Primary Progressive Multiple Sclerosis presenting under the age of 18 years: fact or fiction?

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Running head: Paediatric onset PPMS

Word Count: 984 Abstract: 100

Title: Paediatric Primary Progressive Multiple Sclerosis

References: 10 Figure: 1 Table: 1

Keywords: Primary Progressive Multiple Sclerosis, Pediatric multiple sclerosis, McDonald criteria, MS mimics, Disease Modifying Therapies

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Abstract

Previous cohort studies on pediatric multiple sclerosis (MS) have reported very low frequencies for a primary progressive MS (PPMS) course ranging from 0 to 7%. We identified six patients presenting prior to the age of 18 years and fulfilling the 2017 McDonald Criteria for primary progressive multiple sclerosis (PPMS). Presentation with progressive neurological symptoms and signs in young people should prompt evaluation for genetic causes such as leukodystrophies, hereditary spastic paraparesis and mitochondrial diseases given the rarity of primary progressive course in pediatric MS. In the absence of an alternative diagnosis, with new therapeutic options becoming available for PPMS, this diagnosis should then be considered.

Introduction

Primary Progressive multiple sclerosis (PPMS) is characterized by sustained disability progression from disease onset with occasional plateaus and infrequent relapses[1]. This subtype is seen in around 10-15% of patients presenting with MS. Adults with PPMS tend to be older and typically present over the age of 50 years[2], suggesting that both the clinical phenotype and the disease course in terms of disability accumulation are, at least in part, age-dependent. Previous cohorts have shown very low frequencies of PPMS in children ranging from 0 to 7%.[3]

Here we describe six patients presenting prior to the age of 18 years with a progressive disease course, neuroimaging features typical of adult MS, and positive CSF oligoclonal bands (OCB), thereby fulfilling the 2017 McDonald Criteria.

Methods

Patients were identified from the National Hospital for Neurology and Neurosurgery (NHNN) in London (UK) and the UK Childhood Inflammatory Demyelination (UK-CID) network. Two pediatric neurologists (YH, OA), and two adult neurologists (OC, RC), retrospectively reviewed the medical records. Mann-Witney test was used to compare the EDSS between the different groups. This study was approved by Great Ormond Street Hospital Research and Development Department (reference 16NC10)

Results

A total of six patients (5 male, 1 female) with a diagnosis of PPMS with symptom onset before the age of 18 years were identified. Four patients were identified from the Queen Square Multiple Sclerosis Centre at the National Hospital for Neurology and Neurosurgery, London, United Kingdom (out of an estimated 500 PPMS patients) and two were identified from the United Kingdom Childhood Inflammatory Demyelination (UK-CID) Network (out of 108 paediatric onset MS).

Age at symptom onset was 11-17 years (median age of 15.5 years). All patients presented with a progressive myelopathy with at least one-year history of progressive deterioration of their balance (n=2) and/or progressive worsening of lower limb function (n=4). All patients had MRI scans of the brain and spinal cord with gadolinium. Dissemination in space on first MRI was seen in all patients with periventricular (n=6), cortical/juxtacortical (n=2), infratentorial (n=3) and spinal cord (n=6) lesions (Figure 1). CSF OCB were detected in 5/5 patients tested. Patients were diagnosed with PPMS 3 to 10 years from symptom onset (median 5.5 years). Patients were empirically investigated by their

physicians to exclude a range of alternative inflammatory and neurometabolic aetiologies, of which none were identified (Table 1).

At two years, all patients developed lower limb spasticity, three patients developed cognitive difficulties, three had visual problems and three had bladder involvement. Three patients (50%) had relapses during the progressive clinical course, two with new onset of painless visual symptoms with blurred vision and reduced visual acuity, and one with worsening of the pre-existent leg weakness and urinary incontinence, with an incomplete recovery after steroids treatment. In all of them, periods between relapses were characterized by continuing progression. Median EDSS at 2 years was 5.5 (range: 4 to 7.5), higher than reported in a cohort of 62 paediatric patients with RRMS in the same catchment area (median EDSS at 2yrs: 5.5 vs 1, P<0.001, Mann-Whitney test) [4]. At final follow-up (median 6.5 years), four patients are wheel chair bound and two are walking with bilateral aids.

