SPECIAL FEATURE

Hypothesis: Phylogenetic Diseases of the Nervous System

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SUMMARY: A few human diseases may be viewed from a phylogenetic perspective. Some metabolic or degenerative diseases selectively affect recently evolved or exclusively mammalian structures of the brain and spare the older structures. Examples include Krabbe's leukodystrophy, olivopontocerebellar atrophy, Friedreich's ataxia, Pick's disease, and Leber's optic atrophy. Some pathologic conditions in man are similar to normal anatomy in other species, although the mechanisms may differ. Congenital muscle fiber-type disproportion in rodents, Dandy-Walker cyst in birds, and agenesis of the corpus callosum in marsupials are representative of this category. Loss of basal dendritic spines from pyramidal cells in Pick's disease is reminiscent of certain large neurons normally found in the cortex of reptiles. Changes in metabolism in the evolution of mammals in general and of man in particular may explain some aspects of 'phylogenetic diseases'. Some potential examples are the shift from predominantly phospholipids to galactolipids in myelin composition as mammals evolved, and the greater toxicity of cyanide and other poisons of oxidative metabolism in mammals than in other vertebrates because of less reliance on anaerobic metabolism as an alternative energy source.

RÉSUMÉ: Certaines maladies humaines peuvent être considérées d'un point de vue phylogénétique. Ainsi certaines entités métaboliques ou dégénératives touchent sélectivement les structures plus récemment évoluées, ou exclusivement mammaliennes, et épargnent les structures plus âgées. Comme exemple citons la leukodystrophie de Krabbe, l'OPCA, l'ataxie de Friedreich, la maladie de Pick et l'atrophie optique de Leber. Certaines conditions pathologiques chez l'homme sont semblables à l'anatomie normale d'autres espèces, même si les mécanismes diffèrent. Dans cette catégorie on retrouve la disproportion congénitale des types de fibres musculaires chez les rongeurs, les kystes Dandy-Walker chez les oiseaux et l'agénésie du corps calleux ches les marsupiaux. La perte des épines dendritiques basales dans les cellules pyramidales de la maladie de Pick rappelle certains gros neurones trouvés normalement dans le cortex des reptiles. Des modifications dans le métabolisme au cours de l'evolution des mammifères, et en particulier de l'homme, expliquent peut-être les "maladies phylogénétiques". Par exemple on peut souligner la modification de la composition de la myéline avec l'évolution, d'une prédominance des phospholipides à celle des galactolipides. On peut également mentionner la cytotoxicité accrue du cyanure et d'autres poisons du métabolisme oxidatif des mammifères, parce qu'ils dépendent moins que d'autres vértébrés du métabolisme anaérobique comme source alternative d'énergie.

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Many malformations of the brain are explained as disorders of embryonic development or arrest in the process of cerebral maturation. If the 1875 hypotheses of Haeckel that 'ontogeny recapitulates phylogeny' is even partially true, then some diseases of the central nervous system might be identified on the basis of similarity to the normal condition in other species of vertebrates.

John Hughlings Jackson in 1884 was the first to clearly articulate a possible relation between evolution and human neurologic disease. Medical aspects of phylogeny were not addressed, however, by the many comparative neuroanatomists of this century whose contributions provided the foundation for further development of this theme. Only recently has the hypothesis of phylogenetic diseases emerged from obscurity as another perspective of pathogenesis of neurologic disease, largely unfamiliar to most medical clinicians and basic neuroscientists. (Roofe and Matzke, 1968; Sarnat and Netsky, 1981).

Some neurologic diseases are distinguished by an apparent selective vulnerability of neural structures evolving late in phylogeny, although the individual diseases are not related. Other pathologic conditions in man may have a physiologic counterpart in nonhuman species of vertebrates. These human diseases resemble stages in phylogenesis rather than arrests in ontogenetic development. The comparison of pathologic conditions in man with the normal state in other animals does not imply that similarities of appearance signify similar mechanisms, particularly since the mechanisms are unknown. The comparisons are useful in understanding the ways in which nervous systems of other species have developed and function differently from the evolved human brain. The following examples are suggested as representative of these concepts.

Human Metabolic or Degenerative Disease Selectively Affecting Recently Evolved Structures

Krabbe's Leukodystrophy

Krabbe's disease is a hereditary progressive neurologic disease of infancy related to deficiencies of galactocerebroside-beta-galactosidase and psychosine galactosidase (Suzuki and Suzuki, 1970; Miyatake and Suzuki, 1972). The resultant accu-

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mulation of galactocerebroside and psychosine produces death of myelin-forming cells and degeneration of white matter of the central nervous system and of peripheral nerves (Norman et al., 1961; Suzuki and Grover, 1970).

