type and duration of an unremitting psychopathological deficit syndrome (20,31,41,43,44,78). Only residues with the component of an irreversible pure defect reveal neuroradiological changes (mainly as to the third and lateral ventricles), but not schizophrenics with complete remissions or typical schizophrenic structural deformations (31,41,78). As to functional state markers, higher levels of dopamine, serotonin and norepinephrine were found in process active stages, not in inactive basic stages (determined by level-1-BS) (7,36,75,69,85); the same is valid, concerning abnormal rhythmicity (alpha- and theta-parenrhythmia) in EEG (82, 102). That the results also of newer studies with PET, SPECT or MRI are often very different and controversial, has not rarely the same reason as the inconsistencies of older findings of biological-psychiatric research, i.e. the insufficient strategy of defining and correlating somatic parameters and actual psychopathological syndromes, exactly at the time of the somatic inquiry.

In the concept of process activity (PA) has been differentiated the degree of PA according to the current psychopathological stage: E.g., stages of higher PA are characterized by distinct cognitive BS and by FRS and second rank symptoms in statu nascendi with marked dynamic instability and fluctuation (69, 72, 93). Glutamate has been found, unlike to the most other amino acids, decreased in serum and in CSF (more in active than in inactive stages), a finding, compatible with the hypothesis that the primary cause of schizophrenia may be a hypofunction of glutamatergic systems with a secondary hyperfunction of dopaminergic systems (18, 80, 85, 97). The fluctuation and paroxysmal occurrence of transition relevant cognitive BS, determined by the BSABS and the criteria of the process activity concept (35, 69; 72: pp 346ff; 93), seem to reflect also an imbalance of neurochemical parameters (36, 51, 52, 62, 76, 80, 91, 116).

As to psychopharmacological treatment, a primary as well as a secondary prevention of psychotic episodes in schizophrenia is most likely possible by using the Jaspersian-Schneiderian PP and the findings of the BS research, founded on this clinical PP (see above). Because the effects of neuroleptics and antidepressants are syndrome-directed and the target syndrome in schizophrenia presents very different types of psychopathological cross-sectional pictures, the usual rough differentiation, e.g. of positive and negative, of acute and chronic, paranoid and non-paranoid schizophrenia is not appropriate for the special indication and choice of a distinct drug and dosing strategy. This is valid for maintenance treatment of patients in remission and for early intervention in the prodromal stages before the first and later psychotic episodes (79, 81). Thus, PhPP has to be seen as an essential prerequisite of an effective psychopharmacological treatment too.

We have elsewhere referred to the positive influence of the Ph PP on style and kind of somatic-psychiatric research, which has to be guided and coordinated by clinical psychiatry (16, 24, 53, 56, 77, 80): We can do scientific work both in clinical and in somatic research only in close relation to the patient (s. 109: pp 119f.).

**References:**


1. American Psychiatric Association Diagnostic and statistical manual of mental disorders (DSM-III-R), 3rd edn revised. Washington, DC: APA. 1987.
2. Armbruster B, Huber G. Die zykloiden und schizoaffektiven Psychosen der Bonner Schizophrenie-studie. In: Seidel K, Neumärker KJ, Schulze HA, eds. Zur Klassifikation endogener Psychosen. Leipzig: Hirzel, 1986:54–62.
3. Bleuler M. Die schizophrenen Geistesstörungen im Lichte langjähriger Kranken-und Familiengeschichten. Stuttgart: Thieme, 1972.




https://doi.org/10.1111/j.1601-5215.2008.00305.x Published online by Cambridge University Press

4. Bleuler M, Huber G, Gross G, Schüttler R. Der langfristige verlauf schizophrener psychosen. Gemeinsame Ergebnisse zweier Untersuchungen. Nervenarzt 1976;**47**:477–481.
5. Chapman J. The early symptoms of schizophrenia. Br J Psychiatry 1966;**112**:225–251.
6. Gross G. Prodrome und Vorpostensyndrome schizophrener Erkrankungen. In: Huber G, ed. Schizophrenie und zyklothymie. Ergebnisse und Probleme. Stuttgart: Thieme, 1969: 177–187.
7. Gross G. ed. Perspektiven psychiatrischer Forschung und Praxis. 9. Weißenauer Schizophrenie-Symposion. Stuttgart: Schattauer, 1994.
8. Gross G. The onset of schizophrenia. Schizophr Res 1997;**28**:187–198.
9. Gross G, Huber G. Schizophrenie – eine provisorische Konvention. Zur problematik einer nosographie der schizophrenien. Psychiatr Praxis 1978;**5**:93–105.
10. Gross G, Huber G. Depressive syndrome im verlauf von schizophrenien. Fortschr Neurol Psychiat 1980;**48**:438–446.
11. Gross G, Huber G. Die Bedeutung diagnostischer konzepte und kriterien für die biologisch-psychiatrische Forschung bei schizophrenen und schizoaffektiven Psychosen. In: Hopf A, Beckmann H, eds. Forschungen zur biologischen Psychiatrie. Berlin: Springer, 1984:54–62.
12. Gross G, Huber G. Classification and prognosis of schizophrenic disorders in the light of the Bonn follow-up studies. Psychopathology 1986;**19**:50–59.
13. Gross G, Huber G. Die Bedeutung der symptome 1. Ranges für die Diagnose und Prognose der Schizophrenie. In: Olbrich HM, ed. Halluzination und wahn. Berlin: Springer, 1987:110–123.
14. Gross G, Huber G. Das basissymptomkonzept idiopathischer Psychosen. Zbl Neurol Psychiat 1989;**252**:1–19.
15. Gross G, Huber G. Möglichkeiten und grenzen einer prädiktion des langfristigen therapieunabhängigen und therapieabhängigen Verlaufs schizophrener und schizoaffektiver Erkrankungen. In: Heinrich K et al., eds. Prädiktoren des therapieverlaufs endogener psychosen. Stuttgart: Schattauer, 1993:17–31.
16. Gross G, Huber G. Do we still need psychopathology, and if so, which psychopathology? Neurol Psychiatry Brain Res 1993;**1**:194–200.
17. Gross G, Huber G. Endogenous-depressive symptoms in the course of schizophrenic disorders. Neurol Psychiatry Brain Res 1995;**3**:183–188.
18. Gross G, Huber G. Psychopathology and biological-psychiatric research. Neurol Psychiatry Brain Res 1995;**3**:161–166.
19. Gross G, Huber G. The true onset of schizophrenia in its meaning for the view of the disorder. Neurol Psychiatry Brain Res 1996;**4**:93–102.
20. Gross G, Huber G. Is schizophrenia a neurodevelopmental disorder? Neurol Psychiatry Brain Res 1997;**5**:57–70.
21. Gross G, Huber G. Prodromes and primary prevention of schizophrenic psychoses. Neurol Psychiatry Brain Res 1998;**6**:51–58.
22. Gross G, Huber G. Schizophrenia: a provisional diagnostic convention. In: Maj M, ed. Evidence and experience in psychiatry. Vol.II, Chapter I. Chichester: Wiley & Sons, 1999:55–58.
23. Gross G, Huber G. Schizophrenia spectrum – where to draw the boundary? In: Maj M, ed. Evidence and experience in psychiatry. Vol.II, Chapter V. Chichester: Wiley & Sons, 1999:395–397.
24. Gross G, Huber G. Kommunikation mit psychisch Kranken und phänomenologische Psychopathologie. In: Bochnik HJ, Oehl W, eds. Begegnungen mit psychisch Kranken.: Sternenfels: Verlag Wissenschaft & Praxis, 2000:157–172.
25. Gross G, Huber G. The relevance of Jaspersian-Schneiderian psychopathology for today's psychiatry. Neurol Psychiatry Brain Res 2000;**8**:53–68.
26. Gross G, Huber G. The long-term course of schizophrenia and related disorders. A critical review. Neurol Psychiatry Brain Res 2000;**8**:121–130.
27. Gross G, Huber G. Psychopathologie des Wahns. Psychonomieprinzip und biologische Wahntheorie. Fortschr Neurol Psychiat 2001;**69**:97–104.
28. Gross G, Huber G. Basic symptoms and prodromal phase of schizophrenia. Neurol Psychiatry Brain Res 2005;**12**:185–198.
29. Gross G, Huber G. The schizophrenia concept of K. Schneider revisited. Neurol Psychiatry Brain Res 2006;**13**:31–40.
30. Gross G, Huber G. Somatically based psychoses and the problem of symptomatic schizophrenia. Neurol Psychiatry Brain Res 2007; **14**:131–142.
31. Gross G, Huber G, Schüttler R. Computerized tomography studies on schizophrenic diseases. Arch Psychiatr Nervenkr 1982;**231**:519–526.
32. Gross G, Huber G, Armbruster B. Schizoaffective psychoses – long term prognosis and symptomatology. In: Marneros A, Tsuang MT, eds. The schizoaffective psychoses. Berlin: Springer, 1986:188–203.
33. Gross G, Huber G, Schüttler R. Long-term course of Schneiderian schizophrenia. In: Marneros A, Tsuang MT, eds. The schizoaffective psychoses. Berlin: Springer, 1986:164–178.
34. Gross G, Huber G, Schüttler R. Prediction factors, anamnestic, clinical and social data of Schneiderian schizophrenia. In: Marneros A, Tsuang MT, eds. The schizoaffective psychoses. Berlin: Springer, 1986:179–187.
35. Gross G, Huber G, Klosterkötter J, Linz M BSABS. Bonner Skala für die Beurteilung von Basissymptomen – Bonn Scale for the Assessment of Basic Symptoms. Springer: Berlin, 1987 (1992) Italian, (1994) Danish, (1995) Spanish, (1996) Japanese edition
36. Gross G, Huber G, Klosterkötter J. Psychopathological–neurochemical correlations in idiopathic psychoses. In: Stefanis C et al., eds. Psychiatry: A world perspective. Vol.2. Amsterdam: Excerpta Medica, 1990:203–208.
37. Gross G, Huber G, Klosterkötter J. Early diagnosis of schizophrenia. Neurol Psychiatry Brain Res 1992;**1**:17–22.
38. Gross G, Huber G, Klosterkötter J. The early phase of schizophrenia and prediction of outcome. Int Clin Psychopharmacol 1998;**13**(suppl. 1):S13–S21.
39. Gross G, Huber G, Klosterkötter J, Linz M. BSABS. Bonn Scale for the Assessment of Basic Symptoms, 2nd edn, Aachen: Shaker, 2008.
40. Herz MI, Lamberti JS. Prodromal symptoms and early intervention in schizophrenia. Neurol Psychiatry Brain Res 1998;**6**:37–44.
41. Huber G. Pneumencephalographische und psychopathologische Bilder bei endogenen Psychosen. Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, H 79. Berlin: Springer, 1957.
42. Huber G. Die coenästhetische Schizophrenie. Fortschr Neurol Psychiat 1957;**25**:491–520.
43. Huber G. Chronische Schizophrenie. Synopsis klinischer und neuroradiologischer Untersuchungen an defektschizophrenen Anstaltspatienten. Heidelberg: Hüthig, 1961.
44. Huber G. Neuroradiologie und Psychiatrie. In: Gruhle HW et al., eds. Psychiatrie der Gegenwart. Forschung und Praxis, Bd. I/B Grundlagenforschung zur Psychiatrie. Berlin: Springer, 1964:253–290.
45. Huber G. Reine Defektsyndrome und Basisstadien endogener Psychosen. Fortschr Neurol Psychiat 1966;**34**:409–426.
46. Huber G. Klinik und Psychopathologie der organischen Psychosen. In: Kisker KP et al., eds, Psychiatrie der Gegenwart. 2.Aufl. Bd.II/2. Berlin: Springer, 1972:71–146.
47. Huber G. (ed.) Verlauf und Ausgang schizophrener Erkrankungen. 2. Weißenauer Schizophrenie-Symposion. Stuttgart: Schattauer, 1973.
48. Huber G. Indizien für die Somatosehypothese bei den Schizophrenien. Fortschr Neurol Psychiat 1976;**44**:77–94.
49. Huber G. Die klinische Psychopathologie von Kurt Schneider. In: Janzarik W, ed. Psychopathologie als Grundlagenwissenschaft. Stuttgart: Enke, 1979:102–111.
50. Huber G. Neuere Ansätze zur Überwindung des Mythos von den sog. Geisteskrankheiten. Fortschr Neurol Psychiat 1979;**47**:449–465.
51. Huber G. (ed.) Endogene Psychosen: Diagnostik, Basissymptome und biologische Parameter. 5. Weißenauer Schizophrenie-Symposion. Stuttgart: Schattauer, 1982.
52. Huber G. Das Konzept substratnaher Basissymptome und seine Bedeutung für Theorie und Therapie schizophrener Erkrankungen. Nervenarzt 1983;**54**:23–32.
53. Huber G. Die Bedeutung von Karl Jaspers für die Psychiatrie der Gegenwart. Nervenarzt 1984;**55**:1–9.
54. Huber G. ed. Basisstadien endogener Psychosen und das Borderline-Problem. 6. Weißenauer Schizophrenie-Symposion. Schattauer, Stuttgart New York 1985.
55. Huber G. Newer concepts of basic disorders and basic symptoms in endogenous psychoses: introduction. In: Pichot P et al., eds. Psychiatry. The state of the art, Vol I. London: Plenum Press, 1985:459–511.
56. Huber G. Negative or basic symptoms in schizophrenic and affective illness: introduction. In: Shagass C et al., eds. Biological Psychiatry. New York, NY: Elsevier, 1986:1136–1162.
57. Huber G. Kurt Schneider. The man and his scientific work. Zbl Neurol Psychiat 1987;**246**:177–191.
58. Huber G. (ed.) Fortschritte in der Psychosenforschung? 7. Weißenauer Schizophrenie-Symposion. Stuttgart: Schattauer, 1987.
59. Huber G Das körperliche Krankheitsmodell der endogenen Psychosen. In: Böcker F, Weig W, eds. Aktuelle Kernfragen in der Psychiatrie. Berlin Heidelberg: Springer, 1988:76–90.
60. Huber G. Stellenwert persönlichkeitsbezogener, psychosozialer und somatischer Bedingungsfaktoren in aktuellen Schizophreniekonzepten. In: Janzarik W, ed. Persönlichkeit und Psychose. Stuttgart: Enke, 1988:128–137.