All patients showed new lesions on repeat MRI imaging. Contrast enhancement was present in 3 out of 4 (75%) during the disease course.

A trial of IV methylprednisolone was unsuccessful in four patients. Three patients were commenced on Azathioprine initially but continued to deteriorate, and one patient (patient 5) had a trial of interferon beta 1a but did not tolerate it. One patient had Haematopoietic stem cell transplantation but continued to progress. All patients were on symptomatic treatment for spasticity and pain, including oral/intra-thecal baclofen, gabapentin and nabiximols.

Discussion

In this case series, we describe six patients presenting with PPMS before the age of 18 years. Any child presenting with progressive neurological decline should have extensive investigations for metabolic, genetic, infective and other inflammatory disorders, as per our patient cohort. The differentials diagnosis includes CNS infections, vasculopathies, hereditary spastic paraparesis (HSP), inherited leukodystrophies and mitochondrial diseases. Leukodystrophies in particular may have overlapping features affecting the white matter on neuroimaging, and present with a chronic progressive clinical course, making differentiation from PPMS sometimes challenging[5]. Prior to the 2010 revised McDonald criteria, PPMS was identified by clinical evaluation only and it is possible that some of the paediatric patients with a progressive clinical course with evidence of demyelination on imaging or brain biopsy may have had an alternative genetic diagnosis.

In all six cases included in this report, the clinical phenotype was of a progressive disease course with worsening neurological disability without sustained improvement in disability, and faster accumulation of disability at 2 years compared to paediatric patients with RRMS[4]. In keeping with other cohorts of PPMS we did not observe the female predominance seen in RRMS. A multicenter study of 101 PPMS patients showed that male sex predicted clinical worsening over 5 years[6] which may explain the worse outcomes seen in this cohort.

Patients with PPMS can have acute attacks (superimposed relapses), and this can be categorised as a primary progressive–active phase[1]. In a cohort of 1419 patients with PPMS, superimposed relapses were associated with a lower risk of confirmed disability progression[7]. This suggests that inflammatory relapses are an important determinant of disability accumulation in progressive onset disease (including PPMS). Clinical relapses were reported in 50% of our patients, higher than reported in adult cohorts[8], suggesting that children may have more inflammation than adults.

In keeping with reports of adult cohorts with PPMS[6, 9] (and the new diagnostic criteria, where the presence of two or more T2-hyperintense lesions in the spinal cord supports the diagnosis of PPMS[10]), we also observed spinal cord lesion predominance (vs brain) at disease onset and contrast enhancement was seen in 3/4 (75%) during the disease course.

Until recently disease modifying therapies (DMTs) were only shown to be effective in RRMS. A relatively small, but steadily rising number of clinical trials have been conducted in PPMS. Recently, Ocrelizumab has become the first DMT to show reduced rates of clinical and MRI-evidenced progression in adult patients with PPMS[11] and it is now licenced for the treatment of early PPMS. With new therapeutic options becoming available, although rare, the diagnosis should be considered in children with a progressive clinical course consistent with PPMS and supportive evidence on imaging and CSF analysis.

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Financial Disclosure

Omar Abdel-Mannan, Rosa Cortese, Wallace Brownlee, Yael Hacohen and Evangeline Wassmer have nothing to disclose.

Cheryl Hemingway has received educational and travel grants from Merck Serono and Bayer and Biogen.

Alan Thompson has received honoraria/support for travel for consultancy from Eisai, Hoffman La Roche, Almirall, and Excemed, and support for travel from the National MS Society for consultancy as chair of the International Progressive MS Alliance Scientific Steering Committee, and member of the NMSS Research Programs Advisory Committee. He receives an honorarium from SAGE Publishers as Editor-in-Chief of Multiple Sclerosis Journal and a free subscription from Elsevier as a board member for the Lancet Neurology.

Olga Ciccarelli receives research funding from UK MS Society, Rosetrees trust and NIHR UCLH BRC and serves as a consultant for Biogen, Novartis, Roche, Genzyme, Teva and GE healthcare. She is on the editorial board of neurology.