




## Review Article

# Pediatric CNS Inflammation and Infection: A Review of Immunopathology and Radiology

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**ABSTRACT:** The innate and adaptive immune systems are critical in defense against pathogens and ensuring homeostasis. The central nervous system (CNS) was initially considered to be impermeable to immune cells due to the blood–brain barrier. However, this has now been debunked, with modern research delineating immune cell trafficking within the CNS, ensuring constant immune surveillance. However, these defenses may be breached in infections, which trigger an inflammatory cascade causing tissue damage. In addition, autoimmune conditions and genetic mutations may also lead to sustained proinflammatory molecule release causing significant CNS damage. Ensuing brain injury from most immune triggers is varied but may be associated with common patterns by virtue of a shared immune driver. MRI plays an important role in identifying these conditions and further enables understanding of their pathophysiology as well as their spatial predilection in the brain. In this review, we discuss basic immunology, the major CNS barriers to infections as well as the current understanding of selected pediatric infections and inflammatory processes.

**RÉSUMÉ :** Les infections et l'inflammation du système nerveux central chez les enfants : revue de l'état des connaissances en immunopathologie et en radiologie. Les systèmes immunitaires naturel et acquis jouent un rôle crucial dans la défense de l'organisme contre les agents pathogènes et par le fait même dans l'équilibre homéostatique. On croyait autrefois que le système nerveux central était impénétrable aux cellules immunitaires en raison de la barrière hématoencéphalique (BHE), mais cette hypothèse a été infirmée grâce aux techniques modernes de recherche sur la circulation des cellules immunitaires dans le SNC, qui assurent une surveillance immunitaire continue. Toutefois, ces moyens de défense peuvent subir des brèches en cas d'infection, ce qui déclenche une série de réactions inflammatoires qui entraînent elles-mêmes des lésions tissulaires. En outre, certaines affections auto-immunes ou mutations génétiques peuvent également provoquer la libération continue de molécules pro-inflammatoires, cause d'une atteinte importante au SNC. Les lésions cérébrales découlant de la plupart des déclencheurs immunitaires sont diverses, mais elles peuvent être associées à des manifestations communes en raison d'un même facteur immunitaire. L'imagerie par résonance magnétique joue un rôle important dans la reconnaissance de ces affections, ce qui permet de mieux comprendre leur physiopathologie ainsi que leur répartition spatiale particulière dans le cerveau. Il sera donc question, dans l'article, de notions fondamentales en immunologie, des principales barrières du SNC aux infections, de même que des connaissances actuelles sur certaines infections et certains processus inflammatoires chez les enfants.

**Keywords:** CNS Inflammation; education; infections of the nervous system; neuroradiology; pediatric neurology

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## Introduction

Inflammation is the cardinal host defense response to invading microbes and injury. This host response has a clear benefit when under siege, particularly when regulated. However, sustained or inappropriate inflammation leads to multiple deleterious effects on the native tissue in the central nervous system (CNS). Neuroinflammatory disorders and neuroinfections are a broad category of disease processes, often with common mechanistic end

points as a result of similar immunopathology. In this review, we briefly discuss key concepts of the immune system, with respect to the CNS, and the current understanding of important pediatric infections and inflammatory conditions.

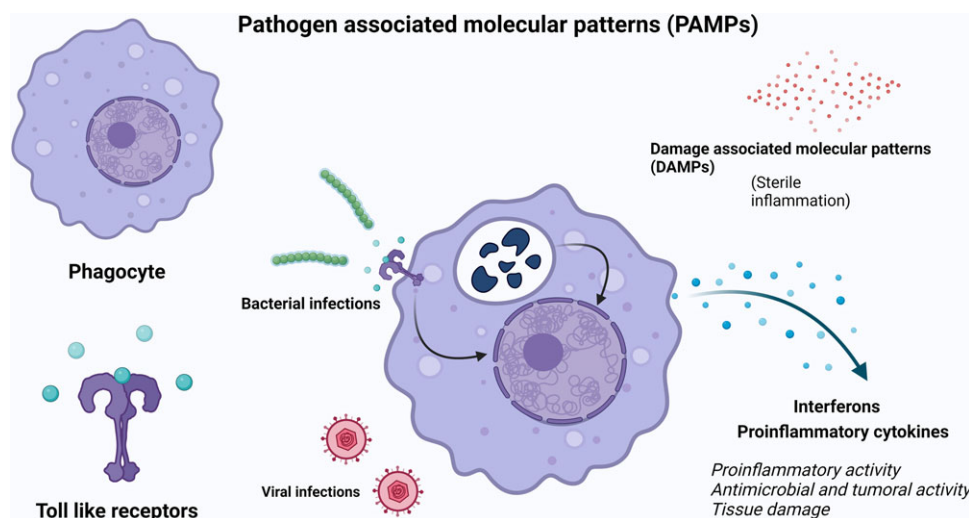
## Innate and adaptive immunity – revisiting basic concepts

Innate immunity (comprised of phagocytic cells, epithelial and endothelial cells, natural killer [NK] cells, innate lymphoid cells and

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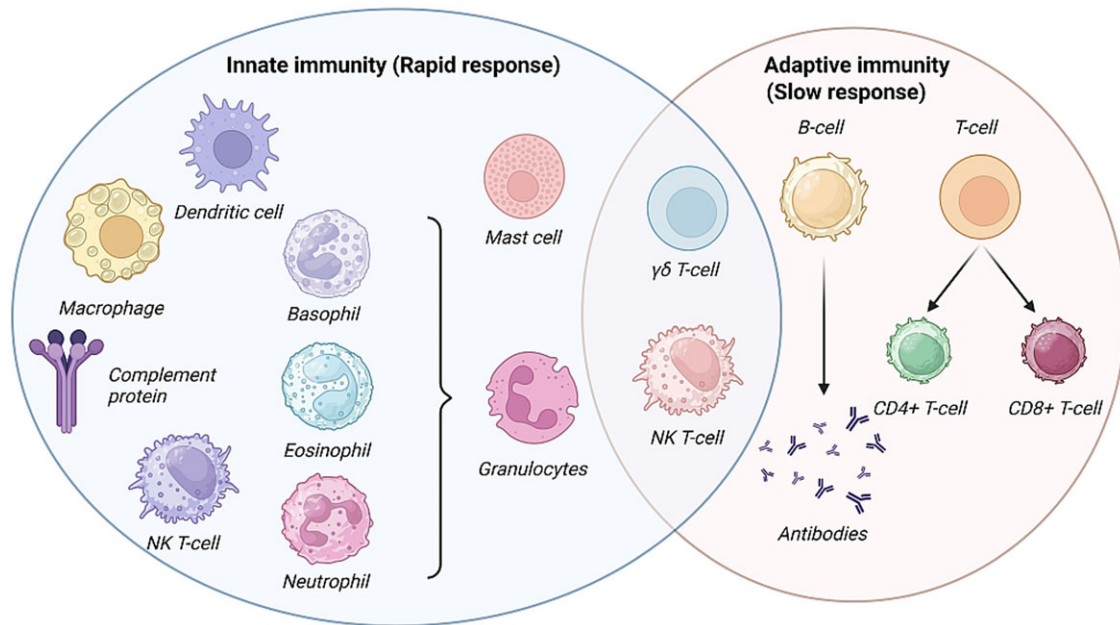
**Figure 1.** Mechanism of action of innate immunity. Identification of PAMPs by PRRs, in this case toll-like receptors/TLRs, leads to activation of signalling pathways which cause production of antimicrobial molecules and incite inflammation. DAMPs on the other hand are released from dead and/or dying host cells causing a sterile inflammatory response. (Created with [BioRender.com](https://www.bio-render.com)). DAMPs = damage associated molecular patterns; PAMPs = pathogen-associated molecular patterns; PRRs = pattern recognition receptors; TLRs = toll-like receptors.

platelets), the first line of defense, is responsible for the prompt detection of pathogens and homeostatic disruptions.<sup>1-3</sup> This is achieved with pattern recognition receptors (PRRs).<sup>2</sup> Multiple subfamilies of PRRs have been identified including Toll-like receptors (TLRs), Nod-like receptors (NLRs), C-type lectin receptors and RIG-like receptors (RLRs).<sup>2</sup> PRRs detect nonspecific “patterns” or structures located on pathogens, collectively called pathogen-associated molecular patterns (PAMPs).<sup>2</sup> Upon PAMP recognition, PRRs initiate signaling pathways that induce antimicrobial effects and incite inflammation.<sup>4</sup> PRRs also respond to “danger” signals or damage associated molecular patterns (DAMPs/alarmins) which originate from endogenous molecules released into the cytoplasm after CNS injury (e.g., heat shock proteins, hyaluronan, uric acid, galectins and thioredoxin)<sup>2</sup> (Fig. 1).

Adaptive immunity provides delayed, but specific and long-lasting immunity. Its major components include B lymphocytes (humoral response) and T lymphocytes (cell-mediated responses).<sup>1</sup> B cells react to specific antigen-stimulating proteins and synthesize immunoglobulins to neutralize pathogens.<sup>1</sup> T-cells are subclassified into CD8 + and CD4 + cells, based on their functions and ability to recognize major histocompatibility complexes (MHC).<sup>1</sup> CD8 + cells provide host defense against intracellular pathogens (e.g., viruses) as they detect surface antigens on infected cells.<sup>1</sup> Upon target binding, CD8+ cells release lytic granules (perforins and granzymes) which perforate cell membranes, thus promoting apoptosis.<sup>1</sup> CD8 + T cells also release cytokines (IFN- $\gamma$ , TNF- $\alpha$ , TNF- $\beta$ ) which inhibit viral replication, activate macrophages and upregulate MHC class I expression (increasing T-cell detection).<sup>1</sup> CD4 + T cells were grouped into Th1 cells (secreting pro-inflammatory molecules e.g., IFN- $\gamma$ , TNF- $\alpha$ , TNF- $\beta$ , IL-1 $\beta$ ) and Th2 cells (secreting anti-inflammatory molecules e.g., IL4, IL-5, IL-6, IL-10, IL-13).<sup>1</sup> Recently, more CD4+ cells have been identified (e.g., Th9, Th17, Th22, T-follicular cells, Treg cells).<sup>1</sup> Most of these secrete proinflammatory cytokines leading to autoimmune and inflammatory diseases.<sup>1</sup> A diagrammatic summary of the various components of innate and adaptive immunity is provided in Figure 2.

### Innate immunity of the CNS: role of the microglia

The innate immune response within the CNS is mediated by resident tissue macrophages, known as microglia.<sup>5</sup> These are derived from primitive yolk sac myeloid progenitors and constitute about 10%–15% of the cell population in the brain.<sup>5,6</sup> Microglia play a vital role in mediating multiple regulatory processes within the brain which are critical for tissue development and maintenance of the neural homeostasis while playing a key role in response to brain injury and tissue repair.<sup>6</sup> In physiological conditions, microglia acquire a relatively inactive phenotype (resting microglia).<sup>5</sup> In this quiescent state, resting microglia demonstrate long cytoplasmic protrusions, a stable cell body with minimal to no movement. This state is regulated by intrinsic factors (e.g. Runx1 [Runt-related transcription factor 1], Irf8 [Interferon regulatory factor 8]) and extrinsic factors (e.g., TREM2 [triggering receptor also expressed on myeloid cells-2], chemokines [CX3CR1 and CD200R]).<sup>6</sup> Additional factors that maintain the resting state of microglia include signals from healthy neurons (CX3CL1, neurotransmitters, neurotrophins and CD22) as well as microRNA-124 (expressed by microglial themselves) which reduces CD46, MHC-II and CD11b which enables maintenance of the quiescent state.<sup>6</sup> Upon exposure to endogenous stimuli, microglia are ‘activated’. There are two polar states of activation, i.e., M1 and M2 phenotypes, which are associated phenomenologically with tissue injury and homeostasis, respectively.<sup>5,6</sup> Typically activated microglia acquire the M1 phenotype and secrete proinflammatory and pro-killing cytokines (IL-1 $\beta$ , IL-6, IL-12, IL-17, IL-18, IL-23, TNF- $\alpha$ , IFN- $\gamma$ , nitric oxide and CCL2), hence serving as the first line of CNS defense effectively purging out pathogens and prompting T-cells to elicit an adaptive immunological response.<sup>6</sup> Alternatively, polarization into the M2 phenotypical state may, though poorly understood, is linked with immunoregulation, suppression of inflammation, tissue repair and injury resolution.<sup>6</sup> Microglia in the M2 state lead to production of IL-4 and IL-10 via Arg1 (arginase 1), Ym1 (chitinase-like protein) and PPAR (peroxisome proliferator-



**Figure 2.** Diagrammatic representation of the components of innate and adaptive immunity. (Created with BioRender.com).

activated receptor).<sup>6</sup> The process of microglial activation is depicted in Figure 3.

### Demystifying “immune privilege” theory of the CNS

Historically, the CNS was erroneously considered to be “immune privileged”.<sup>7</sup> This concept originated from studies that demonstrated the successful survival of implanted neoplasms in neuroparenchyma but not in other tissues.<sup>8</sup> Subsequently, microorganisms and vectors were thought to successfully evade immune recognition in the brain.<sup>8</sup> The contemporaneous understanding of the blood–brain barrier (BBB) eventually deemed it to be responsible for this unique privilege.<sup>8</sup> The BBB was thought to limit immune surveillance offered by peripheral lymphocytes in normal physiological conditions based on the fact that the CNS lacked antigen-presenting cells (APCs) and barely expressed MHC molecules.<sup>9</sup> With an improved understanding of CNS immunity, this dogma has now been modified.<sup>9,10</sup> While there are no APCs in the brain, they exist along CNS vasculature.<sup>9</sup> Neural-derived antigens are identified and released from the CNS and are found in deep cervical lymph nodes draining the CNS.<sup>9</sup> Thus, immune responses can be mounted in these lymphoid structures against antigens within the CNS.<sup>9</sup>

### Barriers to CNS infection

The CNS is protected by an elegant infrastructure of barriers that impede entry and spread of pathogens. In the following discussion, we elaborate on the role of microglia and the BBB in CNS immunity. We also briefly discuss the physiology of other barriers to CNS infection.