 

61. Huber G. Gibt es symptomatische Schizophrenien? Psychiat Neurol Med Psychol 1989;**42**:11–24.
62. Huber G. (ed.) Idiopathische Psychosen. Psychopathologie – Neurobiologie – Therapie. 8. Weißenauer Schizophrenie-Symposion. Stuttgart: Schattauer, 1990
63. Huber G. Klinische und psychopathologische Argumente für eine Differential-typologie idiopathischer Psychosen. In: Simhandl C et al., eds. Klassifikations-probleme in der Psychiatrie. Wien: Ueberreuter, 1990:128–145.
64. Huber G. Disturbances of body sense as a basic symptom of idiopathic psychoses. In: Stefanis C et al., eds. Psychiatry: a world perspective. Vol I. Amsterdam: Excerpta Medica, 1990:304–308.
65. Huber G. Die Konzeption der Einheitspsychose aus der Sicht der Basisstörungslehre. In: Mundt C, Saß H, eds. Für und Wider die Einheitspsychose. Stuttgart: Thieme, 1992:61–72.
66. Huber G. The phenomenological approach to major psychoses in Europe during the past several decades. Neurol Psychiatry Brai Res 1992;**1**:49–53.
67. Huber G. »Cenesthetic schizophrenia« – a subtype of schizophrenic disease. Neurol Psychiatry Brain Res 1992;**1**:54–60.
68. Huber G. Prodrome schizophrener Erkrankungen. Fortschr Neurol Psychiat 1995;**63**:131–138.
69. Huber G. Basissymptom- und Prozeßaktivitätskonzept endogener Psychosen. In: Bräunig P, ed. Emotionspsychopathologie und zykloide Psychosen. Stuttgart: Schattauer, 1995:51–65.
70. Huber G. The heterogeneous course of schizophrenia. Schizophr Res 1997;**28**:177–184.
71. Huber G. Kurt Schneider (1887–1967). In: Schliack H, Hippius H, eds. Nervenärzte. Stuttgart: Thieme, 1998:138–145.
72. Huber G. Psychiatrie. Lehrbuch für Studium und Weiterbildung. 7th edn. Stuttgart: Schattauer, 2005.
73. Huber G. 50 years of schizophrenia research in a personal view. Neurol Psychiatry Brain Res 2006;**13**:41–54.
74. Huber G, Gross G Wahn. Eine deskriptiv-phänomenologische Untersuchung schizophrenen Wahns. Stuttgart: Enke, 1977.
75. Huber G, Gross G. Diagnostic concepts, psychopathological syndromes and somatic changes in schizophrenic diseases. In: Perris C et al., eds. Biological Psychiatry. Amsterdam: Elsevier, 1981:801–804.
76. Huber G, Gross G. The concept of basic symptoms in schizophrenia and schizoaffective psychoses. Recenti Progr Med 1989;**80**:646–652.
77. Huber G, Gross G. Somatische Befunde bei Psychosen. In: Battegay R et al., eds. Handwörterbuch der Psychiatrie. 2nd edn. Stuttgart: Enke, 1992:566–574.
78. Huber G, Gross G. Neuroimaging in der Psychosenforschung. In: Lang W et al., eds. Verhandlungen der Deutschen Gesellschaft für Neurologie in Wien. Wien: Springer 1985:588–592.
79. Huber G, Gross G. Advances in therapy and prevention of schizophrenic disorders? Neurol Psychiatry Brain Res 1997;**5**:1–8.
80. Huber G, Gross G. The basic symptom concept – historical aspects in view of early detection of schizophrenia. Neurol Psychiatry Brain Res 1998;**5**:183–190.
81. Huber G, Gross G. Conventional and newer neuroleptics in the treatment of schizophrenia spectrum disorders. Neurol Psychiatry brain Res 1999;**7**:15–26.
82. Huber G, Penin H. Klinisch-elektroencephalographische Korrelationsuntersuchungen bei Schizophrenen. Fortschr Neurol Psychiat 1968;**36**:641–659.
83. Huber G, Gross G, Schüttler R. Schizophrenie. Eine verlaufs- und sozialpsychiatrische Langzeitstudie. Monographien aus dem Gesamtgebiete der Psychiatrie, Bd 21. Springer, Berlin (Reprint 1984) 1979.
84. Huber G, Gross G, Klosterkötter J. Konzepte und Kriterien affektiver Psychosen. Nervenarzt 1989;**60**:90–94.
85. Huber G, Gross G, Klosterkötter J Amino acids in process active and inactive stages in schizophrenia. In: Stefanis C et al., eds Psychiatry: A world perspective. Vol I. Amsterdam: Excerpta Medica, 1990:209–214.
86. Huber G, Gross G, Schüttler R, Linz M. Longitudinal studies of schizophrenic patients. Schizophr Bull 1980;**6**:592–605.
87. Janzarik W. Strukturdynamische Grundlagen der Psychiatrie. Stuttgart: Enke, 1988.
88. Jaspers K. Allgemeine Psychopathologie. 4th edn. Berlin: Springer, 1946 (9th edn 1973).
89. Kaplan B. (ed.) The inner world of mental illness. New York, NY: Harper & Row, 1964
90. Klosterkötter J. Basissymptome und Endphänomene der Schizophrenie. Berlin: Springer, 1988.
91. Klosterkötter J. Das Forschungswerk Gerd Hubers – Aktualität und Zukunftsperspektive. In: Gross G et al., eds 50 Jahre Psychiatrie. Stuttgart: Schattauer, 1999:199–226.
92. Klosterkötter J. Huber's basic symptoms: a German approach to the initial prodrome of schizophrenia. 2nd International Conference on Early Psychosis, New York. Abstr Vol, 2000:33–34.
93. Klosterkötter J, Gross G Huber G. Das Konzept der Prozeßaktivität bei idiopathischen Psychosen. Nervenarzt 1989;**60**:740–744.
94. Klosterkötter J, Gross G, Huber G et al. Evaluation of the Bonn Scale for the Assessment of Basic Symptoms – BSABS as an instrument for the assessment of schizophrenia proneness: a review of recent findings. Neurol Psychiatry Brain Res 1997;**5**:137–150.
95. Koehler K. Sauer Huber's basic symptoms: Another approach to negative psychopathology in schizophrenia. Compr Psychiatry 1984;**25** 2:174-182.
96. Koehler K, Guth W, Grimm G. First-rank symptoms of schizophrenia in Schneider-oriented German centers. Arch Gen Psychiatry 1977;**34**:810–813.
97. Kornhuber HH Zur Biologie der Schizophrenie. In: Huber G, ed. Idiopathische Psychosen. Psychopathologie, Neurobiologie, Therapie. 8. Weißenauer Schizophrenie-Symposion. Stuttgart: Schattauer, 1990:50–68.
98. Kretschmer E Körperbau und Charakter. 25th edn. Completed by Kretschmer W Springer, Berlin, 1970 1967.
99. Leonhard K. Aufteilung der endogenen Psychosen. 3rd edn. Akademie Verlag, Berlin 1996
100. Mayer-Gross W (1932) Die Schizophrenie. Die Klinik. In: Bumke O, ed. Handbuch der Geisteskrankheiten. Bd.IX, Spez.Teil V. Berlin: Springer, 1966:293–578.
101. Mellor CS. First rank symptoms of schizophrenia. Br J Psychiatry 1970;**117**:15–33.
102. Penin H, Gross G, Huber G. Elektroenzephalographisch-psychopathologische Untersuchungen in Basisstadien endogener Psychosen. In: Huber G, ed. Endogene Psychosen: Diagnostik, Basissymptome und biologische Parameter. 5. Weißenauer Schizophrenie-Symposion. Stuttgart: Schattauer, 1982:247–264.
103. Rao ML, Gross G, Huber G. Altered interrationship of dopamine, prolactin, thyrotropin and thyroid hormone in schizophrenic patients. Eur Arch Psychiatry Neurosci 1984;**234**: 8–12.
104. Schneider K. Die Untergrunddepression. Fortschr Neurol Psychiat 1949;**17**:429–434.
105. Schneider K. Die psychopathischen Persönlichkeiten. 9th edn. Wien: Deuticke,1950.
106. Schneider K. Kraepelin und die gegenwärtige Psychiatrie. Fortschr Neurol Psychiat 1956;**24**:1–7.
107. Schneider K. »Der Psychopath« aus heutiger Sicht. Fortschr Neurol Psychiat 1958;**26**:1–6.
108. Schneider K. Psychiatrie heute. 3rd edn. Stuttgart: Thieme, 1960.
109. Schneider K. Klinische Psychopathologie. 15th unchanged edn. With a commentary by Huber G, Gross G. Stuttgart: Thieme, 2007.
110. Shepherd M. Karl Jaspers: General Psychopathology (books reconsidered). Br J Psychiatry 1982;**141**:310–312.
111. Standage K Psychopathic Personalities: Kurt Schneider (books reconsidered). Br J Psychiatry 1989;**155**:271–273.
112. Strauss JS, Böker W, Brenner HD. Psychosocial treatment of schizophrenia. Huber, Toronto 1987.
113. Süllwold L. Symptome schizophrener Erkrankungen. Uncharakteristische Basisstö-rungen. Monographien aus dem Gesamtgebiete der Psychiatrie, Bd 13. Springer, Berlin 1977.
114. Süllwold L. Der Frankfurter Beschwerdefragebogen. Berlin: Springer, 1991.
115. Süllwold L. Schizophrenie. 3rd edn. Kohlhammer, Stuttgart 1995.
116. Süllwold L, Huber G. Schizophrene Basisstörungen. Monographien aus dem Gesamtgebiete der Psychiatrie, Bd 42. Berlin: Springer, 1986.
117. Weitbrecht HJ. Psychiatrie im Grundriß. 3rd edn. Berlin: Springer, 1973.
118. Zubin J. Closing Comments. In: Häfner H et al., eds. Search for the causes of schizophrenia. Berlin: Springer, 1987:359–365.
119. Zubin J, Spring B. Vulnerability – a new view of schizophrenia. J Abnorm Psychol 1977;**86**:103–126.

