REVIEW

Diagnosis and Management of Children With Atypical Neuroinflammation

Laura Saucier,[1,2] Thomas Rossor,[3,4] Mark P. Gorman,[5] Jonathan D. Santoro,[1,2] and Yael Hacohen[6,7]

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Correspondence
Dr. Hacohen
y.hacohen@ucl.ac.uk

Abstract

Pediatric neuroimmune disorders comprise a heterogeneous group of immune-mediated CNS inflammatory conditions. Some, such as multiple sclerosis, are well defined by validated diagnostic criteria. Others, such as anti-NMDA receptor encephalitis, can be diagnosed with detection of specific autoantibodies. This review addresses neuroimmune disorders that neither feature a diagnosis-defining autoantibody nor meet criteria for a distinct clinicopathologic entity. A broad differential in these cases should include CNS infection, noninflammatory genetic disorders, toxic exposures, metabolic disturbances, and primary psychiatric disorders. Neuroimmune considerations addressed in this review include seronegative autoimmune encephalitis, seronegative demyelinating disorders such as neuromyelitis optica spectrum disorder, and genetic disorders of immune dysregulation or secondary neuroinflammation. In such cases, we recommend a broad diagnostic workup to support the presence of neuroinflammation, exclude non-neuroimmune disorders, detect autoantibodies and other biomarkers of known diseases, identify any potential genetic drivers of neuroinflammation, and provide case-specific insights into pathophysiologic mechanisms of inappropriate immune pathway activation or dysregulation. This review includes an extensive list of useful diagnostic tests and potential implications thereof, as well as a proposed algorithm for the diagnosis and management of the pediatric patient with atypical neuroimmune disorders. In general, first-line acute treatment of neuroimmune disorders begins with steroids, along with consideration of plasmapheresis or IV immunoglobulin. Selection of second-line or maintenance therapy is challenging without a definite, specific diagnosis and the associated benefit of established evidence-based treatment options. Immunotherapies may be considered based on the suspected mechanism of neuroinflammation and the likelihood of relapse. For example, rituximab may be considered for possible antibody-mediated or B-cell–mediated inflammation while anti–interleukin (IL)-6 agents, anti–IL-1 agents, or JAK inhibitors may be considered for certain cases of cytokine-mediated inflammation or innate immune system dysregulation. Care should be taken to monitor response and disease activity, revisit the differential diagnosis in the case of unexpected findings or poor treatment response, and weigh the risks of immunotherapy with the benefits of empiric treatment. Over time, further advancements in biomarker identification and omics research may define specific new clinicopathologic diagnoses and thus obviate the need for "n of 1" approaches to what are currently heterogeneous groups of atypical seronegative neuroimmune disorders.

Introduction

Neuroimmune disorders are an increasingly recognized and heterogeneous group of neurologic conditions characterized by inflammation in the CNS.[1] While all neuroimmune disorders feature heightened or dysregulated immune responses, the underlying pathobiological mechanisms differ widely to include antibody-mediated, T-cell–mediated, and cytokine-mediated inflammation.[1] Classically, neuroimmune conditions have been stratified into disorders of white matter, such as demyelinating disorders,[2] and those of gray matter, such as autoimmune

[1]Division of Neurology, Department of Pediatrics, Children's Hospital Los Angeles, CA; [2]Department of Neurology, Keck School of Medicine of the University of Southern California, Los Angeles; [3]Children's Neurosciences, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, United Kingdom; [4]Department of Women and Children's Health, School of Life Course Sciences (SoLCS), King's College London, United Kingdom; [5]Department of Neurology, Boston Children's Hospital, Harvard Medical School, MA; [6]Department of Neurology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; and [7]Department of Neuroinflammation, Institute of Neurology, University College London, United Kingdom.

Glossary

ADEM = acute disseminated encephalomyelitis; **ADS** = acquired demyelinating syndrome; **AE** = autoimmune encephalitis; **AGS** = Aicardi-Goutières syndrome; **ANE** = acute necrotizing encephalopathy; **ANPRA** = autoantibody-negative but probable AE; **AQP4** = aquaporin 4; **AQP4-Ab** = AQP4 antibody; **BMT** = bone marrow transplant; **CLIPPERS** = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; **DS** = Down syndrome; **FANS** = Fanconi anemia neuroinflammatory syndrome; **FDA** = Food and Drug Administration; **GABA-A** = γ-aminobutyric acid type A; **GFAP** = glial fibrillary acidic protein; **HLH** = hemophagocytic lymphohistiocytosis; **HSCT** = hematopoietic stem cell transplantation; **HSV** = herpes simplex virus; **Ig** = immunoglobulin; **IL** = interleukin; **JAK** = Janus kinase; **LE** = limbic encephalitis; **MOG-Ab** = myelin oligodendrocyte glycoprotein antibody; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated disease; **MS** = multiple sclerosis; **NfL** = neurofilament light chain; **NMDAR** = NMDA receptor; **NMOSD** = neuromyelitis optica spectrum disorder; **TNF** = tumor necrosis factor.

encephalitis (AE).[3] However, in practice, there is considerable overlap. Most of neuroimmune disorders are acquired secondary to a complex interplay between genetics and environment. A small proportion result directly from monogenic disorders of immune dysregulation, which may affect the CNS in isolation or present as a systemic syndrome.[4]

Pediatric neuroimmune disorders may manifest as (1) monophasic presentations, (2) relapsing conditions with discrete episodes of CNS inflammation, and (3) chronic neuroinflammation presenting as progressive deficits with or without superimposed clinical attacks. Some conditions, such as multiple sclerosis (MS), have well-established diagnostic criteria that incorporate typical clinical, radiologic, and laboratory findings. Other conditions, such as myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD),[5] anti-NMDA receptor (NMDAR) encephalitis,[6] and aquaporin 4 antibody (AQP4-Ab)–associated neuromyelitis optica spectrum disorder (NMOSD), require the detection of autoantibodies for diagnosis.[7] In this review, we will focus on the atypical and rare pediatric neuroimmune conditions that lack diagnostic criteria and pathognomonic paraclinical findings and will provide the reader with a summary of published evidence regarding diagnosis and management.

Atypical and "Seronegative" Neuroimmune Disorders in Children

Despite the increasingly widespread availability of antibody testing and recognition of numerous antibody-associated neuroimmune disorders, most of the children with presumed neuroimmune disorders are antibody-negative.[2,8] In clinical practice, these are the most challenging neuroimmunology patients to manage. Because children with presumed seronegative neuroinflammation are often acutely ill, clinicians must often make empiric treatment decisions in the setting of significant diagnostic uncertainty. When evaluating a child with clinical features suggestive of a seronegative neuroimmune disorder, it is important to consider whether the following may be true: (1) the patient has a known antibody, but current tests are either not clinically available or not sufficiently sensitive to detect it; (2) the patient is truly seronegative to all known autoantibodies but instead may have a novel autoantibody yet to be discovered; (3) the patient has an acquired neuroimmune condition that is not antibody-mediated; (4) the patient has an underlying genetic defect driving autoinflammation or other forms of immune dysregulation; or (5) the patient has a primary diagnosis that is not immune-mediated but in some cases may involve secondary inflammation. In the following, we will discuss some of the guiding concepts of seronegative disease and focus on 2 examples in particular—seronegative AE and seronegative demyelinating disorders such as NMOSD.

