Radiologically isolated syndrome in children

Can we predict future events?

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The phenomenon of radiologically isolated syndrome (RIS) in MS represents a key topic of clinical significance. Adults with RIS are asymptomatic at the time of presentation, but have brain MRI scans containing incidental findings highly suggestive of MS, and, importantly, a high rate—59%—of subsequent emergence of new MRI changes[1] and a 5-year risk of clinical events of 34%.[2] Of note, almost 10% of patients with RIS who experienced clinical events received a diagnosis of primary progressive MS in one study.[2] Given the high rate of emergence of new neurologic abnormalities in this population, it is prudent to identify groups in which this phenomenon might exist and to clarify their future risk of relapse.

While the phenomenon has been well described in the adult population, previous studies have not documented its presence in youth. Indeed, a nationwide study in Sweden evaluating all MRI scans performed at a single institution found no children with RIS in the selected year of 2001 and a prevalence of RIS of 0.05%.[3] However, while rare, this phenomenon does exist in children, and important clinical consequences are associated with these radiologic findings. In this edition of *Neurology® Neuroimmunology & Neuroinflammation*, Makhani et al.[4] describe a cohort of youth with RIS and evaluate potential predictors of future and ongoing disease activity. The authors present a cross-national retrospective case series (16 tertiary centers in the United States, Turkey, France, Argentina, Spain, and the United Kingdom) of 38 children who satisfied the 2010 McDonald dissemination in space (DIS) criteria for MS, but were asymptomatic at the time of the MRI scan; follow-up was a median of almost 5 years. Notably, as with their adult counterparts, the youth included in this study had a high likelihood of developing clinical events (42%) and future development of new lesions on MRI (61%). They experienced these events within 1–2 years of initial scan, suggesting the need for close monitoring of this cohort. Spinal cord lesions (hazard ratio 7.8, 95% confidence interval 1.4–43.6, $p = 0.02$) and the presence of CSF oligoclonal bands (OBs) (hazard ratio 10.9, 95% confidence interval 1.4–86.02, $p = 0.02$) increased the risk of the development of clinical events.[4]

Challenges related to identifying RIS in the pediatric population are many, as asymptomatic children who satisfy the DIS criteria are potentially great in number. Approximately, 1/5 of healthy youth may have incidental findings on MRI,[5] with 6% in 1 population having periventricular white matter abnormalities.[6] Determining which patients are in need of surveillance and which patients may have abnormalities due to one-time events in the past is, therefore, of importance. Notably, while the authors used 2010 McDonald DIS criteria to identify their cohort, their cohort was drawn from specialized MS centers. Thus, selection bias may have allowed for the inclusion of patients with images, which were most highly suggestive of MS. It is unknown whether DIS criteria, applied to a general pediatric population, will be sensitive enough to differentiate those youth with high risk of relapse from those with static lesions originating from a previous, unknown insult. Thus, future studies must focus on refining the inclusion criteria for this subgroup of patients. Limitations of the study include its retrospective nature and potential for selection bias. Importantly, however, the authors have highlighted the existence of this subgroup in the pediatric population, and that the rate of development of new lesions and clinical events may be high.

Whether identification of RIS implies a need for therapeutic intervention is an important area of controversy and future inquiry. Cross-sectional analysis of cortical involvement in adult RIS subjects has shown lower cortical volumes and mean thalamic volumes in comparison to healthy controls, as well as correlations between the white matter lesion volume and regional cortical thickness.[7] The relevance of these results for pediatric cohorts has not been

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studied. However, multiple studies suggest the presence of degenerative biology from onset in pediatric MS, including failure of age-expected brain growth[8] and a change in white matter growth trajectory after a single event.[9] Furthermore, natural history studies of pediatric onset MS suggest the time of onset of secondary progression to be in the mid-30s. Given this background, future studies must examine the question of the value of intervention with MS therapies at the time RIS is found in high risk youth (e.g., with positive CSF oligoclonal bands or spinal cord lesions).

Access to MRI around the world has increased significantly in the past decade. In 2014, countries such as the United States, Germany, Japan, and Turkey had rates of MRI of more than 100 per 1,000 population,[10] and Canadian statistics suggest an almost doubling of MRI use between 2006 and 2014.[10,11] With it has come the inevitable rise in incidental MRI findings in asymptomatic individuals. Understanding the clinical relevance of these findings is of great importance, particularly in a phenomenon in which findings suggest the presence of a chronic, degenerative process such as MS. This phenomenon will not go away: The study by Makhani et al. emphasizes the presence of these findings in youth, and, importantly, a rate of emergence of new lesions or clinical findings equivalent to that in the adult population. How these youth should be followed and treated and how the development of sensitive criteria that can be tested more broadly are important subjects of future inquiry.

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