# BRIDGES BETWEEN NEUROLOGY AND PSYCHIATRY

## Post stroke dementia, depression and fatigue

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Stroke is a major cause of long-term physical, cognitive and emotional disability. Cognitive impairment as a sequella after ischemic stroke is a major issue and might be the only preventable form of dementia of late life. The diagnosis of post stroke dementia (PSD) requires evidence of temporal relation between clinically defined stroke and cognitive decline, presence of focal neurological symptoms and signs and usually fluctuating course. However, the current criteria are insufficient and ill defined. The incidence of PSD varies between studies because of different diagnostic criteria and characteristics of study populations. Still, it is generally accepted that approximately 25% of all ischemic stroke patients will develop dementia within 3–6 months. Risk factors for developing PSD include: age, female sex, low level of education, diabetes mellitus, cigarette smoking, white matter changes, left side infarct and volume of infarct. Mortality is afflicted by PSD and the mean survival in PSD is approximately 3–5 years. The mechanism of PSD by which stroke patients may develop is still not entirely clear and include: multi-infarcts, strategic single infarct (thalamus, hypocampus etc.), chronic hypoperfusion and associated degenerative process (Alzheimer's disease). There is lack of data regarding primary and secondary prevention of PSD.

PSD is the most frequent and important neuro–psychiatric consequence of stroke. At least 30% of stroke survivors experience depression both early and late after stroke. Estimated PSD incidents range from 18% to 61% due to methodological differences, such as the point at which patients are assessed in relation to stroke onset and of instruments and criteria used. Depression might be resolved spontaneously within several months in a majority of stroke survivors. Several studies have shown that mortality was higher in stroke patients with depression and treatment with antidepressants might have significant benefit especially during the first 6 months poststroke. However, currently there is insufficient evidence to support routine use of antidepressants for the prevention of depression. Fatigue is defined as a state of general tiredness that is the result of overexertion and can be ameliorated by rest. 'Pathological' fatigue is a state characterized by weariness unrelated to previous exertion levels and is usually not ameliorated by rest; it is chronic in nature and has multiple or unknown causes. There are several aspects of fatigue such as physical, somatic, mental and psychological fatigue. Fatigue is a frequent and often disabling poststroke sequela but there have been only a few investigations on the subject. Fatigue was usually considered as a symptom of depression, however, one study found that 38% of poststroke patients with severe fatigue were also depressed. In another systematic study it was found that 68% of poststroke patients reported fatigue problems and 78% felt lack of energy. Fatigue independently predicted decreased functional independence and mortality. Currently no specific treatment was proven effective for this disabling poststroke sequela. The lecture will cover both depression and fatigue problems in stroke patients.




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# SCIENTIFIC WORKSHOP: EPILEPSY THERAPY

## Optimizing epilepsy therapy – individual approach

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With introduction of many new antiepileptic drugs over the past 10–15 years, more patients can achieve seizure freedom. Recent studies showed that with optimal drug regimen this can be as high as 65–70% (1). However, some seizure types such as the localization-related epilepsy are more difficult to control (1,2) than others (e.g. idiopathic generalized epilepsy) and require further EEG evaluation. A significant number of patients that continue to experience seizures have mesial temporal lobe epilepsy (3), although their seizure frequency may be decreased by optimal AEDs. Because of the refractorness of their seizures, these patients should be included in further presurgical evaluation, that usually begins with long-term video/EEG telemetry.

Video/EEG monitoring has become a crucial part of evaluation of epilepsy patients (4–6). It includes placement of scalp EEG electrodes for several days or occasionally as long as few weeks. The idea is to perform a simultaneous video and EEG recording of a sufficient number of patients' characteristic seizures and interictal activity, as a condition necessary for more precise lateralization and possible localization of seizure focus. Despite the fact that in the past epilepsy patients were referred for the presurgical telemetry almost two decades after their first seizure, the continuous monitoring has proven to be cost-beneficial and, consequently, has been introduced rapidly in many institutions. There are at least two important benefits from the continuous EEG monitoring: first, an exclusion of patients with autonomic behavioral non-epileptic events and their utilization of the emergency care and of the AED (5). A number of studies showed that up to 30% of patients can be misdiagnosed preceeding the video/EEG evaluation (5). Secondly, telemetry offers a superior localization of seizure region in epilepsy patients, or can suggest a need for further intracranial video/EEG monitoring (3,7). Recently, we showed that self-reported seizure frequency did not predict time to first seizure during video/EEG telemetry. This is an important finding, because it suggests that great majority of patients with refractory seizures are good candidates for video/EEG telemetry and should not be excluded from further EEG diagnosis. Although it is difficult to predict a refractory state, self-reported seizure frequency by itself is somewhat biased in its estimate. Many studies indicate that patients underestimate their seizure frequency (8). For example, Blum et al. (9) found that 30% of patients monitored in the epilepsy unit denied all their seizures. In their study most of the seizures originating within the left temporal lobe were denied, and approximately 50% of seizures were denied that started in the right temporal lobe These data suggest that refractory epilepsy cannot be defined only by self-reported seizure rates, because of the potential bias. Much better estimate for seizure refracterness is a failure of the first two antiepileptic drugs in the course of at least two years (10–16). The goal should be to offer these patients EEG telemetry if further evaluation is necessary, and select them for prospective epilepsy surgery.

**References:**

1. Kwan P, Brodie MJ. Clinical trials of antiepileptic medications in newly diagnosed patients with epilepsy. Neurology 2003;**60**(suppl. 4):S2–12.
2. Stephen LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? Epilepsia 2001;**42**:357–362.
3. Serles W, Pataraia E, Bacher J, et al. Clinical seizure lateralization in mesial temporal lobe epilepsy: differences between patients with unitemporal and bitemporal interictal spikes. Neurology 1998;**50**:742–747.
4. Attarian H, Dowling J, Carter J, Gilliam F. Video EEG monitoring prior to vagal nerve stimulator implantation. Neurology 2003;**61**:402–403.
5. Martin RC, Gilliam FG, Kilgore M, Faught E, Kuzniecky R. Improved health care resource utilization following video-EEG-confirmed diagnosis of nonepileptic psychogenic seizures. Seizure 1998;**7**:385–390.
6. Rose AB, McCabe PH, Gilliam FG, et al. Occurrence of seizure clusters and status epilepticus during inpatient video-EEG monitoring. Neurology 2003;**60**:975–978.
7. Kuzniecky R, Suggs S, Gaudier J, Faught E. Lateralization of epileptic foci by magnetic resonance imaging in temporal lobe epilepsy. J Neuroimaging 1991;**1**:163–167.
8. Dalrymple J, Appleby J. Cross sectional study of reporting of epileptic seizures to general practitioners. BMJ 2000;**320**:94–97.
9. Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. Neurology 1996;**47**:260–264.
10. Leidy NK, Elixhauser A, Vickrey B, Means E, Willian MK. Seizure frequency and the health-related quality of life of adults with epilepsy. Neurology 1999;**53**:162–166.
11. Berg AT, Langfitt J, Shinnar S, et al. How long does it take for partial epilepsy to become intractable? Neurology 2003;**60**:186–190.
12. Brodie MJ, Kwan P. Staged approach to epilepsy management. Neurology 2002;**58** (suppl. 5):S2–S8.
13. Campos MG, Godoy J, Mesa MT, Torrealba G, Gejman R, Huete I. Temporal lobe epilepsy surgery with limited resources: results and economic considerations. Epilepsia 2000;**41**(suppl. 4):S18–S21.
14. Trevathan E, Gilliam F. Lost years: delayed referral for surgically treatable epilepsy. Neurology 2003;**61**:432–433.
15. Tureczek IE, Fandino-Franky J, Wieser HG. Comparison of the epilepsy surgery programs in Cartagena, Colombia, and Zurich, Switzerland. Epilepsia 2000;**41**(suppl. 4):S35–S40.
16. H. Hećimović, Attarian, H. Fessler III, A.J. Eisenman, L. Altay-Erbayat, E. Lynch, T. Brown, K. Vahle, T. Ojemann, J. Dowling, J. Gilliam F. Time to first intracranial EEG seizure is not predicted by prior scalp EEG monitoring or general anesthesia, AES 2002.

## Therapeutic strategies for epilepsies

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**Objectives:** Treatment of epilepsies has become much more complex than ten years ago. In the following chapter aims of the treatment, indications for drug treatment or surgical treatment are discussed. Treatment requirements have to be differentiated in those for continous long-term treatment and those for acute interventional therapy. For continous long-term treatment permanent efficacy, tolerable side effects, simple handling, compliance and optimal benefit relation has to be guaranteed. For acute interventional treatment a fast uptake of the drug, rapid effect, safety and optimal logistics are of special importance.



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**Aims of the treatment:** The definition of the aim of the treatment depends on the clinical condition and the individual situation of the patient. The first aim is to obtain seizure control without side effects and social integration. 'It is difficult to treat patients who did not become seizure free adapted aims have to be defined every year. A next step could be to obtain seizure control with tolerable side effects and very difficult to treat patients even only a reduction of severe seizures (frequency and intensity) or day time seizures whereas nocturnal seizures may be more easily be tolerated. Another important aim is the prevention of cognitive decline and injuries by the seizures.

**Treatment requirements:** For continuous long-term treatment the following requirements should be fullfilled:

Permanent efficacy of the anticonvulsive drug (no tolerance), tolerable side effects, simple handling of the application and optimal conditions for continuous compliance of the patient. Additionally an optimal cause benefit relation should be established. For an acute interventional treatment it is more important to provide a very fast uptake of the drug with rapid effect and high safety. In addition simple logistics are important. In addition to the well-known drugs of the first drug generation (phenytoin, phenobarbital and benzodiazepines) parenteral applications of levetiracetam and valproate can be used now for emergency cases. Phosphenytoin offers advantages compared to phenytoin (improved tolerability, i.m. injection) but the logistics requiring cooling are difficult to handle outside the emergency room. Midazolam can be used as buccal application instead or in addition to rectal or intravenous benzodiazepines. After the first treatment patients should receive an emergency identity card which contains the most important informations concerning the seizure signs, postictal behaviour, classification, necessary treatment, address of the neurologist, previous and present medication and additional diseases. This emergency identity card is written in three languages (English, French, German) and can be requested at the 'Verein zur Hilfe Epilepsiekranker Erlangen e.V.').

**Treatment options:** In addition to counselling of the patient and avoiding trigger factors treatment with anticonvulsive drugs most often is performed after two spontaneous epileptic seizures. In special cases after one tonic clonic seizure (e.g. if there is a genetic disposition in the family and general spike wave in the EEG or a pathological neurological finding or epilepsies in the elderly). Anticonvulsant drugs can be divided in drugs of the first generation brom, phenobarbital, primidone, phenytoin, carbamazepine, benzodiazepines and valproate and the drugs of the second generation (felbamate, gabapentine, lamotrigine, levetiracetam, oxcarbazepine, pregabalin tiagabine, topiramate, vigabatrin, zonisamide). In case of pharmacoresistent epilepsies surgery is to be considered (table 1).