When defining a group by the lack of a disease-specific biomarker, it is important to consider the sensitivity and specificity of the different antibody detection methods. False-negative results may arise because of imperfect assay sensitivity, high thresholds for detection, or suboptimal timing of sample collection. Efforts to reduce false-positive rates have led to higher thresholds for defining positivity.[9] The related consequence of this improved specificity is decreased sensitivity, resulting in "falsely seronegative" cases in which the antibody is present but at levels below the threshold for positivity. Moreover, there have been reports of patients who tested negative at onset but seroconvert to AQP4-Ab or MOG-Ab positivity months to years thereafter.[10,11] All results must be considered in the clinical context. Table 1 summarizes key reasons for false-negative results. In general, a higher pretest probability for a given diagnosis increases the positive predictive value of even a low-titer positive antibody result and decreases the negative predictive value of a negative result.

In some cases of true seronegative neuroimmune disorders, there may be a novel unidentified autoantibody present. An in-depth review of autoantibody discovery is out of the scope of this review. In general, there are several techniques for antibody discovery that are performed only in research settings. Utility of such testing on an individual patient basis may be limited. There are 2 main approaches for identification of novel autoantibodies, the candidate approach and agnostic antigen discovery methods, both of which have an established

Table 1 Reasons for False-Negative Results

Assay sensitivity	• Cell-based assays are typically superior to other diagnostic assays, including ELISA • Live cell-based assays may be more sensitive compared with fixed cell-based assays (e.g., MOG-Ab) but take longer to result • Thresholds for positivity differ by laboratory and assay; higher thresholds reduce false positives but increase the risk of false negatives
Serum vs CSF	• For some autoantibodies, CSF testing is more sensitive (e.g., NMDAR-Ab); for others, serum testing is more sensitive (e.g., MOG, AQP4, and LGI-1 Abs) • For some autoantibodies, CSF testing may be less specific (e.g., MOG-Ab); for others, serum testing may be less specific (e.g., GAD65-Ab)
Timing	• Antibody titers may be higher during the acute attack than in remission, during which time they may fluctuate below the level of detection • For certain autoantibodies, there are isolated reports of initially seronegative patients (even when testing during a clinical attack) subsequently seroconverting to positive
Treatment	• A postimmunotherapy and especially post–plasma exchange autoantibody test may be falsely negative because of treatment effect
Human error	• If there is high clinical suspicion for a particular autoantibody, it would be reasonable to retest

Abbreviations: AQP4 = aquaporin 4; LGI-1 = leucine-rich glioma inactivated 1; MOG = myelin oligodendrocyte glycoprotein; MOG-Ab = MOG antibody; NMDAR = NMDA receptor.

record of successful application. The candidate antibody approach involves a priori identification of antigens in the affected CNS tissue that are hypothesized to present a possible target of neuroinflammation. The agnostic antigen discovery approach involves application of patient serum or CSF to either (1) brain sections and/or neuronal cultures or (2) phage-display immunoprecipitation sequencing[12]; if antibody binding is observed, the antigen can then be immunoprecipitated bound to the patient-derived immunoglobulin (Ig) G and the immunoprecipitate will be analyzed to identify specific target antigens.[13]

Seronegative AE

After exclusion of toxic-metabolic derangements and CNS infection, subacute polysymptomatic encephalopathy with neuropsychiatric symptoms, movement disorders, and/or seizures is highly suggestive of immune-mediated encephalitis, particularly in the setting of inflammatory CSF or findings compatible with limbic encephalitis (LE) on MRI. The most common autoantibodies in pediatric AE are MOG and NMDAR; glutamic acid decarboxylase and γ-aminobutyric acid type A (GABA-A) receptor antibodies are uncommon, and other antibodies such as contactin-associated protein-like 2 and leucine-rich glioma inactivated 1 are rare.[14]

Even with strong clinical and paraclinical evidence of immune-mediated encephalitis, many patients with suspected AE are seronegative to all known autoantibodies. In general, seronegative AE can be stratified into definite autoimmune LE and autoantibody-negative but probable AE (ANPRA).[3]

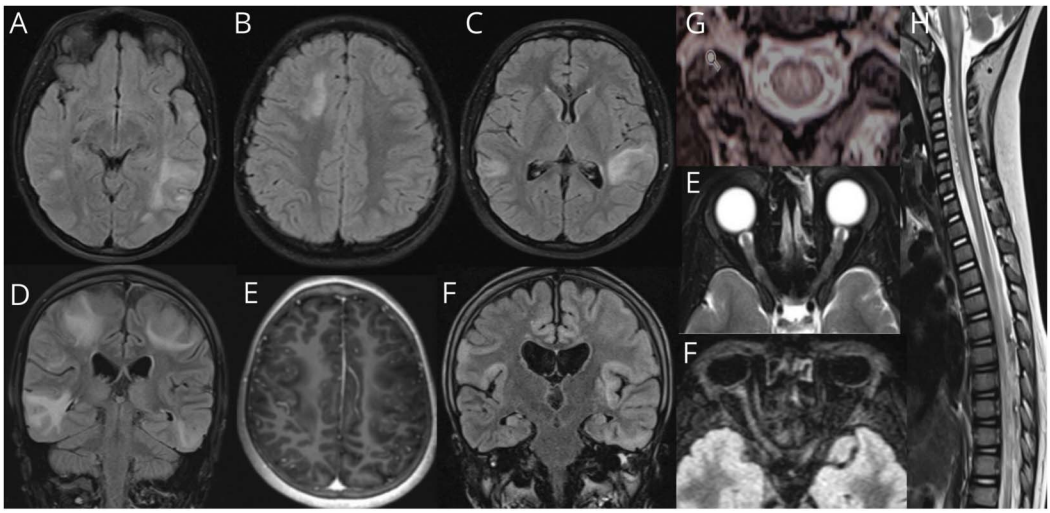
The diagnosis of definite autoimmune LE requires (1) subacute onset of memory deficits, seizures, or psychiatric symptoms referable to the limbic system; (2) bilateral T2 hyperintensities on brain MRI with disproportionate involvement of the mesial temporal lobes; and (3) either CSF pleocytosis or electrographic abnormalities of the temporal lobes. Other causes such as herpes simplex virus (HSV) encephalitis must be excluded. In children, this clinicoradiologic phenotype is nearly always seronegative.[15] Regardless of antibody status, early treatment with steroids and rituximab improves outcomes and reduces risk of postencephalitis temporal lobe epilepsy.[16] Therefore, after excluding CNS infections, immunotherapy should neither be delayed pending antibody results nor withheld in the setting of seronegativity if a patient meets criteria for definite autoimmune LE.

