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Understanding Pediatric Multiple Sclerosis: Clinical Presentation, Diagnostic Criteria, Therapeutic Advances, and Supportive Care Approaches

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Abstract

Pediatric multiple sclerosis (MS) is a chronic, immune-mediated demyelinating disorder of the central nervous system (CNS) that accounts for approximately 2–5% of all MS cases. Increasing recognition, improved imaging, and updated diagnostic criteria have facilitated earlier diagnosis. Pediatric MS differs from adult-onset disease in clinical presentation, relapse frequency, and neurodevelopmental impact. Children often present with multifocal neurological deficits and more frequent relapses but demonstrate superior recovery due to enhanced neuroplasticity. Timely diagnosis and initiation of disease-modifying therapies (DMTs) are critical to prevent irreversible neurological injury and cognitive decline. Recent advances, including high-efficacy B-cell-targeted therapies, Bruton's tyrosine kinase (BTK) inhibitors, and remyelination strategies, are transforming treatment paradigms. This review summarizes current understanding of pediatric MS, including epidemiology, pathophysiology, clinical features, diagnosis, differential diagnosis, therapeutic options, supportive care, and future directions.

Keywords: Pediatric Multiple Sclerosis; Demyelination; Neuroimmunology; Disease-modifying Therapy; B-cell Therapy; Remyelination; Cognitive Rehabilitation

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by inflammation, demyelination, and axonal injury in the CNS. While primarily diagnosed in young adults, approximately 2–5% of cases manifest during childhood or adolescence [1,2]. Pediatric MS (PMS) constitutes a distinct subgroup with unique clinical, biological, and psychosocial characteristics.

Children often present with multifocal neurological symptoms and higher relapse rates compared with adults, yet their recovery is typically more complete due to superior remyelination and neuroplasticity [3-6]. Nevertheless, early onset implies a longer disease duration, increasing the risk of cognitive deficits, psychosocial stress, and academic challenges.

High-resolution magnetic resonance imaging (MRI), updated International Pediatric MS Study Group (IPMSSG) criteria, and improved clinician awareness have enhanced early recognition. This review summarizes pediatric MS, highlighting clinical presentation, pathophysiology, diagnosis, differential diagnosis, management, emerging therapies, and supportive interventions.

Epidemiology

Pediatric MS typically presents between ages 10 and 16, though cases as young as 2 years have been reported5. Incidence varies globally from 0.2 to 2.9 per 100,000 children per year, with a latitude gradient similar to adult MS6. Post-pubertal female predominance suggests hormonal modulation of immune function.

Genetic susceptibility is well established, with HLA-DRB1*15:01 significantly increasing risk [7]. Environmental factors—including Epstein–Barr virus infection, vitamin D deficiency, obesity, and low sunlight exposure—act as potential triggers [8,9]. Pediatric MS is associated with a higher relapse frequency in early disease, emphasizing the importance of early, effective therapy [10].

Pathophysiology

Pediatric MS results from an aberrant immune response targeting CNS myelin and oligodendrocytes. Autoreactive CD4+ T cells infiltrate the CNS, releasing pro-inflammatory cytokines that recruit macrophages and microglia [11]. B cells contribute via antigen presentation, cytokine release, and production of anti-myelin antibodies [12].

Demyelination disrupts saltatory conduction, causing reversible neurological deficits, while chronic axonal injury underlies permanent disability [12,13]. Compared with adults, children exhibit more active inflammatory lesions on MRI but retain greater capacity for remyelination [14]. Emerging studies highlight roles for mitochondrial dysfunction, oxidative stress, and microglial activation in disease progression.

Clinical Presentation

Most pediatric MS patients exhibit a relapsing–remitting course [15]. Progressive phenotypes are rare. Common initial manifestations include:

- **Optic neuritis (25–35%):** unilateral, painful vision loss.
- **Transverse myelitis:** motor weakness, sensory changes, bladder/bowel dysfunction.
- **Brainstem or cerebellar involvement:** ataxia, tremor, dysarthria, diplopia, vertigo.
- **Multifocal deficits:** reflecting dissemination in space.
- **Cognitive and behavioral impairment:** deficits in attention, processing speed, and memory affect up to one-third of children [16].

Relapses are frequent but often resolve more completely than in adults. Recurrent attacks may accumulate into lasting neurological or cognitive deficits. Fatigue, mood changes, and psychosocial impact are common.

Diagnosis

Diagnosis requires dissemination in space (DIS) and dissemination in time (DIT) per 2017 McDonald criteria [17].

Investigations include:

- **MRI of brain and spine:** ovoid periventricular, juxtacortical, and infratentorial lesions; gadolinium enhancement indicates active inflammation.
- **CSF analysis:** oligoclonal bands in ~70% of cases.
- **Evoked potentials:** visual evoked potentials (VEPs) detect subclinical optic nerve involvement.
- **Serology:** MOG-IgG and AQP4-IgG to exclude MOGAD and NMOSD [18].
- **Laboratory testing:** rule out infectious, metabolic, or mitochondrial mimics.