Treatment of epilepsies can be differentiated in several phases according to the cause for the epilepsy of the patient. In case of previously untreated epilepsies the first monotherapy should performed as easy to handle for the patient as possible. For this aim with several drugs a once daily application in adults can be used. In most cases the slogan: 'go slow, start low' should be noticed. As long as seizures occur during treatment an increase of the dosage of the anticonvulsant should be performed. This remains true until side effects occur. The serum concentrations of different antiepileptic drugs of different anticonvulsants only provide an orienting glance through the window of the therapeutic range. There are no absolute upper and lower limits of serum concentrations. Especially the serum concentrations of new antiepileptic drugs are of limited value. During phenytoin treatment serum concentrations are recommended because phenytoine has a nonlinear pharmacokenetic which may lead to severe intoxications. Important criteria for the selection of anticonvulsants are the electroclinical syndrome (focal or generalizied symptomatic or idiopathic), the experience with the efficacy of the anticonvulsive drugs in different epileptic syndromes, its pharmacology, known adverse effects and the tolerability for the patient. Some epileptic syndromes which require special treatment are mentioned briefly. Benign partial epilepsy should be treated with sulthiame (1). Dravet syndrome should not be treated in the first year with lamotrigine (2). Lennox–Gastaut-syndrome due to neuronal ceroid lipofuszinosis could be improved with lamotrigine and valproate (3). In some patients with myoclonic epilepsy Genton (4) described the improvement by levetiracetam. Most often the classification to focal or primarily generalized seizures and epileptic syndromes are used for the choice of anticonvulsive treatment. For focal epilepsies carbamazepine, oxcarbazepine, lamotrigine, gabapentine, pregabalin, tiagabine, vigabatrin, zonisamid, phenytoin, phenobarbital, levetiracetam are licenced. For generalized epilepsies, primary generalized epilepsies with absences ethosuximid zonisamid (myoclonic seizures) can be used. A broad spectrum of efficacy for focal and generalized epilepsies is known for valproate, lamotrigine, topiramate and elbamate. Felbamate plays no major role in the epilepsy treatment because of serious side effects with hepatotoxicity and agranulocytosis.

Advantages and disadvantages of new antiepileptic drugs are discussed in detail (5,6) elsewhere. In addition to the selection of anticonvulsive drug with regard to the classification additional disturbances of the patient have to be taken into account (table 2). The frequent occurrence of polycystic ovaries and hypoandrogenism associated with weight gain and hyperinsulinemia in women taking valproate for epilepsy was reported. After replacing valproate by lamotrigine the body mass index and fasting serum insuline and testosterone concentrations decreased during the first year after. The total number of polycystic ovaries in these women decreased from twenty during valproate medication to eleven, one year after replacing valproate by lamotrigine (7). The results of an expert rating as well as epilepsies in the elderly for the use of different anticonvulsants in focal and generalized epilepsies are demonstrated. In difficult to treat generalized epilepsies with myoclonic seizures valproate is ineffective in 20%. In childhood absence epilepsies 60% of patients respond to the first antiepileptic drug and seizure controll can be obtained in 90%. Valproate and ethosuximide have an equivalent efficacy. In case of combination of absence seizures with tonic clonic seizures valproate or lamotrigine has to be choosen because ethosuximide does not inhibit tonic clonic seizures. Concerning the choice of anticonvulsive medication in the management of difficult to treat idiopathic epilepsies a survey was provided by Perucca (8).

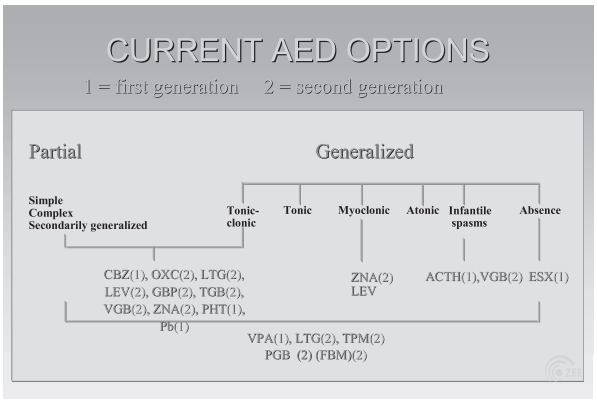


Table 1: Current AED options of the first and second generation. CBZ, carbamazepine; LEV, levetiracetam; VBG, vigabatrin; OXC, oxcabazepine; GBP, gabapentine; ZNA, zonisamide; LTG, lamotrigine; TGB, tiagabin; PHT, phenytoin; ESX, ethosuximide; VPM, valproate; TPM, topiramate; FBm, felbamate; ACTH, adrenocorticotropic hormone; Pb, phenobarbital; PGB, pregabalin




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Use of anticonvulsants in case of additional disturbances

| Disturbances | Use with caution or contraindicated | Alternative (if indicated for syndrome) |
|---|---|---|
| cardic rhythm | CBZ, PHT | LTG, PGB, VGB, TPM, LEV |
| liver | FBM, VPA, CBZ, PHT, LTG | PGB, VGB,(TPM), LEV |
| porphyria | CBZ, PHT, VPA, Pb, Pr, FBM, SUX | PGB, (LTG), VGB, OXC, LEV |
| kidney | GBP, TPM (renal calculus), LTG, VGB, LEV, PGB | CBZ, PHT, OXC, LEV* |
| pancreas | VPA | CBZ, PHT, (LTG), VGB, OXC,TPM, LEV |
| leukopenia | FBM, CBZ, PHT, ETHO, SUL, LTG, TPM | PGB, DZP, LTG, LEV |
| diabetes | PHT, (TPM) | PGB, DZP, LTG, LEV |
| coagulation | VPA | PGB, DZP, LTG, OXC, TPM, LEV |
| exanthema | CBZ, LTG, PHT | VPA, PGB, TPM, VGB, OXC |
| osteoporosis | CBZ, PHT, Pb, Pr, VPA | LTG, OXC, PGB, TPM, VGB, LEV |
| hypothyreosis | CBZ, PHT, OXC | LTG, OXC, PGB, VPA,TPM, VGB, LEV |
| dupuytren | Pb, Pr | PGB, OXC, VPA, LTG, TPM, VGB, LEV |
| L.E. | ETHO, PHT, Pr | PGB, TPM, VGB |
| alopecia | VPA, PHT, Pr | PGB, (LTG), OXC, TPM, VGB, LEV |
| weight | VPA↑, PGB↑, VGB↑,TPM↓, FBM↓ | CBZ, LTG, PHT, OXC, LEV |
| myasthenia | DZP, CLOB, PHT | VPA, PGB, CBZ, LTG, OXC, TPM, LEV |
| psychosis | ETHO, VGB, TGB, TPM, LEV | CBZ, OXC, VPA, PGB, (PHT) |
| eye,visual field, sense of colour | VGB,TPM, BZD, TGB?, PGB?, PHT, CBZ | LTG, LEV |

* adjustment of dosage

H. Stefan 2005

Table 2: CBZ, carbamazepine; PHT, phenytoin; FBM, felbamate; VPA, valproate; LTG, lamotrigine; Pb, phenobarbital; SUX, suximide; GBP, gabapentine; Pr, primidon; TPM, topamax; VBG, vigabatrin; PGB, pregabalin; ETHO, ethosuximide; OXC, oxcarbazepine; ↑ = increase; ↓ = decrease

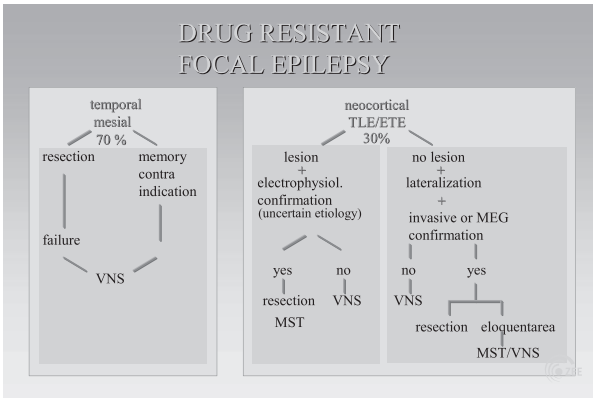


Fig. 1. Decision path for drugs, epilepsy surgery or vagus stimulation modified according to Benbadis et al 2000. VNS, vagus nerve stimulation; MST, multiple subpial transaction; MEG,magnetoencephalography.

**Difficult to treat and pharmacoresistant epilepsies:** After the first anticonvulsive drug has been titrated up to side effects without controlling the seizures we speak of a difficult to treat epilepsy. Seizure control with a second drug may be obtained in 13 to 15% and by using a third or multiple drugs an additional 4% (9). The comparison of the effect of drug treatment and epilepsy surgery in patients with temporal lobe epilepsies has been evaluated by Wiebe et al. (10). After one year of treatment at least two antiepileptic drugs (cabamazepine, valproate, phenytoin) patients became seizure free in 8% and in the controlled population using surgery in 38%. Therefore patients with focal epilepsies who failed to respond to anticonvulsive treatment the possibility of epilepsy surgery or electro-stimulation should be evaluated. Therapeutic strategies for epilepsy surgery, electro-stimulation or diet are discussed with regard to the number of antiepileptic drugs, hemispheric dominance, location of the epileptogenic tissue in temporal or extra temporal areas or generalized epilepsies (Fig. 1). Magnetoencephalography provides a new non invasive tool for localisation of focal epileptic activity in relation to functional important brain areas (11). If still necessary invasive recordings can be more selectively planned using MEG information or even avoided. This offers in some cases a short cut way for the treatment decision path. Because larger sections often are associated with deficits a tailoring of resections is strongly recommended. In addition to resection and electrostimulation gamma knife surgery in mesial temporal lobe epilepsy and fractionated radiotherapy focal sterotactic radiotherapy (12,13) can be performed. Epilepsy therapy for the 21st century offers new perspectives of treatment like direct stimulation of the brain (14) or local applications of antiepileptic drugs (15) and transplantations.

**References:**


1. Rating D, Wolf C, Bast T. Sulthiame as monotherapy in children with bening childhood epilepsy with centrotemporal spikes: A six-month randomized, double-blind, placebo-controlled study. Epilepsia 2000;**41**:1284–1288.
2. Dulac O. Epileptic encephalopathy. Epilepsia 2001;**3**:23–26.
3. Aberg LE, Backman M, Kirveskori E, Santavuori P. Epilepsy and antiepileptic drug therapy in juvenile neruonal ceroid lipofuscinosis. Epilepsia 2000;**41**:1296–1302.
4. Genton P, Gelisse P. Suppression of post-hypoxic and post-encephalitic myoclonus with levetiracetam. Neurology 2001;**57**:1144–1145.
5. Stefan H, Feuerstein TJ. Novel anticonvulsant drugs. Pharmacol Ther 2007;**113:**165–183.
6. Stefan H, Steinhoff BJ. Emerging drugs for epilepsy and other treatment options. Eur J Neurol 2007;**14**:1154–1161.
7. Jouko IT, Isojärvi IT, Rättyä J, Myllylä VV, Knip M, Koivunen R, Pakarinen AJ, Tekay A, Tapanainen JS. Valproate, Lamotrigine and Insulin + Medical Risks in Women with Epilepsy. Ann Neurol 1998;**43**:446–450.
8. Perucca E. Clinical pharmacology and therapeutic use of the new antiepileptic drugs. Fundam Clin Pharmacol 2001;**15**:405–417.
9. Kwan P, Brodie MJ. Refractory epilepsy: a progressive, intractable but preventable condition? Seizure 2002;**2**:77–84.
10. Wiebe E. Comparison of effect of drug treatment and epilepsy surgery. N Engl J.Med 2001;**2**:345–5.
11. Stefan H, Hummel C, Scheler G, Genow A, Druschky K, Tilz C, Kaltenhäuser M, Hopfengärtner R, Buchfelder M, Romstöck J. Magnetic brain source imaging of focal epileptic activity: a synapsis of 455 cases. Brain 2003;**126**:1–10.
12. Stefan H. Epilepsien: Diagnose und Behandlung 1999, Georg Thieme Verlag, 3. Auflage.
13. Regis J, Bartholomei F, Rey M, Hayashi M, Chauvel P, Peragut J-C. Gamma knife surgery for mesial temporal lobe epilepsy. J Neurosurg 2000;**93**:141–146.
14. Rektor I, Kuba R. Neurostimulation in Neurology, Teaching Course Epilepsy, 6th EFNS Congress, Vienna Oct 2000.
15. Boison D, Scheurer L, Teseng JL, Aebischer P, Mohler H. Seizure suppression in kindled rats by intraventricular grafting of an adenosine releasing synthetic polymer. Exp Neurol 1999;**160**:174–74.
16. Benbadis SR, Tatum WO, Vale FL. An algorithmic approach to medically intractable epilepsy. Neurology 2000;**55**:1780–1784.