#### The blood–brain barrier (BBB)

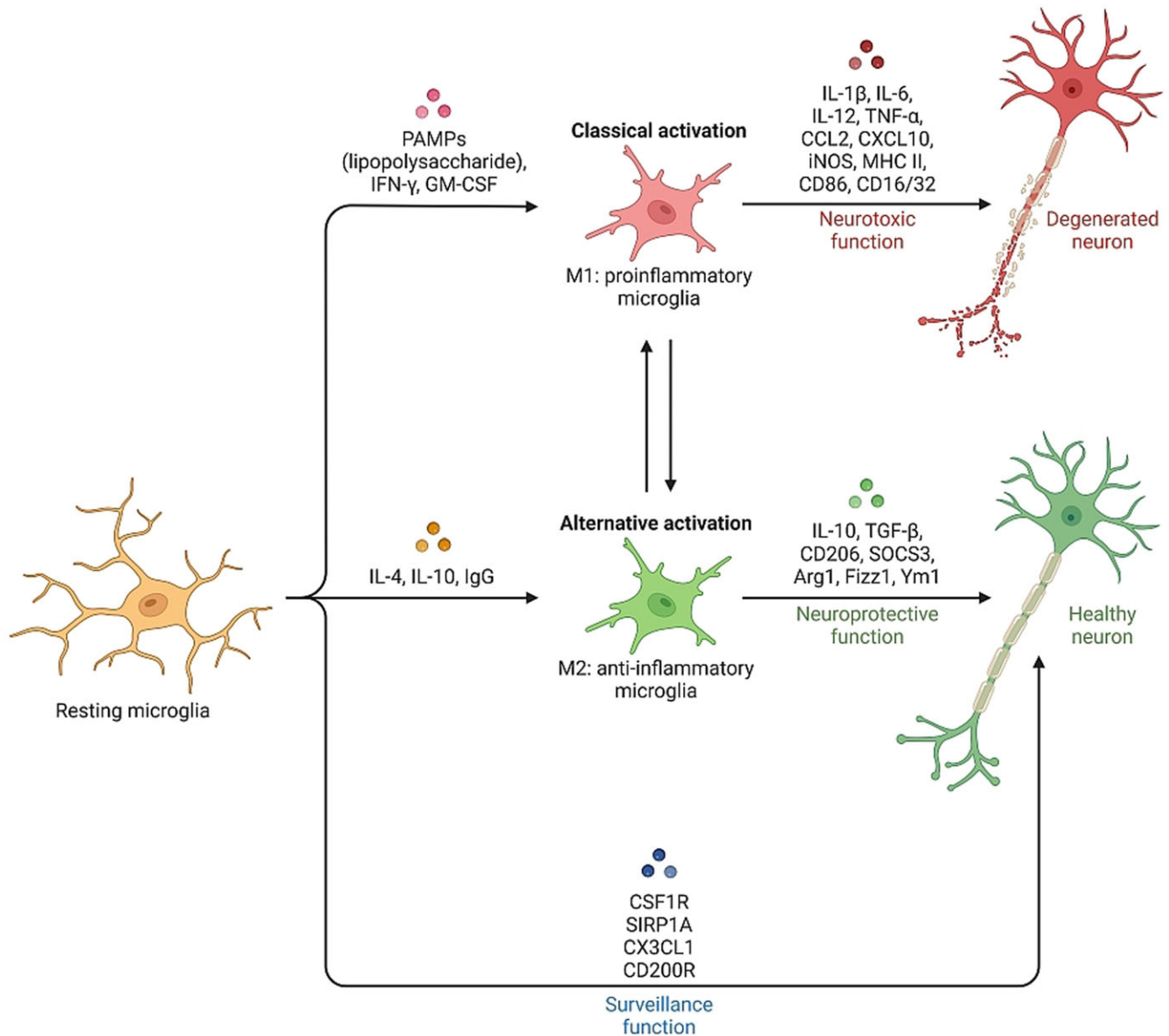
The BBB forms the physical and immunological barrier in the brain parenchyma. The BBB is composed of endothelial cells expressing tight junctions (TJs), basement membrane and pericytes<sup>11</sup> (Fig. 4). It prevents the entry of micro-organisms as well as neurotoxic

components in plasma.<sup>12</sup> A variety of enzymes, transporters and efflux pumps are also present, thus ensuring optimal transport of nutrients into the CNS and toxic metabolites out of it.<sup>13</sup> The TJs of the BBB are composed of transmembrane proteins such as claudin-5, occludin and junctional adhesion molecules (JAM).<sup>13</sup> Claudin-5 forms a diffusion barrier for small molecules while occludin regulates the movement of calcium across the BBB in addition to ensuring TJ stability.<sup>13</sup> Some authors suggest that JAM-A, JAM-B and JAM-C play a role in regulating the BBB stability and the migration of immune cells across it.<sup>13</sup> Other transmembrane proteins include platelet endothelial cell adhesion molecule 1 (PECAM-1) and CD99 which contribute to vascular integrity and mediate leukocyte trafficking, respectively.<sup>14,15</sup>

#### Immune trafficking across the BBB

Immune surveillance of the CNS is carried out by peripherally activated T-cells which traverse the BBB to gain access to the perivascular and subarachnoid spaces, even in normal physiological states.<sup>16</sup> This is due to the special properties of the BBB, which, unlike peripheral endothelium, lacks P-selectin protein and expresses an atypical chemokine receptor 1 (ACKR1).<sup>13</sup> The physiological immune entry is restricted to just T-cells which are independent of these trafficking cues.<sup>13</sup> T-cell entry is a complex, multistep process involving initial tether (capture) onto the endothelium, followed by selectin-facilitated rolling, effectively reducing the speed of the T-cells.<sup>17</sup> Chemotactic cues are later recognized allowing integrin-mediated cell arrest, crawling and finally diapedesis across the BBB.<sup>17</sup>

During neuroinflammation, endothelial cells upregulate vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM1). These interact with  $\alpha$ L $\beta$ 2 and  $\alpha$ 4 $\beta$ 1 on CD4+ T-cells, resulting in T cell arrest.<sup>18</sup> Multiple studies have proposed that activated leukocyte cell adhesion molecule (ALCAM), melanoma cell adhesion molecule (MCAM) and nerve injury-induced protein (ninjurin-1) also play a role in the



**Figure 3.** Schematic depicting microglial polarization states and function. Under physiological conditions microglia perform active surveillance of the CNS (blue pathway). Multiple factors (e.g., colony stimulating factor 1 receptor [CSF1R], signal regulatory protein CD172 [SIRP1A], chemokine [CX3CL1 and CD200R]), help maintain this state. When triggered (red pathway) (e.g., exposure to lipopolysaccharide [LPS], IFN- $\gamma$ , or GM-CSF), microglia acquire M1 phenotype (pro-inflammatory) which leads to neurotoxicity. Alternate pathway activation by IL-1, IgG, or IL-10 causes microglia to attain an anti-inflammatory (M2) state (green pathway) ensuring neuroprotection. (Created with BioRender.com). CNS = central nervous system; GM-CSF = Granulocyte-macrophage colony-stimulating factor.

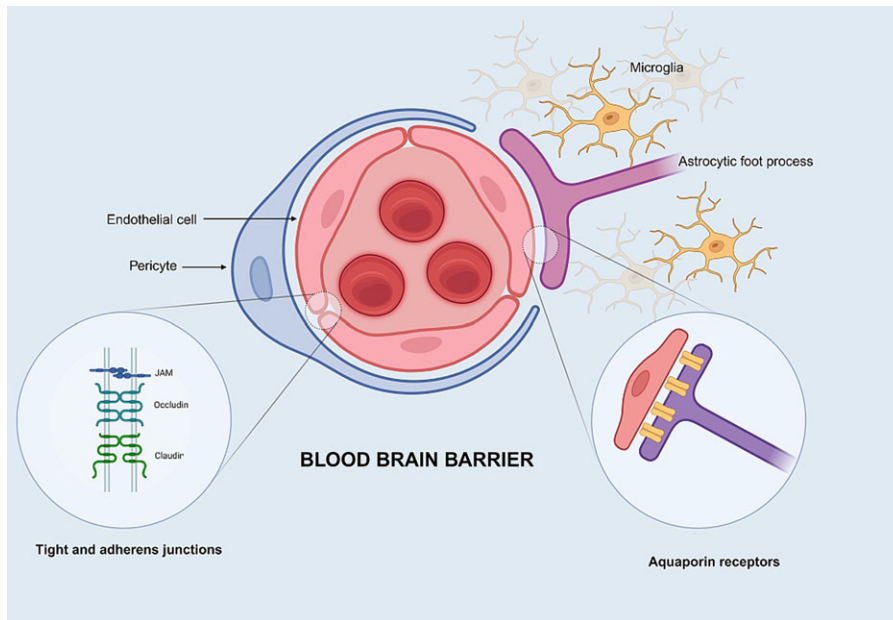
migration of T-cells across the BBB in conditions such as autoimmune encephalomyelitis and multiple sclerosis.<sup>13,19</sup> It must be mentioned that the precise migration mechanisms of other immune cells (B cells, neutrophils, monocytes and dendritic cells) across the BBB are not fully understood.<sup>13</sup> B cell migration is thought to be mediated by endothelial ICAM-1 with  $\alpha 4\beta 1$  integrin, chemokines (CCL2 and CXCL8) and ALCAM.<sup>20</sup>

#### Exit pathway of T-cells

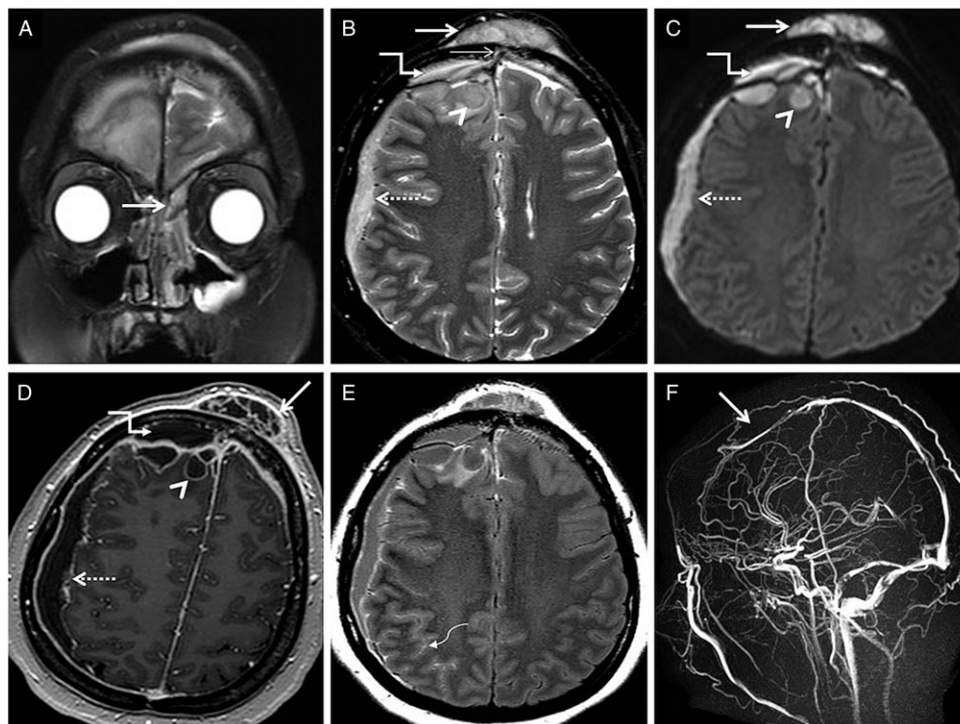
Interstitial fluid flows into the CSF across a paravascular route, termed glymphatics. CSF is eventually resorbed by arachnoid granulations into the dural venous blood.<sup>16</sup> Lymphatic vessels have

been identified draining the CNS in close association with dural venous sinuses.<sup>21,22</sup> These lymphatics drain the interstitial fluid and CSF into deep cervical lymph nodes and contain immune cells, which suggests T-cells and MHC class II-positive myeloid cells are drained into peripheral lymph nodes.<sup>16</sup>

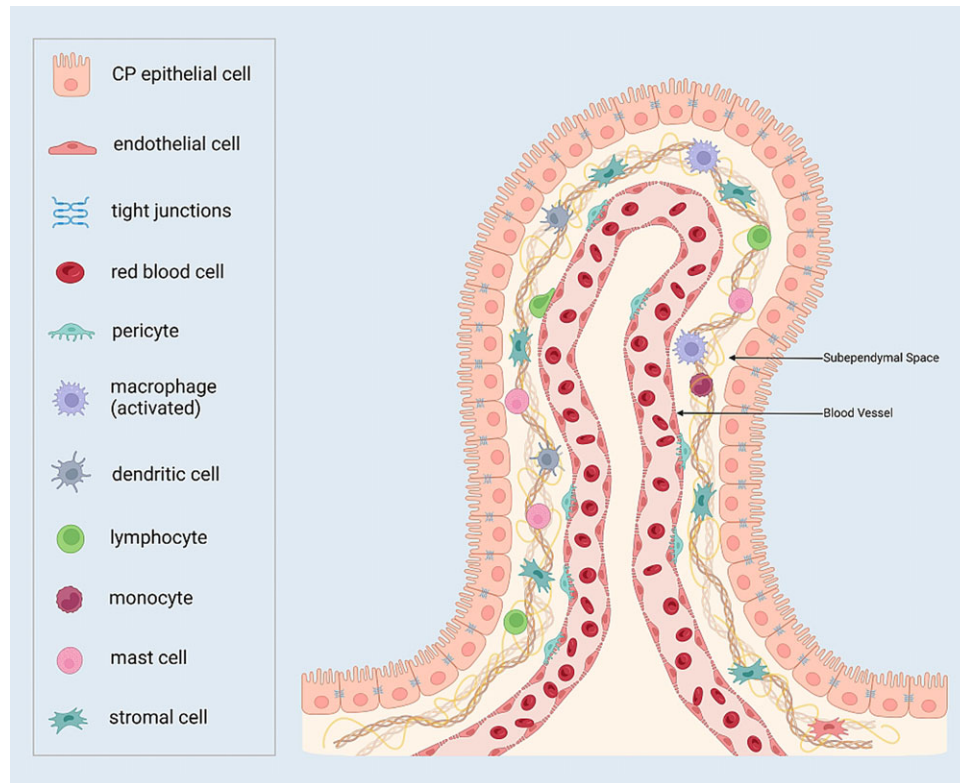
Dural lymphatics express CCL21 chemokines which contribute to the migration of CCR7-expressing cells (dendritic cells and some T cells).<sup>21,22</sup> Hypothesizing from this, the lymphatic network is thought to permit the migration of antigen-presenting cells (APCs) into cervical lymph nodes, thereby initiating a T cell response against antigens, including autoantigens.<sup>16</sup> This is seconded by the reduced severity of experimental autoimmune encephalomyelitis, following the removal of cervical lymph nodes.<sup>16,23</sup>



**Figure 4.** Anatomy of the blood-brain barrier. (Created with BioRender.com).



**Figure 5.** Pott's puffy tumor is a prototypical example of infection breaching multiple CNS barriers to gain access to the brain parenchyma. This example demonstrates Pott's puffy tumor secondary to complicated frontal sinusitis in a 14-year-old year old presenting with fever, facial swelling and altered sensorium. Coronal fat-saturated T2-weighted sequence (A) through the face reveals heterogeneous contents within the left frontal sinus (arrow), obstructing the left fronto-ethmoid drainage pathway. Hyperintense mucosal thickening is also seen in the left maxillary sinus. Axial fat-saturated T2-weighted (B), diffusion-weighted (C), and contrast-enhanced axial 3D-T1 (D) sequences reveal multicompartiment extra-calvarial and intracranial infective collections. A large, loculated heterogeneous abscess, with restricted diffusion, is seen in the frontal scalp tissues demonstrating peripheral enhancement and multiple septations within (arrows in B-D). Note the ill-defined T2-weighted hyperintensity in the frontal bone, representing osteomyelitis, with a focal bony breach (thin arrow in B). Intracranially, similar collections are seen in the right frontal epidural space (stepped arrows in B-D) and the right frontoparietal subdural spaces (dotted arrow in B-D) representing empyemas, as well as within the right frontal lobe parenchyma (arrowheads in B-D) representing abscesses. Contrast-enhanced axial FLAIR sequence (E) also reveals enhancement within the right parietal sulcal spaces, suggestive of meningitis (curved arrow). Phase contrast MR venography (F) reveals loss of flow signals along the rostral segment of the superior sagittal sinus due to infective thrombophlebitis. Overall, these findings are a prototypical representation of microorganisms breaching multiple physical and physiological CNS barriers. CNS = central nervous system; FLAIR = Fluid Attenuated Inversion Recovery.



