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# FEATURES OF DIFFERENTIAL DIAGNOSIS OF ENCEPHALITIS, ENCEPHALOMYELITIS, AND DISSEMINATED ENCEPHALOMYELITIS IN CHILDREN: CONTEMPORARY CLINICAL, NEUROIMAGING, AND NEUROIMMUNOLOGICAL APPROACHES

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**Abstract**

**Background.** Encephalitis, encephalomyelitis, and acute disseminated encephalomyelitis represent a heterogeneous spectrum of inflammatory neurological disorders in children. Their clinical manifestations frequently overlap, creating substantial diagnostic challenges, particularly during the early stages of disease. The emergence of autoimmune encephalitis syndromes, myelin oligodendrocyte glycoprotein antibody-associated disease, and improved molecular diagnostic techniques has fundamentally transformed pediatric neuroinflammatory diagnostics.

**Materials and Methods.** A narrative analytical review of peer-reviewed publications, international diagnostic criteria, observational studies, and consensus recommendations was conducted. Particular attention was paid to clinical phenotyping, magnetic resonance imaging, electroencephalography, cerebrospinal fluid molecular testing, neuronal autoantibodies, and myelin oligodendrocyte glycoprotein antibodies.

**Results.** Major distinguishing characteristics of infectious, antibody-mediated, and demyelinating inflammatory disorders were systematically evaluated. An original conceptual framework, PED-NEURODIFF, was developed to organize diagnostic decisions through sequential assessment of inflammatory encephalopathy, spinal cord involvement, neuroimaging patterns, etiological biomarkers, and longitudinal disease evolution.

**Conclusion.** Accurate differentiation of pediatric encephalitis and encephalomyelitis requires an integrated diagnostic approach rather than reliance on individual clinical or laboratory findings. Combining clinical assessment, neuroimaging, electroencephalography, molecular microbiology, and targeted autoantibody testing may facilitate earlier etiological classification, appropriate treatment selection, and long-term neurological surveillance.

**Keywords:** pediatric encephalitis, encephalomyelitis, acute disseminated encephalomyelitis, autoimmune encephalitis, MOG antibody-associated disease, differential diagnosis, magnetic resonance imaging, cerebrospinal fluid, neuroinflammation, demyelination.

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# ОСОБЕННОСТИ ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ ЭНЦЕФАЛИТА, ЭНЦЕФАЛОМИЕЛИТА И ДИССЕМИНИРОВАННОГО ЭНЦЕФАЛОМИЕЛИТА У ДЕТЕЙ: СОВРЕМЕННЫЕ КЛИНИЧЕСКИЕ, НЕЙРОВИЗУАЛИЗАЦИОННЫЕ И НЕЙРОИММУНОЛОГИЧЕСКИЕ ПОДХОДЫ

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**Аннотация**

**Актуальность.** Энцефалит, энцефаломиелит и острый диссеминированный энцефаломиелит представляют собой гетерогенную группу воспалительных заболеваний центральной нервной системы у детей. Сходство клинических проявлений, включая энцефалопатию, судорожные приступы, очаговый неврологический дефицит и изменения магнитно-резонансной томографии, существенно затрудняет раннюю дифференциальную диагностику. Выявление новых аутоиммунных синдромов, MOG-ассоциированного заболевания и совершенствование молекулярно-генетических методов исследования расширили возможности установления этиологии нейровоспалительных процессов.

**Материалы и методы.** Выполнен аналитический обзор научных публикаций, международных диагностических критериев, клинических исследований и консенсусных рекомендаций. Изучены особенности неврологической симптоматики, магнитно-резонансной томографии, электроэнцефалографии, исследования цереброспинальной жидкости, молекулярной диагностики инфекций и определения специфических аутоантител.

**Результаты.** Систематизированы ключевые дифференциально-диагностические характеристики воспалительных и демиелинизирующих заболеваний головного и спинного мозга. Разработана авторская концептуальная модель PED-NEURODIFF, объединяющая оценку энцефалопатии, поражения спинного мозга, нейровизуализационных паттернов, иммунологических биомаркеров и динамики заболевания.

**Заключение.** Дифференциальная диагностика нейровоспалительных заболеваний у детей должна основываться на комплексной интерпретации клинических, нейрофизиологических, нейровизуализационных и лабораторных данных. Предложенная модель может использоваться как организационная основа диагностического процесса и требует последующей клинической валидации.

**Ключевые слова:** энцефалит, энцефаломиелит, острый диссеминированный энцефаломиелит, детская неврология, аутоиммунный энцефалит, MOG-ассоциированное заболевание, дифференциальная диагностика, нейровизуализация, цереброспинальная жидкость.

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## BOLALARDA ENSEFALIT, ENSEFALOMIYELIT VA DISSEMINATSIYALANGAN ENSEFALOMIYELITNING DIFFERENSIAL DIAGNOSTIKASI XUSUSIYATLARI: ZAMONAVIY KLINIK, NEYROVIZUALIZATSION VA NEYROIMMUNOLOGIK YONDASHUVLAR

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**Annotatsiya**

**Dolzarbligi.** Ensefalit, ensefalomiyelit va o‘tkir disseminatsiyalangan ensefalomiyelit bolalarda markaziy asab tizimining turli etiologiyaga ega yallig‘lanish kasalliklari hisoblanadi. Ushbu kasalliklarda ensefalopatiya, tutqanoq xurujlari, o‘choqli nevrologik nuqson va magnit-rezonans tomografiyadagi o‘zgarishlarning o‘xshashligi erta differensial diagnostikani murakkablashtiradi. Autoimmun ensefalit, miyelinning oligodendrotsitar glikoproteiniga qarshi antitanachalar bilan bog‘liq kasallik va molekulyar diagnostika usullarining rivojlanishi neyroyallig‘lanish jarayonlari etiologiyasini aniqlash imkoniyatlarini kengaytirdi.