The distribution of lesions in the brain and spinal cord strongly suggests an evolutionary pattern because the tracts involved are almost exclusively mammalian structures (Sarnat and Netsky, 1981). Phylogenetically old and constant pathways found in all classes of vertebrates are spared. These structures include the olfactory tracts, fornix, mammillothalamic fasciculus (tract of Vicq d'Azyr), stria medullaris, and medial longitudinal fasciculus. By contrast, the corticospinal tracts, subcortical white matter of the centrum semiovale, and dorsal columns of the spinal cord are severely affected (Normal et al., 1961). The selectivity of the damage suggests that a metabolic change has occurred in the evolution of mammals so that the new, uniquely mammalian pathways use galactocerebroside more than phylogenetically older tracts, or have fewer alternative pathways upon which to rely. Biochemical analysis of cerebral lipids show that mammals have more galactolipids but less phospholipids (expressed as mg per 100 mg dry weight of myelin) than lower vertebrates such as fishes and amphibians (Cuzner et al., 1965; Smith, 1967; Ramsey, 1981). If these ratios can be shown to differ between the corticospinal tract and the fornix or olfactory tract in man, these data would support the evolutionary theory of selective involvement. By contrast with Krabbe's disease, in Niemann-Pick disease (deficiency of sphinogomyelinase needed for phospholipid metabolism) there is no selectivity of involvement of new or old structures of the brain.

While phylogenetically old tracts generally have an earlier onset of myelination than recent pathways, the selective involvement cannot be explained on this basis because some structures myelinating early also are involved early. Spinal nerve roots are one example. The progressive degeneration involves tracts already myelinated earlier and does not simply prevent the myelination of still immature pathways.

An additional phylogenetic aspect of Krabbe's disease is the demonstration of congenital muscle fiber type disproportion (CMFTD) in at least some cases (Martin et al., 1976; Dehkharghani et al., 1981). CMFTD is not a characteristic finding of denervation atrophy of muscle. Peripheral neuropathy in Krabbe's disease causes a reduction in the number of functional motor nerve fibers in the perinatal period and early infancy, resulting in giant fetal motor units (see CMFTD, this paper; Sarnat, 1983).

Pick's Disease

This disease, formerly in the category of 'presenile demetias', involves the atrophy of associative areas of the cerebral cortex but spares primary motor and sensory gyri. Frontal and neocortical portions of the temporal lobes are especially affected. Paleocortex (hippocampus) and archicortex (amygdala) remain uninvolved. As the phylogenetic scale of mammals is ascended, the progressive expansion of the cerebral cortex is accomplished mainly by the addition of new secondary and tertiary 'associative' regions in the neocortex.

Golgi impregnations of cerebral cortical neurons in cases of Pick's disease show a unique dendritic pattern not encountered in Alzheimer disease or other degenerative dementias (Wechsler et al., 1982). Golgi impregnations of pyramidal neurons from the frontal gyri demonstrate long, spineless, uncomplicated dendritic branches or decreased numbers of basilar dendrites. This configuration is reminiscent of the branching patterns of the 'candelabra' cells normally occurring in the less complex three-layered cerebral cortex of reptiles. These pyramidal neurons also have multiple, long, proximal dendritic segments devoid of spines, and minimal branching of even the spine-covered distal segments (Ulinski, 1977). Pyramidal cells in the normal trilaminar paleocortex comprising Ammon's horn in man do not lack dendritic spines as in Pick's disease (Cajal, 1968). Whether electrotonic junctions occur at the synapses of the abnormal neurons in Pick's disease, as they do in reptiles, is not yet known.

Spinocerebellar Degenerations

Friedreich's ataxia and olivo-ponto-cerebellar atrophy are progressive diseases of the central nervous system affecting almost exclusively those structures of mammals either absent or rudimentary in lower vertebrates. The phylogenetically oldest portions of the cerebellar vermis (archicerebellum and paleocerebellum) are spared together with other old components of the cerebellar system, such as the dorsal and medial accessory olivary nuclei (Norman and Ulrich, 1958). The mammalian neocerebellar hemispheres, principal inferior olivary nuclei, and pontine nuclei are severely affected. The dorsal spinocerebellar tract, a more recent evolutionary acquisition than the ventral spinocerebellar tract, is more affected. Dorsal columns and corticospinal tracts, also mammalian development, may be involved.

