Chapter 19: Multiple Sclerosis and Demyelinating Disorders

Supplemental Material

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Pediatric Onset MS

Although commonly assumed to be an adult disorder, MS is also seen in children, with 2% to 10% of cases having a pediatric onset (Yeh, 2021). Approximately 20,000 children are known to suffer from MS in the United States (MacAllister et al., 2007). The frequency of pediatric onset MS (POMS) is about 1.35 to 2.5 per 100,000 (Gadoth, 2003), with a mean age of onset between eight and 14 years of age, with onset prior to 10 years of age being least common and indicative of a poor prognosis. While the gender distribution is similar to adult MS, the ethnic distribution is different in POMS, with more African American and Latino children being susceptible. Comparable to adult MS, children initially present with symptoms of sensory disturbances, optic neuritis, brainstem related symptoms, motor deficits, and gait disorders (Patel, Bhise, & Krupp, 2009). Optic neuritis is the most common symptom at onset, followed by sensory disturbances. Transverse myelitis is also more common among children than adults. It is estimated that approximately 90% or more of POMS suffer from a relapsing–remitting course with 2.3% to 7% experiencing a primary progressive course (Ness et al., 2007).

Disease burden measured by MRI is typically greater in POMS, but the progression is slower than with adults and irreversible disability takes longer to develop (Yeh, 2021). A recent study also showed that the time from pediatric onset to disability has gotten considerably longer in recent years. Baroncini et al. (2021) found that the cumulative risk of reaching disability milestones (EDSS scores of 4.0 and 6.0) gradually decreased over time when this was examined

in four different time epochs (< 1993, 1993–1999, 2000–2006, 2007–2013). They estimated that the risk of persistent disability had been reduced by 50% to 70%. As to the cause of this reduction, they noted that a greater number of the POMS in the later epochs had been treated with disease modifying therapies (DMTs) and that they had been given earlier and for a longer period of time.

The time for conversion to a secondary progressive course is longer in children than adults and children typically have a less progressive course. Indicators of a poor prognosis include short (less than one year) interval before the first and second attack, incomplete recovery after the first attack, and a secondary progressive course, which is more common following a greater number of attacks in the first two to five years (Ness et al., 2007). Similar to adult MS, fatigue and psychiatric issues are a frequent concern in POMS. Rates of at least mild fatigue have been reported to exceed 50% in POMS, with this being severe enough to affect school and recreational activities in about 40% (Carroll et al., 2015). With this said, rates have been found to be highly variable across studies, with a review of 12 articles reporting rates of at least some fatigue in POMS ranging from 9% to 76% (Carroll et al.). Upwards of 48% of children report experiencing some sort of affective disorder (Chitnis et al., 2011). Finally, cognitive disturbances are estimated to occur in as many as 77% of children, and include difficulties in complex attention, working memory, processing speed, language (confrontation naming and receptive functions), visuomotor integration, and executive functioning (Chitnis et al., 2011; MacAllister et al., 2005; Patel et al., 2009; Yeh, 2021). Taken together, these factors are known to have a substantial impact on a child's academic achievement, psychosocial adjustment, and overall quality of life.

A recent population-based study by Boesen et al. (2021) examined school performance, psychiatric comorbidity, and healthcare utilization in 92 pediatric MS cases, comparing them to a matched control group. Using the Danish National Health Registry, they did not find any differences in grades between the MS group and the matched control or another chronic illness group. Interestingly, these authors found that levels of psychiatric comorbidity (broadly considered) were higher in children with MS compared with both healthy children and children with other chronic diseases. Specifically, risk was over three times greater in the MS compared with the matched control group, and nearly twice the risk even compared to the chronic illness group.

Depression in MS—Functional Imaging Studies and Treatment Outcomes

Functional brain variables in relation to emotional functioning in MS have been examined in only a limited way in MS. Although not examining depression per se, Passamonti and colleagues (2009) explored emotional processing in a small group (n=12) of relapsing-remitting PwMS. They found that, compared with controls, MS participants showed a lack of functional connectivity between the amygdala and the PFC during an emotional processing task involving the matching of affective faces. Although the MS participants in the study were not clinically depressed, they reported significantly higher scores on depression measures than controls. These authors suggested that reduced functional connectivity could reflect a disruption in an important affective processing system in the brain of PwMS early in the disease process that might ultimately put them at risk for emotional difficulties such as depression.

Another functional neuroimaging study by Riccelli and colleagues (2016) reported reduced connectivity between the hippocampus and amygdala, as well as the dorsolateral and

ventrolateral prefrontal cortices in PwMS, on the other. Additionally, when the participants were exposed to facial images of sadness and anger, increased activation in the prefrontal cortex was found.

Depression has been shown to be treatable through brief and even telephone-based cognitive behavioral therapy (CBT; Mohr, Hart, Julian, & al., 2005; Mohr et al., 2000), as well as group therapy. Additionally, CBT has been shown to be effective via computerized versions that are self-administered (Ratajska et al., 2019). Moderate effect sizes have been reported for CBT, regardless of format (Hind et al., 2014). Because of these types of studies, the American Academy of Neurology has recommended CBT to treat depression in MS (Minden et al., 2014).

Also, cognitive-behavioral stress management training has been shown to reduce emotional distress in MS (Fischer et al., 1994). Nonetheless, depression has historically been undertreated in MS, despite the fact that it is unlikely to remit spontaneously. Successful treatment of depression is associated with greater adherence to immunotherapy.

Unfortunately, even the most promising interventions for depression are effective in only about 50% of PwMS (Ehde et al., 2008; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). Depression in MS negatively affects quality of life, adaptive functioning and well-being (Vargas & Arnett, 2010), interferes with medication adherence (Bruce, Hancock, Arnett, & Lynch, 2010), and may increase mortality (Feinstein, O'Conner, & Feinstein, 2002). There is a need for developing models with greater explanatory power that could result in the development of better treatments to reduce depression in MS.