The diagnosis of ANPRA is more challenging.[3] In the absence of LE and any identifiable autoantibodies, the 2016 Graus criteria[3] allow only for the diagnosis of possible or probable seronegative AE. Diagnosis of possible AE requires subacute onset of neurocognitive or psychiatric changes along with at least 1 supporting feature—a focal CNS deficit, seizures, CSF pleocytosis, or radiographic evidence of inflammation. ANPRA diagnosis requires at least 2 supporting paraclinical findings of inflammation—abnormal CSF (pleocytosis, oligoclonal bands, elevated IgG index), MRI consistent with encephalitis, or inflammatory histopathology on brain biopsy. Seronegative AE almost certainly represents a heterogeneous collection of various etiologies. Brain MRI is usually normal while EEG is typically abnormal with slowing and/or epileptiform discharges. Although paraneoplastic antibody testing and body imaging are frequently performed, associated tumors are rare in pediatric populations. In 1 retrospective cohort, patients with ANPRA seem to have similarly severe initial presentations but worse outcomes compared with those with LE or acute disseminated encephalomyelitis (ADEM).[17]

Seronegative Demyelinating Disorders

The differential diagnosis for pediatric demyelinating disorders (ADEM, optic neuritis, transverse myelitis) includes MS, MOGAD, NMOSD, glial fibrillary acidic protein (GFAP) astrocytopathy, CNS vasculitis, neurosarcoidosis, and other systemic rheumatologic disorders with CNS manifestations.[2] In addition, it is important to consider nonimmune-mediated diseases such as neoplasm, infection (e.g., infectious encephalomyelitis or acute flaccid myelitis), vascular injury (e.g., spinal cord infarct secondary to fibrocartilaginous emboli), and genetic/metabolic conditions (e.g., mitochondrial and metabolic disorders), particularly in patients who do not

Figure 1 Imaging Features of Children With Primary and Secondary Inflammation Mimicking MOGAD



(A) Axial FLAIR T2-weighted scan of the brain showing ill-defined lesions evolving in the cortical and subcortical white matter in a child with seronegative ADEM. These have completely resolved in a follow-up scan 2 months later (not shown). (B, C) Axial FLAIR T2-weighted scans demonstrating new lesion at the time of relapse 6 months from onset with encephalopathy and seizures. (D) Coronal FLAIR T2-weighted scan demonstrating confluent hyperintensities bilaterally predominantly in the frontotemporal cortex with associated gadolinium enhancement (E) in a child with Takayasu's arteritis and new-onset encephalopathy. (F) Coronal FLAIR T2-weighted scan demonstrating bilateral cortical lesion in a child with encephalopathy and seizures with a known diagnosis of genetic CNS HLH. (G) Axial gradient-echo T2-weighted scan of the cord showing the central lesion with a H-sign in a child with seronegative myelitis. (E) T2-weighted imaging showing seronegative bilateral optic neuritis. (F) Axial gadolinium-enhanced fat sat T1-weighted scan of the brain showing longitudinal optic nerve involvement. (H) Longitudinal extensive transverse myelitis in a child with a mitochondrial disease. ADEM = acute disseminated encephalomyelitis; FLAIR = fluid-attenuated inversion recovery; HLH = hemophagocytic lymphohistiocytosis; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.

respond to immunotherapy. Figure 1 illustrates key mimics of MOGAD in children.

Among children, approximately 30% of first-time acquired demyelinating syndromes (ADSs) are MOG-Ab positive, less than 5% are AQP4-Ab positive, and up to 25% meet criteria for MS.[2] Pediatric ADS is often seronegative, including approximately 50% of ADEM, 50% of optic neuritis, and up to 80% of transverse myelitis.[18] Particularly in the pediatric population, seronegative non-MS demyelination is typically postinfectious and monophasic, with a low risk of relapse when compared with MS, AQP4-Ab NMOSD, and even MOGAD.[19]

In contrast to monophasic ADS, most relapsing ADS in children is either MS- or antibody-associated. In 1 study of 110 children with relapsing demyelinating disease, 83% of non-MS patients were positive for either MOG or AQP4 antibody.[20] In the rare cases of suspected seronegative relapsing demyelination, further investigation for alternative diagnosis should occur in parallel with empiric treatment, with immunotherapy agents chosen based on the suspected mechanism of inflammation, severity of the disease, and degree of recovery from relapse.

Perhaps, the best described form of relapsing antibody-negative non-MS demyelination is seronegative NMOSD. Unlike AQP4-Ab–positive cases, seronegative NMOSD is likely a heterogeneous group with diverse underlying pathophysiology. Overall, seronegative patients are believed to have a lower relapse risk.[21] Treatment of seronegative NMOSD is addressed later in this review.

Monogenetic Disorders Associated With Neuroinflammation

Recent advancements in genetic testing have enhanced the identification and diagnosis of monogenetic neuroinflammatory disorders. To identify these conditions, previous diagnostic approaches emphasized the importance of "red flag" features such as very early age at onset, preexisting developmental delay, multisystem involvement, supportive family history, and parental consanguinity.[22] Such features remain clinically useful, and targeted single-gene or genetic panel testing may be considered in selected cases. In 1 cohort of 60 patients with features suspicious for genetic neuroinflammatory disease, a 257-gene panel led to a definitive diagnosis in 20% over a 2-year period.[23] More widespread application of whole-exome and genome sequencing has now detected a genetic basis for some neuroinflammatory disorders even in the absence of classic "red flag" features.

In certain cases, a specific genetic diagnosis may lead to targeted treatment and markedly improved outcomes. Examples of this paradigm include the following: (1) type 1 interferonopathies such as Aicardi-Goutières syndrome (AGS) with potential response to Janus kinase (JAK) inhibitors,[23] (2) cryopyrin-

associated periodic syndromes (related to pathogenic *NLRP3* variants) that improve with anti–interleukin-1 (IL-1) agents (e.g., anakinra and canakinumab),[24] (3) *RANBP2*-associated acute necrotizing encephalopathy (ANE) that may respond to early high-dose corticosteroids and tocilizumab,[25,26] (4) deficiency of adenosine deaminase 2 as a cause of recurrent inflammatory strokes that can be prevented with tumor necrosis factor (TNF)–α inhibitors,[27] and (5) *CTLA4* haploinsufficiency with response to abatacept.[28] Some of these treatments are very rarely, if ever, used as empiric treatment in neuroimmunology, highlighting the importance of a precise genetic diagnosis to allow for targeted therapies that would otherwise not be considered.