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# SCIENTIFIC WORKSHOP: CLINICAL PSYCHOIMMUNOLOGY

## Basic aspects of psychoneuroimmunology: neuroendocrinological and metabolic aspects

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The relationship between psychiatric illness and immune system was first observed in 1927 by Wagner-Jauregg, the only psychiatrist who ever awarded Noble prize for his work on malaria inoculation in the treatment of dementia paralytica. In recent years many studies have been carried out on the relationship between psychological stress, depression and immune system. Some melanoma and chronic hepatitis patients when treated with pro-inflammatory cytokines such as interferon-α and interleukin-2 developed neuropsychiatric complications including depression. In major depression, activation of the inflammatory response system (IRS) and, increased concentrations of plasma pro-inflammatory cytokines, prostaglandin E2 and negative immuno-regulatory cytokines in peripheral blood have been reported. The changes in blood cytokines have also been reported to occur in other psychiatric disorders such as schizophrenia, bipolar mania and anxiety disorders (1,2). The imbalances between the pro- and anti-inflammatory cytokines in patients with psychiatric disorders were reversed by the effective medication (1,3).

In animal studies, different stressors are reported to increase interleukin-1 messenger RNA expression in the hypothalamus (4), elevate interleukin-1 activity in cell culture supernatants (5), and enhance the interleukin-1 in the hypothalamus (6), increase interleukin-1β and TNF-α by isolated alveolar macrophages (7), and increase the plasma concentrations of interleukin-6 (8, 9). In the olfactory bulbectomised rat model of depression, the pro-inflammatory cytokines were found to be increased in the blood and brain in association with depressive-like behaviour and cytokine changes were normalized after chronic treatment with antidepressants (10). The proinflammatory cytokines have been shown to enhance corticotrophin releasing factor (CRF) in the hypothalamus which in turn activates hypothalamo–pituitary–adrenal (HPA) axis. This result in persistently high cortisol concentrations; such changes are commonly observed in the depressed patients. In addition, CRF again increases the release of pro-inflammatory cytokines from macrophages which further contributes to the activation of HPA axis. Such changes induce the glucocorticoid receptor tolerance which enhances the impairment of the negative feedback mechanism of the HPA axis. In chronic stress, the arginine vasopressin (AVP) was also found to be responsible enhancing effect of CRF on the HPA axis. The pro-inflammatory cytokine, IL1β was shown to be responsible for the shift from CRF to AVP in the activation of anterior pituitary in chronic stress thereby further enhancing the hypercortisolaemia. The chronic increase in cortisol is considered to contribute to neurodegenerative changes in the brain. This is probably due to the increased cortisol impairing the synthesis of neurotrophic factors such as brain derived neurotrophic factor (BDNF) and thus preventing neuronal repair. The chronic hypercortisolaemia, combined with the changes in the brain induced by chronic low grade inflammation, may contribute to neuronal apoptosis. It is hypothesized that such inflammatory assaults are compounded by the synthesis of beta amyloid plaques and neurofibrillary tangles. These changes could account for the increase in incidence in dementia in middle aged and elderly depressed patients.

In recent years, the link between cytokines and the serotonergic turnover through tryptophan metabolism has become of interest. It is reported that cytokines such as IL-2 and IFN-γ reduce the synthesis of 5-HT by stimulating the activity of indoleamine 2,3 dioxygenase (IDO), an enzyme which converts tryptophan, the precursor of 5-HT, to kynurenine. Kynurenine is further metabolized to kynurenic acid (KYNA), 3-hydroxykynurenine (3OHK) and quinolinic acid (QA) by kynurenine aminotransferase, kynurenine 3-monooxygenase (kynurenine 3-hydroxylase) and kynureninase respectively (11). Both kynurenine 3-monooxygenase and kynurenase are also shown to be activated by IFN-γ and TNF-α (12). 3OHK is neurotoxic and apoptotic while QA is the excitotoxic N-methyl-D-aspartate (NMDA) receptor agonist (13). Conversely KYNA, the synthesis of which is decreased in depression, is an antagonist of all three ionotropic excitatory amino acid receptors (14) and α7-nicotinic acetylcholine receptor (α7-nAChR) (15).

In the brain, tryptophan catabolism occurs in the astrocytes and microglia though 60% of brain kynurenine is contributed from the periphery (16). The astrocytes are shown to produce mainly KYNA whereas microglia and macrophages produced mainly 3OHK and QA (17–19). The astrocytes have been demonstrated to metabolise the QA produced by the neighbouring microglia. The protective effect of KYNA against excitotoxic effect of QA has also been detected in neuronal cell cultures. Tryptophan breakdown has been found to be increased but KYNA, the neuroprotective metabolite, is decreased in both depressed and schizophrenic patients compared to healthy controls; no significant changes occur in the group of patients with bipolar mania. Moreover, in the patients with schizophrenia, the neurotoxic 3OHK is significantly increased compared to healthy controls. Antidepressant or antipsychotic treatment did not correct the reduction in plasma KYNA even though the rise in 3OHK could be corrected to a certain extent. Such changes in these metabolites are reflected also in the cerebrospinal fluid of depressed and schizophrenic patients. The plasma 3OHK concentration has been shown to be correlated with CSF kynurenines; CSF KYNA concentrations are positively associated with response to treatment. These findings lead to the hypothesis that the reduced neuroprotective metabolite, and increased neurodegenerative metabolites, result in an imbalance neuroprotection–neurodegeneration in the brain might further induce the apoptosis of the neuroprotective astrocytes. The vulnerability to stress is thereby enhanced.

In rats treated with chronic interferon-α both depressive-like behaviour together with a loss of astrocytes in dentate gyrus of hippocampus has been observed. The loss of astrocytes is not corrected by the antidepressant treatment. Thus, following treatment, even though depressed patients showed recovery from depressive symptoms they frequently relapse. Furthermore, the interval between depressive episodes is often shorter and there is higher chance of recurrence. Regarding the relationship between immune system abnormalities, tryptophan metabolism changes and neurotransmitter changes, it is important to consider the changes in




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terms of the imbalance between the interactive systems. For example, kynurenic acid interacts with other neurochemical systems, such as glutamatergic and dopaminergic systems: since kynurenic acid has antagonistic effect not only on the glutamatergic NMDA receptors but also on α-7 nicotinic acetylcholine receptor the changes could indirectly influence the dopaminergic neurotransmission. Therefore, both marked increases and decreases in KYNA are likely to be detrimental to the dopaminergic and glutamatergic systems which emphasises that the optimal balance between neuroprotective and neurotoxic metabolites of the kynurenic pathway is necessary for the normal neuronal functions.

In conclusion, the neuroprotection–neurodegeneration balance is superimposed on the changes in HPA axis and oxidative stress. Such an interaction between immune system, neuroendocrine and neurotransmitter systems plays an important role in the development of major psychiatric disorders and contributes to impaired cognitive function and dementia.

**References:**


1. Kim YK, Myint AM, Lee BH, Han CS, Lee HJ, Kim DJ, et al. Th1, Th2 and Th3 cytokine alteration in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2004;**28**:1129–1134.
2. Kim MS, Choi IY, Lee SH, Hong SH, Shin T, Kim HM. The oriental medicine "Cool-Cool (Cool-X-A)" inhibits inflammatory cytokine production and migration in mast cells. Biol Pharm Bull 2004;**27**:34–37.
3. Myint AM, Leonard BE, Steinbusch HW, Kim YK. Th1, Th2, and Th3 cytokine alterations in major depression. J Affect Disord 2005; 88: 167–73.
4. Minami M, Kuraishi Y, Yamaguchi T, Nakai S, Hirai Y, Satoh M. Immobilization stress induces interleukin-1 beta mRNA in the rat hypothalamus. Neurosci Lett 1991;**123**:254–256.
5. Khlusov IA, Dygai AM, Gol'dberg ED. The adrenergic regulation of interleukin production by bone marrow cells during immobilization stress. Biull Eksp Biol Med 1993;**116**:570–572.
6. Shintani F, Nakaki T, Kanba S, Kato R, Asai M. Role of interleukin-1 in stress responses. A putative neurotransmitter. Mol Neurobiol 1995;**10**:47–71.
7. Persoons JH, Schornagel K, Breve J, Berkenbosch F, Kraal G. Acute stress affects cytokines and nitric oxide production by alveolar macrophages differently. Am J Respir Crit Care Med 1995;**152**:619–624.
8. Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS. Exposure to physical and psychological stressors elevates plasma interleukin 6: relationship to the activation of hypothalamic-pituitary-adrenal axis. Endocrinology 1993;**133**:2523–2530.
9. Shizuya K, Komori T, Fujiwara R, Miyahara S, Ohmori M, Nomura J. The influence of restraint stress on the expression of mRNAs for IL-6 and the IL-6 receptor in the hypothalamus and midbrain of the rat. Life Sci 1997;61:PL 135–140.
10. Song C, Leonard BE. The olfactory bulbectomised rat as a model of depression. Neurosci Biobehav Rev 2005;**29**:627–647.
11. Bender DA. The kynurenine pathway of tryptophan metabolism. In: Stones TW, ed. Quinolinic acid and kynurenines. Boca Raton, Florida, FL: CRC Press, 1989;3–38.
12. Chiarugi A, Calvani M, Meli E, Traggiai E, Moroni F. Synthesis and release of neurotoxic kynurenine metabolites by human monocyte-derived macrophages. J Neuroimmunol 2001;**120**:190–198.
13. Schwarcz R, Whetsell WO Jr, Mangano RM. Quinolinic acid: an endogenous metabolite that produces axon-sparing lesions in rat brain. Science 1983;**219**:316–318.
14. Perkins MN, Stone TW. An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid. Brain Res 1982;**247**:184–187.
15. Hilmas C, Pereira EF, Alkondon M, Rassoulpour A, Schwarcz R, Albuquerque EX. The brain metabolite kynurenic acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications. J Neurosci 2001;**21**:7463–7473.
16. Gal EM, Sherman AD. L-kynurenine: its synthesis and possible regulatory function in brain. Neurochem Res 1980;**5**:223–239.
17. Guillemin GJ, Smythe G, Takikawa O, Brew BJ. Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. Glia 2005;**49**:15–23.
18. Guillemin GJ, Kerr SJ, Smythe GA, Smith DG, Kapoor V, Armati PJ, et al. Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection. J Neurochem 2001;**78**:842–853.
19. Guillemin GJ, Smith DG, Kerr SJ, Smythe GA, Kapoor V, Armati PJ, et al. Characterisation of kynurenine pathway metabolism in human astrocytes and implications in neuropathogenesis. Redox Rep 2000;**5**:108–111.


