

# The epidemiology of acquired demyelinating syndrome in children: a complex opportunity to investigate the etiopathogenesis of multiple sclerosis

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Multiple sclerosis is a neuroinflammatory and neurodegenerative polyfactorial disorder of the central nervous system normally affecting young adults and potentially leading to severe disability. How genetic and environmental factors individually or in combination contribute to the disease pathogenesis remains to be unraveled.<sup>1</sup> Clinical onset of multiple sclerosis typically occurs between 20 years and 40 years of age; prevalence is over 100 per 100 000 and incidence is 4 to 6 per 100 000/year in White populations.

Pediatric-onset multiple sclerosis (pedMS) represents 3% to 10% of all multiple sclerosis onsets. Its annual incidence is up to 3 per 100 000 children, increases with age, and is of a relapsing-remitting nature; the primary progressive manifestation is very uncommon.<sup>2</sup> PedMS is one of the possible outcomes of an acquired demyelinating syndrome (ADS) among children, but its proportion out of all ADS at onset is debated. Other multiphasic diseases (e.g. neuromyelitis optica spectrum disorders [NMOSD], anti-myelin associated oligodendrocyte glycoprotein disorder [MOGAD], or monophasic events like acute disseminated encephalomyelitis [ADEM] or clinically isolated syndromes) need to be considered in the diagnostic interpretation of first onset of ADS in children for all consequent relevant therapeutical and prognostic implications.

In a study conducted of a large cohort of UK children, Abdel-Mannan et al. report that pedMS is diagnosed in 19% of children with ADS and that, based on a 10-year follow-up, 68% of all ADS has a monophasic presentation.<sup>3</sup> Interestingly, in a Sardinian pediatric population, multiple sclerosis was diagnosed in 72% of first ADS cases.<sup>4</sup>

A number of factors contribute to the diagnostic and prognostic complexity of ADS in children. Epidemiological differences across studies are confounded by age: the definition of a 'pediatric' population may range from less than 16 years<sup>3</sup> to less than 18 years of age.<sup>4</sup> The length of follow-up periods as well as the retrospective (from adult multiple series) versus prospective nature of data collection (i.e. pediatric registries) also affect the proportion of

multiple sclerosis diagnosed over ADS series. The age at onset of pedMS is higher than that in a monophasic ADS and a greater probability for a multifocal relapsing-remitting inflammatory disease (pedMS) with increased age is corroborated by a more frequent association with brain abnormalities during magnetic resonance imaging (MRI) and the evidence of intrathecal synthesis of oligoclonal immunoglobulin G (IgG) in the cerebrospinal fluid. Differential diagnosis with other neuroinflammatory or systemic inflammatory conditions may be more challenging than in adults and especially in ADEM-like onsets.

Abdel-Mannan et al. report that 4% of ADS were reclassified in acute necrotizing encephalopathy, primary hemophagocytic lymphohistiocytosis, anti-NMDA receptor encephalitis, vitamin B12 deficiency, and Sjögren syndrome.<sup>3</sup> Although over 95% of pedMS already meet the 2017 revised McDonald criteria at presentation,<sup>3,5</sup> epidemiological, clinical, and MRI differences are reported between early (i.e. >11y, 0.6% of all cases) and late-onset pedMS. An even sex distribution or a male preponderance, brainstem involvement, encephalopathy, ill-defined T2-hyperintensive lesions, deep gray matter involvement with fewer enhancing lesions on MRI, neutrophilic pleocytosis, higher percentage of monocytes, and the absence of intrathecal IgG synthesis are more frequently associated with pedMS of earlier onset. Comparing the proportion of NMOSD in ADS at onset across studies in children is hampered by heterogeneous case definitions and their retrospective nature; NMOSD diagnostic criteria only became available in 2015.

Epidemiological studies of ADS among children represent a complex yet unique opportunity to investigate multiple sclerosis etiopathogenesis for the much shorter latency period from etiopathogenetic processes to disease onset. Whether multiple sclerosis onset in children is linked to a higher pathogenetic load differing across populations, what the role of the developing brain is in such pathogenesis, and whether the more frequent adult multiple sclerosis instead depends on a lifetime accumulation of exposures remain to be elucidated.

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