Leber's Optic Atrophy

This rare hereditary disease results from progressive degeneration of retinal ganglion cells and secondary degeneration of optic nerve fibers from the macula, and lateral geniculate neurons. Other parts of the nervous system usually are not affected, but the disorder occasionally is associated with features of spinocerebellar degeneration or with additional signs and symptoms including seizures, mental retardation loss of proprioception, and spasticity (Woodworth et al., 1959; Bruyn and Went, 1964).

All vertebrates have eyes and optic nerves, although they may be secondarily small and vestigial in some blind species of fishes and in salamanders living in dark caves. The reason Leber's optic atrophy is proposed as a phylogenetic disease is that only in mammals do most optic nerve fibers terminate in the lateral geniculate body of the thalamus. In all nonmammalian vertebrates, more than 90 percent of optic nerve fibers project to the optic tectum (superior colliculus of mammals) and pretectal area; only a few end in the thalamus, in the nucleus rotundus (pulvinar) and primordium of the lateral geniculate body (Sarnat and Netsky, 1981). In mammals, this ratio is reversed. Most optic nerve fibers, therefore, are not homologous structures between mammals and other vertebrates.

We propose that this evolutionary development has resulted in a metabolic alteration rendering the newer fibers sensitive to an as yet unproved agent. A failure in the conversion of cyanide to thiocyanate has been suggested as the genetic defect in Leber's optic atrophy (Adams et al., 1966). Chronic ingestion of a cyanogenic glycoside, the cassava bean, is responsible for the spastic-ataxic syndrome of tropical Africa (Osuntokun et al., 1970).

Greater vulnerability to cyanide of a newer mammalian than of older reptilian structures of the brain is an untested hypothesis.

Cyanide poisons the cytochrome oxidase system of mitochondrial respiration. This pathogenesis of Leber's optic atrophy would be consistent with both the clinicopathologic findings and with evolutionary aspects. In experimental cyanide intoxication of mammals, electrical activity is first depressed in the cerebral cortex and later in the basal ganglia and upper midbrain; most of the brainstem is not depressed; electrical activity in the spinal cord actually increases (Ward and Wheatley, 1947). Among vertebrates, neuronal oxidative metabolism is less crucial in many species of amphibians and reptiles than in mammals. For example, the freshwater turtle survives prolonged underwater dives of more than a week with zero oxygen tensions in its blood, and diving iguana lizards remain submerged for as long as 4½ hours with severe lactic acidosis (Moberly, 1968). By contrast, the bottle-nosed porpoise, an intelligent mammal, has a maximum diving time of only 5 minutes and well conditioned human swimmers can hold their breath for only 2-3 minutes.

Human Disorders Resembling Normal Conditions of Other Species

Congenital Muscle Fiber Type Disproportion (CMFTD)

CMFTD is a 'congenital myopathy' defined by histochemical features of the muscle biopsy, but clinically associated with dysmorphic facies, muscular hypotonia and nonprogressive weakness, normal intelligence, and a normal chromosomal karyotype (Brooke, 1973). Type I muscle fibers are uniformly small, and type II fibers become hypertrophic; a disproportion also applies to the ratio of fiber types in most cases as numerical predominance of type I fibers. Muscle fibers are otherwise mature, and degenerative changes are not found. The findings are demonstrable in the neonatal period (Fardeau et al., 1975; Sarnat, 1978).

CMFTD does not correspond to any normal stage of ontogenesis of human striated muscle. It is, however, the normal adult condition of the mouse, rat, and other rodents (Sarnat and Netsky, 1981). A theory to explain the pathogenesis of this condition proposes that a teratogenic insult during early development causes an accelerated rate of physiologic cell death of spinal motor neuroblasts. Surviving motor neurons then innervate larger than normal numbers of muscle fibers. Stimulation of these giant motor units does not provide sufficient trophic influence for the growth in size of the individual muscle fibers, but does accomplish maturation and conversion of the motor units to type I (Sarnat, 1983). Phylogenetically, most species of the same class produce a relatively equal population of embryonic neuroblasts of the same type. The attrition related to the embryonic process of cell death is species-specific and the outcome differs greatly in the adult of the species. For example, turtles and snakes, both reptiles, produce equal numbers of thoracic spinal motor neuroblasts. In snakes, however, the number of cells surviving to innervate the large paraspinal muscles greatly exceeds the few surviving thoracic motor neurons of turtles, whose paraspinal muscles are rendered vestigial by the development of the carapace or shell. Another species-specific example of the balance between the production of excess neuroblasts and later culmination by cell death of those not successfully matched with target cells is found in the mesencephalic trigeminal nucleus; adult beavers have six times as many neurons in this nucleus as do hamsters, although both species produce an approximately equal surplus of neuroblasts (Katz and Lasek, 1978).