**Materiallar va usullar.** Ilmiy maqolalar, xalqaro diagnostik mezonlar, klinik tadqiqotlar va konsensus tavsiyalari tahlil qilindi. Nevrologik simptomlar, magnit-rezonans tomografiya,

elektroensefalografiya, orqa miya suyuqligi tahlili, infeksiyalarning molekulyar diagnostikasi va maxsus autoantitanachalarni aniqlash usullari o‘rganildi.

**Natijalar.** Bosh miya va orqa miyaning yallig‘lanish hamda demiyelinizatsion kasalliklariga xos muhim differensial-diagnostik belgilar tizimlashtirildi. Ensefalopatiya, orqa miya zararlanishi, neyrovizualizatsion belgilar, immunologik biomarkerlar va kasallikning vaqt davomida kechishini birlashtiruvchi PED-NEURODIFF mualliflik konseptual modeli taklif etildi.

**Xulosa.** Bolalarda neyroyallig‘lanish kasalliklarining differensial diagnostikasi klinik, neyrofiziologik, neyrovizualizatsion va laborator ma’lumotlarni kompleks baholashga asoslanishi kerak. Taklif etilgan model diagnostik jarayonni tizimlashtirishda yordam berishi mumkin, biroq klinik validatsiyani talab qiladi.

**Kalit so‘zlar:** ensefalit, ensefalomiyelit, o‘tkir disseminatsiyalangan ensefalomiyelit, bolalar nevrologiyasi, autoimmun ensefalit, MOG-assotsiatsiyalangan kasallik, differensial diagnostika, neyrovizualizatsiya, orqa miya suyuqligi.

**Introduction.** Inflammatory diseases of the central nervous system constitute an important group of neurological disorders in childhood because of their potential to cause acute cerebral dysfunction, progressive neurological deterioration, epilepsy, motor disability, cognitive impairment, and long-term neuropsychological consequences. Among these conditions, encephalitis, encephalomyelitis, and acute disseminated encephalomyelitis (ADEM) are particularly challenging to differentiate because they may share similar clinical presentations, cerebrospinal fluid abnormalities, and magnetic resonance imaging findings. Nevertheless, the underlying pathophysiological mechanisms, disease trajectories, and therapeutic approaches may differ substantially [1, 2, 3]. The term *encephalitis* denotes inflammation of the brain parenchyma and encompasses infectious, autoimmune, and other inflammatory etiologies. International Encephalitis Consortium criteria emphasize altered mental status lasting at least 24 hours without an alternative explanation as the principal clinical criterion, supported by additional features such as fever, seizures, focal neurological abnormalities, cerebrospinal fluid pleocytosis, electroencephalographic changes, or neuroimaging evidence of inflammation [1]. Importantly, encephalitis should be distinguished from encephalopathy, which describes cerebral dysfunction without necessarily establishing an inflammatory mechanism. Metabolic disturbances, toxic exposures, systemic infection, hypoxic injury, and mitochondrial disorders may produce severe encephalopathy without primary brain inflammation. Failure to recognize this distinction can result in inappropriate etiological classification and delayed treatment of the underlying disorder [2, 4].

The epidemiology of encephalitis is characterized by substantial heterogeneity. Population-based investigations have demonstrated that infectious and autoimmune etiologies contribute to the overall disease burden, while a considerable proportion of patients remain without a confirmed causative diagnosis despite extensive testing. Granerod and colleagues identified diverse infectious and immune-mediated causes in a prospective multicenter study, whereas the California Encephalitis Project highlighted the limitations of conventional diagnostic methods and the frequency of unresolved cases [3, 4]. Molecular diagnostic technologies have improved the detection of neurotropic pathogens, particularly herpes simplex virus, enteroviruses, and other infectious agents. Updated laboratory guidance emphasizes that molecular testing should be selected according to clinical presentation, exposure history, specimen type, and disease timing. Metagenomic next-generation sequencing offers additional diagnostic opportunities for selected unexplained cases, although it does not replace targeted molecular assays or careful clinical interpretation [5, 6]. In parallel with developments in infectious disease diagnostics, the identification of antibodies against neuronal surface proteins has transformed the conceptual framework of autoimmune encephalitis. Graus and colleagues proposed a syndrome-based approach that permits early recognition of probable autoimmune encephalitis before the availability of confirmatory antibody results [7]. Pediatric autoimmune encephalitis has additional diagnostic characteristics. Behavioral changes, developmental regression, abnormal movements, sleep disturbances, speech dysfunction, and seizures may predominate over classical memory impairment or psychiatric symptoms. Cellucci and colleagues therefore proposed pediatric-specific diagnostic

pathways incorporating developmental considerations, neurological examination, brain imaging, electroencephalography, and cerebrospinal fluid analysis [8].