The evolution of a genetics-forward approach in the field of neuroimmunology is exemplified by hemophagocytic lymphohistiocytosis (HLH). Primary (familial) HLH is caused by sequence variation in one of several genes affecting lymphocyte cytotoxicity and is associated with CNS involvement in approximately 63% of patients.[29] Previously, HLH as a cause of neurologic symptoms was typically only considered in patients with severe, multisystemic inflammation and characteristic laboratory findings such as cytopenia and markedly elevated ferritin. However, CNS involvement can be the initial or sole manifestation of HLH in some patients without any systemic manifestations.[30] Common features of CNS-restricted HLH include seizures, ataxia, multifocal white matter contrast-enhancing T2 hyperintense lesions with a predilection for the cerebellum, and microhemorrhages on susceptibility-weighted imaging.[30,31] These features are nonspecific, and thus, CNS-restricted HLH can mimic numerous conditions including demyelinating disorders, CNS vasculitis, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), and neuroinfectious diseases. In a cohort of 12 adults with CLIPPERS or CLIPPERS-like conditions, one-third had HLH gene mutations,[32] highlighting the importance of genetic testing in patients with a presumptive diagnosis of CLIPPERS, which lacks a diagnostic biomarker. While several treatments can transiently improve symptoms of HLH, hematopoietic stem cell transplantation (HSCT) is the definitive treatment. In an international survey, HSCT was associated with reduced mortality in CNS-restricted HLH (15.7% vs 71.4%).[33] HLH relapses can occur after HSCT, especially in the setting of reduced chimerism, and longitudinal monitoring is warranted.[34] Asymptomatic siblings of clinically affected probands with CNS-restricted HLH have also been diagnosed, leading to pre-emptive HSCT and prevention of neurologic sequelae.[34]

Down syndrome (DS) is another example of a genetically determined increased risk of immune dysregulation and autoimmunity. In this disorder, upregulated interferon signaling is the direct product of the trisomy of chromosome 21, which encodes multiple interferon receptor genes.[35] Patients with DS carry a higher risk of systemic autoimmune diseases such as type I diabetes, Celiac disease, and Hashimoto thyroiditis. Furthermore, emerging evidence suggests that DS regression disorder, a neuropsychiatric condition characterized by acute-to-subacute onset of sleep and behavioral disturbances, psychiatric symptoms, catatonia, and other motor abnormalities, in otherwise healthy individuals with DS may also have roots in interferon-mediated inflammation and respond to immunosuppression.[36]

In still other genetic conditions, the primary gene mutation does not directly affect immune function but instead may drive or trigger immune responsiveness to neuropathology. This has been reported in *SHANK3*-associated Phelan-McDermid syndrome,[37] in which some individuals experience an immunotherapy-responsive neurocognitive regression. Other genetic disorders may generate secondary neuroinflammation as a byproduct of aberrant antigen exposure or immunogenic neoantigen production. As an example, *FADD* gene loss-of-function mutations impair apoptosis and thus chronically expose the immune system to cellular components recognized as damaged or foreign; this has been associated with the development of dramatic FADD-associated neuroinflammation.[33] Another group of disorders—including AGS, Fanconi anemia, SNORD118-associated Labrune syndrome, CTC1-associated Coats plus syndrome, TREX1-associated retinal vasculopathy with cerebral leukoencephalopathy, and systemic manifestations—all disrupt the repair, maintenance, integrity, and/or processing of nucleic acids. The resultant abnormal genetic material, recognized by the immune system as nonself, may trigger the apparent neuroinflammation that can be associated with these conditions. As such, there may be a role for immunotherapy in certain cases. Notably, there is evidence for JAK inhibitors to treat AGS, an interferonopathy caused by genetic defects in host nucleic acid degradation that drive an interferon-mediated inflammatory response to the accumulated DNA and/or RNA.[23] A recently identified disorder of potentially similar pathophysiology is Fanconi anemia neuroinflammatory syndrome (FANS). Fanconi anemia is a genetic disorder associated with faulty DNA repair, and FANS is a progressive disorder characterized by severe chronic and recurrent brain inflammation associated with evidence of microvasculopathy, calcifications, multifocal contrast-enhancing T2 hyperintense lesions on MRI, and necrotic tumefactive lesions.[38] As FANS tends to arise several years after bone marrow transplant (BMT) among patients with Fanconi anemia with high chimerism and good graft health, it is likely that the neuroinflammation is not due to primary immune dysregulation because the hematopoietic immune system is derived from the unaffected donor. Instead, the pathogenesis is likely related to an immune response to the abnormal nucleic acids in tissues, such as the brain and endothelium, which were not "cured" by BMT.

Finally, associated neuroinflammatory pathology has also been reported in some mitochondrial disorders. These conditions, although not classically considered "autoimmune," can mimic primary neuroinflammatory diseases and may be partially responsive to immunotherapy.[39] Although the mechanisms are complex, malfunctioning mitochondria may

either contribute to a proinflammatory milieu or interfere with anti-inflammatory tissue maintenance.

Diagnostic Approach for Suspected Neuroimmune Disorders in Children

All children with suspected neuroimmune conditions should be investigated with neuroimaging, lumbar puncture, and relevant autoantibodies. An EEG can evaluate for electrographic evidence of encephalopathy and cortical irritability in cases of suspected AE with or without seizures. Investigations to exclude infection should include CSF gram stain, culture, and PCR tests, which are often available as panels of typical microbes known to cause encephalitis/meningitis. As indicated by the index of suspicion, further infectious studies such as pathogen-specific testing or unbiased metagenomic next-generation sequencing may be considered. Other diagnostic workup for atypical neuroimmune disorders may include a paraneoplastic screen (i.e., if the phenotype suggests OMS or anti-NMDAR encephalitis), systemic rheumatologic workup, genetic testing, and brain biopsy. Table 2 summarizes diagnostic workup and potential treatment implications of positive results.

Neuroimaging

Conventional MRI of the brain, spinal cord, and orbit with contrast is essential in nearly all cases of suspected neuroinflammation,[40] particularly because of the common occurrence of asymptomatic or subclinical lesions among young children. Although MRI changes are included as paraclinical evidence of inflammation in the Graus[3] and Cellucci[41] criteria, imaging results are normal in approximately half of the children with anti-NMDAR encephalitis and in 37% of those with autoimmune encephalopathy, regardless of antibody status. In fact, in cases of AE, a normal brain MRI in a child with severe polysymptomatic encephalopathy can help support the diagnosis and rule out other conditions such as CNS infections and neurometabolic disorders.

Repeat intra-attack imaging, particularly in the absence of a clear diagnosis, may reveal new lesions (radiologic lag[42,43]), now a well-recognized feature in MOGAD, with 25% of patients with encephalitis[44] and 10% with myelopathy[45] presenting with initially normal MRI. The presence or absence of gadolinium enhancement can indicate active lesions but may also persist because of chronic damage to the blood-brain barrier.[46]

Emerging neuroimaging techniques may enhance our ability to monitor disease activity and assess treatment responses.[47] Longitudinal assessments of brain volume, which correlate with cognitive testing in adults with MS, hold potential for interpreting pediatric neurocognitive evaluations.[48] Volumetric scans can reveal widespread axonal injury, neuronal loss, and specific cortical and deep gray matter atrophy.[49] Advanced imaging can reflect underlying pathologic changes in both myelin and axons in demyelinating diseases, as well as structural connectivity and neurotransmitter dynamics in AE. It is important to note that implementing these advanced imaging methods in clinical practice is challenging, with interpretation complicated by factors such as neuroplasticity, remyelination, and aging. Because children are often very ill during the acute stage, many of these techniques can only be performed during follow-up and results may vary based on the timing of the scans or medication (including anesthetics). While these modalities are currently used primarily in research settings, their validation in specific neuroimmune conditions may lead to broader application, including in seronegative patients.