## Clinical immunology


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The increase of the incidence of various autoimmune disorders was just recently demonstrated in pedigrees with spectrum psychoses (1) confirming indirectly also the described overlap of genes in between schizophrenia and affective spectrum (2). The common pathogenetic pathway could be the immune inflammatory reaction pattern. In any case, immune dysfunction and various pathogens including viruses, bacteria and protozoa, seem involved in the pathogenesis in a subgroup of psychoses although the exact pathomechanisms remain to be elucidated. This evolving evidence of a gene immune pathogen connection in psychoses would represent a similarity to autoimmune disorders in general (compare 3). It is expected that there are further interactions, with the endocrine system, with neuroprotection respectively neurodegeneration, and neuroplasticity, and metabolic responses, but also with yet unknown factors which may be unique to the brain itself, not least the yet poorly described role of immune cell trafficking through CSF spaces and the CNS, previously thought to be very limited or excluded and understood as the immune privilege of the brain, a dogma which was recently challenged (4,5). According to the mild encephalitis (ME) hypothesis (6) a subgroup of affective and schizophrenic spectrum psychoses may be causally related to an underlying mild inflammatory process, be it agent induced or from autoimmune origin. Focusing on the possible role of Borna disease virus (BDV) in such framework, collected was considerable evidence that in a small number of cases BDV may be the initiating or causal agent (7). Various infectious agents and autoimmune mechanisms/antigens could be involved, eventually representing a diverse spectrum of specific causes and common pathogenetic pathways. Such scenario could plausibly explain that a number of non-specific treatments are useful. Nevertheless, in severe or chronic or therapy resistant cases there may be special need to differentiate specific causes/mechanisms, and apply differentiated therapies. We therefore attempted to improve differential diagnosis, by blood and CSF investigations, brain imaging, and selected specific approaches. Cerebrospinal fluid investigation is key in known neurologic chronic meningoencephalitis, though with limited sensitivity. In patients with psychoses about 50% of patients showed some CSF abnormalities. Regarding specific causes, each of them appeared to be rare, including cases of suggestive BDV ME, suggestive Lupus erythematodes ME, or ME possibly related to Sjögren syndrome, or to autoimmune thyreoditis, or ME from autoimmune induced streptococcal disease. Guided by such differential diagnoses diversified treatment approaches were applied in therapy resistant cases: cerebrospinal fluid filtration in suggested BDV induced immune pathological disorder, anti-inflammatory treatment or immune modulation, antibiotic treatment combined with tonsillectomy in streptococcal induced autoimmune disorder. Non-specific treatments were continued in parallel or not. In some cases full remission was obtained with such specified treatments. These preliminary data suggest, future research should be directed to improve further differential diagnosis and differential therapy (8).




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**References:**

1. Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, Mortensen PB. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. Am J Psychiatry 2006; **163:**521–528.
2. Berrettini W. Bipolar disorder and schizophrenia: not so distant relatives? World Psychiatry 2003; **2:**68–72.
3. Rioux JD, Abbas AK. Paths to understanding the genetic basis of autoimmune disease. Nature 2005;**435:**584–589.
4. Engelhardt B. Regulation of immune cell entry into the central nervous system. Results Probl Cell Differ 2006;**43:**259–280.
5. Meinl E, Krumbholz M, Hohlfeld R. B Lineage cells in the inflammatory central nervous system environment: migration, maintenance, local antibody production, and therapeutic modulation. Ann Neurol 2006;**59:**880–892.
6. Bechter K. Mild encephalitis underlying psychiatric disorder – a reconsideration and hypothesis exemplified on Borna disease. Neurol Psychiatry Brain Res 2001;**9:**55–70.
7. Bechter K, Herzog S, Schreiner V, Brinkmeier H, Aulkemeyer P, Weber F, Wollinsky KH, Schüttler R. Borna disease virus-related therapy-resistant depression improved after cerebrospinal fluid filtration. J Psychiatric Res 2000;**34:** 393–396.
8. Bechter K. Infektionen und Depression – Allgemeine Aspekte und spezifische Auslöser. Neurotransmitter 2008;**1:**46–50.




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# SCIENTIFIC WORKSHOP: FREQUENT PAIN SYNDROMES IN EVERYDAY NEUROLOGICAL PRACTICE

## Current aspects of pain management – pain therapy defined by neuro-psychological mechanisms

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Acute nociceptive pain arises from an activation of nociceptors, i.e. free nerve endings in the peripheral tissue which alert the body to potential or actual tissue damage via intensity-coded signaling. Most nociceptors are polymodal: they respond to noxious heat, strong mechanical or chemical stimuli. Nociceptors can be sensitized (primary hyperalgesia) by a plethora of exogenous and endogenous chemical stimuli including neuropeptides, prostaglandins, bradykinin, histamine, serotonin, neurotrophins, cytokines, protones and $K^+$ ions. The factors that modify the transduction mechanism are either released by the surrounding tissue or the nerve endings (neurogenic inflammation).

Neuropathic pain results from damage to the peripheral nerve, the spinal ganglion/dorsal root, or the central nervous system (e.g. spinal cord injury or central poststroke pain). It is characterized by a complex combination of sensory deficits including partial or complete loss of sensation and dysaesthesia or paraesthesia. Nerve injury leading to neuromas containing regenerating axon sprouts most commonly reduces the threshold of nociceptor terminals to heat and mechanical stimuli and, thus, increases and maintains the afferent input. This pain state is probably often independent of additional peripheral stimuli. It also involves spontaneous activity or paroxysmal generation of action potentials in large myelinated A-beta fibers which normally signal innocuous sensations. Like other persistent pain syndromes neuropathic pain offers no biological advantage. Traumatic injury of peripheral nerves also increases the excitability of nociceptors in and around nerve trunks and involves components released from nerve terminals (neurogenic inflammation), as well as immunological and vascular components from cells resident within, or recruited into the affected area.

Action potentials generated in nociceptors, as well as injured nerve fibers release excitatory neurotransmitters at their synaptic terminals such as L-glutamate and substance P, and trigger cellular events in the central nervous system that extend over different time frames. The co-release of L-glutamate and substance P is strongly implicated in the sensitization of spinofugally projecting multireceptive neurons in the dorsal horn of the spinal cord. Excitatory glutamatergic synaptic transmission in the mammalian brain is mediated by the activation of ionotropic and metabotropic receptors. The various ionotropic and metabotropic subtypes of glutamate receptors (including their splice-variants) are thought to be often co-localized on neurons. The ionotropic receptors are subdivided in AMPA, kainate and NMDA (N-methyl-D-aspartate) receptors. The NMDA receptor is distinctive in being both ligand-gated and voltage-gated and selectively permeable to $Ca2^+$. Synaptic efficacy in multireceptive (wide-dynamic-range) neurons which integrate and process sensory information from noxious and non-noxious somatic activity in the spinal cord dorsal horn increases with repetitive stimulation. Some of these spinofugally projecting neurons then respond more intensely to noxious stimuli (hyperalgesia), or previously not painful stimuli evoke pain (mechanical, thermal, or chemical allodynia; causalgia). This sensitization of central neurons is associated with a reduction in pain threshold and a spread of pain sensitivity to non-injured areas. This heightened synaptic transmission leads to an amplification of pain responses. The molecular mechanisms underlying the generation and maintenance of this form of synaptic plasticity share striking similarities with memory processes reflected in long-term potentiation and long-term depression.

The importance of multireceptive neurons in the establishment of hyperalgesia and allodynia suggests a strategic focus for drug treatment or interventions by peripheral stimulation on this first stage of sensory integration in the CNS. The central sensitization of somatosensory processing is prevented most effectively by blocking glutamatergic synaptic transmission by compounds such as flupirtine which reduces the discharge activity of most central neurons.

Recent results suggest that the analgesic, muscle-relaxant and neuroprotective agent flupirtine opens G-protein-activated inwardly rectifying $K^+$ channels and, thus, indirectly prevents the activation of voltage-sensitive NMDA channels. A significant (and growing) body of genetic, molecular, physiological and pharmacological evidence now exists to indicate that a variety of $K^+$ channels represent particularly interesting targets for the treatment of diseases such as epilepsy and neuropathic pain.

In conclusion, acquisition and storage of aversive social and somatic memories is one of the basic principles of nervous systems. In the absence of reinforcement, the behavioral response will gradually diminish to be finally extinct. Research over the last decades has shown that pain syndromes may arise from a variety of physiological and pharmacologically distinct systems. A multitude of components released from nerve terminals or non-synaptically from neighboring neurons, glia cells, the immune system or from the circulation participate in the integration and maintenance of somatosensory information in the pain matrix to finally build the memory of pain. Besides in somatosensory areas in the thalamus and the neocortex, activity-dependent gene expression also induces long-term alterations in the excitability of neurons in limbic structures, such as the prefrontal cortex, anterior cingulate cortex, amygdala and hippocampus, structures considered as gateways to emotions. It is to be expected that conventional analgesics often show only limited therapeutic value in the treatment of this multitude of dynamic changes that operate to produce the symptoms. Novel compounds and new regimes for drug treatment to prevent activity-dependent long-term changes in transducing and suppressive systems are emerging to help the patient to cope with pain and subsequently with comorbidities such as poor sleep, depressed mood, and anxiety. All treatment strategies must consider the prominent role of anxiety in chronic pain states.




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## Approach to the headache patient in everyday clinical practice

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Headache is one of the most common medical complaints. While episodic tension-type headache is common in population-based studies, migraine is the most common diagnosis in patients presenting to primary care physicians with headache. Migraine and tension-type headaches affect women more often than men. Migraine is an episodic headache that may be classified into three types: Migraine with aura, Migraine without aura and Migraine variants (retinal migraine, ophthalmoplegic migraine, familial hemiplegic migraine) (1). Migraine is thought to have a polygenetic and multifactor etiology. No consistent genetic basis has been established for migraine, with the exception of familial hemiplegic migraine. All of the phenomena that occur with migraine can not be explained by single theory. The vascular theory of migraine, which suggested that vascular headaches such as migraine and cluster headaches were caused by the dilatation of blood vessels, while the aura of migraine resulted from vasoconstriction, is no longer considered viable. According to modern theory, a primary neuronal dysfunction leads to a sequence of changes intracranially and extracranially that account for migraine, including the three phases of premonitory symptoms, aura, and headache. Genetic and environmental factors are important in pathophysiology of migraine (2). Pathogenesis of migraine includes role of trigeminovascular system, cortical spreading depression, and serotonin and calcitonin gene-related peptide (CGRP) concentration. Migraine with aura has been linked to right-to-left cardiac shunts, usually in the setting of a patent foramen ovale (PFO). The mechanism of the association between right-to-left cardiac shunt and migraine is not known.

**Clinical manifestations:** Migraine commonly begins early in the morning but can occur at any time. Nocturnal headaches, which awaken the patient from sleep, characteristically occur with cluster headaches, but migraine can awaken patients as well. The headache is lateralized during severe migraine attacks in 60–70% of patients, but in up to 30% of patients pain is localized bifrontally. Usually, pain is gradual in onset, following a crescendo pattern with gradual but complete resolution. Rapid head motion, sneezing, straining, constant motion, or physical exertion can worsened migraine headache. Many individuals report photophobia or phonophobia during attacks, leading many migraine sufferers to seek relief by lying down in a darkened, quiet room. Migraine aura is the complex of neurological symptoms that accompanies migraine headache. Auras are thought to be caused by cortical spreading depression occurring in regions of the cortex that correspond to the clinical manifestations of the aura. Manifestations of aura are visual disturbances, sensory symptoms, motor weakness and speech disturbances (3).

**Diagnostic testing:** Neuroimaging is not necessary in most patients with migraine but is recommended for patients with an unexplained abnormal finding on neurological examination, patients with atypical headache features or headaches that do not fulfill the strict definition of migraine or other primary headache disorder. Severe, sudden headache is also indication for neuroimaging because of the suspicion of subarachnoid hemorrhage (4).