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis represents one of the most extensively characterized antibody-mediated syndromes. The disease may present with behavioral disturbances, movement disorders, seizures, dysautonomia, language regression, and fluctuating consciousness. Dalmau and colleagues established its relationship with antibodies targeting neuronal NMDARs, while subsequent investigations demonstrated the clinical relevance of early recognition and appropriate immunotherapy [9, 10]. International pediatric recommendations further emphasize that autoimmune encephalitis requires timely recognition, exclusion of important mimics, and coordinated management by pediatric neurologists, infectious disease specialists, neuroimmunologists, and intensive care clinicians [11]. A particularly important diagnostic phenomenon is autoimmune encephalitis developing after herpes simplex encephalitis. Armangue and colleagues demonstrated that patients recovering from confirmed herpes simplex encephalitis may subsequently develop neurological deterioration associated with neuronal autoantibodies. Such deterioration may be misinterpreted as persistent viral replication or treatment failure unless the possibility of a secondary autoimmune process is considered [12].

The term *encephalomyelitis* refers to inflammatory involvement of both the brain and spinal cord. It is primarily an anatomical and clinical description rather than a single etiological diagnosis. Encephalomyelitis may result from direct infection, postinfectious inflammation, antibody-mediated demyelination, systemic autoimmune disease, or other neuroinflammatory mechanisms. Consequently, the presence of spinal cord involvement modifies the diagnostic investigation but does not independently determine whether the process is infectious or autoimmune.

ADEM is a specific clinical syndrome within the broader spectrum of acquired inflammatory demyelinating disorders. The International Pediatric Multiple Sclerosis Study Group diagnostic framework emphasizes a first polyfocal inflammatory demyelinating event accompanied by encephalopathy that cannot be explained by fever or another systemic illness. Magnetic resonance imaging typically demonstrates multifocal, frequently bilateral, poorly demarcated lesions involving cerebral white matter, sometimes accompanied by deep gray matter or spinal cord abnormalities [13, 14]. Pohl and colleagues described ADEM as predominantly a disorder of childhood, commonly presenting after an infectious illness and usually following a monophasic course. Nevertheless, its diagnosis remains challenging because of overlap with pediatric multiple sclerosis, neuromyelitis optica spectrum disorder, autoimmune encephalitis, and other inflammatory conditions [15]. The discovery of antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) has fundamentally changed the interpretation of pediatric demyelinating syndromes. International diagnostic criteria published in 2023 established MOG antibody-associated disease (MOGAD) as a distinct immune-mediated disorder that may present with ADEM, optic neuritis, transverse myelitis, cortical encephalitis, or brainstem involvement [16].

Prospective pediatric investigations have shown that MOG-IgG status provides important diagnostic and prognostic information in children presenting with acquired demyelinating syndromes. However, positive antibody testing must be interpreted in conjunction with the clinical phenotype, assay methodology, and antibody level because low-positive results may have limited specificity [17]. Recent studies further emphasize that MOGAD-like encephalitic presentations can occur even without detectable MOG-IgG. Olivé-Cirera and colleagues demonstrated overlapping clinical and neuroimaging characteristics among antibody-positive and antibody-negative pediatric encephalitic syndromes, indicating that clinical phenotyping cannot be replaced by isolated serological testing [18]. An updated pediatric neuroradiological review published in October 2026 emphasized the importance of comprehensive MRI assessment of the brain, optic pathways, and spinal cord in distinguishing MOGAD, ADEM, multiple sclerosis, and related neuroinflammatory conditions [19].

The differential diagnosis also includes aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4-NMOSD), for which international diagnostic criteria emphasize characteristic clinical syndromes and disease-specific antibody testing. Moreover, multiple sclerosis diagnostic criteria have evolved substantially, with the 2024 McDonald revisions incorporating

additional anatomical and biomarker evidence. Nevertheless, diagnostic caution remains essential in children presenting with an ADEM-like first attack [20, 21, 22]. Inflammatory disorders involving the spinal cord require additional differentiation from acute flaccid myelitis, which predominantly affects spinal cord gray matter and may be associated with enterovirus infection. Surveillance investigations and subsequent reviews have established characteristic patterns of acute flaccid weakness, anterior horn involvement, and respiratory complications [23, 24, 25]. Other inflammatory syndromes, including glial fibrillary acidic protein (GFAP) astrocytopathy, may produce overlapping encephalitic and myelitic manifestations. Recognition of these disorders has expanded the diagnostic spectrum of inflammatory central nervous system diseases and increased the importance of carefully selected antibody investigations [26]. Current approaches therefore require integration of clinical phenomenology, neuroanatomical localization, magnetic resonance imaging, electroencephalography, cerebrospinal fluid investigation, microbiological testing, and targeted neuroimmunological assays.

**Materials and methods.** This study was designed as a narrative analytical review with subsequent development of a conceptual diagnostic decision-making framework for pediatric inflammatory disorders of the central nervous system. The literature analysis focused on international consensus statements, clinical diagnostic criteria, observational cohort studies, systematic reviews, and peer-reviewed articles published primarily between 2007 and 2026. Earlier foundational studies were included when essential for understanding the evolution of diagnostic definitions or disease classification. Particular attention was given to consensus criteria developed by the International Encephalitis Consortium, International Pediatric Multiple Sclerosis Study Group, International MOGAD Panel, and international working groups studying autoimmune encephalitis and neuromyelitis optica spectrum disorder.

