Letters

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Pediatric MS patients with a primary progressive-like disease may still have relevant inflammatory activity and may benefit from regular MS treatment

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In childhood, multiple sclerosis (MS) with a primary progressive disease course is very rare.[1,2] Therefore, we read the recent article of Abdel-Mannan et al.[3] presenting six pediatric patients fulfilling McDonald 2017 criteria for primary progressive MS (PPMS) with great interest. All patients presented with a progressive myelopathy, including progressive balance, and/or lower limb function impairment for at least 1 year. During follow-up, they had an ongoing progressive disease course, without sustained improvement and with a faster decline of Expanded Disability Status Scale (EDSS) compared to pediatric relapsing-remitting MS patients. In the four patients treated with intravenous methylprednisolone (ivMP), this treatment was unsuccessful. Patients continued to progress despite immunomodulatory treatment (azathioprine or hematopoietic stem cell transplantation). Only one patient was started on first-line disease-modifying therapy (DMT) for MS (interferon-beta-1a) but did not tolerate this. Although rare, Abdel-Mannan et al.[3] plead for recognition of PPMS in childhood in order to start registered PPMS treatment in these patients in hope to prevent further deterioration.

In our national cohort of pediatric patients with demyelinating diseases in the Netherlands (PROUD-kids study; PRedicting OUtcome in acquired Demyelinating syndromes in childhood), we identified two pediatric MS patients who presented with a progressive decline of balance, coordination, and motor function. In addition, one patient had progressive vision loss. At symptom onset, these patients were 8 and 13 years old (a boy and a girl, respectively). At the time of presentation in our National Pediatric MS center in Rotterdam, they already deteriorated for 9.2 and 1.3 years, respectively. Comparable with the cases described by Abdel-Mannan et al.,[3] magnetic resonance (MR) imaging of our patients showed typical MS lesions with presence of periventricular, juxtacortical, infratentorial, and spinal cord lesions (Figure 1); presence of unique oligoclonal bands in cerebrospinal fluid; and no indication for other diagnoses in additional investigations in both. They also responded poorly to ivMP, with no to minimal clinical improvement.

Interestingly, in contrast to the continuing progression Abdel-Mannan et al.[3] described in all their patients despite treatment (no DMTs), our patients stabilized after starting second-line DMTs. Directly after MS diagnosis, both were started on Natalizumab, and recently one patient changed to Fingolimod due to positive John Cunningham virus. Within a follow-up of 2.1 years after starting treatment, a relevant improvement in EDSS was observed from 3.5 to 3.0 and 4.0 to 3.5, respectively. In addition, they had no relapses and MR imaging of brain and spinal cord showed no new lesions during follow-up. Even though they presented with a primary progressive-like disease course and did not respond well to steroids; in our opinion, the observed response to second-line DMTs may indicate relevant inflammatory activity in these pediatric patients. This is in line with the higher inflammatory activity observed in pediatric compared to adult MS patients with a relapsing disease course.[4,5] In conclusion, in our view pediatric MS patients with a primary progressive-like disease course differ from adult PPMS patients. Therefore, we argue that all pediatric MS patients with a primary progressive-like disease course should receive regular first-line or second-line MS treatment.