CSF and Serum Biomarkers

Emerging fluid biomarkers of cellular injury in neuroimmune disorders include GFAP, a marker of astrocyte activation and damage, as well as neurofilament light chain (NfL), tau, and ubiquitin carboxy-terminal hydrolase, markers of neuronal injury. Current data support both NfL and GFAP as biomarkers in MS; NfL correlates with inflammatory disease activity while GFAP correlates with neurodegeneration and disability.[50] Although these biomarkers could plausibly be used to monitor disease activity and treatment response in non-MS neuroimmune disorders as well, they are nonspecific and their utility in clinical practice is not yet well established. Fluid biomarkers may also generate clues regarding diagnosis and pathophysiology. For example, consistent with the astrocytopathy underlying AQP4 disease, AQP4-Ab NMOSD cases exhibit higher serum GFAP levels than seronegative NMOSD.[21]

CSF neopterin is the product of cytokine-induced macrophage activation and a biomarker of innate immune system inflammation. It is nonspecific, elevated in both infectious and inflammatory conditions, including some metabolic/genetic diseases with secondary inflammation.[23] Situations in which neopterin can be helpful include distinguishing between seronegative AE and primary psychiatric disease or between neuroinflammatory and noninflammatory causes of encephalopathy. Furthermore, in the right clinical context, significantly elevated neopterin can indicate an interferonopathy.

Cytokine analysis offers further potential to discriminate between disease entities, delineate underlying disease mechanisms, identify therapeutic targets (such as tocilizumab for IL-6 elevations and anakinra for IL-1 elevations), and predict disease course. For example, compared with other patients with refractory status epilepticus, those with cryptogenic new-onset refractory status epilepticus (NORSE) demonstrated more significant innate immune activation with elevations of CXCL8, CCL2, and MIP-1α; higher levels of these proinflammatory cytokines predicted worse outcomes.[51]

The Role of Brain Biopsy

Among children with severe atypical neuroinflammation, a brain biopsy may be considered. The primary goal is often to

Table 2 Recommended Neurodiagnostic and Laboratory Studies

	Indications	Implications
Electrophysiologic studies (first-line)		
EEG	Concern for AE, seizures, status epilepticus, some cases of encephalopathy	• Contributes to diagnostic criteria for AE even if seizure is not identified
Electrophysiologic studies (second-line)		
Nerve conduction/EMG	Concern for central and peripheral demyelination, Isaac/Morvan syndrome	• Identifies peripheral nervous system involvement that may require treatment and/or provide diagnostic clues
Neuroimaging (first-line)		
MRI brain, spine and orbits w/wo contrast	All cases	• Identification of symptomatic or asymptomatic cord and brain lesions, particularly when prominent symptoms (i.e., encephalopathy) may limit localizing power of the neurologic examination • Coronal postgadolinium T1 fat-saturated MRI has very high sensitivity to detect acute pretreated optic neuritis
Neuroimaging (second-line)		
MR spectroscopy	Differential includes tumor, metabolic/mitochondrial disease, or leukodystrophy	• May provide diagnostic insights for atypical lesions or individuals with multisystem disease
MR angiograph	Concern for vasculitis	• Abnormal in medium and large vessel vasculitis, but typically normal in small vessel vasculitis
Vessel wall imaging	Concern for vasculitis	• Suboptimal sensitivity and specificity but may indicate vessel wall inflammation and support a diagnosis of vasculitis
Serum studies (first-line)		
Basic laboratory results: CBC with diff, complete metabolic panel	All cases	
Nonspecific inflammatory markers: CRP, ESR	All cases	
OCBs by IEF ***Collect paired serum and CSF samples**	All cases	See CSF studies further
Autoimmune encephalopathy/encephalitis panel (including NMDAR antibody)	Suspected AE, presence of new-onset seizures with encephalopathy	• Seropositivity defines AE type, informs treatment, predicts course and outcome
MOG-Ab	Demyelinating disease (including ON, TM, ADEM), encephalitis/meningoencephalitis, aseptic meningitis	• Diagnosis and management for MOGAD
AQP4 antibody	Demyelinating disease, particularly if suspicious for NMOSD	• Diagnosis and management for AQP4 NMOSD
Serum studies (second-line, when clinically indicated)		
GFAP antibody	Atypical demyelinating disease	• Diagnosis and management for GFAP antibody-associated astrocytopathy
Neurofascin/paranoidal antibodies	Concern for combined central and peripheral demyelination	• Diagnosis and management of neurofascin antibody–associated CCPD
Infectious mimic rule-out: consider HIV, syphilis, tuberculosis, EBV, *Bartonella*, coxsackie, enterovirus, mycoplasma, arboviruses (including WNV), endemic dimorphic fungi	Fever or systemic signs of infection; concerning exposure history; rhombencephalitis, meningoencephalitis, atypical ADEM, or other demyelination; enterovirus studies for possible AFM; parasite testing if eosinophilia	• Pathogen-directed antimicrobial management • Avoiding unnecessary immunotherapy, although infection-associated inflammation may still respond to steroids
Systemic rheumatologic laboratory results: ANA, C3, C4, antiphospholipid antibodies, dsDNA, smith, RNP, SSA, SSB, ANCA, Celiac antibodies	Rheumatologic screen (ANA) indicated in most cases; additional testing if systemic symptoms, positive ANA, concern for vasculitis	• Diagnosis and management of underlying rheumatologic disease with consideration of cyclophosphamide for CNS involvement