Diagnostic findings were organized into clinical, neuroanatomical, radiological, cerebrospinal fluid, electroencephalographic, microbiological, immunological, and longitudinal domains. Clinical characteristics were assessed with emphasis on altered mental status, seizures, behavioral abnormalities, multifocal neurological deficits, optic pathway dysfunction, spinal cord syndromes, and movement disorders. Neuroimaging findings were evaluated according to lesion distribution, anatomical localization, signal characteristics, contrast enhancement, diffusion abnormalities, and temporal evolution. Laboratory investigations were considered according to their potential to establish infection, support central nervous system inflammation, identify disease-associated antibodies, or exclude alternative metabolic and systemic disorders. An original conceptual framework designated PED-NEURODIFF (Pediatric Neuroinflammatory Differential Diagnosis Framework) was developed through qualitative integration of the reviewed diagnostic principles. The framework was designed to support sequential clinical reasoning rather than to provide a numerical diagnostic score. Its main purpose is to organize differential diagnosis, guide appropriate investigations, and reduce the risk of premature etiological classification. No patient-level clinical dataset was analyzed. No original cohort, diagnostic accuracy estimates, sensitivity calculations, statistical comparisons, or independent meta-analysis were conducted. The manuscript therefore presents a structured narrative synthesis and a conceptual diagnostic model rather than results from a prospective or retrospective clinical investigation.

**Results**

**Clinical differentiation of encephalitis, encephalomyelitis, and ADEM.** The analytical synthesis identified several important distinctions between the major diagnostic categories. Infectious encephalitis is characterized by direct or infection-associated inflammation of the brain, often accompanied by fever, headache, altered consciousness, seizures, and focal neurological abnormalities. However, fever is neither universally present nor specific for an infectious etiology. Autoimmune encephalitis may demonstrate similar abnormalities but frequently includes prominent behavioral disturbances, movement disorders, language regression, sleep dysfunction, or autonomic instability. These features are particularly relevant in younger children, whose developmental stage may prevent reliable assessment of memory impairment and psychiatric symptoms. Encephalomyelitis is defined by simultaneous or sequential involvement of cerebral and spinal cord structures. Clinically, it may present with encephalopathy accompanied by weakness, sensory

deficits, sphincter dysfunction, or signs of a spinal cord lesion. The condition requires further etiological classification. ADEM is generally associated with acute encephalopathy and multifocal neurological deficits, frequently occurring after a recent infection. The presence of widespread demyelinating lesions supports the diagnosis, but the initial episode must be differentiated from MOGAD, pediatric multiple sclerosis, and other inflammatory syndromes. The clinical syndrome should therefore be established before assigning an etiological diagnosis.

**Table 1. Differential clinical characteristics of major pediatric neuroinflammatory syndromes**

| Clinical feature | Infectious encephalitis | Autoimmune encephalitis | Encephalomyelitis | ADEM |
|---|---|---|---|---|
| Principal process | Infectious or infection-associated brain inflammation | Immune-mediated cerebral inflammation | Combined brain and spinal cord inflammation | Acute inflammatory demyelination |
| Typical onset | Acute or subacute | Acute or subacute | Acute or subacute | Usually acute or subacute |
| Fever | Common in several etiologies | Possible, particularly at onset | Variable | May precede onset |
| Encephalopathy | Frequent and diagnostically important | Frequent but phenotype-dependent | Variable | Required by classical pediatric criteria |
| Seizures | Common in several forms | Common in selected syndromes | Possible | Possible |
| Behavioral changes | Possible | Often prominent | Possible | May accompany encephalopathy |
| Spinal cord dysfunction | Not obligatory | Possible in selected disorders | Defining anatomical component | May be present |
| Multifocal demyelination | Not obligatory | Not typical of all forms | Depends on etiology | Characteristic |
| Disease-specific testing | Pathogen-directed investigations | Neuronal antibody testing | Etiology-dependent | MOG-IgG and alternative disease exclusion |
| Longitudinal course | Depends on pathogen | Monophasic or relapsing | Depends on cause | Classically monophasic, requiring follow-up |

**Magnetic resonance imaging as a differential diagnostic instrument.** Magnetic resonance imaging represents a central component of pediatric neuroinflammatory diagnosis because lesion topography may provide important evidence regarding the underlying pathological process. In herpes simplex encephalitis, inflammatory abnormalities often involve temporal and insular cortical structures. Diffusion restriction, cortical edema, and occasionally hemorrhagic changes may occur. However, lesion distribution varies with age and disease stage, and atypical presentations are possible. Autoimmune encephalitis may involve mesial temporal structures, cortical regions, basal ganglia, or other cerebral areas. Importantly, a normal brain MRI does not exclude autoimmune encephalitis, particularly anti-NMDAR encephalitis. ADEM typically demonstrates large, bilateral, asymmetrical, poorly marginated hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery sequences. Lesions may involve subcortical and deep white matter, thalami, basal ganglia, brainstem, cerebellum, and spinal cord. MOGAD can demonstrate

ADEM-like lesions, cortical abnormalities, optic neuritis, and longitudinally extensive spinal cord inflammation. Cortical encephalitis associated with MOG-IgG may present with seizures and prominent cortical fluid-attenuated inversion recovery hyperintensity. Pediatric multiple sclerosis more typically produces well-defined periventricular, juxtacortical, infratentorial, and spinal cord lesions, although overlap with other inflammatory disorders must be considered. AQP4-NMOSD may involve long segments of the spinal cord, optic pathways, brainstem, and periependymal regions. In contrast, acute flaccid myelitis frequently demonstrates abnormalities predominantly affecting spinal cord gray matter.

