Pediatric multiple sclerosis

The 2015 Sydney Carter Award Lecture

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In 1952, Sydney Carter, MD (1912–2005; Professor Emeritus, Columbia University), was asked to establish the first independent child neurology program at Columbia Presbyterian Hospital. Prior to this, children with neurologic disorders were largely cared for by general pediatricians, or on occasion, and often with trepidation, by adult neurologists. Dr. Carter recognized the unique care needs of the pediatric neurology patient. He prioritized the requirement to harmonize neuroscience and neurodevelopment, and advocated the need to identify the hallmarks of neurologic illness in the context of the developing central and peripheral nervous systems, and to foster training programs specifically in Child Neurology.

It is my sincere honor to be the 2015 Sydney Carter Award recipient, and to pay service to the many colleagues whose dedication, brilliance, and compassion have contributed immeasurably to the content of this lecture. In my lecture, and herein, I summarize the learning curve and milestones achieved in pediatric multiple sclerosis (MS) care and research to date. I have endeavored to mention the work of international colleagues and to emphasize the Canadian Pediatric Demyelinating Disease program. The Canadian program began with a 3-year survey of over 2,400 pediatric health care providers^{1–3} to estimate the annual incidence of acute demyelination in Canadian children.⁴ Through the creation of the Canadian Pediatric Demyelinating Disease Network with funding by the Multiple Sclerosis Scientific Research Foundation, a prospective cohort (2004–present), a centralized database, biorepository, and high-quality research MRI dataset have contributed to our understanding of the clinical, genetic, epidemiologic, and imaging characteristics of MS in children.

Just as Dr. Carter identified a fundamental need for pediatric neurology, formal programs for pediatric-onset MS were also born from recognition of a clinical care need. Before 1980, search of the English literature yielded fewer than 30 publications on the topic of pediatric MS, and many believed that MS was a disease solely of adults (reviewed in Ref. 5). The available MS diagnostic criteria proposed by Poser et al.⁶ specifically excluded the diagnosis of MS in persons younger than 10 years, and did not formally comment on MS in youth. Further complicating the diagnosis and care of pediatric patients with MS is the fact that approximately 70% of pediatric patients with acute demyelination will have a transient illness without clinical or MRI evidence of new lesions over time. Acute disseminated encephalomyelitis (ADEM) typifies monophasic demyelination, particularly in young children. Distinguishing such patients from the 30% ultimately confirmed to have MS has been the focus of much of the research performed in the last 15 years.^{7–9}

The diagnosis of MS rests on clinical features. There are no diagnostically specific genetic mutations or biomarkers for MS. Given this, an initial priority was to define the clinical features of pediatric-onset MS. Since 1980, several key articles have characterized MS onset in childhood,^{10–21} and led to a multinational collaboration.²² The tendency for very young patients with MS to manifest with polyfocal neurologic deficits and a high frequency of brainstem symptoms at onset were noted. Over the next 5 years, several key observations emerged: (1) children and adolescents experience relapsing neurologic deficits typical of adult-onset relapsing-remitting MS but do not appear to experience primary progressive MS²³; (2) CSF analysis reveals the presence of intrathecal oligoclonal bands, a hallmark of MS in adults, in 60%–95% of pediatric patients, but less commonly in younger children²⁴; (3) over 95% of pediatric patients with MS recover well, in terms of physical functioning, from acute episodes early in their disease²⁵; (4) cognitive impairment occurs in approximately 30% of pediatric patients with MS^{26–32} and correlates with MRI measures (reduced brain volume, altered resting state and functional connectivity, and reduced tissue integrity)^{33–38}; (5) pediatric patients with MS have higher relapse frequency in the first few years postonset, as compared to patients with adult-onset MS^{39,40}; and (6) time from first attack to secondary progressive MS (a stage of the disease characterized by progressive accrual of neurologic impairment not linked to discrete relapses) appears to take approximately 10 years longer in pediatric-onset patients, although the age at which such deficits appear occurs at a younger age than occurs in adult-onset MS.⁴¹