Diagnosis may be deferred in children with a first demyelinating episode until recurrence or new MRI lesions are observed.

Differential Diagnosis

Differentiating pediatric MS from other demyelinating disorders is critical [19-21]. Key conditions include:

1. Acute Disseminated Encephalomyelitis (ADEM)

- Typically monophasic, often post-infectious.
- Presents with encephalopathy, polyfocal deficits, and sometimes seizures.
- **MRI:** large, bilateral, poorly demarcated lesions, often involving deep gray matter.
- **CSF:** mild lymphocytosis; transient oligoclonal bands.
- Distinguishing feature: single episode; absence of new lesions over time favors ADEM.

2. MOG Antibody–Associated Disease (MOGAD)

- Presents with optic neuritis, transverse myelitis, or ADEM-like syndromes.
- **MRI:** confluent, sometimes ADEM-like lesions; central gray matter spinal cord involvement.
- **Serology:** MOG-IgG positive.
- **Clinical course:** relapsing or monophasic; treatment differs from MS.

3. Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Severe bilateral optic neuritis, longitudinally extensive transverse myelitis (LETM), area postrema syndrome.
- **Serology:** AQP4-IgG positive.
- **MRI:** LETM ≥3 vertebral segments; peri ependymal brainstem lesions.
- Some MS therapies worsen NMOSD, making differentiation critical.

4. Leukodystrophies

- Genetic white matter disorders, often progressive.
- **MRI:** symmetric diffuse hypomyelination.
- **CSF:** usually normal; no oligoclonal bands.
- **Clinical:** developmental delay or systemic involvement.

5. Metabolic/Mitochondrial Disorders

- Progressive neurological decline with multisystem involvement.
- **MRI:** symmetric white matter, basal ganglia, or brainstem lesions.
- **Laboratory:** elevated lactate, specific metabolic markers.

6. Autoimmune Encephalitis

- Subacute cognitive decline, seizures, and psychiatric symptoms.
- **MRI:** cortical/subcortical hyperintensities; rarely confluent white matter lesions.
- **Serology:** disease-specific autoantibodies (e.g., NMDAR, LGI1).

Features	Pediatric MS	ADEM	MOGAD	NMOSD	Leukodystrophy	Metabolic/ Mitochondrial
Age	10–16 yrs	<10 yrs common	Any age	Any age	Early childhood	Variable
Course	Relapsing	Monophasic	Relapsing/ Monophasic	Relapsing	Progressive	Progressive
MRI	Ovoid periventricular/ juxtacortical lesions	Bilateral, large, poorly demarcated	Confluent, sometimes ADEM-like	LETM, brainstem	Symmetric, diffuse	Symmetric, basal ganglia/ brainstem
CSF	Oligoclonal bands ~70%	Mild lymphocytosis	Usually negative	Often negative	Usually normal	Variable metabolic markers
Serology	Negative	Negative	MOG-IgG	AQP4-IgG	Negative	Genetic/ metabolic
Encephalopathy	Rare	Common	Sometimes	Rare	Rare	Sometimes

Table 1 : Comparative Diagnostic Table.

Management

Acute Relapse Treatment

- High-dose intravenous methylprednisolone 20–30 mg/kg/day (max 1 g/day) for 3–5 days [22].
- Plasma exchange or IVIG for steroid-refractory relapses.

Disease-Modifying Therapy (DMT)

- **First-line:** interferon-β and glatiramer acetate [23].
- **High-efficacy/oral therapies:** fingolimod [24], natalizumab [25], ocrelizumab/rituximab [26].
- **Monitoring:** MRI, blood counts, liver function, growth, thyroid function.

Emerging and Novel Therapies

- **B-cell-targeted therapies:** ocrelizumab, ofatumumab, rituximab [27,28].
- **BTK inhibitors:** tolebrutinib, evobrutinib [29].
- **Remyelination strategies:** clemastine fumarate, metformin, PIPE-307 [30].
- **AI-driven predictive models:** for individualized therapy planning [31].

Supportive and Symptomatic Care

- Physical/occupational therapy for mobility and coordination.
- Cognitive rehabilitation for attention, memory, and executive deficits.
- Psychological support, school accommodations, fatigue management.
- Family education and transition planning to adult care.

Prognosis

Children recover well from individual relapses but are at risk for cognitive deficits and early cumulative disability [32,33]. Early DMT initiation and supportive interventions improve long-term neurological and academic outcomes [34].

Future Directions

Research is shifting toward precision medicine and neuroregenerative approaches, including biomarker discovery, gut–brain axis studies, gene–environment interactions, AI-driven predictive tools, and pediatric-specific clinical trials of DMTs and remyelination therapies.

Conclusion

Pediatric MS is a rare but increasingly recognized neuroimmunological disorder with distinct challenges. Early diagnosis, differentiation from other demyelinating disorders, and prompt initiation of DMTs—including novel B-cell and BTK-targeted therapies—are critical. Multidisciplinary care integrating pharmacologic, cognitive, psychological, and social support optimizes long-term outcomes.

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