**Table 2. Comparative MRI features in the differential diagnosis of pediatric neuroinflammation**

| Disorder | Predominant anatomical distribution | Typical MRI characteristics | Important diagnostic consideration |
|---|---|---|---|
| Herpes simplex encephalitis | Temporal, insular and other cortical regions | T2/FLAIR abnormalities, diffusion restriction, possible hemorrhage | Normal early imaging does not exclude infection |
| Anti-NMDAR encephalitis | Variable; MRI may be normal | Normal findings or nonspecific inflammatory abnormalities | Normal MRI does not exclude disease |
| ADEM | Bilateral white matter, deep gray nuclei, brainstem or cord | Large, poorly demarcated T2/FLAIR lesions | Clinical encephalopathy remains essential |
| MOGAD | White matter, cortex, optic nerves and spinal cord | ADEM-like lesions, cortical inflammation, longitudinally extensive myelitis | Requires appropriate antibody interpretation |
| Multiple sclerosis | Periventricular, juxtacortical, infratentorial and spinal regions | More sharply defined demyelinating lesions | Apply age-appropriate criteria and exclude mimics |
| AQP4-NMOSD | Optic nerves, spinal cord, brainstem, periependymal regions | Longitudinally extensive myelitis and other characteristic patterns | Serum AQP4-IgG is diagnostically important |
| Acute flaccid myelitis | Spinal cord gray matter | Longitudinal central cord abnormalities, often anterior horn predominant | Consider enterovirus-associated disease |
| GFAP astrocytopathy | Brain, meninges and sometimes spinal cord | Variable inflammatory changes; possible radial enhancement | CSF GFAP-IgG may support diagnosis |

**Cerebrospinal fluid analysis.** Cerebrospinal fluid investigation provides essential information regarding inflammatory activity and may identify specific infectious or autoimmune etiologies. In infectious encephalitis, cerebrospinal fluid may demonstrate pleocytosis, increased protein concentration, or other inflammatory changes. However, the absence of marked pleocytosis does not exclude infection, especially early in the disease course or in selected populations. Polymerase chain reaction testing for herpes simplex virus is particularly important because delayed diagnosis can result in severe neurological injury. An initially negative result does not definitively exclude herpes simplex encephalitis when clinical suspicion remains high. Enterovirus molecular testing may establish an infectious cause, although detection from respiratory or gastrointestinal specimens must be distinguished from direct evidence of central nervous system infection. Autoimmune encephalitis may be accompanied by lymphocytic pleocytosis, intrathecal immunoglobulin synthesis, or oligoclonal bands. Nevertheless, normal routine cerebrospinal fluid

findings do not exclude all forms of autoimmune encephalitis. For suspected anti-NMDAR encephalitis, cerebrospinal fluid antibody testing is particularly important, since interpretation of serum-only results may be less reliable. In ADEM, mild inflammatory cerebrospinal fluid abnormalities may occur, but no routine cerebrospinal fluid finding is sufficiently specific to confirm the syndrome independently. Serum MOG-IgG testing using a validated cell-based assay is essential when MOGAD is suspected. Low-positive results require particular caution, and antibody detection should be considered in the context of a compatible clinical demyelinating phenotype. Likewise, AQP4-IgG testing is important when the phenotype suggests neuromyelitis optica spectrum disorder.

**Table 3. Diagnostic contribution of cerebrospinal fluid and serological investigations**

| Investigation | Principal diagnostic purpose | Interpretation and limitations |
|---|---|---|
| CSF cell count and differential | Establish inflammatory activity | Pleocytosis is nonspecific; normal findings do not exclude all causes |
| CSF protein and glucose | Characterize inflammatory or infectious processes | Must be interpreted with age and systemic parameters |
| HSV-1/2 PCR | Identify herpes simplex CNS infection | Repeat if initial testing is negative and suspicion remains high |
| Enterovirus PCR | Identify enteroviral CNS infection | Extra-CSF positivity may not prove direct CNS infection |
| CSF bacterial studies | Exclude bacterial meningitis or meningoencephalitis | Urgent when compatible with clinical presentation |
| CSF NMDAR-IgG | Support anti-NMDAR encephalitis diagnosis | Clinical phenotype and antibody specificity remain essential |
| Serum MOG-IgG | Identify MOGAD in compatible acquired demyelinating syndromes | Use validated cell-based assays; interpret low-positive results cautiously |
| Serum AQP4-IgG | Support diagnosis of AQP4-NMOSD | Requires a compatible clinical and imaging phenotype |
| CSF oligoclonal bands | Evaluate intrathecal immunoglobulin synthesis | Supportive but not specific for multiple sclerosis |
| CSF GFAP-IgG | Assess suspected autoimmune GFAP astrocytopathy | Interpret in clinical and radiological context |
| Metagenomic sequencing | Investigate selected unexplained infections | Resource-dependent; not a substitute for targeted urgent testing |

**Development of the PED-NEURODIFF diagnostic framework.** The reviewed evidence supports a structured clinical approach in which immediate neurological assessment is followed by neuroanatomical localization, exclusion of treatable infections, targeted neuroimmunological investigations, and longitudinal reassessment. The proposed PED-NEURODIFF framework begins with determination of whether the child has a true encephalitic syndrome or an alternative form of encephalopathy. The subsequent stage involves recognition of associated neurological manifestations, including seizures, optic neuritis, myelopathy, movement disorders, and peripheral or lower motor neuron weakness. When encephalitic manifestations dominate, infectious and autoimmune causes are investigated in parallel according to clinical risk. When multifocal neurological deficits are accompanied by widespread demyelinating MRI abnormalities, ADEM and MOGAD become particularly relevant diagnostic considerations. The identification of spinal cord involvement requires differentiation between inflammatory white matter myelitis, anterior horn gray matter injury, and other structural or metabolic abnormalities. Finally, follow-up clinical and imaging assessment helps distinguish monophasic inflammatory disorders from relapsing demyelinating diseases.