**Figure 6.** Diagrammatic representation of the choroid plexus demonstrating the blood-CSF barrier. Blood vessels within the choroid plexus are devoid of tight junctions. However, the outer epithelial layer demonstrates tight junctions which limits and monitors egress of molecules into the CSF. The subependymal space is patrolled by cells of innate and adaptive immunity even under normal physiological states. (Created with [BioRender.com](https://www.biorender.com)). CSF = cerebrospinal fluid.

## Other barriers to CNS infection

### Skull and meninges

The skull vault forms an obvious physical barrier, protecting the brain from exogenous pathogens.<sup>10</sup> Defects in the skull vault, including remnant embryonic connections, can be a source of entry for infections.<sup>24</sup> Within diploic spaces of the skull, pockets of marrow are present, which connect to the dural vasculature via diploic veins. Owing to a chemokine gradient between marrow and dura, egress of marrow-derived B cells takes place.<sup>11</sup> B cell population expresses surface receptors which on engagement are activated and differentiate into antibody-secreting plasma cells.<sup>10</sup> The dural blood vessels are devoid of TJs and are lined by meningeal macrophages.<sup>11</sup> Additional dural immune cells (T cells, B cells, dendritic cells, plasma cells, innate lymphoid cells and mast cells) are also encountered in peri-sinus spaces.<sup>11</sup> Circulating microorganisms are most likely to exit across the fenestrated dural vessels hence explaining the need for a plethora of immune cells within the dura.<sup>11</sup>

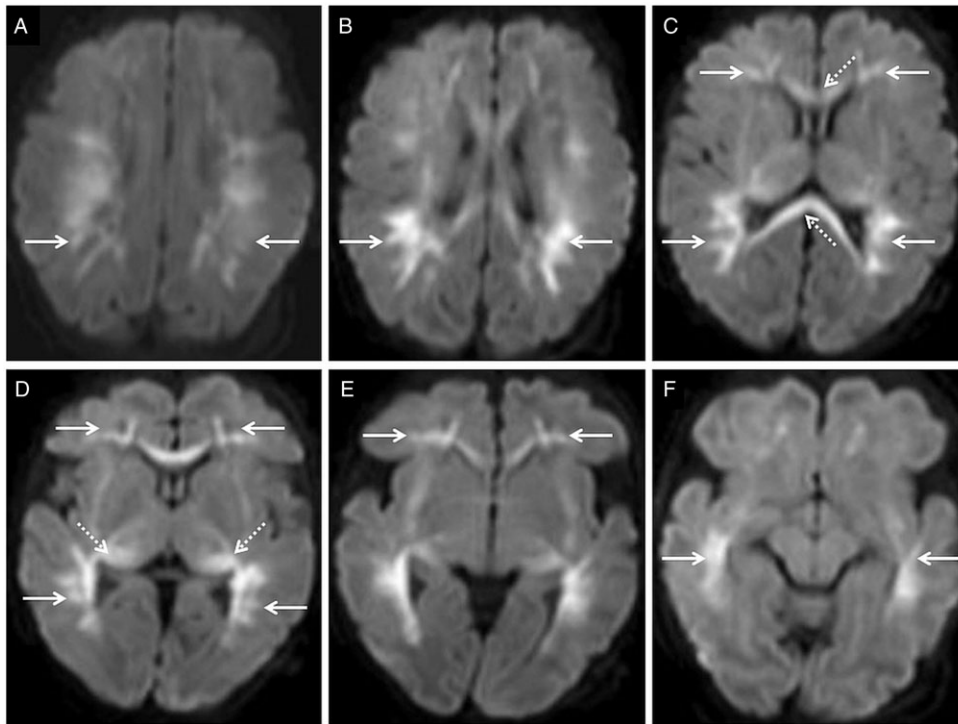
Unlike the dural vasculature, blood vessels in the arachnoid mater demonstrate TJs.<sup>11</sup> Nevertheless, microorganisms can still infect the CSF, particularly when the walls of blood vessels are infected, initiating a chain of inflammatory responses (meningitis).<sup>11</sup> Fibroblasts within the arachnoid mater are also connected via TJs which limit the free diffusion of solutes and other water-soluble substances.<sup>13</sup> They express efflux pumps which enable adequate transport of toxins out of the CSF.<sup>13</sup> Pial blood vessels that penetrate the brain also demonstrate TJs and are defended by perivascular macrophages<sup>11</sup> (Fig. 5)

### Blood-cerebrospinal fluid barrier (BCSFB)

The choroid plexus projects into the ventricles of the brain and produces CSF. Blood vessels within the CP are devoid of TJs, thus permitting extravasation of blood-borne molecules into the CP stroma.<sup>11,13</sup> However, the CP stroma is patrolled by numerous cells of innate and adaptive immunity even under normal physiological states.<sup>11,13</sup> Additionally, the layer of epithelial cells lining the CP has TJs (occludin, claudin-1, -2, -3, -11, JAM-A and zonula occludens-1, -2, -3) which form a barrier between blood and CSF<sup>11,13</sup> (Fig. 6). In a pathological state, the integrity of this epithelial layer may be disrupted allowing pathogens to access the ventricular CSF, thereby inciting an inflammatory response known as ventriculitis.<sup>11</sup>

### Nasal epithelium and olfactory bulbs

Olfactory sensory neurons are located in the upper nasal airway and contain nonmotile sensory cilia (which bind to odor molecules) and an axon (responsible for signal transmission to the brain).<sup>25</sup> The axons traverse the cribriform plate and synapse with neurons in the olfactory bulb.<sup>25</sup> Given its location, the nasal mucosa is constantly exposed to air-borne microbes. However, the nasal mucosa is protected by macrophages, T- and B-cells. Nevertheless, certain neurotropic viruses may evade these defenses and travel along the olfactory sensory neurons across the cribriform plate to gain access to the olfactory bulbs, hence bypassing other CNS defenses.<sup>11</sup> In response, the immune system attempts to purge these microbes while limiting cellular damage by releasing non-cytolytic cytokines and interferons (IFN- $\gamma$  by CD4+



**Figure 7.** Parechoviral infection in a neonate presenting with fever and seizures. Diffusion-weighted imaging (DWI; A-F) reveals near symmetric restricted diffusion (ADC not shown) extensively involving the cerebral white matter bilaterally. Note the linear, radiating pattern of the signal abnormality (arrows) towards the subcortical and juxta-cortical white matter. Restricted diffusion is also noted in the corpus callosum (dotted arrows in C) and the dorsolateral thalami (dotted arrows in D), suggestive of preWallerian degeneration ADC = apparent diffusion coefficient.

and 8+ as well as natural killer/NK cells).<sup>11</sup> Once cleared, CD8+ cells establish permanent residency in the olfactory system, preventing re-infection.<sup>11</sup>

### Selected radio-pathological considerations

In this section we discuss some of the current understanding of rather uncommon infections and neuroinflammatory disorders we have encountered in our clinical practice.

#### Infections

##### *Parechovirus encephalitis*

The *Parechovirus A* (PeV-A) or the Human Parechovirus (HPeV), is a single-stranded RNA virus belonging to the *Picornaviridae* family.<sup>26,27</sup> Of the 19 known genotypes, PeV-A3 commonly affects young infants.<sup>27</sup> It is contracted via respiratory or gastrointestinal routes; CNS infection is secondary to hematogenous dissemination.<sup>27</sup> Maternofetal transmission is not uncommon (30%-50%).<sup>27</sup>

Symptomatology may vary from minor gastroenteritis or respiratory symptoms to fever, rash, irritability and sepsis with occasional CSF pleocytosis.<sup>27</sup> Children < 2 years of age are at the highest risk of infection, with illness being particularly severe in children < 6 months of age (27).<sup>27</sup>

Following infection, innate and adaptive immune responses are triggered. PRRs (TLRs, retinoic acid inducible gene I, and melanoma differentiation-associated gene 5) form the main defense mechanisms.<sup>26</sup> TLR7 and TLR8 identify the viral RNA and activate the NF- $\kappa$ B signalling pathway leading to the secretion of pro-inflammatory cytokines (IFN- $\beta$ , TNF- $\alpha$ , IL-6).<sup>26</sup> The role of T-cell immunity in parechoviral infection is not understood, though an increased T-cell proliferation has been noted in response to PeV-A1 capsids.<sup>26</sup> Owing to the immature immune system in neonates, the elevated levels of pro-inflammatory cytokines and systemic inflammatory response have been linked to the severe pathogenesis of parechoviral infection.<sup>26</sup> Neonatal sepsis

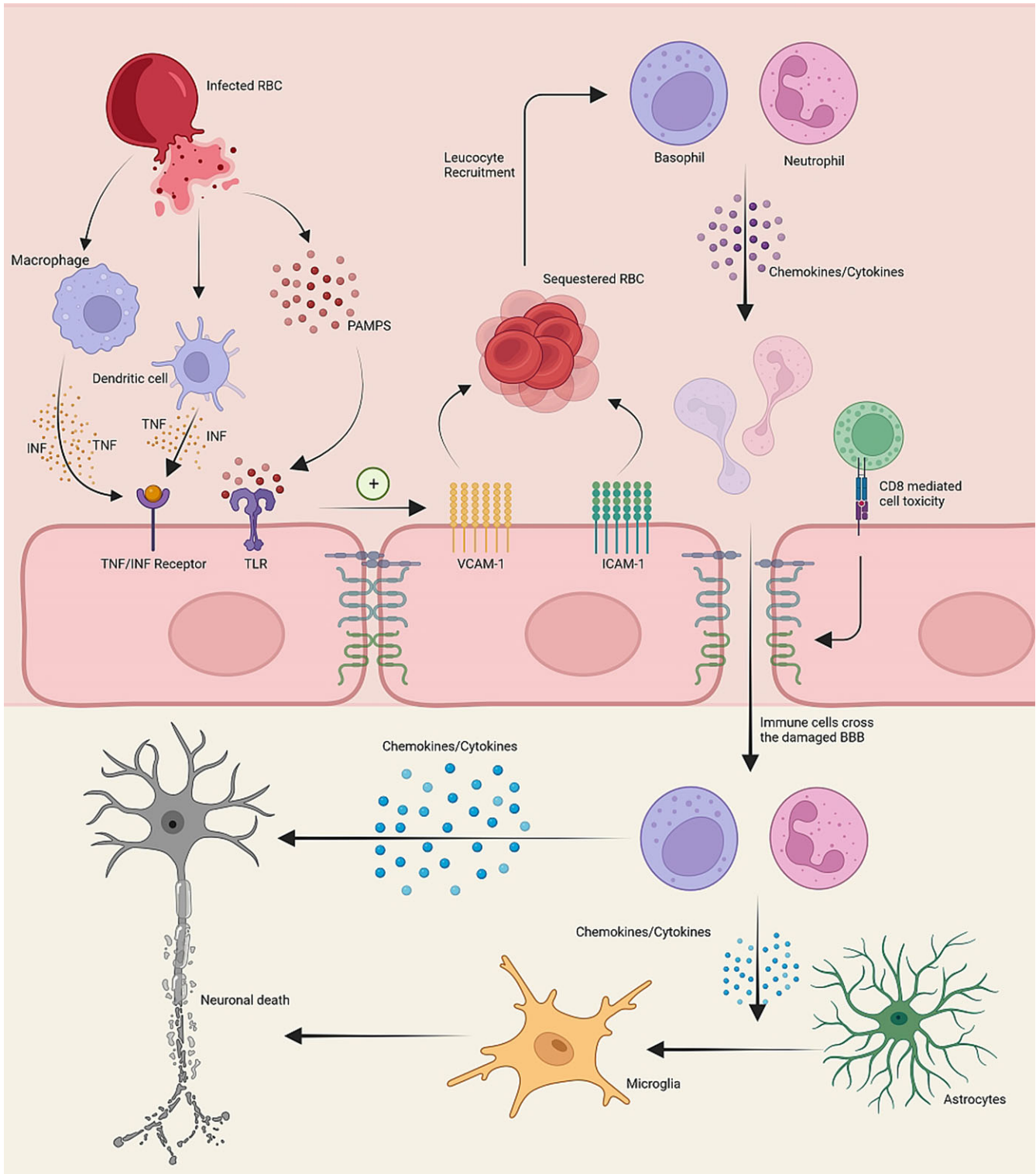
(systemic inflammatory response syndrome) is a severe, but common, manifestation of PeV-A3 and is associated with increased vascular permeability and reduced BBB function, allowing leakage of the virus into the CNS.<sup>26</sup> Preferential neuroaxonal tropism may be one cause of the distinct imaging pattern of the white matter involvement.<sup>28</sup> Given the radiating pattern of involvement, the hypothesis of perivenular invasion or venous ischemia has also been proposed. This is supported by the postmortem examinations of two premature neonates, in which only periventricular inflammatory changes with marked macrophage infiltration and moderate astrocytosis were observed.<sup>27,29</sup>

On cranial ultrasound, hyperechogenicity in the periventricular and deep white matter may be seen. On MRI, diffuse, multifocal signal abnormality and restricted diffusion in the subcortical white matter, with a frontal predominance, is a common finding<sup>27</sup> (Fig. 7). Branching T1- and T2 shortening along the deep medullary veins is also a common finding.<sup>27</sup> Thalamic involvement may be seen while the basal ganglia, hippocampal formations and posterior fossa structures may be spared.<sup>27</sup> Additionally, a lactate peak may be encountered on MR spectroscopy; however, contrast-enhanced MRI, MR angiography and MR venography are typically normal.<sup>27</sup>