Continued

Table 2 Recommended Neurodiagnostic and Laboratory Studies *(continued)*

	Indications	Implications
HLH studies: ferritin, fibrinogen, triglycerides, soluble IL2 receptor, CXCL9, IL-18, NK cell function/CD107a assay, perforin/granzyme B, XIAP protein, SAP protein	Concern for CNS HLH with or without systemic symptoms; MRI with T2 hyperintensities and numerous avidly enhancing lesions and microhemorrhages (may not be present early)	• Management of underlying provoking infection/malignancy for secondary HLH • Consideration of bone marrow transplant for primary HLH • Steroids, if used before testing, may normalize results so important to obtain before immunotherapy when possible
Cytokines (including IL-1 and IL-6)	Peri-infectious and atypical presentations	• Elevations in proinflammatory cytokines may provide insights into underlying pathophysiology and possible therapeutic targets (e.g., tocilizumab for elevated IL-6)
CSF studies (first-line)		
Routine studies: cell count with differential, protein, glucose	All cases	• Basic studies provide diagnostic insight and may prompt additional studies (i.e., expanded infectious workup for high cell count)
IgG index and OCBs	All cases	• CSF-restricted OCBs or elevated IgG index supports but does not confirm neuroinflammation and may further indicate possible lymphocyte/B-cell involvement • May suggest possible role for B-cell depletion therapy
Autoimmune encephalopathy/encephalitis panel (including NMDAR antibody)	Suspected AE, presence of new-onset seizures with encephalopathy	• Seropositivity defines AE type, informs treatment, predicts course and outcome
Infectious studies: meningitis/encephalitis PCR panel, culture, case-specific pathogen testing, unbiased mNGS	Case-specific; culture and PCR panel for common CNS pathogens indicated in many cases; HSV and VZV PCR critical for LE	• Pathogen-directed antimicrobial management • Avoiding unnecessary immunotherapy, although infection-associated inflammation may still respond to steroids
CSF studies (second-line)		
Cytokines (including IL-1 and IL-6)	Peri-infectious and atypical presentations	• Elevations in proinflammatory cytokines may provide insights into underlying pathophysiology and possible therapeutic targets (e.g., tocilizumab for elevated IL-6)
MOG-Ab	High suspicion for MOGAD (particularly if serum MOG is negative)	• Poor sensitivity and specificity, difficult to interpret at this time; isolated CSF MOG-Ab is rare in MOGAD but has been described in adults and may indicate more severe disease
AQP4 antibody	Demyelinating disease, particularly if suspicious for NMOSD	• AQP4 antibody assays are more sensitive in the serum, but identification in the CSF can support a diagnosis of AQP4+ NMO
GFAP antibody	Atypical demyelinating disease	• Diagnosis and management for GFAP antibody-associated astrocytopathy
Neopterin	Nearly all cases where neuroinflammatory disease is presumed	• Indicates macrophage/monocyte activation, innate immune system activation • Provides evidence of inflammatory or infectious process as opposed to a noninflammatory neurologic, genetic, or psychiatric process • Often very high with infection and interferonopathies
Lymphocyte subsets	Atypical cases in which immunotherapy choice is unclear	• Increased T or B cells may provide insights into underlying pathophysiology and possible therapeutic targets (e.g., B-cell depletion therapy in the case of increased B cells)
Other diagnostic workup		
Genetic studies: whole-exome or whole-genome, mitochondrial sequencing, gene panels—leukodystrophy, autoinflammatory, immunodeficiency, etc	Atypical or very young–onset neuroinflammation, symmetric findings on MRI, progressive clinical and/or radiographic disease, case-specific genes (e.g., RANBP2 for ANE), and HLA (e.g., HLAB27 for Bechet)	• Diagnosis and management of underlying genetic disease • Avoids invasive procedures, such as biopsy

Continued

Table 2 Recommended Neurodiagnostic and Laboratory Studies *(continued)*

	Indications	Implications
Ophthalmologic examination, evaluation for retinal disease, fluorescein angiography, OCT, VEP	Optic neuropathy, neuroretinitis, vasculitis, demyelinating disease	• Provides diagnostic clues • Should be considered in cases of ADEM when unable to definitively exclude optic neuritis by history and examination
Body imaging: chest x-ray, MRI or CT chest/abdomen/pelvis, MR, or C	Chest x-ray for sarcoidosis; paraneoplastic screen for AE or OMAS with MRI or CT; MR or CT angio to evaluate for extra-CNS vasculitis; PET if concern for sarcoidosis or cancer	• Provides diagnostic clues (e.g., hilar lymphadenopathy in sarcoidosis) and identifies possible systemic involvement • Identifies possible biopsy targets outside the CNS to avoid brain biopsy in cases with non-CNS involvement
Brain biopsy	Rules out neoplasm/histiocytic disease or focal CNS infection; definitive diagnosis of sarcoidosis, granulomatous disease, small vessel vasculitis	• Rules in or out particular diagnoses • Provides mechanistic insights into the underlying disease process that may have treatment implications (e.g., consider TNF-α inhibitors if noninfectious granulomas are detected, or immunotherapeutic agents with T-cell activity if tissue shows significant T-cell predominant infiltrate)
Neurocognitive assessments[a] **• Attention: Digit Span, TMT, SDMT** **• Executive: BRIEF, CASE** **• Global: CASE, NPI-Q** **• Memory: BRIEF, CMS, CVLT-C, RCFT**	Deficits on certain neurocognitive tests may aid in localization of lesion(s) and/or confirm degree of disability that may be subtle on neurologic examination	• Typically, neurocognitive assessments will lack a baseline and must be interpreted with caution in the context of clinical examination and neurodiagnostic data • Assessments at or near presentation may allow for a cognitive biomarker of improvement after treatment initiation • Larger, more comprehensive, neurocognitive batteries are beneficial for longitudinal follow-up and should be guided by the multidisciplinary team that includes a neuropsychologist when possible

Abbreviations: ADEM = acute disseminated encephalomyelitis; ANE = acute necrotizing encephalopathy; AQP4 = aquaporin 4; BRIEF = Behavior Rating Inventory of Executive Function; CASE = Clinical Assessment Scale for Autoimmune Encephalitis; CMS = Children's Memory Scale; CVLT-C = California Verbal Learning Test for Children; GFAP = glial fibrillary acidic protein; HLH = hemophagocytic lymphohistiocytosis; HSV = herpes simplex virus; mNGS = metagenomic next-generation sequencing; MOG-Ab = myelin oligodendrocyte glycoprotein antibody; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; NMDAR = NMDA receptor; OCB = oligoclonal band; OCT = optical coherence tomography; ON = optic neuritis; RCFT = Rey Complex Figure Test; SDMT = Symbol Digit Modality Test; TM = transverse myelitis; TMT = Trail Making Test; TNF = tumor necrosis factor; VEP = visual evoked potential.
[a] List provided is not inclusive of all cognitive tests that could potentially be used.

exclude alternative diagnoses such as CNS infection or malignancy.[52] Histopathology may also characterize inflammation to guide immunotherapy or even confirm a suspected diagnosis, such as CNS vasculitis or neurosarcoidosis. Both conditions are rare in the pediatric populations but are difficult to diagnose conclusively without tissue. It is important to note that in a retrospective review of 21 children who underwent brain biopsy for suspected CNS vasculitis, two-thirds were found to have alternative diagnoses (e.g., MOGAD, anti–GABA-A receptor encephalitis, CNS-HLH, and AGS) that could have been identified without biopsy. This study supports careful and extensive diagnostic approaches before embarking on an invasive procedure such as brain biopsy.[53]

The Role of Genetic Testing

When the clinician is faced with a patient with severe, unexplained neuroinflammation, and particularly in cases refractory to conventional immunotherapies, genetic testing should be performed. In such patients, the use of rapid whole-exome or genome sequencing can identify monogenetic conditions in as many as 20% of patients, obviating the need for invasive and often nondiagnostic brain biopsies.[53] In addition to diagnosing genetic neuroinflammatory disorders that may be amenable to targeted effective treatments, whole-genome and exome sequencing may also identify monogenetic noninflammatory disorders that mimic neuroinflammation clinically or radiographically (e.g., *ATP1A3* mutations). In such patients, unnecessary and potentially harmful immunotherapies can be avoided.[54]

Treatment Approach for Atypical or Seronegative Neuroimmune Disorders in Children

The decision to initiate empiric treatment for potential neuroinflammation can be relatively straightforward when the phenotype is strongly suggestive of a specific diagnosis, such as anti-NMDAR encephalitis.[55] In cases of atypical neuroinflammation, however, clinicians must balance the risk of disease progression and disability accrual against both treatment-associated risks and diagnostic overshadowing.