**Table 4. Original PED-NEURODIFF diagnostic decision framework**

| Diagnostic domain | Key clinical question | Principal investigation | Decision-making significance |
|---|---|---|---|
| P - Presentation | Is there encephalitis, encephalopathy, or isolated myelopathy? | Neurological examination, systemic assessment | Establishes the initial syndrome |
| E - Etiology | Could the presentation represent treatable infection? | CSF studies, pathogen-directed molecular testing | Guides urgent antimicrobial investigation |
| D - Distribution | Which cerebral and spinal structures are affected? | Brain and spinal MRI | Identifies the anatomical pattern |
| N - Neurophysiology | Are seizures or diffuse cerebral dysfunction present? | EEG and continuous monitoring when indicated | Detects electrographic seizures and encephalopathy |
| I - Immunology | Is an antibody-associated disorder suspected? | Targeted neuronal, MOG-IgG and AQP4-IgG testing | Supports immune-mediated classification |
| R - Reassessment | Do the findings evolve as expected? | Repeat clinical and imaging assessment | Identifies diagnostic inconsistencies |
| O - Other diagnoses | Are metabolic, genetic, vascular, toxic or neoplastic causes possible? | Targeted investigations | Reduces diagnostic anchoring |
| D - Disease course | Is the event monophasic or relapsing? | Longitudinal clinical and MRI follow-up | Supports final classification |
| I - Integration | Are the findings mutually consistent? | Multidisciplinary review | Prevents reliance on isolated results |
| F - Functional outcome | What neurological deficits require follow-up? | Developmental and functional assessment | Guides surveillance and rehabilitation |

**Evaluation of diagnostic concordance.** The analytical review identified diagnostic concordance as a key principle of disease classification. An isolated abnormal antibody result is insufficient when the clinical and radiological phenotype is incompatible with the proposed disease. Conversely, negative antibody testing does not exclude all immune-mediated neurological conditions. Similarly, the presence of fever or cerebrospinal fluid pleocytosis cannot independently distinguish infection from postinfectious or autoimmune inflammation. The most reliable diagnostic classification therefore emerges when clinical presentation, neuroimaging distribution, laboratory findings, and disease evolution support the same pathophysiological interpretation.

**Table 5. Proposed indicators for future clinical validation of PED-NEURODIFF**

| Endpoint | Proposed assessment | Research significance |
|---|---|---|
| Etiological diagnostic agreement | Final multidisciplinary diagnosis | Evaluates overall classification accuracy |
| Time to etiological diagnosis | Interval from presentation to diagnosis | Measures diagnostic efficiency |
| Sensitivity for infectious encephalitis | Comparison with accepted reference diagnosis | Evaluates safety of infection recognition |
| Specificity for ADEM and MOGAD | Consensus-based reference classification | Assesses differential diagnostic performance |

| | | |
|---|---|---|
| Time to appropriate treatment | Interval to syndrome-specific management | Evaluates clinical pathway efficiency |
| Frequency of diagnostic reclassification | Follow-up clinical and MRI reassessment | Identifies early diagnostic uncertainty |
| Neurological outcome | Functional and neurological scales | Assesses clinical relevance |
| Neurocognitive outcome | Age-appropriate developmental testing | Measures long-term consequences |

**Discussion.** The differential diagnosis of encephalitis, encephalomyelitis, and ADEM in children remains challenging because the clinical presentation frequently reflects the anatomical distribution of inflammation rather than its underlying cause. The diagnostic definitions proposed by the International Encephalitis Consortium provide an important framework for recognizing encephalitis, but they do not independently establish infectious or autoimmune etiology. This distinction is particularly important in children with systemic infection, metabolic disturbances, prolonged seizures, or medication-related encephalopathy [1, 2]. Population-based studies have consistently demonstrated that a substantial proportion of encephalitis cases remain etiologically unresolved. Granerod and colleagues highlighted the heterogeneity of infectious and autoimmune etiologies, while Glaser and colleagues emphasized the limitations of broad but non-targeted diagnostic testing [3, 4]. Modern molecular microbiology has improved etiological identification, but the diagnostic interpretation of a positive result requires attention to specimen characteristics and the patient's clinical presentation. The 2024 IDSA–ASM laboratory guidance recommends targeted molecular testing and recognizes the possibility of false-negative results, particularly when sampling occurs early in the disease course [5]. Metagenomic next-generation sequencing represents an important additional diagnostic strategy. Wilson and colleagues demonstrated its value in selected patients with meningitis and encephalitis, although the sensitivity of the method varies with pathogen abundance, specimen quality, and bioinformatic analysis. Furthermore, incidental microbial detection does not necessarily establish disease causation [6].

A major advance in the field has been the recognition of autoimmune encephalitis as a distinct group of treatable neurological disorders. Graus and colleagues proposed clinical criteria that prioritize syndrome recognition and permit early diagnostic consideration before confirmatory antibody testing becomes available [7]. However, diagnostic criteria developed for adults require adaptation to pediatric developmental characteristics. Cellucci and colleagues emphasized that behavioral changes, developmental regression, reduced speech, abnormal movements, and seizures may be more informative than classical psychiatric manifestations in young children [8]. Anti-NMDAR encephalitis illustrates these challenges. Dalmau and colleagues demonstrated the association between neuronal antibodies and characteristic neurological manifestations. Later studies confirmed the importance of comprehensive clinical assessment and longitudinal evaluation [9].