##### *Cerebral malaria*

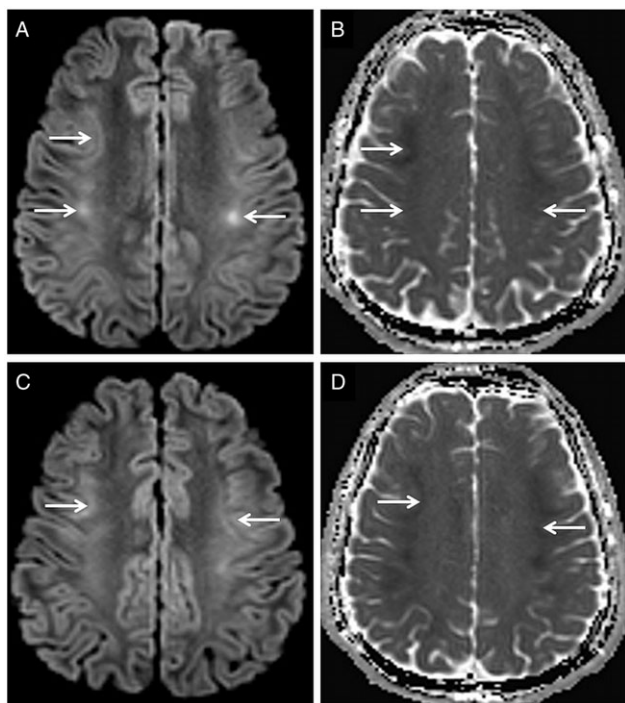
Malaria is a mosquito-borne disease, transmitted through the bite of a Plasmodium-infected female Anopheles mosquito. While multiple species are known to cause malaria, *P. falciparum* and *P. vivax* are the main cause of complications in humans, including cerebral malaria (CM).<sup>30</sup> CM commonly presents with impairment in consciousness and encephalopathy, with or without seizures, eventually progressing to coma.<sup>30</sup> Despite treatment, focal neurological signs and symptoms may persist, with signs of brainstem dysfunction being common in pediatric survivors.<sup>30</sup>

Understanding the pathogenesis of CM has been confounded by the fact that plasmodium-infected red blood cells (PRBCs)



**Figure 8.** Pathophysiology of cerebral malaria. The rupture of infected red blood cells leads to the release of merozoites which activate macrophages and dendritic cells which in turn causes the release of TNF and IFN- $\gamma$ . These increase the expression of VCAM1 and ICAM1 on the endothelial cells in the BBB which further recruits more infected RBS, hence promoting inflammation and stimulating pro-coagulation pathways. PRRs detect malarial PAMPs and trigger the secretion of cytokines including IL-6, IL-12, and TNF. This also leads to increased recruitment of basophils, neutrophils, and NK cells. Upon activation these cells release chemokines (MIP-1  $\alpha$  and MIP-1 $\beta$ ) which damage the integrity of the BBB. In addition, the endothelial cells of the BBB present the malarial antigen to CD8+ T cells in the brain which incites CD8+ T cell-mediated endothelial cell death (mediated by granzyme B). Following BBB breakdown, parasite-derived proteins and peripheral immune cells gain access to the brain. This triggers astrocyte and microglial activation which increases proinflammatory cytokines and chemokines production (e.g., MAP kinase-mediated cytotoxic pathway) which causes axonal loss. (Created with [BioRender.com](https://www.biorender.com/)). BBB = blood-brain barrier; NK = natural killer; PRRs = pattern recognition receptors.





**Figure 9.** Cerebral malaria in patient presenting to the emergency department in deep coma. Axial DWI (A, C) and corresponding ADC (B, D) images show restricted diffusion involving the juxta- and subcortical white matter bilaterally. A diagnosis of CM was made based on peripheral smears and the patient survived after intensive treatment with anti-malarial regimens and supportive management. ADC = apparent diffusion coefficient; CM = cerebral malaria; DWI = diffusion-weighted imaging.

remain within the vascular lumen and do not physically damage the parenchyma.<sup>30</sup> It is now known that cerebral microcirculatory disturbances cause the clinical manifestations of CM.<sup>31</sup> PRBCs undergo a process known as sequestration, by virtue of which they adhere to the endothelium with the help of a specific cell-surface ligand (*P. falciparum* erythrocyte membrane protein 1).<sup>31</sup> It is encoded by a variable gene (*var-gene*) and interacts with host adhesion receptors (ICAM-1, EPCR, CD36).<sup>30</sup> Sequestration subsequently leads to multiple downstream cerebrovascular effects such as vasoconstriction, cerebral blood flow impediment, luminal obstruction and BBB disruption.<sup>31</sup> Apart from these mechanical effects, an alternate hypothesis related to cytokine storm has also been proposed based on the observation of increased neutrophil activation and increased production of cytokines (TNF, IFN- $\gamma$ , IL-2, IL-6, IL-8 and IL-10)<sup>30</sup> (Fig. 8).

The neuroimaging features of CM are variable, especially due to isolated case reports and small case series. Typical imaging findings include diffuse neuroparenchymal swelling with increased T2 signal intensity, affecting the cerebral hemispheres more than the posterior fossa structures.<sup>33</sup> In a cohort of 120 Malawian patients with CM, Potchen et al found moderate-to-severe cerebral edema, resulting in narrowing of CSF spaces and uncus herniation, was the most prevalent finding (47.5%).<sup>32</sup> Some variability in the distribution was also noted, with 24.6% and 7.0% demonstrating supratentorial and infratentorial swelling respectively.<sup>32</sup> In a study of pediatric patients admitted with CM by Seydel et al, 21 (81%) out of the 25 patients who died demonstrated MRI evidence of severe brain swelling at the time of admission (odds ratio for brain

swelling among patients who died vs. survivors was 14.0; 95% CI, 4.5–43.4). These patients died as a result of respiratory arrest, consistent with the effects of elevated intracranial pressure. However, in this study, it was noted that brain swelling in the setting of CM does not always translate into fatality as the authors found that approximately 65% of the patients with severely increased brain volume survived with long-term outcomes similar to survivors with normal brain volumes. They concluded that interventions to decrease brain swelling and to sustain respiration temporarily could reduce mortality without an increased in morbidity.<sup>34</sup>

Signal alterations in the deep gray nuclei have also been described. Hyperintense T2 signals in the basal ganglia was common in the study conducted by Potchen et al (84.2%); predominant involvement of the globus pallidus was seen in a few cases.<sup>32</sup> Restricted diffusion in the basal ganglia was also seen (42%).<sup>32</sup> Thalamic involvement (64.2%) was observed, but associated restricted diffusion was uncommon.<sup>32</sup> Petechial cerebral hemorrhagic foci may also be noted on susceptibility weighted images (SWI).<sup>33</sup>

Potchen et al also described T2-hyperintense cortical swelling (61.7%), typically not following a vascular distribution, however, cortical restricted diffusion was noted in 20.8% of cases.<sup>32</sup> These areas of restricted diffusion resolve in survivors, with no sequelae after a month, but persist or worsen in patients who succumb to the illness. The etiology of this phenomenon is still not completely understood.<sup>33</sup>

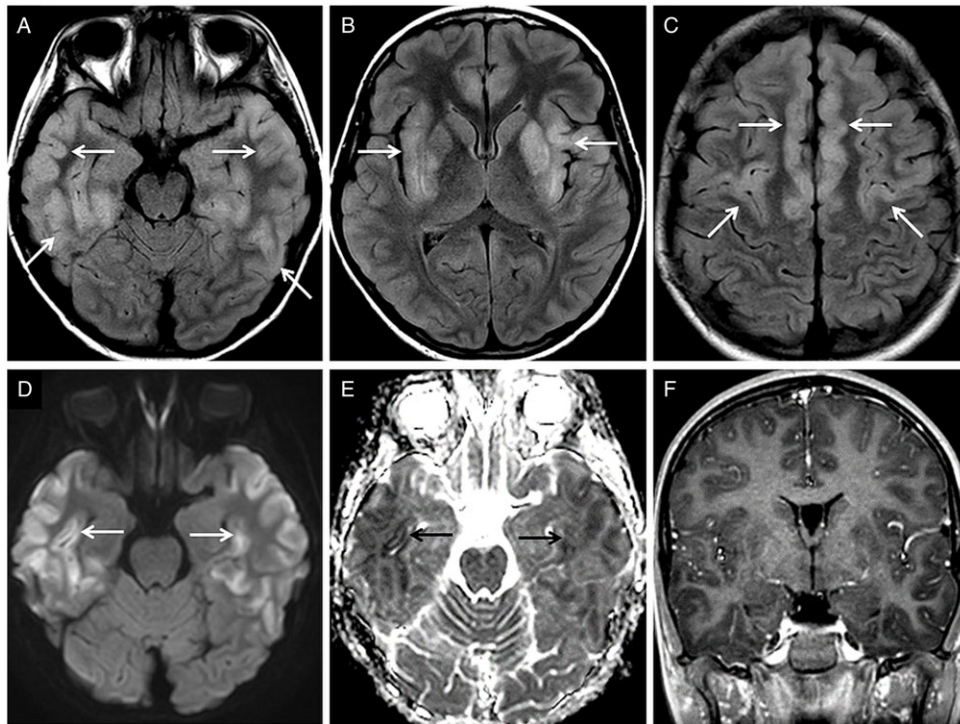
Increased T2 signal in the white matter (71.7%) was commonly accompanied by DWI abnormalities (45.0%) in the study by Potchen et al.<sup>32</sup> Callosal T2 hyperintensity was also seen in (49.2%) commonly in the absence of other white matter changes.<sup>32</sup> In their cohort, cerebellar involvement was not uncommon (49.2%), ranging from diffuse involvement to multifocal areas or unifocal lesions, while restricted diffusion in the cerebellum was uncommon.<sup>32</sup> In our experience, we have encountered a case of CM showing restricted diffusion and T2-prolongation involving the juxta- and subcortical white matter, with a near symmetric distribution (Fig. 9).

Approximately 30% of those who survive CM develop structural brain abnormalities and are often associated with seizures, developmental delay, behavioral problems and multiple neurological deficits.<sup>33</sup> Volume loss of the brain parenchyma is the most common finding, seen as early as within 2 weeks after coma resolution. Periventricular and subcortical T2 hyperintense signal abnormality in almost 47% and 18% of all cases, respectively. Focal areas of cerebral cortical defects / encephalomalacia and isolated vermian atrophy may also be encountered.<sup>33</sup>

### Inflammatory basis of epilepsy syndromes

#### Febrile infection-related epilepsy syndrome (FIRES)

Status epilepticus (SE) is a common neurological condition, occasionally preceded by febrile illness in some patients.<sup>35</sup> This entity has various names including new-onset refractory SE (NORSE), febrile illness-related epilepsy syndrome (FIRES), acute encephalitis with refractory repetitive partial seizures (AERRPS) and devastating epilepsy in school-age children (DESC).<sup>35</sup> NORSE is defined as a clinical presentation, not a specific diagnosis, in patients with new onset of refractory SE without a clear acute /active structural or toxic-metabolic etiology.<sup>35</sup> FIRES, a subcategory of NORSE, present following a febrile illness with fever occurring 2

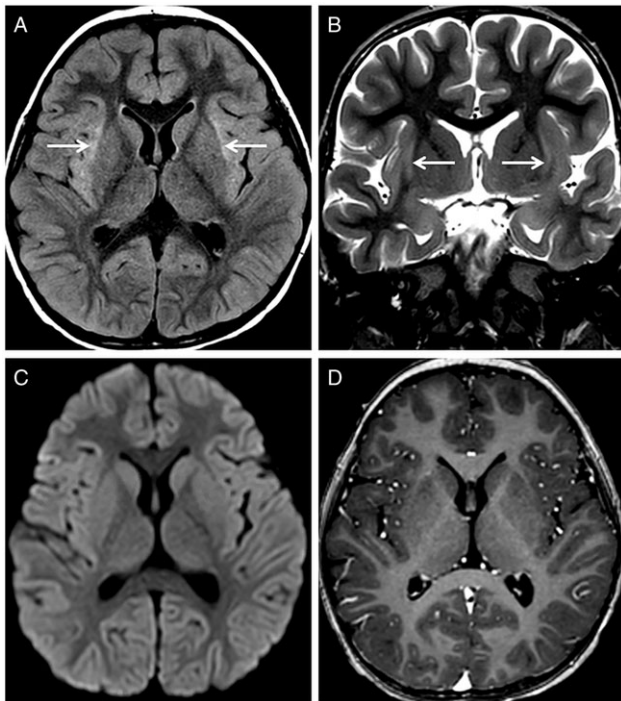


**Figure 10.** FIERES in a 10-year-old presenting with acute failure of verbalization, reduced ambulation and poor intake along with abnormal repetitive movements of hands and pursing of lips. Axial FLAIR sequence (A-C) shows extensive, symmetric, gyriform hyperintense cortical swelling in the temporal lobes (A), the insula (B), and the frontal lobes (with a mesial predominance; C). Similar hyperintense swelling is seen involving the lentiform nuclei bilaterally. Axial DWI (D) and ADC (E) sequences show corresponding gyriform restricted diffusion in the temporal lobes. There was no restricted diffusion seen in the rest of the affected brain parenchyma. Coronal contrast-enhanced 3D-T1 sequence (F) reveals no evidence of contrast enhancement. A differential diagnosis of infection, including viral etiologies such as herpes, as well as anti-NMDAR encephalitis were considered at the time of initial presentation. A biopsy of the temporal lobe revealed focal spongiotic changes with apoptotic neurons and neuronal loss but no immunohistochemistry was negative. Based on the clinical presentation and the pathological results, FIERES was considered and the patient was treated with methylprednisolone, IV immunoglobulin and plasma exchange (PLEX). ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; FIERES = febrile infection-related epilepsy syndrome.