**Supplemental data
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The 1990s also saw the rapid increase in availability of MRI and the subsequent visualization of MS lesions in the brain, optic nerves, and spinal cord in adults with MS. The characteristic distribution of lesions in periventricular and juxtacortical white matter, the typical occurrence of numerous T2-bright lesions even early in the disease course, and the ability of gadolinium dye to outline disruption of the blood–brain barrier in acute lesions led to inclusion of specific MRI features in the McDonald MS diagnostic criteria.^{e2,e3} The diagnostic criteria for MS were further revised in 2010^{e4} and for the first time formally provide diagnostic criteria for pediatric-onset MS. Evidence that patients with pediatric-onset MS also harbor lesions in the CNS regions commonly targeted

in adult-onset disease^{e5} and identification of MRI lesion patterns that distinguish pediatric MS from ADEM^{e6,e7} aided in the capacity for more accurate MS diagnosis in children.^{e8,e9} Application of the 2010 MS criteria permits MS diagnosis to be established at the time of an incident attack in selected patients, clearly leading to a more prompt diagnosis,^{e9} but should be applied cautiously in children younger than 11 years and is not applicable in children with a first attack meeting criteria for ADEM. The figure illustrates the MRI features of pediatric MS, including visualization of cortical lesions using 7T MRI.

The ability to identify pediatric MS at the time of disease onset provides an opportunity for early disease treatment. Level 1A evidence of efficacy of immunomodulatory therapies for MS in adults, notably interferon β -1a, interferon β -1b, and glatiramer acetate, was established through large phase III trials. Patients with pediatric-onset MS were not included in these pivotal studies, and to date, only isolated case reports and retrospective case series address the use of these first-line therapies in patients with MS younger than 18 years.^{e10–e14} Consensus regarding the use of first-line and some second-line therapies in pediatric MS was published to aid clinicians and to advocate for access for patients.^{e15,e16} There are now more than 15 approved therapies for MS in adults, including higher potency infusion therapies and oral medications, with several further agents soon to gain regulatory approval. Both the Food and Drug Agency in the United States and the European Medicine Agency require pediatric investigational plans for all newly approved therapies. An international consensus meeting was held to articulate considerations for the safe conduct of clinical trials for pediatric MS.^{e17} The rarity of pediatric-onset MS, considerations of immune, multiorgan, and CNS maturity, fertility and endocrine implications, and patient and parental attitudes to participation in rigorous clinical trials are key considerations.²² The launch of several phase III clinical trials in pediatric MS over the last 3 years will yield data on some of these key considerations.

Key opportunities to better understand MS pathobiology have been born through the care and evaluation of pediatric MS cohorts. Although the etiology of MS remains incompletely understood, a complex interplay between host genetic factors and environmental exposures that influence peripheral and possibly CNS-specific immune cell function is likely operative. Epidemiologic studies implicate month of birth,^{e18,e19} place of residence during childhood,^{e20} limited childhood outdoor play, low levels of sun exposure,^{e21} lack of ingestion of vitamin D supplements before adulthood,^{e22,e23} secondhand smoke exposure,^{e24} early puberty in girls,^{e25} and obesity during adolescence^{e26,e27} as risk factors for MS. Collectively, these