Although exclusion of infections should be part of the diagnostic process of any child with neuroinflammation, infectious workup beyond a negative CSF enterovirus PCR, HSV PCR, and gram stain should not delay first-line

immunotherapy for suspected infectious vs inflammatory CNS disease in immunocompetent children among whom there is a low suspicion for fungal or mycobacterial infection. As such, immunotherapy should be initiated while awaiting diagnostic results in most circumstances. Acute first-line immunotherapy for most neuroimmune disorders consists of steroids, IVIgs, and plasma exchange, alone or in combination.

Selection of second-line treatment may depend on the clinicoradiologic phenotype and/or the suspected underlying pathophysiologic mechanism of neuroinflammation. For example, in children with seronegative AE or NMOSD, rituximab should be a primary consideration.[16] In children with acute atypical CNS demyelination, suspected ANE, or life-threatening inflammatory malignant cerebral edema, expeditious treatment with tocilizumab may be indicated.[56] For histopathology consistent with granulomatous disease, a TNF-α inhibitor may be effective.[57]

Paraclinical data supporting predominately innate vs adaptive immune system–mediated neuroinflammation can further inform treatment decisions. When dysregulation of the innate immune system is suspected, CSF cytokine measurements can guide targeted therapy with anti–IL-6 monoclonal antibodies (such as tocilizumab) or IL-1 monoclonal antibodies (such as anakinra) and can support use of JAK inhibitors when multiple CSF cytokines are elevated. JAK inhibitors may also be indicated in suspected interferonopathies,[23] including those with elevated CSF neopterin and IL-2. Regarding treatments targeting the adaptive immune system, rituximab is a reasonable option for undefined neuroimmune disorders with evidence of lymphocyte involvement, particularly those in which CSF studies reveal restricted oligoclonal bands, elevated IgG index, or high B-cell number. Cyclophosphamide may be considered for severe non-MS demyelinating diseases and other severe adaptive immune-mediated neuroinflammatory conditions, especially when CSF studies or brain biopsy indicate T-cell involvement. In such cases, one may also consider mycophenolate mofetil, another broad-spectrum agent with a more favorable side-effect profile, but the 3-month delay to peak efficacy often limits its use in the acute and subacute setting.

Treatment of a Child With Presumed Seronegative AE

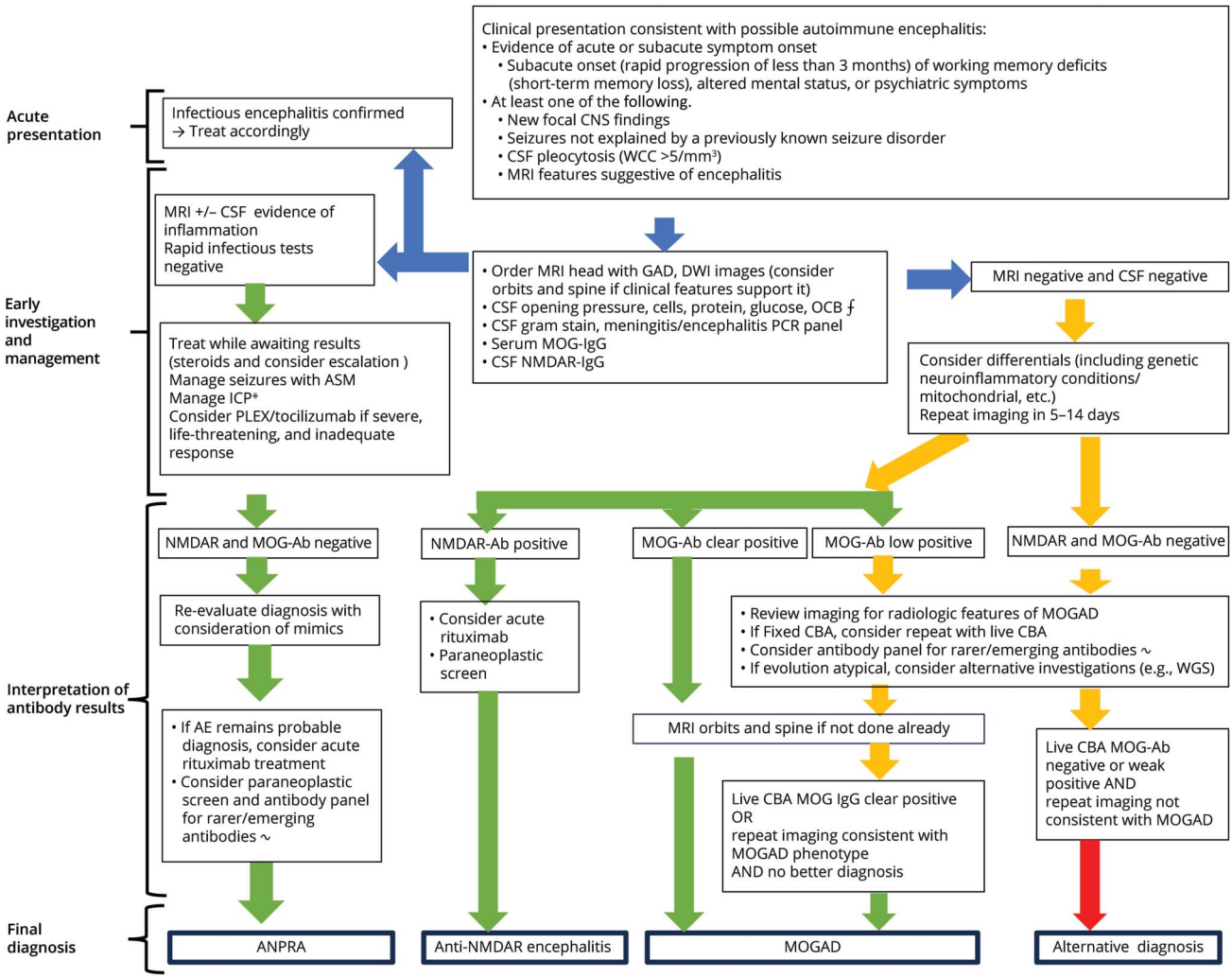
With emerging data supporting the importance of early treatment for AE, the clinician is under greater pressure to initiate acute treatment in parallel with pending diagnostic investigations. We propose a diagnostic algorithm (Figure 2), applicable to any episode of suspected encephalitis in children. Acute treatment of seronegative AE that meets diagnostic criteria and/or has evidence of CNS inflammation is similar to that of seropositive AE, first-line treatment and strong consideration of early rituximab,[16] which should be prioritized in all but mild cases of AE. Rituximab improves outcomes in anti-NMDAR encephalitis, particularly when administered early in the course, and was found to be effective in adult patients with LE irrespective of antibody status.[16] Beyond rituximab, third-line and fourth-line treatment considerations in cases of severe and refractory AE include anti–IL-6 agents and cyclophosphamide. Most seronegative AE is monophasic, and therefore, maintenance treatment is rarely indicated. A key challenge when managing these children is to distinguish between ongoing inflammation requiring escalation and residual symptoms, for example, in the psychiatric or neurocognitive domains. Evaluating for evidence of inflammation on MRI and abnormal background on the EEG (not believed to be secondary to seizures) can be a useful marker. Intrathecal oligoclonal bands can persist outside the acute event and should not be used in isolation as a marker of relapse.