weeks to 24 hours prior to onset of refractory SE.<sup>35</sup> The exact etiology of FIERES is unknown. While few cases have tested positive for mycoplasma and adenovirus, however, no pathogen has been isolated in a vast majority of cases.<sup>36</sup> Autoimmunity has also been implicated with reports of anti-glutamate receptor antibodies or anti-glutamic acid decarboxylase antibodies and IL6/IL8 obtained from CSF.<sup>36</sup> Genes including SCN2A and PCDH19 have been reported.<sup>37</sup> Febrile illness causes the release of pro-inflammatory cytokines and chemokines which lower the seizure threshold secondary to ion channel function modification while promoting neuronal excitability.<sup>36</sup> These may also prime innate immunity activation in seizure-prone areas of the brain and alter cellular components in the BBB, thereby triggering a neuroinflammatory cascade.<sup>36</sup> Activation of microglial NLRP3 inflammasome/IL1 axis has been proposed, leading to a proinflammatory-proconvulsive milieu.<sup>36</sup> FIERES also shows elevation of pro-inflammatory profile including interleukin IL-6, C-X-X motif chemokine ligand 8 (CXCL8) and C-C motif ligand L3 and 4 (CCL4 and CCL3) as well as IL-1 $\beta$ .<sup>36,37</sup> IL-1 $\beta$  in particular lowers the seizure threshold and is endogenously antagonized by IL-1Ra, encoded by the IL1RN gene.<sup>38</sup> Patients with the variable number of tandem repeat (VNTR) allele of the IL1RN, RN2, carry a higher risk of FIERES as the presence of RN2 is associated with reduced IL1RN-mRNA expression and enhanced IL-1 $\beta$  production.<sup>38</sup> FIERES typically affects children at a median age of 6–8 years. FIERES has 3 stages of disease evolution.<sup>36</sup> The initial prodromal stage (approximately 13 days) is characterized by febrile illness (respiratory or gastrointestinal infection).<sup>36,37</sup> This is followed by a new onset of seizures, which increase in frequency,

eventually evolving into refractory SE.<sup>36</sup> At this stage, most patients have recovered from fever.<sup>36</sup> The final chronic stage ensues with patients requiring multiple anti-seizure medications with varying grades of residual disability. Seizures are typically multifocal or generalized, evolving into super-refractory SE reaching up to several seizures each day.<sup>36,39</sup>

The major role of MRI, in patients with FIERES, is to exclude other clinical mimics. The NORSE Institute recommends a contrast-enhanced MRI of the brain with MR angiography and MR venography within the first 24 hours of symptom onset.<sup>40</sup> Most patients have an unremarkable initial MRI examination, though unilateral or bilateral temporal lobe signal abnormalities have been reported.<sup>40</sup> Description of the spatial involvement of the temporal lobe is heterogeneous in literature, with authors reporting hippocampal, mesial temporal or just temporal lobe involvement.<sup>40</sup> Cortical edema with T2/FLAIR hyperintensity and/or restricted diffusion may also be noted reflecting impairment of the Na/ATPase pump function<sup>40</sup> (Fig. 10). Bilateral involvement of the basal ganglia is another frequent abnormality reported in the acute FIERES.<sup>40</sup> Basal ganglia involvement may affect the striatal inhibitory function and reduce the seizure threshold, however, the exact mechanism leading to signal alterations in the basal ganglia is unclear. Involvement of the insular/peri-insular regions and the cerebral cortices (focal or diffuse) may also be noted.<sup>40</sup> Symmetric T2/FLAIR hyperintensity involving the caudate, referred to as the 'caudate sign' has been reported, however, this is neither diagnostic nor pathognomonic for NORSE or FIERES<sup>41</sup> (Fig. 11). Involvement of thalami, brainstem and cerebellum is



**Figure 11.** Claustral sign in a 3-year-old with suspected FIRES presenting with multiple seizures, following a bout of febrile illness. Axial FLAIR (A) and coronal T2-weighted (B) sequences reveal hyperintensities in the subinsular regions/claustrum bilaterally (arrows). Axial DWI (C) and axial contrast-enhanced 3D-T1 sequence (D) demonstrate no corresponding restricted diffusion or contrast enhancement, respectively. DWI = diffusion-weighted imaging; FIRES = febrile infection-related epilepsy syndrome.

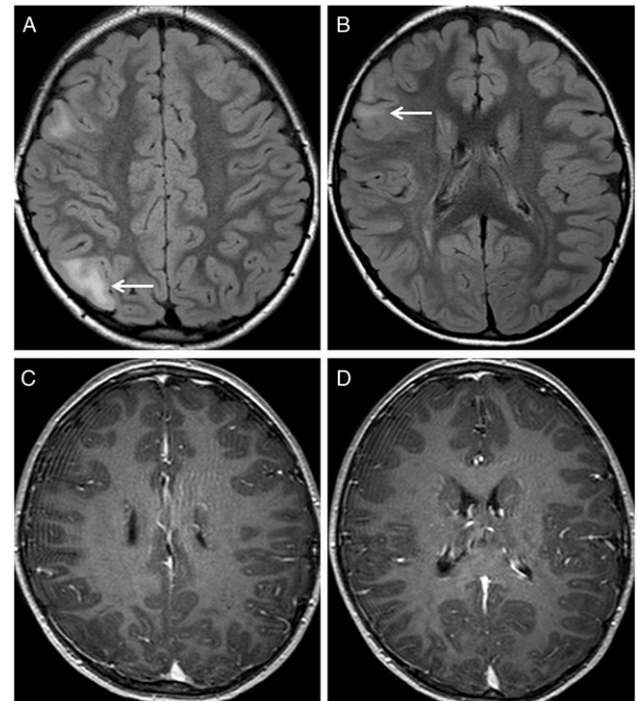
rare. Following contrast administration, parenchymal or leptomeningeal enhancement may be seen.<sup>40</sup>

Imaging in the chronic phase may reveal normal MRI appearances or global parenchymal atrophy with ex-vacuo dilation of the ventricles.<sup>40</sup> Atrophy and/or T2 hyperintensity within the mesial temporal lobes is not uncommon.<sup>40</sup> Abnormal white matter T2/FLAIR hyperintensities may be seen in the deep and/or subcortical white matter.<sup>40</sup> Similar signal changes may be seen in the insular and peri-insular as well as the deep grey nuclei and cortices.<sup>40</sup> Ependymal enhancement and signal abnormalities in the substantia nigra and corticospinal tracts have been described in single case reports.<sup>40</sup>

#### *Rasmussen's encephalitis (RE)*

RE is a rare chronic neurological disorder of unknown origin, classically causing drug-resistant focal epilepsy with progressive unihemispheric atrophy.<sup>42,43</sup> RE may begin anytime between infancy and adulthood, with a median age of 6 years.<sup>43</sup> Some may present with a prodromal period of hemiparesis or episodic seizures progressing to the acute phase characterized by frequent seizures arising from one cerebral hemisphere.<sup>43</sup> Nearly half the patients present with *epilepsia partialis continua*.<sup>43</sup> Untreated patients develop hemiparesis, hemianopia, cognitive decline and dysphasia (when the language dominant hemisphere is affected).<sup>43</sup>

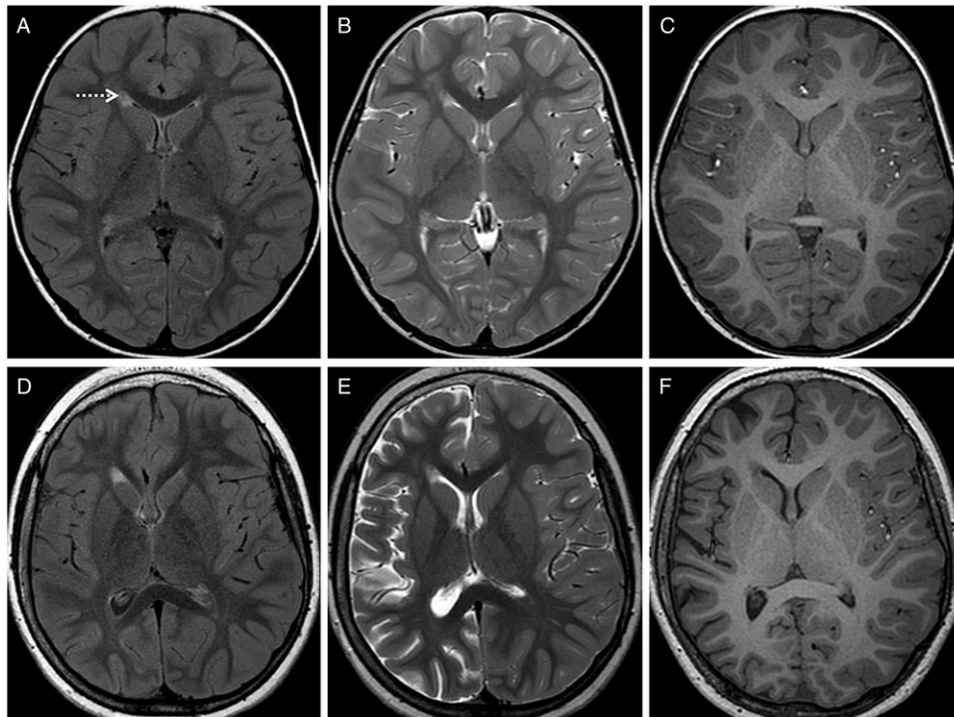
At present there is no obvious cause known to trigger RE. Viral infections were considered to be a trigger, however, to date no study has proved viral replication in the brain parenchyma of patients with RE.<sup>42,44</sup> Autoantibodies against GluR3 were considered, however, these were found only in a few patients with proven RE.<sup>43</sup> More recently, cytotoxic T cells have been evaluated in the pathogenesis of RE; pathological specimens have



**Figure 12.** Rasmussen encephalitis in a 6-year-old patient presenting with sudden onset absence-like complex partial seizures originating from the right hemisphere. Axial FLAIR sequence (A, B) shows areas ill-defined areas of hyperintense signal involving the cortex and the juxtacortical white matter of the right parietal (A) and frontal (B) lobes. DWI (not shown) revealed no restricted diffusion in these locations. Corresponding contrast-enhanced 3D-T1 sequence (C, D) reveals no evidence of enhancement in these regions. DWI = diffusion-weighted imaging.

revealed that cytotoxic CD8+ T cell lymphocytes form the majority of infiltrated T cells in RE with 10% of which are granzyme-B positive CD8+ T cells.<sup>42</sup> This is viewed as compelling evidence of neuronal destruction and astrocytic degeneration caused by cytotoxic T cells, which gives rise to seizures.<sup>42</sup> Research has also shown certain genes (encoding interferon- $\gamma$ , CCL5, CCL22, CCL23, CXCL9, CXCL10 and Fas ligand) were expressed in RE which are related to the activation and recruitment of T cells to sites of inflammation.<sup>43</sup> Activation of microglia has also been evaluated; their activation closely follows the T-cell infiltration patterns and progression of cortical damage.<sup>42,43</sup> Activated microglia release interleukin 1 and other pro-inflammatory cytokines which participate in the seizure induction. Activated microglia may also take part in complement-mediated synaptic dysfunction which increases neuronal excitability.<sup>42,43</sup>

MRI forms the mainstay in the evaluation of RE. Typical MRI features include preferential atrophy of the frontal lobe and insula with volume loss of the caudate head, together leading to ex-vacuo enlargement of the CSF spaces<sup>42</sup> (Fig. 12). Volume loss typically ensues 4 months following symptom onset. Intra- and/or subcortical T2/FLAIR may also be observed<sup>42,44</sup> (Fig. 13). Areas of increased signals have been shown to correspond to sites of increased T cells, microglial nodules and GFAP + astrocytes. Most tissue loss is noted within the initial 12 months of disease onset; with disease progression, cortical atrophy develops in the rest of the hemisphere.<sup>42,44</sup> Fluorodeoxyglucose-positron emission tomography shows hypometabolism in the affected hemisphere while single photon emission computed tomography may show interictal hypoperfusion and ictal hyperperfusion of focal parenchymal lesions in patients with RE.<sup>42</sup>



**Figure 13.** Evolution of Rasmussen encephalitis. Axial FLAIR (A) and axial T2-weighted (B) sequences reveal a small nonspecific focus of hyperintensity in the right frontal lobe (dotted arrows). Axial 3D-T1 sequence (C) shows normal volume of the right cerebral hemisphere. Follow-up MRI (D-F) obtained after 3 years due to medically refractory focal epilepsy, occurring multiple times daily, and emerging left hemiparesis. Axial FLAIR (D), axial T2-weighted (E), and axial 3D-T1 (F) sequences reveal marked volume loss of the right cerebral hemisphere, seen in the form of ex-vacuo dilation of the right lateral ventricle and prominence of the sulcal spaces. Note, apart from non-specific FLAIR/T2 hyperintensity along the right frontal horn, there is no other signal abnormality seen in the rest of the brain parenchyma.

## Autoimmune encephalitis

### Anti-NMDAR encephalitis

The N-methyl-D-aspartate receptor (NMDAR) is an ionotropic glutamate receptor, centered in the postsynaptic compartment.<sup>45</sup> It is comprised of two GluN1 and two GluN2 or GluN3 subunits; GluN1 and GluN3 bind glycine while GluN2 binds glutamate.<sup>45</sup> Autoantibodies against the GluN1 subunit of the NMDAR are the most common form of autoimmune encephalitis, especially in children.<sup>46,47</sup>

Tumors and post-viral states are common immunologic triggers linked to anti-NMDAR encephalitis.<sup>48</sup> However, in nearly half of the cases, the immunologic triggers remain unknown.<sup>48</sup> Tumors containing nervous tissues expressing NMDAR (e.g., ovarian teratomas) incite expansion of T and B cells while virus-induced neuronal damage leads to direct transport of the receptors to draining lymph nodes or APC uptake stimulating memory B expansion.<sup>46</sup> Upon exposure to NMDAR, naïve B cells are activated and enter the CNS via the choroid plexus.<sup>48</sup> Tumors also present potential ligands for the innate PRRs, including, but not limited to TLRs.<sup>46</sup> The activation of innate immunity-mediated cytokines and TLR ligands leads to BBB disruption, allowing B cell infiltration.<sup>46</sup> Interaction with the autoantibodies causes internalization of the NMDARs leading to decreased receptor density on cell surfaces and eventual imbalance between excitatory and inhibitory neurotransmitters<sup>45</sup> (Fig. 14).