Figure The cardinal MRI features of multiple sclerosis (MS) in children

(A) Axial fluid-attenuated inversion recovery (FLAIR) image demonstrates multifocal areas of increased signal in the periventricular, juxtacortical, callosal, and deep white matter. In the right periventricular white matter, lesions have coalesced, leading to a large area of abnormal periventricular white matter. (B) Axial T1-weighted image postgadolinium infusion of the same patient as in (A) shows a T1 hypointense lesion (black hole) with a rim of enhancement. The area of confluent abnormal T2 signal in the right periventricular white matter is also hypointense in this T1 sequence, indicative of lesion chronicity. (C) Sagittal FLAIR image highlights prominent lesions emanating from the corpus callosum (Dawson fingers), a key feature of MS in both children and adults, and (D) 7T MRI magnetization-prepared rapid gradient echo image with arrows pointing to cortical lesions in an adolescent patient with MS. Leukocortical lesions (cortical lesions that abut the white matter) and intracortical lesions (lesions that are located entirely within the cortex) are visualized on 7T MRI. Subpial lesions are much less readily visualized and sequence optimization to improve detection of subpial lesions is ongoing.

epidemiologic studies implicate childhood through adolescence as the key time wherein MS risk is defined. As such, patients with pediatric-onset MS provide a unique window into genetic signatures and environmental exposures experienced in close proximity to disease onset. Indeed, pediatric patients with MS (but not children with monophasic demyelination) are more likely than healthy youth to have at least one of the MS-implicated human leukocyte antigen (HLA) risk alleles^{e28} and to have a higher proportion of MS-risk single nucleotide polymorphisms.^{e29} The vast majority of children with MS studied have low circulating vitamin D concentrations.^{7,e30} Over 80% of pediatric patients with MS have serologic evidence of remote infection with Epstein-Barr virus (EBV), which compares to a prevalence of approximately 40% in regionally and age-matched healthy peers.^{7,23,e30,e31} Patients with pediatric MS also shed EBV in saliva far more frequently than EBV-exposed healthy youth, suggesting a possible impairment in host control of EBV latency in MS.^{e32} The presence of any 1 or all 3 of the most strongly associated risk factors (HLA-DRB1501 allele, low vitamin D concentrations, and remote EBV infection) is not sufficient for MS, as evidenced by the fact that all 3 risk factors exist in over 50% of children with monophasic demyelination.⁷ More interesting perhaps is that the absence of all 3 factors portends a 95% likelihood of monophasic demyelination.⁷

In addition to evaluation of putative risk factors for MS, pediatric patients with MS also provide an opportunity to characterize the immunologic signature of the disease at a point inherently more representative of the earliest timepoint in immune dysregulation, and at a point in time when extraneous alternations that may emerge with age are less likely to be operative. Miniaturization of assays, given the smaller blood sample volumes obtained from children, was an essential first step before analysis of immune cell subset responses to specific mitogens and intracellular cytokine analyses could be performed. Heightened T-cell responses to myelin antigens,^{e33} and preliminary suggestion of premature aging of the regulatory T-cell population^{e34} in pediatric patients with MS, point to impaired immune regulation as a key inciting component of MS biology. Peripheral T-cell responses are not the sole immunologic component of MS. Proteomic analyses of CSF reveal distinctive patterns in pediatric patients with MS, with a prominent representation of axoglial but not traditionally implicated proteins such as those associated with compact myelin,^{e35} suggestive of early neurodegenerative as well as immune biology. Circulating antibodies to myelin proteins have also been studied. While the presence of anti-myelin basic protein antibodies does not distinguish children with MS from those with other autoimmune diseases or

from healthy children,^{e36} recent work has demonstrated that myelin oligodendroglial antibodies are rare in children or adults with MS,^{e37,e38} are present in a subset of patients who are negative for anti-aquaporin 4 antibodies but have clinical features suggestive of neuromyelitis optica spectrum disorder,^{e39,e40} and are present in 25%–50% of children with ADEM.^{e38,e41–e43}

At the time of the present lectureship, there are 63 accredited Pediatric Neurology residency programs in the United States, a true legacy to the memory of Dr. Sydney Carter. The field of pediatric MS care and research has also benefitted from a similar Himalayan growth curve. The International Pediatric Multiple Sclerosis Study Group (www.ipmssg.org), created in 2004, now includes over 150 clinicians and researchers from over 40 countries. A search of PubMed for the last 3 years now identifies over 140 new peer-reviewed pediatric MS manuscripts per year.