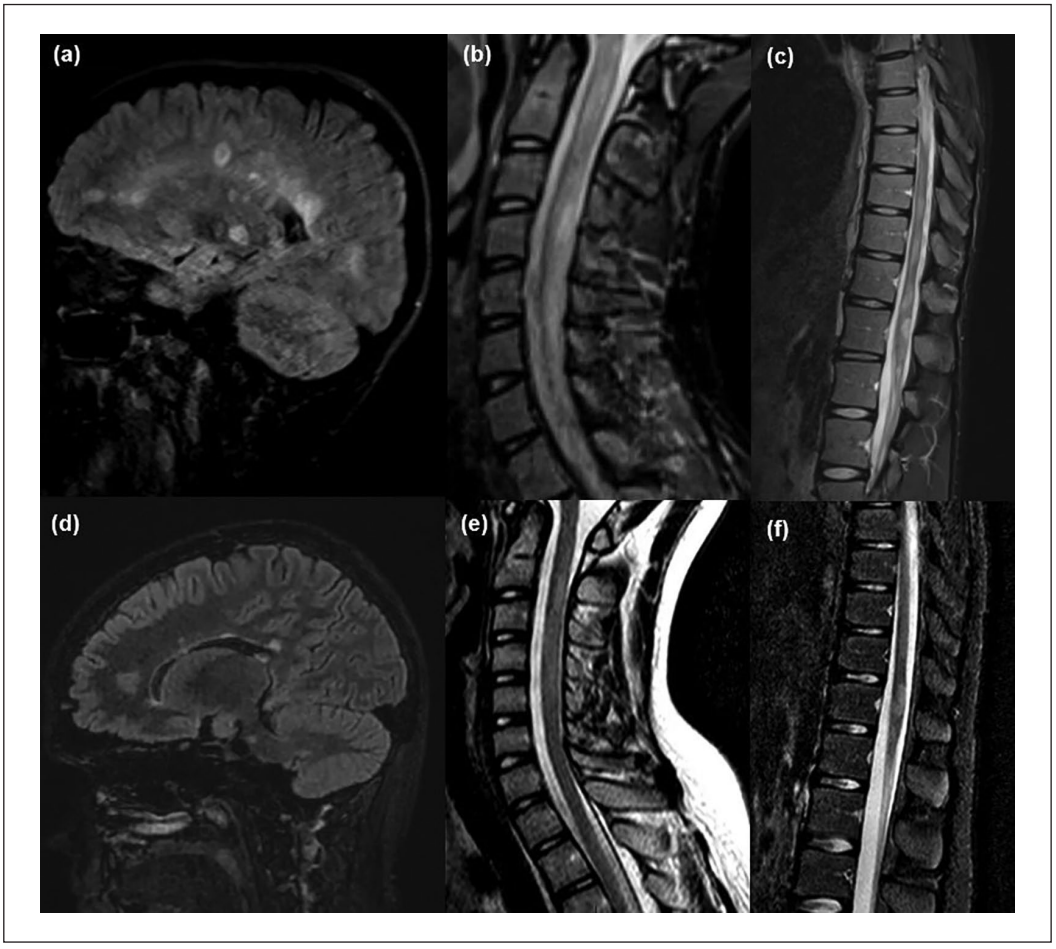

Figure 1. MR images of the (a–c) boy and (d–f) girl with a primary progressive-like disease course from first presentation. Sagittal FLAIR-weighted brain images show (a, d) multiple supratentorial and (d) infratentorial hyperintens white matter lesions. T2-weighted spinal cord MRI scan shows (b, e) cervical as well as (c, f) thoracolumbar involvement in both patients.

Declaration of Conflicting Interests

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Switching from natalizumab to ocrelizumab in patients with multiple sclerosis

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Natalizumab, a monoclonal antibody against alpha-4 integrin, is a highly effective disease-modifying therapy (DMT) for relapsing remitting multiple sclerosis (MS).[1] Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML), especially in patients who are John Cunningham virus antibody positive (JCV-Ab+).[2] Switching to another DMT is one strategy to mitigate PML risk, but a long washout period can precipitate disease activity. Ocrelizumab, a humanized anti-CD20 monoclonal antibody that depletes B lymphocytes,[3] could be an effective secondary therapy. As of January 2020, seven cases of carryover PML have occurred in patients who switched from natalizumab to ocrelizumab, raising safety concerns about this transition.[4] We reviewed our cases of natalizumab to ocrelizumab transition to assess the safety and efficacy of our protocol.

We retrospectively identified 28 patients (mean age: 40 ± 12 years, 21 (75%) female, median extended disability status scale (EDSS): 1.5 (0–6.5)) from Columbia University Irving Medical Center who switched directly from natalizumab to ocrelizumab between March 2017 to May 2019. The mean disease duration from MS symptom onset to natalizumab discontinuation was 8 ± 6 years, and the median number of natalizumab infusions was 36 (2–110). Natalizumab was the first DMT in 10 (36%) patients. No patient had a clinical relapse within 12 months of transition.

The reasons for switch included PML risk ($n=18$), secondary progressive MS ($n=5$), infusion frequency ($n=4$), and pregnancy planning ($n=1$). Seventeen (61%) patients tested JCV-Ab+ (median titer: 0.54 (0.21–3.12)), and four patients had titers >1.5. There was no correlation between the proportion of JCV-Ab+ patients and natalizumab duration. All JCV-Ab+ patients had a magnetic resonance imaging (MRI) brain before receiving ocrelizumab. One individual had cerebrospinal fluid (CSF) testing for JCV in the setting of new, non-enhancing T2 lesions.

The median natalizumab wash out period was 44 days (35–83). Every patient had a follow-up 3T MRI, which occurred at a median of 6 months after their first full ocrelizumab dose. New, non-enhancing T2 lesions were present in the brain MRIs of four patients, three of whom were JCV-Ab+ (titers: 0.31–0.46). All lesions appeared consistent with MS, and we observed no association between washout time and T2 lesion formation. Two of the four patients had subsequent MRIs, which showed stable demyelinating lesions. No relapses occurred in the transition period, although the EDSS score increased in one patient with progressive MS. By 6 months, CD19% was zero in 21 of 23 patients. Adverse events were limited to minor infusion reactions in nine (32%) patients. No serious infections, including PML, have occurred in the mean 22 ± 8 months of clinical follow-up.

A standardized approach to natalizumab cessation is currently lacking, although experts recommend a short washout period to reduce disease activity. Therefore, the absence of relapses in our cohort may partly derive from the median 6-week transition window. Our results are also concordant with a retrospective analysis of rituximab, which demonstrated a low relapse rate after transition.[5] Since ocrelizumab achieves suppression of circulating CD19+ lymphocytes by week 2,[3] its rapid biological effects make it an appealing alternative to other DMTs after natalizumab cessation.