Titulaer and colleagues showed that clinical outcomes may improve with appropriate treatment, but functional recovery can extend over a prolonged period. Consequently, early diagnostic uncertainty should not be confused with irreversible neurological injury [10]. International pediatric recommendations by Nosadini and colleagues support timely recognition of anti-NMDAR encephalitis and emphasize coordinated specialist management. Nevertheless, the decision to initiate immunotherapy must be considered alongside urgent evaluation and treatment of potentially serious infectious mimics [11]. An important example of overlapping disease mechanisms is autoimmune encephalitis following herpes simplex encephalitis. Armangue and colleagues demonstrated that neurological relapse after virologically established herpes simplex encephalitis may arise from a secondary autoimmune process. The differential diagnosis in such cases requires renewed clinical examination, electroencephalography, neuroimaging, and appropriately timed cerebrospinal fluid testing [12].

The distinction between ADEM and other pediatric demyelinating disorders also has important consequences for diagnostic classification. The International Pediatric Multiple Sclerosis Study Group criteria define ADEM through a combination of encephalopathy and polyfocal

inflammatory demyelination, rather than MRI abnormalities alone [13]. Tenembaum and colleagues emphasized the typically postinfectious and monophasic clinical presentation of ADEM. However, they also noted that the differential diagnosis encompasses multiple sclerosis and other inflammatory disorders, necessitating continued observation after the acute episode [14].

Pohl and colleagues reinforced the importance of clinical encephalopathy and characteristic imaging patterns while recognizing that recurrent neurological events may require diagnostic reconsideration [15]. The introduction of MOGAD diagnostic criteria has fundamentally changed the interpretation of ADEM-like presentations. Banwell and colleagues established that serum MOG-IgG detected by validated cell-based assays, together with a compatible clinical syndrome and exclusion of alternative diagnoses, forms the basis of MOGAD classification [16].

Hennes and colleagues demonstrated the prognostic relevance of MOG antibodies in pediatric acquired demyelinating syndromes. Their findings support the importance of evaluating antibody status while acknowledging that long-term disease behavior remains heterogeneous [17]. The recent study by Olivé-Cirera and colleagues is particularly relevant because it describes pediatric MOGAD-like encephalitic phenotypes among children without detectable MOG antibodies. These observations indicate that imaging patterns, although clinically informative, cannot independently establish antibody-defined disease [18]. Aw-Zoretic's 2026 review similarly emphasized the need to integrate neuroimaging with age, clinical phenotype, optic nerve involvement, spinal cord abnormalities, and antibody testing. The increasing recognition of cortical encephalitis and gray matter predominant presentations expands the differential diagnosis beyond classical white matter demyelination [19].

AQP4-NMOSD represents another important consideration. Wingerchuk and colleagues established international diagnostic criteria emphasizing core clinical characteristics and serum AQP4-IgG testing. In pediatric patients, severe optic neuritis, longitudinally extensive myelitis, and characteristic brainstem syndromes should prompt careful evaluation for this disorder [20]. Multiple sclerosis must be considered particularly in adolescents with recurrent neurological events and characteristic demyelinating lesions. The revised McDonald criteria published by Montalban and colleagues in 2025 incorporate additional anatomical locations and selected biomarkers. However, their application requires appropriate exclusion of alternative inflammatory diseases, especially MOGAD and AQP4-NMOSD [21]. The earlier McDonald framework described by Thompson and colleagues remains important for understanding diagnostic evolution and the interpretation of dissemination in space and time. In children with an ADEM-like initial event, longitudinal clinical and imaging information is especially valuable in preventing premature classification as multiple sclerosis [22]. Spinal cord involvement may further complicate differential diagnosis. Sejvar and colleagues characterized acute flaccid myelitis as a syndrome associated with acute limb weakness and lesions predominantly involving spinal cord gray matter [23]. Messacar and colleagues demonstrated epidemiological and biological evidence linking enterovirus D68 with acute flaccid myelitis. This association highlights the importance of respiratory and stool investigations in selected patients, particularly because cerebrospinal fluid testing may fail to identify the implicated virus [24]. Murphy and colleagues further emphasized that acute flaccid myelitis differs from classical inflammatory demyelinating myelitis in its clinical distribution and neuroanatomical characteristics. Severe asymmetrical flaccid weakness, reduced reflexes, and anterior horn involvement may provide important diagnostic clues [25].

Autoimmune GFAP astrocytopathy expands the spectrum of potential causes of encephalomyelitis. Shan and colleagues described variable presentations involving the brain, meninges, and spinal cord, sometimes accompanied by characteristic radial perivascular enhancement. However, this radiological finding is not universally present and cannot independently establish the diagnosis [26]. Best-practice recommendations by Abboud and colleagues underscore the importance of comprehensive diagnostic assessment before attributing encephalitic manifestations to a single immune mechanism. Normal MRI findings, nonspecific cerebrospinal fluid changes, and negative antibody testing do not exclude every form of autoimmune encephalitis [27].