Pediatric MS research is no longer in its infancy. We have matured through the development of pediatric MS diagnostic criteria, have learned from adult-onset MS and confirmed shared genetic and environmental risk determinants, have identified cognitive impairment as a critical outcome of pediatric-onset MS, and have proposed models for clinical therapeutic trials for pediatric MS. It is now time for the field to take independent steps from those of researchers into adult MS and investigate aspects of MS that may be unique or differentially expressed in pediatric MS, such as gut microbiome–dietary relationships, thymic maturation and the influence of MS and MS therapies on this process, and structure–function relationships in the maturing CNS visualized by advanced imaging. Immunologic insights in the youngest patients with MS may teach us about the inciting biology of MS, a window into the disease no longer visible by adulthood. It is plausible that future neuroprotective strategies may be maximally beneficial in the pediatric MS population treated before permanent CNS injury and at a time of greater CNS resiliency. Specific priorities for the near future include immunophenotyping of individual patients to evaluate not only their immune cell repertoire, intracellular cytokine production, and cellular age (as estimated by telomere length), but also to evaluate their own immune responses to a given therapy. Can we more accurately define treatment response, and in so doing, provide more effective treatment with less risk? Understanding the impact of MS at the individual level also requires evaluation of CNS reserve. Exercise, intellectual enrichment, and potentially modulation of the gut microbiome and maintenance of vitamin D sufficiency may be “wellness” strategies with even more potential for benefit when enacted in patients with pediatric MS who are still availed of the heightened plasticity of youth. The benefit of mitigating the lifetime impact of MS is incalculable and

represents the overarching milestone to be achieved in the field of pediatric MS.

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B. Banwell receives remuneration for work as a central MRI reviewer for Novartis, and for her work as a Chief Editor of *Multiple Sclerosis and Related Disorders*. Dr. Banwell serves as an unpaid consultant on pediatric trial design for Novartis, Sanofi, Biogen-Idec, and Teva Neuroscience. Go to Neurology.org for full disclosures.

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regained his memory. The head trauma amnesia cure myth remains a popular theme in Bollywood movies to this day and newspaper articles, such as the one on the 39-year-old jawan,² strengthen the myth.

Author Response: Mary V. Spiers, Philadelphia: I thank Dr. Sethi for relating this story after reading my article.¹ It is a testament to the myth's strength that the reporter did not consider alternate diagnostic possibilities but simply frames the soldier's story as a second blow amnesia cure.

It is assumed the soldier had an initial brain injury, causing identity loss. The myth of a blow to the head causing identity loss amnesia is widely believed by the public (80%).³ The soldier was reportedly with 2 others during the accident, but were they questioned? Furthermore, the soldier's memory was restored with the presumed physical jolt, but belief or mental health status were not considered. In another case, following a car accident, a woman's belief that sleep contributed to memory

loss (as seen in the movie "50 First Dates") appeared to be a contributing factor in her ability to remember information from the previous day.⁴

Multiple possibilities, including an amnesic fugue state, should be considered by those evaluating the soldier, but any evidence found that contradicts the myth will probably not get the same press coverage.

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CORRECTION

Pediatric multiple sclerosis: The 2015 Sydney Carter Award Lecture

In the Special Article "Pediatric multiple sclerosis: The 2015 Sydney Carter Award Lecture" by B. Banwell,¹ there is a misspelling throughout the article. All instances should read "Sidney" rather than "Sydney" as originally published. The author regrets the errors. In addition, the author wishes to add the following sentence and reference: "A 1956 article by Drs. Low and Carter² described 7 children with acute neurologic illness, 3 of whom experienced relapsing disease and 4 with single events. Neuroimaging at that time was restricted to pneumoencephalograms and skull X-rays, which were noninformative. The rarity of pediatric-onset MS and the challenges faced by child neurologists in making such a diagnosis are well-described."

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