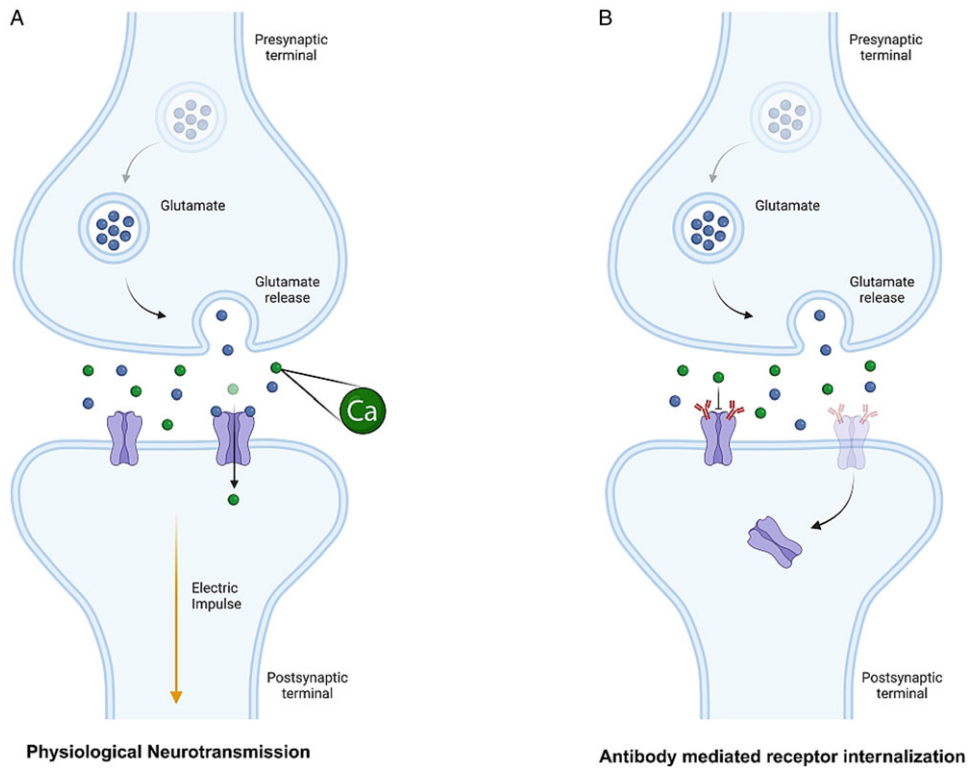
NMDAR encephalitis often shows a progressive clinical worsening. An initial viral-like prodrome may be encountered (fever, malaise, headache, etc).<sup>49</sup> This is subsequently followed by psychiatric symptoms (anxiety, depression, schizophrenia, psychosis) with progression to temporal lobe dysfunction (amnesia and seizures).<sup>49</sup> Ultimately, severe residual neurologic deficits may

be seen (impairments of memory and psychiatric symptoms).<sup>49</sup> Early diagnosis and treatment may be associated with a good prognosis and neurological outcomes, with patients returning to baseline.<sup>49</sup>

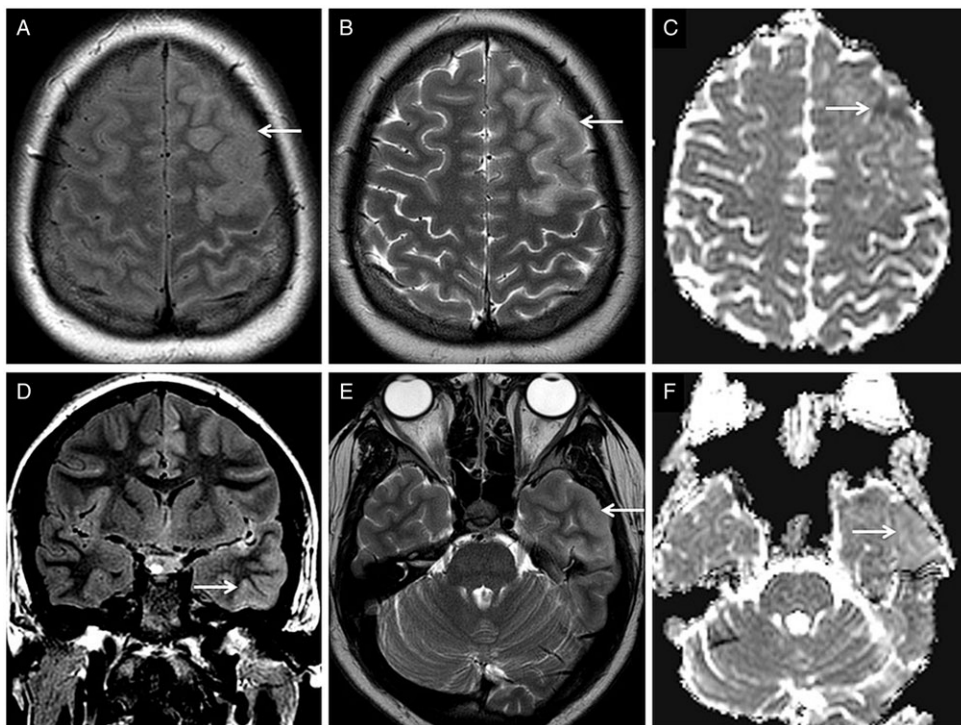
Most patients with anti-NMDAR encephalitis have normal brain MRI examinations at presentation (89%) and on follow-up (79%).<sup>49</sup> Non-specific T2/FLAIR hyperintensity involving grey and/or white matter with variable supra- and infratentorial distribution has been described.<sup>49</sup> In a study of 53 patients with anti-NMDAR encephalitis, including pediatric and adult patients, Zhang et al divided brain lesions into 4 groups: type 1 (normal MRI; 53%), type 2 (isolated hippocampal involvement; 13%), type 3 (lesions sparing the hippocampus; 13%) and type 4 (combined hippocampus and other focal brain involvement' 21%).<sup>5</sup> Apart from the hippocampus, lesions were found in the frontal lobes, cingulate gyri, middle cerebellar peduncles, corpus callosum, insula, basal ganglia, thalami and brainstem.<sup>50</sup> They found no statistical difference in the imaging manifestations between pediatric and adult groups ( $p = 0.982$ ).<sup>50</sup> Hippocampal involvement was associated with a poor neurological outcome.<sup>50</sup> The presence of restricted diffusion is uncommon and should prompt further evaluation of the etiologies including seizures, infectious encephalitis and vasculitis.<sup>51,52</sup> (Fig. 15). Rare manifestations include isolated contrast enhancement of the leptomeninges and cranial nerve enhancement<sup>51,52</sup> (Fig. 16).

### Neurological manifestations in monogenic autoimmune disorders

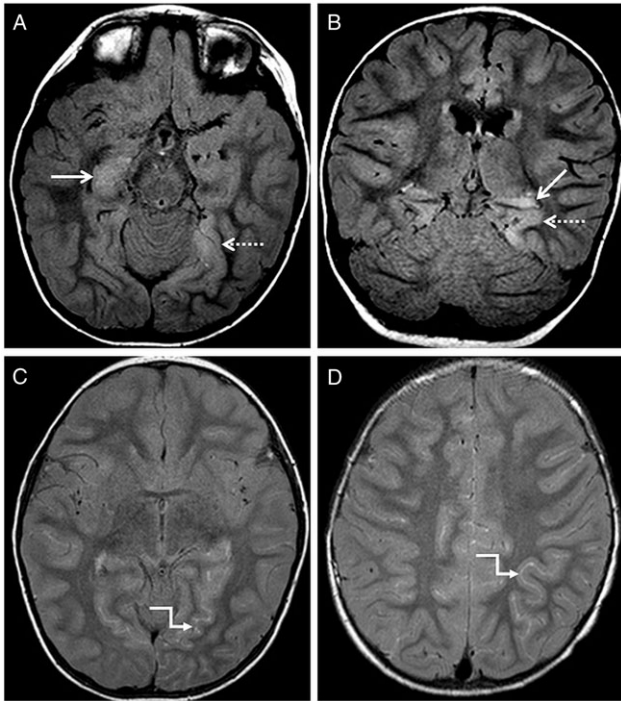
The monogenic autoimmune disorders affecting the CNS are further classified into Interleukin-1b mediated disorders, type 1



**Figure 14.** Pathophysiology of anti-NMDAR encephalitis. (A) Simplified diagrammatic representation of neurotransmission at a glutamatergic synapse and (B) simplified diagrammatic representation of antibody-mediated internalization. Binding of antibodies to the GluN1 subunit causes crosslinking of NMDAR, hence forming clusters (not shown). These are removed from the post-synaptic surface by endocytosis (receptor internalization). This eventually leads to a decreased density of NMDAR at the postsynaptic membrane. The net result is slowing down of glutamate evoked postsynaptic impulses. (Created with [BioRender.com](https://www.biorender.com)). NMDAR, N-methyl-D-aspartate receptor.



**Figure 15.** Imaging findings in a 12-year-old patient with anti-NMDAR encephalitis. Axial FLAIR (A) and T2 (B) images reveal abnormal hyperintense swelling of the left frontal cortices (arrow), with resultant effacement of the left frontal sulci. Abnormal signal is also seen involving the subjacent white matter. Axial ADC (C) obtained at the corresponding level shows patchy areas low signals representing restricted diffusion (arrow) on the background of hyperintense signals representing vasogenic edema. Coronal FLAIR (D), axial T2 (E), axial ADC (F) images obtained through the temporal lobes reveals similar hyperintense swelling of the left anterolateral temporal cortices (arrows). Contrast was not administered as the patient was suffering from concomitant chronic renal failure. ADC = apparent diffusion coefficient; NMDAR = N-methyl-D-aspartate receptor.



**Figure 16.** Atypical imaging presentation of anti-NMDAR encephalitis in a 2-year-old presenting with new-onset seizures, behavioral changes, aphasia, and fever. Axial (A) and coronal oblique FLAIR (B) sequences reveal hyperintense signal abnormality within the hippocampal formations bilaterally (arrows) as well as gyriform, FLAIR hyperintense swelling of the left occipitotemporal gyrus (dotted arrow in A) and the left parahippocampal gyrus (dotted arrow in B). Contrast-enhanced axial FLAIR images (C, D) reveal diffuse leptomeningeal enhancement (stepped arrows) along both cerebral hemispheres. The patient received high-dose intravenous steroids with clinical status reaching back to baseline within a few weeks. NMDAR = N-methyl-D-aspartate receptor.

interferonopathies, hemophagocytic syndromes and immunodeficiency disorders. In this section, we discuss the current understanding of acute necrotizing encephalopathy and familial hemophagocytic lymphohistiocytosis.

#### *Acute necrotizing encephalopathy (ANE) vs acute necrotizing encephalopathy 1 (ANE1)*

ANE is a distinct parainfectious encephalopathy, triggered by a viral infection (influenza A, influenza B, novel influenza A/H1N1, parainfluenza, human herpes virus 6, herpes 7, etc.). While the pathomechanisms of ANE are still unclear, it is thought to be an exaggerated immune response to the viral infection (cytokine storm), resulting in multisystem involvement. The CNS manifestation of this is seen in the form of increased BBB permeability.<sup>53</sup> Research shows, that a CD56+ natural killer (NK) may be involved.<sup>53</sup> Elevation of other cytokines has also been described, with IL-6 and TNF- $\alpha$  playing a major role in neurotoxicity and BBB endothelial damage, respectively.<sup>53</sup> The outcome of ANE varies depending on the causative organism. In a study by Khamis et al, the rate of pediatric intensive care unit admission was 100% and 77% for influenza and non-influenza cases, respectively. The authors also found a higher mortality rate in patients with ANE secondary to influenza infection (42% vs 11% among those due to non-influenza infection)<sup>54</sup>

ANE was initially thought to have a geographic distribution but is now considered a global phenomenon. Multiple cases of recurrent and/or familial ANE were reported suggesting an

inherited disposition. Missense mutations in the Ran Binding Protein 2 (RANBP2), the gene encoding the nuclear pore protein, were found to be the susceptibility allele for familial/recurrent cases, with an autosomal dominant inheritance.<sup>55</sup> This form of ANE has since been classified as “ANE1”.<sup>53</sup> Mutations in SCN1A R1575C and carnitine palmitoyl transferase II genes have also been linked to ANE1.<sup>56–61</sup>

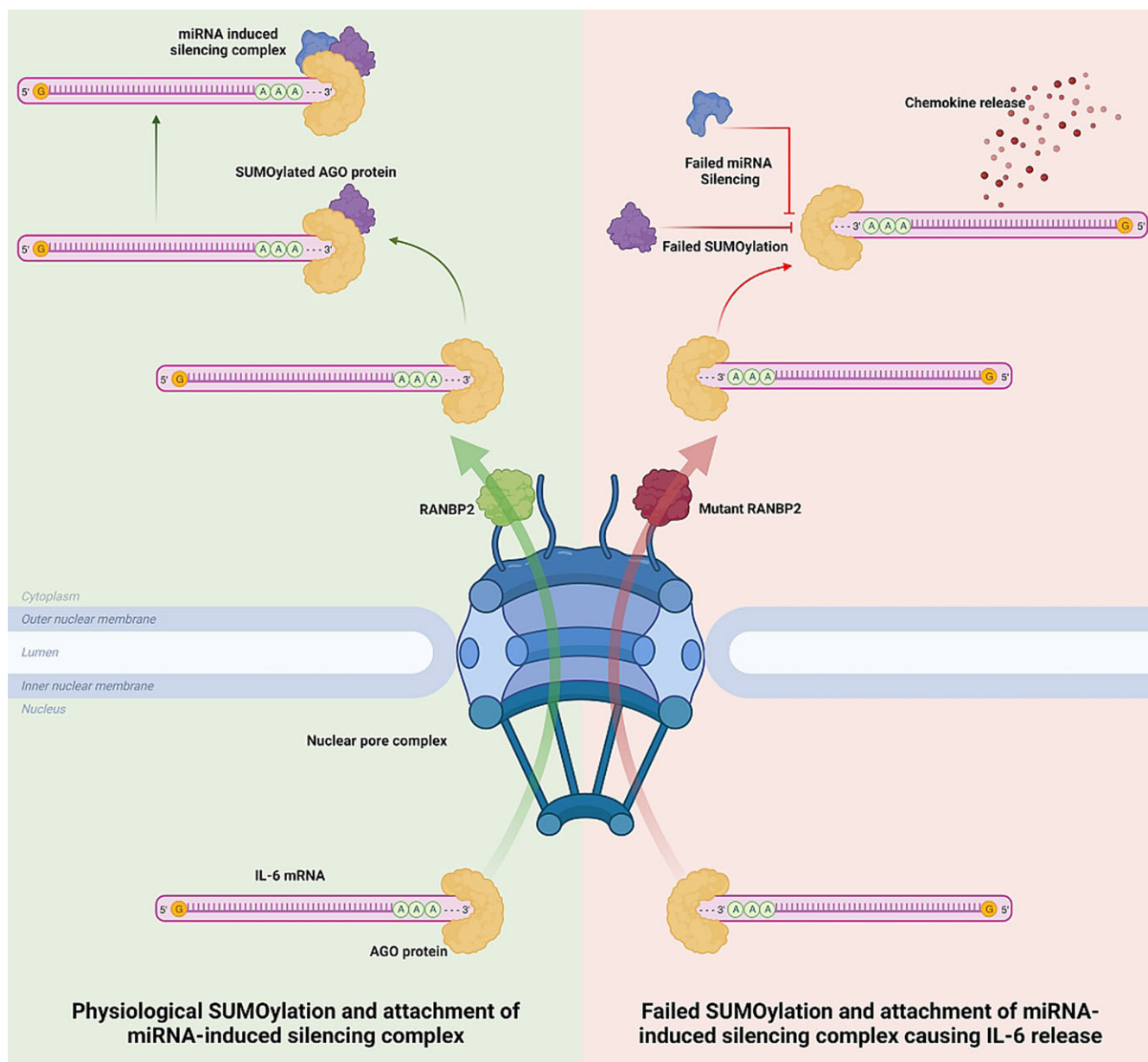
RANBP2 is located on the cytoplasmic surface of the nuclear pore. It performs several functions such as protein transport facilitation, intracellular trafficking, neuronal energy maintenance and regulation of specific subsets of mRNAs.<sup>53,62</sup> Specifically, RANBP2 is a small ubiquitin-related modifier (SUMO) pathway protein that attaches and stabilizes target proteins (SUMOylation), thus enabling them to perform vital cellular functions.<sup>24</sup> In this context, RANBP2-mediated SUMOylation of Argonaute or AGO proteins ensure the silencing of ANE-related cytokines (IL-6, TNF $\alpha$ ), STAT1 activity and type 1 interferon.<sup>24</sup> Failure of these silencing mechanisms leads to persistent cytokine production increased glutamatergic CNS excitotoxicity and eventual CNS injury<sup>63,64</sup> (Fig. 17).