The ratio of motor neurons to muscle fibers in a given muscle is species-specific. It differs between mouse and man, and probably also between type I and II motor units in the mouse. CMFTD is thus normal in the mouse, but appears in man only if the normal size of the human motor unit is not maintained during fetal development. The weakness associated with the hypoplastic type I muscle fibers is partially compensated by work hypertrophy of type II fibers belonging to the few surviving normal sized motor units.

Dandy-Walker Malformation

This cause of congenital hydrocephalus is usually associated with failure of the lateral and median foramena (of Luschka and Magendie) to normally form in the posterior velum of the cerebellum during embryonic life, although this defect is not demonstrated in all postmortem cases and controversy still exists regarding the mechanism of cyst formation (D'Agostino et al., 1963; Hart et al., 1972). The posterior half of the fourth ventricle balloons into the cisterna magna as the ventricular fluid produced by the choroid plexuses is obstructed from normal access to the subarachnoid space and intraventricular pressure increases. The posterior part of the cerebellar vermis is poorly formed, its space occupied by the fourth ventricular 'cyst'. In addition, disturbances in neuronal migrations in the medulla and heterotopias of inferior olivary nuclei commonly occur, (Hanaway and Netsky, 1971; Hart et al., 1972), but whether this feature is a primary dysgenesis or secondary to anatomic distortion is uncertain. The vermis normally develops before the foramina open, consistent with a primary dysgenesis, but early normal formation might be followed by regression, with the same end-results by late fetal life. Rare cases are associated with multiple formations of the brainstem and cerebellum suggesting a hindrance of neuroblastic proliferation and migration from rhombencephalic cytogenic zones of the entire alar plate, with persistence of the anterior membranous area (Janzer and Friede, 1982). Most cases of Dandy-Walker syndrome are not associated with severe dysgenesis of the brainstem or cerebellum except for the constant feature of posterior vermal dysgenesis or absence.

Free communication for the flow of cerebrospinal fluid between the ventricular system and the subarachnoid space is necessary only in mammals. The caudal part of the roof of the fourth ventricle in birds is an expanded membranous pouch of ependyma and pia mater. The large surface of this semipermeable pouch or cyst allows sufficient exchange of water and solutes between the ventricle and subarachnoid space that equilibrium is maintained (Jones and Dolman, 1979). A fourth ventricular protrusion also appears transiently in mammalian embryos before the foramen of Magendie opens. Reptiles have a condition similar to birds, but fishes and amphibians have only a small subarachnoid space around the brain (Sarnat and Netsky, 1981). The rudimentary subarachnoid space around the brainstem and cerebellum in frogs communicates with the fourth ventricle through special pores in the posterior tela of the hindbrain (Tornheim and Foltz, 1979), unlike the more advanced reptiles and birds. Among mammals, the sizes of the median and lateral apertures of the fourth ventricular outlet are inversely related, and some species with large lateral foramina lack of median aperture (Cammermeyer, 1971).

Dandy-Walker malformation in man thus corresponds, at least in part, to the normal condition of birds, not only because of failure of the foramina to form in some cases, but mainly because of the cystic expansion of the forth ventricle. Such a generous reservoir of cerebrospinal fluid contained in an absorptive membrane is not practical in mammals because the expanded cerebral cortex occupies so much intracranial volume that space is not available to accommodate large fluid-filled cavities.

Congenital Absence of the Corpus Callosum

Complete or partial absence of the corpus callosum not only accompanies severe cerebral malformations such as holoprosencephaly, but more commonly exists as a relatively asymptomatic and isolated anomaly of the brain in some people, both retarded and normal (Loeser and Alvord, 1968; Ettlinger et al., 1974). Some cases are genetically determined and associated with myoclonic epilepsy.