When approaching AE treatment, it is important to consider that the differential includes noninflammatory diagnoses such as primary psychiatric disorders, epileptic encephalopathies, and genetic/metabolic diseases. Therefore, while expeditious treatment of suspected AE with first-line treatments is warranted, it is equally critical to avoid unnecessary risks of additional immunosuppressive treatments without convincing evidence of neuroinflammation after extensive diagnostic testing. Fortunately, most pending tests will have resulted by the time that a clinician must initiate second-line and third-line immunotherapy for AE. In addition, it is also important to avoid escalating immunotherapy for sequelae of previous AE without evidence of active disease. In the absence of relapsed or refractory inflammation, postencephalitis epilepsy and neurocognitive impairment are typically sequelae of previous injury and, therefore, not indications for further immunosuppression. For example, patients with LE may develop postencephalitis epilepsy, likely related to insults to the temporal lobe. Such epilepsy should be treated with antiseizure medications and consideration of epilepsy surgery as opposed to immunotherapy.

Treatment of Children With Presumed Seronegative Demyelination

Acute treatment of most forms of inflammatory demyelination involves steroids and consideration of plasma exchange. However, of note, seronegative NMOSD may be less steroid-responsive than AQP4-Ab NMOSD. In contrast to AQP4-Ab NMOSD, which requires lifelong immunosuppression, seronegative disease may not. Highly effective treatment options for AQP4-Ab NMOSD include B-cell depletion (e.g., rituximab and inebilizumab), terminal complement inhibition (e.g., eculizumab and ravulizumab), and IL-6 inhibition (e.g., satralizumab).[58] There are no Food and Drug Administration (FDA)–approved treatments for pediatric AQP4-Ab NMOSD currently, although rituximab is a common immunotherapy choice. Because anti-CD20 therapies such as rituximab are highly effective in reducing relapse in both AQP4-Ab NMOSD and MS, it is also a reasonable choice for maintenance treatment in seronegative pediatric NMOSD as well, particularly if there is a suspicion for sub-detection threshold AQP4 antibody present. Unfortunately, the N-Momentum trial demonstrating efficacy of inebilizumab-

Figure 2 Diagnostic Algorithm for a Child Presenting With Suspected Encephalitis



*Consideration should be given to raised ICP, particularly with a rapid deterioration. Neurosurgery should be involved for possible decompressive craniectomy or external ventricular drainage if indicated. ƒFor autoimmune encephalitis, rituximab can be used along with first-line immunotherapy, typically without the need for ongoing maintenance dosing outside the acute period. For severe presentations in the ICU, early PLEX should be considered (risk-benefit should be considered particularly in centers with less experience in younger patients and in patients with severe encephalopathy and agitation, which may only tolerate PLEX in the ICU setting). Plasma exchange is most often used in cases of severe or life-threatening dysautonomia, refractory seizures, or severe refractory encephalitis. IL-6 receptor blockade (tocilizumab) may also be beneficial, and evidence of elevated IL-6 in the CSF may identify patients in whom this may be more effective. ∿Further investigations may be considered but remain within the scope of research. These include CSF MOG IgG testing and wider autoantibody testing. CBA = cell-based assay; ICU = intensive care unit; ICP = intracranial pressure; Ig = immunoglobulin; IL = interleukin; MOG-Ab = myelin oligodendrocyte glycoprotein antibody; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; PLEX = plasma exchange.

induced B-cell depletion in AQP4-Ab NMOSD was not powered sufficiently to detect a statistically significant benefit to seronegative patients.[59] Similarly, of the other clinical trials investigating treatments now FDA-approved for adult AQP4-Ab NMOSD, only the SAkuraSky trial of satralizumab included any substantial number of seronegative patients; this trial found that relapse rates of AQP4-Ab–negative patients with NMOSD may have decreased on satralizumab, but the effect was far greater among AQP4-Ab–positive patients.[60]

Evaluating Treatment Response

The assessment of clinical response to immunotherapy can be difficult. First, the natural history of many neuroinflammatory disorders features episodic relapse followed by some degree of recovery, which may be conflated with immunotherapy response, particularly as relapse often prompts escalation of treatment. Second, considering both placebo effect and regression to the mean, clinicians should avoid equating post-immunotherapy clinical improvement with definitive proof of underlying neuroinflammation, particularly when improvement is subjective. Objective improvement of abnormal findings on neurologic examination, MRI, and/or EEG can increase confidence in immunotherapy response. Although neuropsychological testing and various bedside evaluations (modified Rankin Scale, Expanded Disability Status Scale, Montreal Cognitive Assessment, Clinical Assessment Scale in Autoimmune Encephalitis) can be used to monitor clinical status and assess outcomes, brain development in childhood

can present additional challenges when interpreting outcomes in the pediatric population. Because a child's neurocognitive baseline is not static but instead advances over time, it is exceedingly difficult to quantify lost neurocognitive potential. Projections of a specific child's expected developmental trajectory from a previous baseline are imprecise and unreliable, and comparison with peers is limited by considerable neurocognitive heterogeneity between age-matched children. Similar limitations affect the application of MRI-based brain volumetry in assessing outcomes of pediatric patients. Furthermore, certain biological biomarkers, including NfL, change over the course of normal childhood, thus confounding potential trends associated with disease activity and/or treatment response. Standardized care paradigms with consistent definitions of "adequate" and "insufficient" therapeutic responses are the first step to advance clinical care, especially when clinical trials are challenged by disease rarity. Development of rigorous outcome metrics is essential to better appreciate and manage long-term morbidity. Pathobiological insights will continue to be gained both within specific neuroimmune conditions and across conditions that share core mechanisms, including the interplay between genetics, infectious exposures, and host immune balance. Ultimately, the clinician must weigh the risks of any therapeutic intervention against the available biomarkers, clinical scenario, and literature because each clinical scenario will be unique.

Conclusion and Future Direction

Children with neuroimmune conditions often present acutely ill with highly inflammatory disease. Yet, permanent disability can be mitigated by immunotherapy and the pediatric brain's remarkable capacity for neuroplasticity and repair. In this review, we focused on children with atypical neuroinflammatory conditions. In these cases, clinicians should consider a broad differential, seek pathophysiologic insights with extensive diagnostic studies, and be sure to revisit the presumed diagnosis in the cases of unexpected clinical trajectories or poor immunotherapy response. We provided a table to summarize key investigations and their utility in clinical practice, as well as an algorithm for managing atypical suspected neuroinflammation in the context of an acute/subacute encephalopathy. Although acute first-line treatment of suspected immune-mediated encephalitis is similar for most presentations, second-line treatments differ by suspected pathophysiology and phenotype. Overall, with a paucity of data to support specific immunotherapies for seronegative neuroimmune disorders, insights into case-specific pathophysiology will drive management decisions.

Author Contributions

L. Saucier: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. T. Rossor: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M.P. Gorman: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J.D. Santoro: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. Y. Hacohen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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