**Treatment of migraine:** Treatment of migraine headache includes control of the individual attack and prevention. Prophylactic migraine treatment may be indicated if patients are having more than four headaches per month, the headaches last longer than 12 h, or they account for a significant amount of total disability. The main goal of prophylactic treatment is to reduce attack frequency, severity and duration, improve responsiveness to treatment of acute attacks and to reduce disability. The choice of prophylactic agent depends upon the individual situation, associated medical problems, and presence of conditions that are comorbid with migraine such as depression, mania, anxiety, panic, Raynaud's syndrome, epilepsy, and stroke. Prophylactic migraine medications that have proven high efficacy in clinical trials include propranolol, metoprolol, timolol, amitriptyline, topiramate, and valproate. The abortive (symptomatic) therapy of migraine ranges from the use of simple analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to triptans or the less commonly used dihydroergotamine. Abortive treatments are usually more effective if they are given early in the course of the headache. In some patients with migraine mild analgetics including non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen may be sufficient. If one NSAID is ineffective, a different drug may be tried.

Triptans are the serotonin 1 b/1 d agonists that are considered to be 'specific' therapies for acute migraine since all of the triptans inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem. Triptans inhibit transmission in the trigeminal nucleus caudalis, thereby blocking afferent input to second order neurons. They may also activate 5-HT 1 b/1 d receptors in descending brainstem pain modulating pathways and thereby inhibit dural nociception. The available triptans include sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan. Sumatriptan can be given as a subcutaneous injection (usually administered by autoinjector in the thigh), as a nasal spray, or orally. Zolmitriptan is also available for both nasal and oral use. The others are available for oral use only. A number of randomized, controlled trials and systematic reviews have found all of the triptans to be effective for the treatment of acute migraine. The choice of serotonin agonist should be individualized. Ergotamine and dihydroergotamine (DHE 45) are group of medications that bind to 5HT 1 b/d receptors, just as triptans do. Ergots should be avoided in patients with coronary artery disease because they cause sustained coronary artery constriction, peripheral vascular disease, hypertension, and hepatic or renal disease. Similar to the triptans, DHE 45 is contraindicated in patients with hypertension or ischemic heart disease, in combination with MAO inhibitors, and in the elderly. Nonpharmacologic management of headache includes relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy. Hypnosis, acupuncture and transcutaneous electrical nerve stimulation sometimes may be also helpful in treatment of migraine headache (5).

**References:**

1. Lovrenčić-Huzjan A, Demarin V, Rundek T, Vuković V. Role of vertebral artery hypoplasia in migraine. Cephalalgia 1998;**18**:684–686.
2. Ducros A, Tournier-Lasserve E, Bousser MG. The genetics of migraine. Lancet Neurol 2002;**1**:285–291.
3. Demarin V, Vuković V, Huzjan Lovrenčić V, Lušić I, Jančuljak D, Wilheim K, Zurak N. Evidence based guidelines for treatment of primary headaches. Acta Clin Croat 2005;**44**:139–183.
4. Demarin V, Vuković V. Migrena-patogeneza, dijagnostika, klinička slika. Medix 2005;**11** 29:52–57.
5. Lipton RB, Bigal ME, Diamond M et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;**68**:343–349.

## Intention of modern pain management in patients with low back pain syndrome: flupirtine in Germany – long-term experience

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Chronic low back pain (CLBP) is one of the most frequent and most expensive diseases in the world. In Germany half of the




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population is suffering from back pain, 38% episodically, 12% daily. 25% of the population are at least once every year in medical treatment because of back pain. The total cost for CLBP in Germany (80 million inhabitants) is 25 bill € annually, the major part of which (78%) is for sick leave and early retirements. Even though only 10% of acute back pain becomes CLBP early intervention and effective treatment is of paramount importance for the prevention of chronification.

Thorough physical, neurological, psychological and functional examination reveal in most cases the myofascial system with changes in muscles and tendons tension as well as psychological disorders to be of much greater importance than inflammation and herniated discs. Consequently X-ray, CT and MRT are only second-line diagnostic tools. Better information is gained from objective parameters such as pressure pain threshold (PPTh), pressure pain tolerance (PPT) and tissue compliance (TC). The treatment of pain should always be based on underlying mechanism, e.g. chronic vs. acute, nociceptive vs. neuropathic, inflammation vs. tension. In all cases where tension plays a major role as well as in all patients whose pain is on the way to becoming chronic, flupirtine (Katadolon) with its unique mode of action has proven to be more effective and safer than other strategies, especially NSAIDs.

Being the only available selective neuronal potassium channel opener (SNEPCO) the substance provides via hyperpolarisation of the neuronal membranes:

i) Analgesia by down-regulating nociceptive activation, nociceptive sensitisation and pain chronification by reducing excitability of nociceptive neurons;

ii) Neuroprotection reducing intracellular $Ca^{++}$ concentration;

iii) Muscle-relaxation by down-regulating spinal motorial reflexes, thus normalising muscle tension by reducing nociception-based spinal motor-efferent.

Following this, flupirtine (Katadolon®) is in German guidelines for pharmacological treatment of CLBP provided by the two major German Pain-Societies (Deutsche Gesellschaft für Schmerztherapie and Deutsche Gesellschaft zum Studium des Schmerzes) recommended as first line substance for all types of back pain from day seven on, if muscle tension and chronification processes are present.



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# SCIENTIFIC WORKSHOP: LINK BETWEEN PSYCHOSIS AND OTHER PSYCHIATRIC DISORDERS

## Classification of psychiatric disorders: Is there a need for change?

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In order to understand each other in our profession i.e. psychiatry, we have to have officially accepted standards when it comes to the determination of basic units i.e. disorders. In comparison to most of the medical disciplines, which call the basic units diseases, we call them disorders in the field of psychiatry. The reason is that we, in the field of psychiatry, don't have enough knowledge about the etiological factors, the pathological substrates, pathophysiology, often not even about the typical clinical picture, the type of successful therapy, the clinical process or prognosis, but all of this has to be defined in order to discuss a disease. This has led to the fact that classifications of psychiatric disorders have to be changed, corrected and added relatively often. In 1992, the World Health Organization has issued 'The ICD-10 Clasification of Mental and Behavioural Disorders', which we have translated into Croatian in 1999, when it came into force by the decision of the Ministry of Health. This classification has to a large extent the terminology and the criteria for the definition of various disorders. We have a similar situation with the changes in the American classification DSM-IV, which also significantly differs from DSM-III.

We know that currently a new version of the classification of psychiatric disorders is being developed by the World Health Organization. It is justified to ask the following questions: Is this necessary? Why is it necessary? Why don't we develop a classification that we won't have to change, a long-term classification?

In order to develop a long-term classification, we would have to have clearly and precisely defined units that we classify, i.e. diseases, what means that a specific state of disease could be defined as disease and not as disorder. Can we do this now? Can we, for example, define schizophrenia by etiological factors, pathological anatomic and physiological determinants, a clinical pattern, progress, therapy or prognosis? We cannot define hardly anything out of the previously mentioned, and quite often we have a similar case with a series of other psychiatric disorders. Can we define depression, posttraumatic stress disorder and a series of other psychiatric disorders? In practice, we actually cannot talk about a structured validity of psychiatric disorders since these are actually disorders, and disorders therefore are almost always only defined by symptoms. This means that we classify diagnoses, and the diagnoses are actually the names of the disorders, but not the diseases. Disorders differ from diseases also by the fact that we define a predictive validity for the disorder (we determine the predictive validity arbitrarily), whereas for the disease (self-explanatory), a structured validity is defined (e.g. progressive paralysis). Since schizophrenia complies with the mentioned disorder, but not the disease, since we, i.e. the psychiatrists, defined (chose) the symptoms, by which we define its borders and try to define the therapy (which today fortunately is relatively good), it is not long-term determined, it is not a nosologic entity, rather just a diagnostic entity. That this is the fact is best proven in practice by the fact that one of the subcategories of schizophrenia 'schizoaffective disorder', in the former ninth revised version of the International Classification is defined as subcategory of schizophrenia (295.7), and today, in the tenth revised version of the International Classification it is defined as a separate diagnostic category ( F 25). This is to a large extent a consequence of the arbitrary definition and non-psychiatric characteristics (e.g. the duration of the disease, the intensity of the disease, the level of disability or similar).

The fact alone that there are currently two valid classifications of psychological disorders in the world that significantly differ by a series of criteria, it is not difficult to conclude that there are still numerous dilemmas, not only with regards to how to define individual diseases, but also hot to determine the therapeutic guidelines, what is even more important in terms of practice.

In the conclusion it has to be pointed out that a series of new, above all morphological findings, and the finding in the field of pharmacogenomics opens up the possibility not only to scientists but also to clinical staff to change the classification of diseases (and not of disorders). It is justified to believe that the perception of the specific aspect of clinical patterns and their changes contribute to the aim to get further new findings and thus enable the development of a 'long-term classification' of psychological diseases and not disorders.

## Rational and effective therapy for psychosis – applicability of different antipsychotics and antidepressants in combined therapy

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Drug treatment of psychotic disorders is unfortunately too often associated with partial remissions, frequent relapse or recurrence as well as with persistent residual symptoms, distress and low level of well-being and quality of life. The use of a single mental health medication is always the simplest and safest, but very often not the most effective treatment. Even more, monotherapy is generally insufficient for complete or satisfying treatment response. It is increasingly being recognized that single antipsychotics are not effective in treating the entire range of symptoms in psychosis, as well as antidepressants in monotherapy do not cover all aspects of depression. Many patients not only benefit for multiple mental health medication, but also polypharmacy regime may be fundamental for maintaining and achieving their recovery. Polypharmacy with different antipsychotics and antidepressants in combined therapy may be the key element in the effective treatment of psychotic disorders with depressive syndromes, as well as in depressive disorders with psychotic features.




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# SCIENTIFIC WORKSHOP: INTRODUCTION INTO DIAGNOSTIC AND STATISTICAL INTERPRETATION OF CEREBROSPINAL FLUID DATA. TRAINING IN THE USE OF REIBERGRAMS WITH A NEW SOFTWARE

## Statistical evaluation of intrathecal protein synthesis in CSF/serum quotient diagrams

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**Abstract:** The protein concentrations in cerebrospinal fluid depend on blood concentration, blood-CSF barrier function and intrathecal synthesis. Therefore, the interpretation of CSF protein data on the base of absolute CSF concentrations or isolated CSF/serum quotients is not sufficient. The quantitation of intrathecal synthesis in quotient diagrams (Reibergrams) is well established in routine diagnosis of neurological diseases(1,2) with software supported CSF data reports. This diagnostic interpretation method in CSF/Serum quotient diagrams is now supplemented by a new statistics software for the numerical and graphical evaluation of patient groups. This is reached by
(i) transfer of Albumin, IgG, IgA and IgM data from tables into Reibergrams; (ii) comparison of patient groups in a single diagram; (iii) group statistics for quantitative intrathecal Ig-synthesis; (iv) disease course for a single patient; and (v) therapy control data in a single diagram together with the easy export of graphical CSF data and statistics into research publication.
This communication is to report the mathematical base. With a representative example, we demonstrate the application: a comparison of age-related intrathecal IgG, IgA and IgM synthesis in groups of patients with early onset multiple sclerosis between 7 and 30 years (Reiber H. et al unpublished data).

**Introduction:** As a main target of Cerebrospinal fluid analysis, we detect intrathecal synthesis of the immonuglobulins IgG, IgA and IgM with reference to the albumin quotient, which is the parameter for the individual blood-CSF barrier function. The nonlinear reference range of blood-derived proteins in CSF (Fig.1) is based on the physiologically and theoretically derived hyperbolic functions (2) replacing older linear Index calculations which lead to false interpretations (1). This recent evaluation concept is presented in the CSF data report to the clinician either graphically in the Reibergrams (see Fig. 2) or numerically by calculation of the intrathecally synthesized amount ($Ig_{loc}$) in mg/l CSF or as the relative intrathecal fraction ($Ig_{IF}$) in % of total Ig CSF concentration (1).