The corpus callosum interconnects associative sensory areas of the neucortical hemispheres in all placental mammals. It is largest in man and other primates in whom these parts of the brain are best developed. The number of callosal fibers originating in primary sensory neocortex, particularly that related to distal extremities, is relatively small in the monkey (Pandya and Vignolo, 1969). These connections cannot be demonstrated in the cat or raccoon (Welker and Seidenstein, 1959; Ebner and Myers, 1965). The visual associative areas are interconnected through the corpus callosum, but the primary striate cortex does not contribute callosal fibers in cat, raccoon or monkey (Meyers, 1962; Ebner and Myers, 1965).

The corpus callosum normally is lacking in marsupials, such as the opossum or kangaroo, and in monotremes such as the platypus. Other forebrain commissures are developed in these species and include the psalterium (hippocamal commissure) and anterior commissure (Heath and Jones, 1971). The corpus callosum is not formed in nonmammalian vertebrates, but these animals lack a six-layered neocortex.

Lipomas sometimes occur within the corpus callosum (Zettner and Netsky, 1960). These tumors may be rests of primitive meninx. The incompletely differentiated meninges and perimeningeal space of lower vertebrates contain gelatinous and fatty tissue to protect the brain instead of the fluid-filled subarachnoid space of mammals (Sarnat and Netsky, 1981).

Comment

The phylogenetic hypothesis does not presume to explain the pathogenesis of disease, to imply that individual cases are the result of faulty evolution or to account for clinical symptoms and signs. The proposed group of unrelated human disorders illustrate that some conditions may be better suited to species other than man. In our species they are not in physiologic balance because of additional developments. Phylogenesis thus is not a mechanism of disease, but rather a perspective through which normal and abnormal human anatomy and physiology may be compared with other less complex species that have developed divergent adaptations and 'evolved' along lines different from man.

The mechanism of evolution is incompletely understood, and the Darwinian theory of natural selection explains only some phenomena. Genetic mutations giving rise to new types of organisms are not single, and every genetic modification improving chances of survival is accompanied by multiple other changes neither increasing nor decreasing rates of survival. Such changes may be anatomic or metabolic. Neuronal aggregates and their connections also may assume new functions without major genetic modification or anatomic restructuring. An example is the adaptation of brainstem nuclei and their ascending projections in fishes related to the lateral line system to serve an auditory function in terrestrial vertebrates. This functional shift is observed not only in the evolution of amphibians from a lungfish-like ancestor, but is repeated ontogenetically in the metamorphosis of tadpole to frog.

Although we recognize several neurologic diseases in which recently evolved structures of the brain are disproportionately involved, we are unable to identify the converse: diseases selectively affecting phylogenetically old structures and sparing the new. The probable reason is that many early evolved parts of the brain are essential to survival, such as the vital autonomic centers of the brainstem; their degeneration would be lethal in early embryologic development, precluding clinical expression. Leigh's subacute necrotising encephalopathy may be a possible representative of this category, but the degenerative process does not involve the old parts of the brain exclusively.

Arguments against the phylogenetic theory of selective anatomic or metabolic involvement might be raised that in some patients additional structures not corresponding to evolutionary patterns are involved. For example, absence of the corpus callosum may only be one part of a complex cerebral dysgenesis. More than one mechanism may be operating. A severely dysplastic or nearly absent neocortex generates neither normal intra- nor interhemispheric neuronal connections. This condition is not a phylogenetic disease, but probably is unrelated to callosal agenesis as an isolated anomaly of an otherwise apparently normal brain. Similarly, the rare cases of Dandy-Walker syndrome associated with severe dysplasias of the rhombencephalon probably have somewhat different or multiple pathogenetic mechanisms than the more common, less complex anomaly. In olivopontocerebellar atrophy, motor neurons and autonomic neurons occasionally are affected. If the pathogenesis is metabolic, the biochemical deficiency probably indeed also affects some older structures as well, and the disparity is relative, just as the differences in ratios of the various lipid components of myelin between different classes of vertebrates are only quantitative or relative.

The evolutionary concept may lead to new approaches in the investigation and understanding of some diseases, using the almost untapped knowledge of comparative neuranatomy and neurochemistry of vertebrates that, simple or complex, differ from man. In these 'lower' animals, nature has conveniently isolated neural systems without the embellishments of mammalian development. Metabolic changes in the evolution of mammals from ancestral vertebrate may be studied by comparing the brains of representative modern species of nonmammalian vertebrates with that of man. The insight thus gained may yield clues regarding the function and metabolism of the human brain in neurologic disease.

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