ANE1 is usually preceded by a nonspecific infection which triggers downstream hyperinflammatory mechanisms. Clinically, the disease is divided into 3 phases prodrome (fever, diarrhea, vomiting, upper respiratory tract infection), acute encephalopathy (seizure, altered consciousness, focal neurologic deficits) and recovery.<sup>65</sup> The clinical course is diverse ranging from mild encephalopathy to a fulminant course leading to death.<sup>65</sup>

Neuroimaging manifestations include symmetric involvement of bilateral thalami with a characteristic trilaminar pattern. This pattern refers to a central core of T2 hyperintensity representing perivascular hemorrhage and neuronal/glial necrosis, surrounded by a zone of cytotoxic edema, seen as restricted diffusion, due to vascular congestion and oligodendrocyte swelling.<sup>55</sup> The outermost zone represents extravasation/vasogenic edema and demonstrates T2-shine through<sup>55</sup> (Fig. 18). ANE1 has an increased predisposition to involve amygdala, hippocampus and medial temporal lobes compared to sporadic ANE.<sup>56</sup> Involvement of the cerebral hemispherical white matter, brainstem and cerebellum may also be noted.<sup>66–68</sup> Uncommon manifestations include isolated involvement of the cerebral parenchyma, internal capsule and the corpus callosum.<sup>69</sup> The presence of cavitation and hemorrhage is linked to adverse clinical outcomes in pediatric ANE1.<sup>70</sup>

#### *Familial hemophagocytic lymphohistiocytosis (FHLH)*

Familial hemophagocytic lymphohistiocytosis (FHLH) is an autosomal recessive disorder with various subtypes (deficient genes): FHL1 (unknown), FHL2 (PRF1), FHL3 (Munc13-4 protein on UNC13D), FHL4 (Syntaxin 11 protein on STX11) and FHL5 (Munc18-2 protein on STXBP2) (71). PRF1 encodes perforin, contained in cytotoxic granules of lymphocytes.<sup>72</sup> Upon exposure to infected cells, CD8+ cytotoxic T cells and NK cells release these perforin-containing cytotoxic granules and granzymes resulting in target cell membrane destabilization and apoptosis.<sup>72</sup> Perforin deficiency leads to the inability of granule content to enter into target cells.<sup>72</sup> A prolonged synapse time ensues between perforin-deficient cytotoxic lymphocytes and target cells causing overproduction of pro-inflammatory cytokines.<sup>72</sup> APCs continue to accumulate and stimulate T cell activation and proliferation leading to excessive lymphohistiocytic proliferation and hypercytokinemia ultimately causing widespread tissue damage and hyperinflammation.<sup>72</sup> UNC13D, STX11 and STXBP2 gene products are important for normal cytotoxic granule exocytosis.<sup>72</sup> Defects in these genes limits the granule contents from being



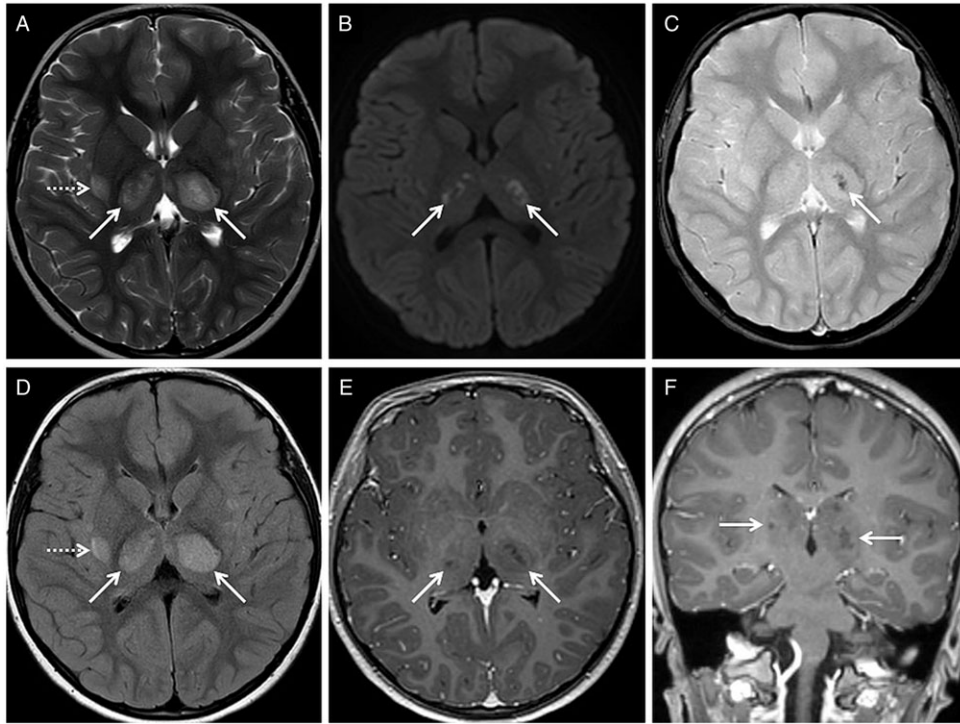
**Figure 17.** Schematic of the ANE1 pathophysiology. The nuclear pore complex is a complex macromolecule located in the nuclear envelope. It serves as an important conduit for transport across the nuclear membrane. Argonaute (AGO protein) is involved in messenger RNA (mRNA) silencing, by facilitating attachment of micro-RNA (miRNA-induced silencing complex; a silencing RNA) to the target IL6 mRNA. The RANBP2-mediated SUMOylation ensures a stable attachment of during AGO to IL-6 mRNA passage during its transport across the nuclear pore protein. The SUMOylated AGO bound IL-6 mRNA later attaches to miRNA-induced silencing complex, thereby ceasing the production of IL-6. While the exact role of mutated RANBP2 interaction in this sequence of events is not clearly delineated, but failure of miRNA-induced silencing complex attachment to an otherwise unstable AGO bound IL-6 mRNA complex may lead to sustained production of cytokines and hypercytokinemia. Adapted from reference 24. (Created with BioRender.com) ANE1 = acute necrotizing encephalopathy.

released into the immunological synapse, hence target cells are not destroyed.<sup>72</sup> HLH is also a manifestation of other genetic diseases, including pigmentary disorders (RAB27A, LYST and AP3B1 mutations), X-linked lymphoproliferative diseases (SH2D1A and XIAP mutations), CDC42 mutations, gain-of-function mutations in NLRC4 and Epstein-Barr virus (EBV) susceptibility disorders (MAGT1, ITK, CD27, CD70, CTPS1, RASGRP1 gene deficiency).<sup>72</sup> Discussion of their pathomechanisms is beyond the scope of this article, but summarized in Figure 19.

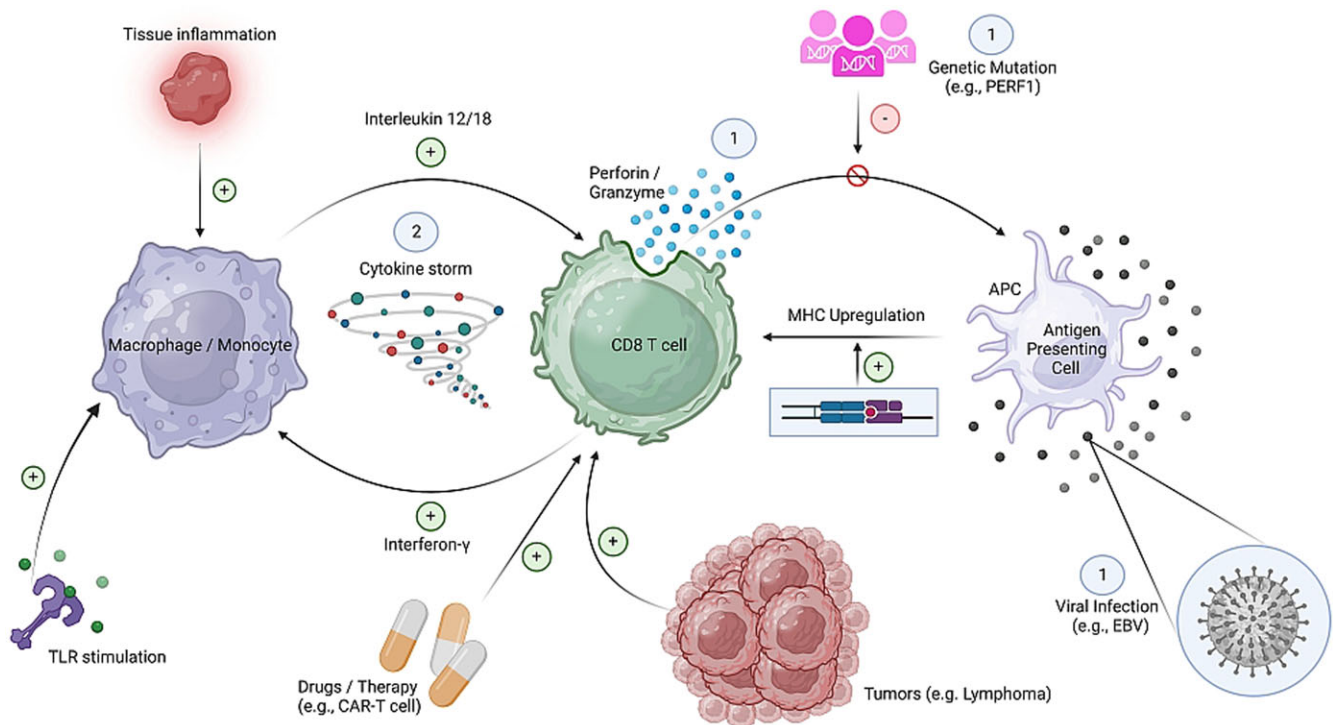
CNS involvement is common in all forms of HLH. The reported incidence of CNS involvement in FHLH is ranges between 18-75%

in FHLH.<sup>73</sup> In a case series ( $n = 38$ ), ataxia/gait disturbances (74%), seizures (50%), headache (47%), visual alterations (45%) and motor impairment (42%) were reported (74). Cranial nerve palsies, papilledema, dysmetria, dysarthria, sensory deficits and behavioral alterations were also reported.<sup>74</sup> Histopathologically, pediatric CNS HLH shows meningeal lymphocytic and macrophage infiltration (stage 1), advancing to perivascular inflammatory infiltrate (stage 2), leading to diffuse parenchymal infiltration, multifocal necrosis and astrogliosis (stage 3).<sup>75</sup>

MRI is the neuroimaging modality of choice for patients with CNS-HLH.<sup>73</sup> In a study of 179 pediatric patients, CNS imaging

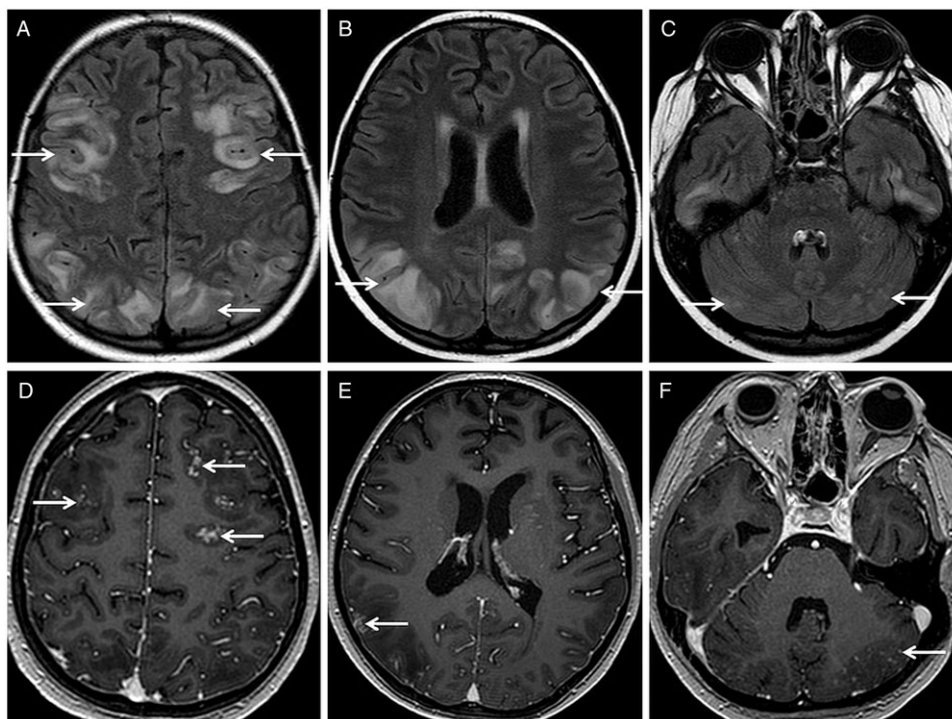


**Figure 18.** ANE1 due to RANBP2 mutation in a 4-year-old child presenting with acute encephalopathy. Axial T2-weighted sequence (A) shows symmetric involvement of bilateral thalami (solid arrows). An evolving trilaminar pattern can be identified with a central area of T2 hyperintensity surrounded by a rim of intermediate signal and a peripheral ring of hyperintensity. A small focus of T2-weighted hyperintensity is also noted along the posterior aspect of the right lentiform nucleus (dotted arrow in A). Axial DWI sequence (B) shows patchy areas of restricted diffusion in the core of the thalamic lesions. Axial multiplanar gradient recalled (MPGR) sequence (C) shows areas of susceptibility within the left thalamic lesion suggesting foci of hemorrhage. Axial FLAIR sequence (D) shows homogeneous hyperintense swelling of the thalami as well as the right lentiform nucleus posteriorly. Axial (E) and coronal (F) contrast-enhanced 3D-T1 sequence shows subtle enhancement within the thalamic lesions. DWI = diffusion-weighted imaging.



