Pediatric Demyelinating Diseases: Multiple Sclerosis or Not?

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Multiple sclerosis, like other autoimmune diseases, starts at a young age with the majority of patients experiencing the initial symptoms between the ages of 20 and 40. However, in a not negligible proportion of patients the onset of MS occurs either at a much older age or during childhood. The pediatric MS population deserves special consideration because of some unique features in this age group. Onset of a chronic disease like MS at such an early age translates into a very long clinical course. Epidemiological data show that most of the pediatric MS patients will remain disability free for longer periods from the time of onset as compared to adult patients. However, even if disability in these cases will appear 20–30 years after the initial symptoms, it will still occur at a young age, probably younger than in patients with adult MS.

Pediatric MS needs special consideration not only because of the above epidemiological parameters, but also because many of the pediatric patients will be diagnosed later with another disease, not multiple sclerosis. Various additional clinical disorders (usually systemic autoimmune diseases or neuromyelitis optica) characterized by episodes of central nervous system demyelination have been increasingly recognized in children. Moreover, a much higher proportion of children (as compared to adults) suffer from a monophasic (and not chronic) demyelinating event such as acute disseminated encephalomyelitis or isolated optic neuritis, and transverse myelitis, often post-infectious. Differentiation between such acute monophasic illnesses and a chronic demyelinating disease is extremely difficult and long clinical and neuroradiological follow-up is needed.

Pediatric multiple sclerosis and neuromyelitis optica have historically been diagnosed using adult criteria and treatment protocols. There is limited information and no controlled scientific data regarding the optimal diagnostic evaluation and treatment (both at the acute stage and in the long term) in pediatric central nervous system demyelinating diseases. Another important issue concerning chronic immunomodulating therapy in this age group is its unknown and possibly harmful effect on normal growth and development.

Trying to deal with the above problems, European and American expert consortiums for pediatric MS formulated consensus recommendations for the diagnosis and the suggested treatment protocols [1-3]. According to these recommendations, the diagnosis of pediatric MS requires multiple episodes of CNS demyelination separated in time and disseminated in space as accepted for adults [4], and there should be no lower age limit (e.g., including cases under the age of 10).

The magnetic resonance imaging scan can be used to fulfill the dissemination in space requirement if the McDonald criteria for a "positive MRI" are met, i.e., the MRI must show three of the four following features: a) nine or more white matter lesions or one gadolinium-enhancing lesion, b) three or more periventricular lesions, c) one juxtacortical lesion, and d) an infratentorial lesion [5]. The combination of an abnormal CSF (either the presence of oligoclonal antibodies or an elevated immunoglobulin G index) and two lesions in the MRI of which one is located in the brain, can also fulfill the dissemination in space criterion. Two main differences apply to pediatric patients as compared to adults: First, in patients younger than 10 years old the dissemination in time and space should preferably be a clinical one, and second, the diagnosis of ADEM should be excluded. This is due to the fact that in the majority of children under 10 years old, the first demyelinating episode carries features resembling ADEM and their MRI scans typically show multiple, variably enhancing lesions within the four critical CNS locations. Therefore, using MRI as a substitute for dissemination in space and time, especially in the initial MRI, is probably not appropriate for the younger group [6].

The above consensus statements were recently validated [7]. Verhey et al., for the Canadian Pediatric Demyelinating Disease Network, described the Canadian experience with pediatric patients. This study showed that 20% of the pediatric patients who suffered from a demyelinat-

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MS = multiple sclerosis

CNS = central nervous system

CSF = cerebrospinal fluid
AFEM = acute disseminated encephalomyelitis

ing episode (57 of 284) were subsequently diagnosed with MS after a median of 188 days. The presence of either one or more T1-weighted hypointense lesions or one or more periventricular lesions was associated with an increased likelihood of MS diagnosis (sensitivity 84%, specificity 93%, positive predictive value 76%, negative predictive value 96%). The risk for MS was higher when both parameters were present [7].

In general, the clinical presentation of pediatric MS is variable. The presenting symptoms in children over age 12 generally include discrete neurological symptoms (i.e., focal motor and sensory deficits) resembling the typical clinically isolated syndromes of adult MS. In younger children the presenting symptoms are more often multifocal and associated with encephalopathy (ADEM or ADEM-like disease) [8].

Environmental factors have been implicated in the susceptibility of children to multiple sclerosis, since the temporal association between exposure to such risk factors and the onset of first symptoms seems to be much tighter than in adults. Three factors seem to be of importance: vitamin D insufficiency, viral infections (particularly Epstein-Barr virus, herpes viruses, varicella zoster), and exposure to cigarette smoke. The role of such environmental factors in the development of multiple sclerosis in young children merits further research [8].

In this issue of *IMAJ*, Achiron et al. [9] describe the prevalence of pediatric MS in Israel. They collected demographic, clinical and imaging data for all patients diagnosed with childhood MS during 15 years and compared them with data of juvenile and adult MS. Their mean follow-up time was 8.4 years. The authors found that childhood-onset MS is rare in Israel, with an incidence of 0.1/100,000 children and that children with MS accounted for only 0.89% of all MS patients. According to their data, the authors concluded that childhood MS does not differ significantly from juvenile and adult-onset MS in terms of clinical, laboratory and imaging fea-

tures. However, two differences between childhood, juvenile and adult MS were highlighted in their cohort. The first is that during a similar follow-up period, none of the patients with childhood MS progressed to significant disability compared to 9.4% of the juvenile and 14.4% of the adult MS patients. Second, the proportion of males was greater in the childhood MS group as compared to juvenile and adult MS groups. Those differences are in accordance with those from the international cohorts [10].

Clinicians who treat patients with pediatric MS face major problems. Making the correct diagnosis is challenging, due to the larger number of inflammatory conditions mimicking MS in this age group. Even among experts in the field there is still uncertainty as to whether a patient who suffered from a single demyelinating episode can be safely given the diagnosis of early MS. Taking into account the recommendations of the international groups that immunomodulatory treatment be started in all active patients in this age group, we propose the following:

- Regarding diagnosis: children suffering from the first MS episode before the age of 10 should experience two separate clinical episodes in order to be diagnosed with definite MS (the "old" Poser's criteria should be used in this group). In those in whom the first demyelinating episode occurred at an age older than 10, the diagnosis of definite MS can be established based on the newer MacDonland criteria, using the MRI findings for determination of dissemination in time and space, and substituting therefore (similarly to the adults) the need for a second confirmed clinical relapse.

- Regarding therapy: there are limited epidemiological and prognostic data in this age group. This complicates the decision significantly whether or not to start a preventive immunomodulatory treatment in the pediatric population. In adult MS, several studies have underlined the importance of initiation of treatment as early as possible [11-13].

Such evidence-based information is lacking for childhood MS. The only reasonable option for the present is to follow the international consortium recommendations. This is particularly important for a small country where pediatric MS seems to be a very rare disease (as shown by Achiron and team, namely, during the last 10 years only 10 new pediatric MS patients were diagnosed in Israel), and there is no way to accumulate significant epidemiological data for the Israeli population in the near future. It is generally advisable that pediatric MS be diagnosed and treated by a team that will include adult MS specialists and, preferably, in the framework of a specialized MS center.

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