A contemporary review by Ferenc and colleagues further highlights the complexity of ADEM pathogenesis, including molecular mimicry, blood–brain barrier dysfunction, neuroinflammation, and immune-mediated demyelination. These mechanisms may explain why clinical symptoms overlap with both infectious and autoimmune encephalitic syndromes [28]. The recognition of cortical MOG-associated encephalitis is another important development. Budhram and colleagues described the syndrome associated with cortical FLAIR hyperintensity and seizures, often referred to as FLAMES. This entity may resemble infectious encephalitis at presentation, particularly when headache, fever, and seizures coexist [29]. Infectious etiologies remain important even when neuroimaging suggests an inflammatory demyelinating process. Fowlkes and colleagues described enterovirus-associated encephalitis, demonstrating that enteroviruses can produce significant cerebral dysfunction and should not be considered exclusively causes of aseptic meningitis [30].

Ambrose and colleagues emphasized that a carefully structured diagnostic strategy can improve etiological investigation in encephalitis. Their findings support the use of symptom-directed investigations and appropriate specimen selection rather than indiscriminate testing [31]. Ellul and Solomon further stressed the need for rapid clinical assessment and appropriate early investigation when encephalitis is suspected. In particular, concern for herpes simplex encephalitis warrants urgent antiviral treatment rather than waiting for confirmatory cerebrospinal fluid results [32]. Reindl and Waters highlighted the importance of interpreting MOG antibodies within a compatible clinical syndrome. They also emphasized that advances in cell-based assays have improved disease specificity but have not eliminated the possibility of misleading results in patients with a low pretest probability [33]. The California Encephalitis Project, described by Glaser and colleagues, demonstrated that extensive infectious testing may still fail to identify a causative pathogen. Consequently, the absence of an established infectious etiology should prompt diagnostic reconsideration without automatically establishing autoimmune disease [34]. Taken together, these investigations support a central principle: anatomical distribution, inflammatory biomarkers, and etiological testing provide complementary rather than interchangeable forms of diagnostic evidence. The proposed PED-NEURODIFF framework was designed around this principle. It aims to prevent premature attribution of a pediatric neuroinflammatory syndrome to infection, autoimmunity, or demyelination on the basis of a single abnormal finding.

Its first advantage is the separation of the clinical syndrome from etiological diagnosis. This distinction is fundamental because encephalopathy, encephalitis, and encephalomyelitis describe different levels of clinical and anatomical interpretation. A second advantage is recognition of the dynamic character of neuroinflammatory disorders. Early imaging findings may be absent or nonspecific, antibody results may become available only after several days, and additional clinical attacks may change the eventual classification. A third advantage is explicit consideration of diagnostic mimics. Metabolic encephalopathies, genetic disorders, acute vascular lesions, central nervous system tumors, systemic inflammatory diseases, toxic conditions, and postictal abnormalities may resemble inflammatory disorders. Nevertheless, the proposed model has limitations. It was developed through qualitative synthesis of published evidence and has not undergone prospective evaluation. Its diagnostic sensitivity, specificity, reproducibility, and influence on clinical outcomes therefore remain unknown.

Further research should evaluate PED-NEURODIFF in prospective multicenter pediatric cohorts. Patients could be categorized according to the initial clinical presentation, followed by standardized investigations and longitudinal reassessment. The primary endpoint could be agreement between the early framework-guided classification and a final multidisciplinary reference diagnosis established after follow-up. Secondary endpoints may include time to etiological diagnosis, frequency of diagnostic reclassification, time to appropriate treatment, neurological disability, cognitive outcomes, and healthcare resource utilization. Methodological safeguards should include blinded adjudication of the final diagnosis, standardized imaging review, laboratory quality control, and adjustment for the availability of advanced antibody and molecular testing. Particular attention should be paid to distinguishing diagnostic accuracy from therapeutic effectiveness. A framework that organizes investigations cannot be considered a proven method of

improving neurological outcomes until that benefit has been demonstrated in appropriately designed clinical research. The future of pediatric neuroinflammatory diagnostics will likely involve further integration of quantitative neuroimaging, advanced molecular microbiology, standardized antibody assays, and longitudinal clinical phenotyping. Machine-learning approaches may provide additional assistance, but their clinical application will require transparent validation, appropriate calibration, and careful evaluation of diagnostic errors.

**Conclusion.** The differential diagnosis of encephalitis, encephalomyelitis, and acute disseminated encephalomyelitis in children represents a complex clinical problem because these conditions share neurological manifestations, inflammatory characteristics, and overlapping neuroimaging findings. Infectious encephalitis requires timely recognition of potentially treatable pathogens, whereas autoimmune encephalitis demands careful assessment of characteristic clinical syndromes and appropriate neuronal antibody testing. ADEM is primarily a clinical and radiological syndrome characterized by encephalopathy and multifocal inflammatory demyelination. The recognition of MOGAD has substantially changed its diagnostic interpretation and requires careful integration of serological, clinical, and radiological findings. The term encephalomyelitis describes combined brain and spinal cord inflammation and does not independently specify an infectious, autoimmune, or demyelinating etiology. Magnetic resonance imaging, electroencephalography, cerebrospinal fluid studies, pathogen-directed molecular testing, and neuroimmunological investigations constitute complementary diagnostic methods. Longitudinal neurological and neuroimaging follow-up remains essential because the initial clinical presentation may evolve into a more specific diagnosis. The proposed PED-NEURODIFF conceptual framework integrates clinical phenotyping, neuroanatomical localization, etiological testing, and reassessment into a structured diagnostic approach. Future prospective validation is necessary to determine whether this framework improves diagnostic accuracy, reduces delays in appropriate treatment, and supports better long-term neurological outcomes in children with inflammatory central nervous system disorders.

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