**Figure 19.** Schematic representation of HLH pathogenesis. (Circuit #1) in patients with familial HLH and some other forms of HLH related to primary EBV infection, genetic defects of virucidal property (e.g., Perforin 1 (PERF1) deficiency) causes sustained presentation of antigens and activation CD8+T cells, amplified by IFN- $\gamma$  release and MHC-I upregulation. Prolonged IFN- $\gamma$  release is also thought to cause tissue macrophage/monocyte activation consequently leading to release of inflammatory mediators (IL-1b, IL-6, IL-18, IL-12). (Circuit #2) macrophages/monocytes are activated by activated by chronic inflammation and TLR stimulation (infection). In HLH associated with malignancies, malignant cells may drive HLH through autonomous cytokine release or presentation of EBV antigen. Drug (CAR-T cell therapy) induced occurs due to activation of therapeutic CD8+ CAR-T cells. (Created with BioRender.com). EBV = Epstein-Barr virus; CAR-T = Chimeric antigen receptor T cell; HLH = hemophagocytic lymphohistiocytosis.





**Figure 20.** HLH in a 12-year-old with long-standing immune dysregulation (fever, cytopenia, splenomegaly). Axial FLAIR (A, B) images reveal bilateral, near-symmetric, gyral FLAIR hyperintensity with cortical swelling with similar signal abnormality in the juxtacortical white matter in the frontal and parietal lobes (arrows in A, B). Axial FLAIR (C) reveals patchy hyperintensities in the cerebellar hemispheres as well (C). Contrast-enhanced axial 3D-T1 sequences (D-F) reveal multiple, punctate foci of cortical enhancement, most accentuated in the frontal lobes, more on the left (arrows in D), with few foci of enhancement in the right parietal lobe (arrow in E), and left cerebellum (arrow in F).

findings were seen in up to 50% of cases with systemic HLH, most of which belonged to the FHLH group.<sup>76</sup> At neuroimaging, pediatric CNS-HLH presents with differing imaging patterns affecting various brain regions including multifocal cerebral and cerebellar white matter lesions, CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) like brainstem lesions and diffuse cerebellar involvement similar to cerebellitis.<sup>77</sup> Atypical findings include diffuse hemorrhagic transformation with bilateral basal ganglia, thalamus and brainstem involvement.<sup>78</sup> Other findings reported in CNS-HLH are nodular or ring-enhancing lesions with restricted diffusion, leptomeningeal enhancement, diffuse cerebral edema, subdural collections as well as calcification and cerebral atrophy in late stages<sup>79–81</sup> (Fig. 20).

#### **SARS-CoV-2 and COVID-19: the novel mimicker**

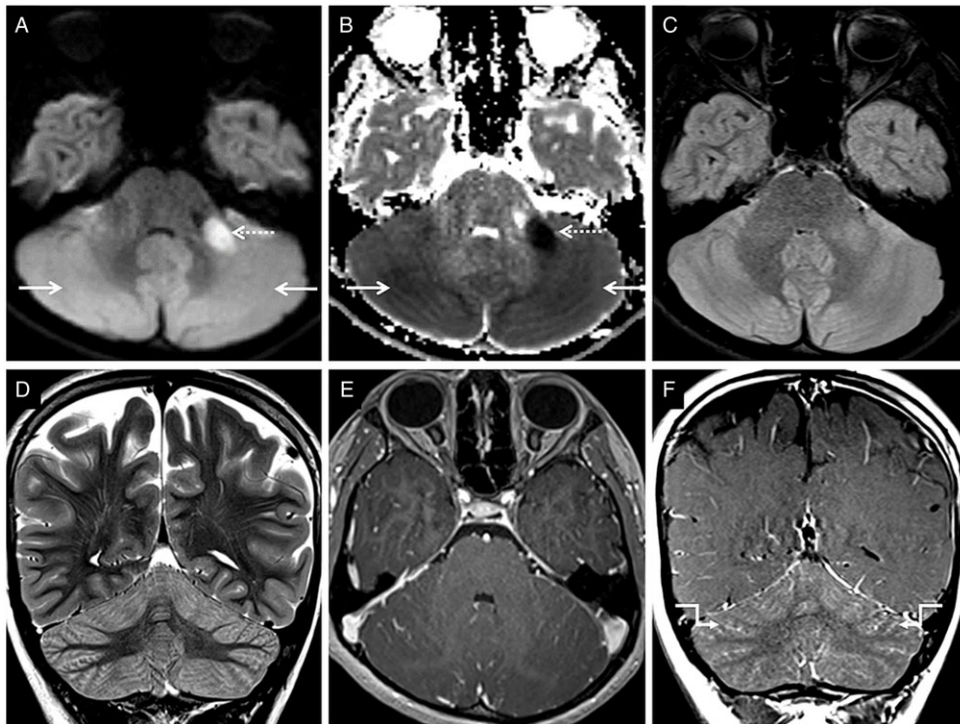
The recent crippling pandemic, termed as Coronavirus disease (COVID-19), is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belonging to the positive-sense single-stranded RNA viruses beta coronavirus ( $\beta$ -CoV) family.<sup>82</sup> The potential mechanisms to explain the SARS-CoV2 neurotropism include angiotensin-converting enzyme 2 receptor (ACE2); neurons, astroglia cells, microglia cells and endothelial cells) mediated direct entry into the neuronal cells secondary to hematogenous spread.<sup>83–85</sup> Of note, the virus is approximately 60–140 nm in diameter allowing it to easily bypass the BBB.<sup>82</sup> Transneuronal dissemination (antegrade or retrograde) is another route for CNS infection. ACE2, transmembrane serine protease 2, and neuropilin-1 (NRP1)

expressed in the olfactory epithelium are thought to facilitate such transneuronal migration of the virus.<sup>82</sup>

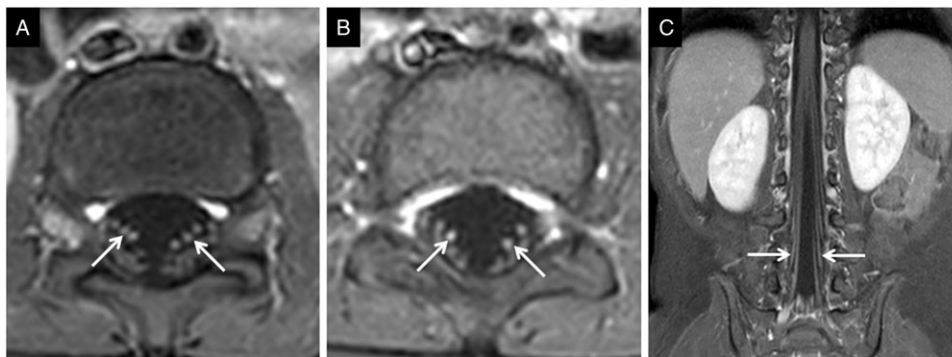
The etiology of CNS manifestations in COVID-19 are multifactorial. Acute respiratory distress syndrome (ARDS), a common complication of pulmonary SARS-CoV-2 infection, causes severe hypoxia leading to accumulation of anaerobic metabolites in the mitochondria and failure of the Na<sup>+</sup> K<sup>+</sup>-ATPase pump leading to cytotoxic edema and cerebral blood flow dysregulation.<sup>82</sup> Neurological manifestations in COVID-19 may also occur from a systemic inflammatory response (cytokine storm) characterized by an exaggeration of pro-inflammatory cytokine and chemokine release causing severe end-organ damage.<sup>82</sup> Studies indicate that SARS-CoV-2 induces proinflammatory cytokine signaling from astrocytes and microglia cells causing a massive release of inflammatory factors (IL-6, IL-12, IL-15, IL-1 $\beta$  and TNF- $\alpha$ ).<sup>82</sup> Immune dysregulation is another underlying mechanism of CNS injury; the virus may induce an increased concentration of proinflammatory CCR6<sup>+</sup> Th17 in CD4<sup>+</sup> T cells and cytotoxic granules in CD8<sup>+</sup> T cells, indicating T cell overactivation and associated immune-mediated CNS damage.<sup>82</sup>

#### **Acute and subacute neurological complications**

Acute encephalopathy or encephalitis typically presents with ill-defined areas of T2/FLAIR hyperintensity of the cortex and hemispherical white matter with gyral swelling; rare deep grey nuclei involvement; microbleeds; and variable contrast enhancement.<sup>86–88</sup> Occasional reports of cerebellitis have also been published<sup>89</sup> (Fig. 21). Parainfectious immune-mediated Guillain-



**Figure 21.** COVID-related cerebellitis in a 6-year-old patient presenting with fever, headache, ataxia and decreased mental status. Axial DWI (A) and ADC (B) sequences reveal extensive restricted diffusion involving both the cerebellar hemispheres (arrows) with a focus of profound restricted diffusion in the left middle cerebellar peduncle (dotted arrows). Axial FLAIR (C) and T2-weighted (D) sequences reveal hyperintense swelling of the cerebellum with effacement of the interfolial spaces and the cerebellopontine angle cisterns. Contrast-enhanced axial 3D-T1 sequence (E) demonstrates no abnormal parenchymal enhancement. Delayed coronal contrast enhanced T1-weighted sequence (F) reveals leptomeningeal enhancement along the cerebellar hemispheres bilaterally. The patient was treated with intravenous immunoglobulins for 10 days along with 10 cycles of plasma exchange (PLEX). ADC = apparent diffusion coefficient; DWI, diffusion-weighted imaging.



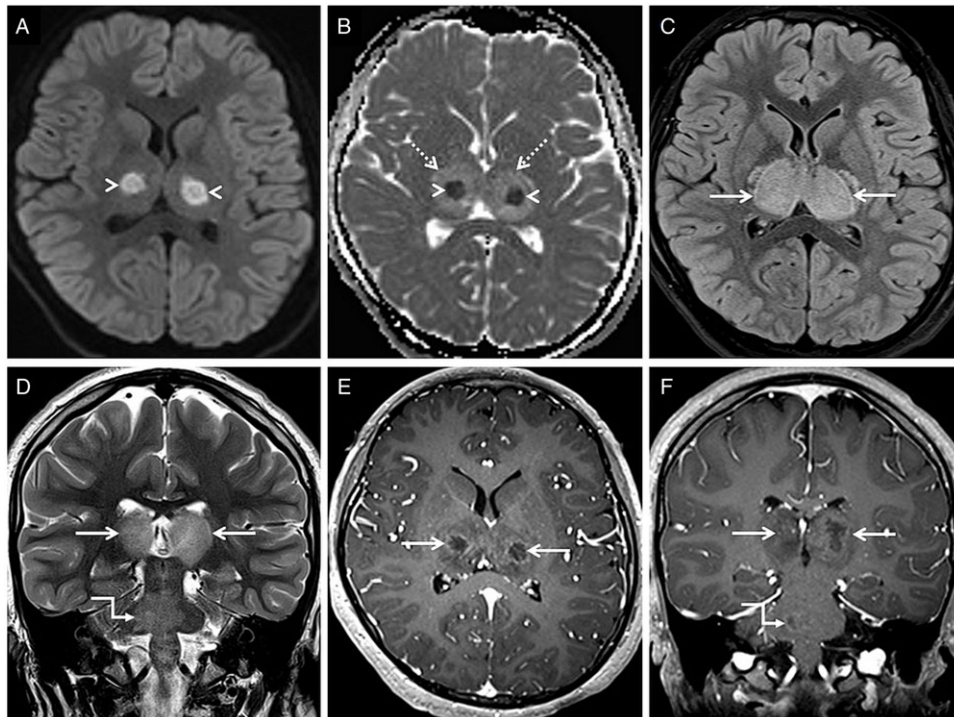
**Figure 22.** Guillain-Barré syndrome (GBS) in a 2-year-old presenting with COVID infection detected on nasopharyngeal swab analysis, presenting with generalized weakness and gait disturbance. Sequential craniocaudal contrast-enhanced axial (A, B) and coronal (C) T1 sequences through the lumbar spine demonstrate enhancing thickening of the ventral cauda equina nerve roots. The patient was treated with a 3-day course of intravenous immunoglobulins.

Barre syndrome and Miller-Fisher variants are characterized by cauda equina nerve root thickening/enhancement and lower cranial nerve enhancement<sup>24</sup> (Fig. 22). On the other hand, endothelial injury and thrombosis lead to vasculitis, acute arterial stroke, venous thromboembolism, microbleeds and parenchymal hemorrhage. Moreover, cytokine and inflammatory mediators result in cerebral endothelial damage and blood-brain barrier

disruption leading to posterior reversible encephalopathy syndrome.<sup>90</sup>

#### *Delayed neurological complications*

The cytotoxic lesions of the corpus callosum splenium are associated with hyperinflammatory illness i.e., pediatric multisystem inflammatory syndrome in children (MIS-C); and the myositis of the neck



**Figure 23.** MRI in an 8-year-old patient presenting with fever and decreased level of consciousness. The patient tested positive for COVID infection. Axial DWI (A) and apparent diffusion coefficient (ADC; B) show areas of restricted diffusion involving both the thalami (arrowheads) with peripheral areas of facilitated diffusion (dotted arrows in B). Axial FLAIR (C) and coronal T2-weighted (D) sequences demonstrate marked swelling of the thalami (arrows). In addition, confluent T2-weighted hyperintensity is seen in the pons (stepped arrow in D), extending into the medulla. Corresponding FLAIR hyperintensity was noted in the affected brainstem (not shown). Contrast-enhanced axial (E) and coronal (F) 3D-T1 sequences show faint irregular enhancement in the thalami (arrows), with a nonenhancing core, corresponding to the areas of restricted diffusion. Subtle, irregular, ring-like enhancement is also seen in the right hemipons (stepped arrow in F). These imaging manifestations suggest a parainfectious CNS complication (ANE) following COVID-19 infection occurring due to a hyperimmune response. ANE = acute necrotizing encephalopathy; CNS = central nervous system; DWI = diffusion-weighted imaging.

and face typically occurs weeks after COVID-19 infection. On imaging, splenic lesions may be seen in up to 60% of children and demonstrate T2 FLAIR hyperintensity with restricted diffusion and postulated to represent intramyelinic edema due to cytokine-mediated glutamate toxicity.<sup>91</sup>

Cytokine storm-induced neuronal and autoimmune injury encompassing acute disseminated encephalomyelitis (ADEM) like phenotype, acute necrotizing encephalopathy (ANE) and transverse myelitis are reported in all phases (Fig. 23). Rarely, ADEM-like imaging phenotype in SARS-CoV-2 occurs due to immune-mediated encephalitis associated with anti-myelin oligodendrocyte (MOG) and Anti-NMDAR antibodies. Pediatric COVID-19-associated ADEM-like phenotype shows better treatment response and outcome on treatment with steroids compared to increased association with severe disease, risk of intracranial hemorrhage and poor outcome in adults.<sup>92,93</sup>

## Conclusion

In this review, we discuss some of the common infective and inflammatory conditions specific to the pediatric population. With an improved understanding of the immune system, the role of innate and adaptive immune mechanisms in the neurological and imaging manifestations of pediatric infections and inflammatory syndromes has now been elucidated. These conditions may utilize similar mechanisms, yet produce clinically and radiographically distinct manifestations with some overlap. Understanding these pathomechanisms is not only critical in

accurate diagnosis but also paves the path for further research in terms of specific targeted treatments.

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