**Statistics in Reibergrams:** The comparison of patient groups in the nonlinear evaluation diagrams needs the reference to the mean values of the reference range in the Reibergrams (Qmean in the Table1 and Fig. 1). This statistical treatment of patient groups is different from the individual data interpretation of a single patient in the routine analysis where we have to detect unambiguously an intrathecal synthesis. In this diagnostic case, the evaluation refers to the upper discrimination line of the reference range (Qlim in the Table1 and Fig.1)

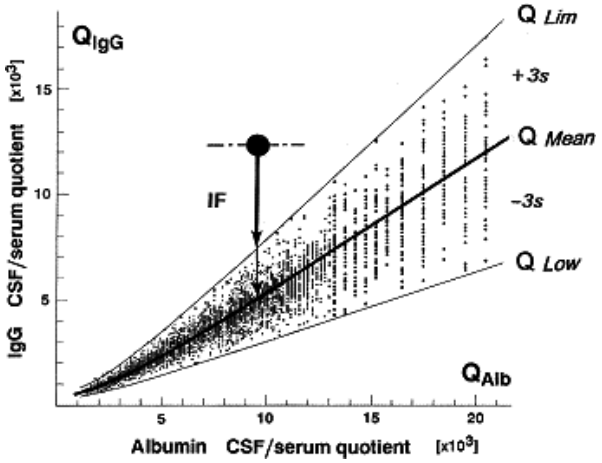


Fig. 1. Hyperbolic functions (2) of the reference range for blood-derived proteins in CSF: QLim = upper border line for diagnostic purpose, Qmean = mean hyperbolic function as reference for statistical evaluation of patient groups.

**Basic calculations:** For statistical evaluation this software (3) uses the functions described below. For this purpose in all functions used for routine analysis the values a/b, $b^2$, c of Qlim (Reiber 1994, http://www.horeiber.de) are replaced by those for the hyperbolic functions of Qmean.

$Q_{mean} = a/b\ (Q_{Alb}{}^2 + b^2)^{0.5} - c$

The mean intrathecal synthesis is calculated correspondingly with:

$Ig_{loc}$ (m) = [QIg – Qmean (Ig)] × Ig serum (as mg/l)

$Ig_{IF}$ (m) = $Ig_{loc}$/Ig(CSF) × 100 (in %).

The calculation examples in Table1 are performed for patient data with QAlb = $40 \times 10^{-3}$ and the corresponding values of a/b, $b^2$, c for Qmean functions of IgG, IgA and IgM:

$Q_{mean}$ (IgG) = $0.65\ (40^2 + 8)^{0.5} - 1.4 = 24.66\ (\times 10^{-3})$

$Q_{mean}$ (IgA) = $0.47\ (40^2 + 27)^{0.5} - 2.1 = 16.86\ (\times 10^{-3})$

$Q_{mean}$ (IgM) = $0.33\ (40^2 + 306)^{0.5} - 5.7 = 8.71\ (\times 10^{-3})$

$IgG_{loc}$ (m) = (65-24.66) × 12.6 = 508.3 (mg/l)

$IgG_{IF}$(m) = 508.3/819 × 100 = 62 (%)




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Table 1. Calculation examples with data from a patient with a neuroborreliosis

| | | Alb | IgG | IgA | IgM |
|---|---|---|---|---|---|
| CSF | mg/l | 1440 | 819 | 113 | 171 |
| Serum | g/l | 36 | 12.6 | 2.7 | 1.8 |
| $Q \bullet 10^3$ | | 40 | 65 | 41.9 | 95 |
| $Q_{mean} \bullet 10^3$ | | | 24.66 | 16.86 | 8.71 |
| $Ig_{Loc}$ (m)* | mg/l | | 508.3 | 67.5 | 155 |
| $Ig_{IF}$ (m)* | % | | 62 | 60 | 91 |
| $Q_{Lim} \bullet 10^3$ | | | 35.6 | 27.9 | 20.7 |
| $Ig_{Loc}$** | mg/l | | 370.4 | 38.1 | 133.7 |
| $Ig_{IF}$** | % | | 45 | 34 | 78 |

*Calculated with reference to Qmean.
**Reference to QLim.

### Evaluation table of the CSF statistics tool (3)

CSF and serum concentration values for albumin, IgG, IgA, IgM or the precalculated CSF/serum quotients, Q, are inserted into the software table ether direct or imported from Excel or text tables. The program calculates quotients and the intrathecal fractions with reference to the Qmean of the reference range. For the subsequently marked groups of patients the program calculates the statistics as shown in Table 2.

Table 2. Statistics evaluation from CSF statistics tool (COMED) for a group of multiple sclerosis patients with the age of 28–29 years (open circles in Fig.2). Data represent mean values (MV), standard deviation (SD) and coefficient of variation (CV) for the number (N) of patients calculated with reference to Qmean. In case of IgIF (m) < 10% the mean data of the group are not significantly different from normal mean. In these cases the subsequent variation values are not calculated (N/A), neither for IF nor for Igloc

| | | IF (%) | Ig Loc (mg/l) | | | | |
|---|---|---|---|---|---|---|---|
| | QAlb | IgG | IgA | IgM | IgG | IgA | IgM |
| MV | 5.34 | 53.70 | 9.25 | 22.57 | 40.07 | 0.49 | 0.80 |
| SD | 5.88 | 56.75 | N/A | 59.72 | 48.80 | N/A | 1.77 |
| CV | 109.98 | 105.68 | N/A | 264.61 | 121.79 | N/A | 219.76 |
| N | 29 | 29 | 29 | 29 | 29 | 28 | 29 |

**Diagrams and group comparison:** In Table 3, the age related data of eight groups of multiple sclerosis patients are shown as a numerical example of the evaluation. For the first time, we are able to get reliable statistical evaluations of CSF immunoglobulin data which are not biased by the variation of the different albumin quotients (age related different, but normal barrier functions). The mean intrathecally synthesized IgG [IgGloc (m) in the Table] increases with age (14.6–40.1 mg/l increase of CSF concentration). The age related decreasing CSF flow rate (increasing QAlb) and the age related increasing serum-IgG lead also to a higher blood-derived IgG fraction with the consequence of a rather constant intrathecal fraction IF varying between 40 and 56%.
[IF = IgGloc (m)/Qmean (IgG) × 100 in %].
The graphical demonstration of the complete group is easily performed and exported from the CSF Statistics tool as shown for two of the groups in Fig. 2.

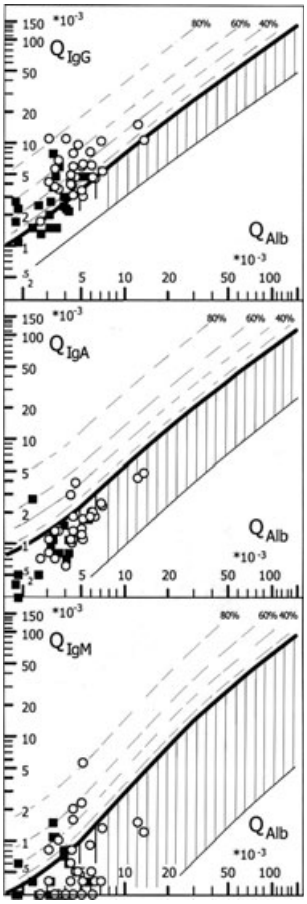


Fig. 2. Multiple sclerosis groups (age 7–11 years and 28–29 years) in Reibergrams, data are complementary to Tables 2 and 3. The diagram is created with CSF statistics tool (3).

Table 3: Age dependent data of MS Patients between the age of 7 and 30 years. Two of the groups (7-11 and 28–29) are shown in Fig. 2. Statistics (Table 2) and the corresponding presentation in Reibergrams (Fig. 2) are created with the CSF statistic tool (COMED)

| Parameter/units | | Mean values | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Age-range | years | 7–11 | 12–13 | 14 | 15–16 | 17–21 | 22–24 | 25–27 | 28–29 |
| N | | 22 | 24 | 18 | 22 | 22 | 23 | 26 | 29 |
| Qalb | $\times 10^3$ | 3.32 | 3.78 | 3.84 | 4.22 | 4.82 | 4.96 | 4.7 | 5.3 |
| IgGloc (m) | mg/l | 14.6 | 26.7 | 18.6 | 28.4 | 28.2 | 24.2 | 34.4 | 40.1 |
| IgGIF (m) | % | 42.8 | 50.7 | 43.6 | 55.7 | 42.7 | 39.8 | 49.1 | 53.7 |
| IgGSer | g/l | 10.1 | 10.7 | 11.1 | 10.7 | 11.0 | 11.8 | 11.5 | 11.4 |


**References: (for download see http://www.horeiber.de)**

1. Reiber H, Peter JB. Cerebrospinal fluid analysis – disease-related data patterns and evaluation programs. J Neurol Sci 2001;**184**:101–122.
2. Reiber H. Flow rate of cerebrospinal fluid (CSF) – a concept common to normal blood-CSF barrier function and to dysfunction in neurological diseases. J Neurol Sci 1994;**122**:189–203.
3. Reiber H and Albaum W. CSF Statistics Tool, COMED Soest, free download from http://www.comed-com.de





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# TEACHING COURSE

## Challenges for young psychiatrists in a united Europe: Setting up a young scientists' task force to focus on networking, mentoring and harmonization of research aims

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**Aims:** Our century is marked by rapid changes in various social areas such as health, communication, ethics, politics and economics that influence the way modern health systems are working and therefore present major challenges for psychiatric professionals as well. To face these aspects and to cover the international character of research, specialised organizations for trainees and young professionals are a powerful tool to give the young executives a voice in the development of research and practice standards and therefore to take influence on their own future and carrier progress (1). Nevertheless, little was done to support young scientists with focus on neuropsychiatric and neuroimmunological research up to now.

**Background:** Based on the UEMS (Union of European Medical Specialists) founded in 1958 that was followed by the constitution of the European Board of Psychiatry in 1992, the European Federation of Psychiatric Trainees EFPT as well as the Wold Association of Young Psychiatric and Trainees WAYPT and the Young Psychiatrists' Council of the World Association of Psychiatry WPA advocate the needs and rights of psychiatric trainees all over the world. Young researchers who are focusing a career within the scientific community should take the opportunity to learn from these political organisations regarding essential networking and integration skills (2,3).

To act as powerful and independent junior research institutions, they have to rely on engaged and courageous young scientists who communicate international and regional research characteristics as well as critical aspects, initiate and realise joint projects and learn from each other to represent a strong advocacy of young researchers regarding adequate mentoring and chances to find their way within this highly competitive field. Moreover, the scientific offspring not only comprises a great pool of young high potentials with new ideas and innovative approaches and moreover provides the future opinion leaders, but presents in particular the base of scientific work and medical progress.




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**Method and conclusion:** To start, the establishment of a national network of trainees with especial interest in science who then get in touch with national leaders in the field of research in psychiatry is advantageous to carry on the project by presenting and promoting the organization on national conferences, to constitute and define structure and leadership as well as to organize the future funding and to implement cooperations with further young trainee and research institutions. Another way to succeed consists in founding a young researchers group within a well-established science organisation and to fall back on senior members of this association to ask them for mentorship and support as done in Germany were a young researchers group with special interest in bipolar disorder was founded within the German Association of Bipolar Disorders.

However, the quantity and quality of scientific success rise with each talent joining the group, therefore and regarding the outstanding experience for members as well as mentors it might be the right time to unify highly qualified young scientists with neuropsychiatric interest across South-Eastern Europe.

**References:**


1. Calliess IT, Treichel K. Sorgen der Weiterbildungsassistenten nach dem Deutschen Ärztetag: Psychiatrie und Psychotherapie – quo vadis. Neurotransmitter Sonderheft 2003;**2**: 49–51.
2. Calliess IT, Treichel K. European Young Psychiatrists Program auf dem AEP-Kongress (Association of European Psychiatrists) in München vom 2 –6.4.2005. Nervenarz t 2005;**76**:655–656.
3. Calliess IT, Schulze TG, Treichel K. 5 Jahre Young Psychiatrists Program – ein Beitrag für den Nachwuchs in der Psychiatrie in Deutschland. Nervenarzt 2006;**77**:1407–1410.





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