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Disease activity in progressive multiple sclerosis can be effectively reduced by cladribine

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ABSTRACT

Background: Evidence suggests people with non-relapsing deteriorating ("progressive") multiple sclerosis (pwPMS) may benefit from disease-modifying immune therapy (DMT). However, only one such treatment (ocrelizumab) has been licensed and is highly restricted to pwPMS suffering from the primary progressive phenotype. The difficulties assessing treatment outcome in pwPMS is one important reason for the lack of respective DMT. The concentration of neurofilaments in the cerebrospinal fluid (CSF) provides a biomarker of neuro-axonal damage, and both neurofilament light (NfL) and heavy chain (NfH) levels have been used as outcome indices and to guide treatment choices.

Methods: We report on two pwPMS, who were treated with subcutaneous cladribine undergoing CSF NfL testing, alongside MRI and clinical follow-up, before and after treatment.

Results: Cladribine treatment was well tolerated without any side effects. CSF NfL after treatment revealed significant reduction (by 73% and 80%, respectively) corroborating the MRI detectable drop in disease activity. Disability mildly progressed in one, and remained stable in the other pwPMS.

Conclusions: pwPMS with detectable disease activity (MRI, elevated NfL) should be considered for DMT. NfL appears to be a sensitive index of treatment effect in pwPMS, and may be a useful outcome in clinical trials targeting this patient group. Over and above its licensed indication (relapsing MS), cladribine may be an effective treatment option for pwPMS.

1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating and degenerative disease of the central nervous system (Compston and Coles 2008), and the most common cause of non-traumatic disability among young adults in the Northern Hemisphere (Mackenzie et al., 2014). Most people with multiple sclerosis (pwMS) will experience a progressive course of their condition at some point. This may be from onset (primary progressive MS) or more commonly following a period dominated by relapses and remissions, which after an average disease duration of 10 years, transitions into "secondary progressive" MS in natural history studies (Leray et al., 2010). Whilst eleven different classes of disease-modifying treatments (DMTs) have been licensed for people with early/relapsing MS in Europe and the USA, there is currently only one such treatment, ocrelizumab, which is partially effective in people with progressive MS (Montalban et al., 2017).

There is, thus, an evident need for more effective DMTs for people with progressive MS (pwPMS). Development of DMTs for this patient population, however, has been slow due to a number of factors including (i) the regulatory environment and its adherence in clinical trials to the expanded disability status scale (EDSS) (Kurtzke 1983) as key primary outcome, in spite of the EDSS' well known shortcomings in terms of precision, and its ambulation bias driving an "eligibility cut-off" based on the ability to walk (Dubuisson et al., 2017a), (ii) the concept of MS, as a "two stage disease" with an early inflammatory followed by a largely non-inflammatory progressive phase (Leray et al., 2010), and (iii) a disregard for the differences in size and connectivity of the cortical representation for upper and lower limb function, and abundance of corticospinal tracts supplying upper compared to lower limbs (Patestas and Gartner 2016) resulting in a physiological

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Glossary

CNS	central nervous system
CSF	cerebrospinal fluid
DMT	disease modifying treatment
DNA	Deoxyribonucleic acid
EDSS	expanded disability scale score
Gd	gadolinium
JC virus	John Cunningham virus
MRI	magnet resonance imaging
MS	multiple sclerosis
NF	neurofilaments
NF-L	neurofilament light chain
OCB	oligoclonal bands
PP	primary progressive
pwMS	people with multiple sclerosis
pwRMS	people with relapsing multiple sclerosis
pwPMS	people with progressive multiple sclerosis
s.c.	subcutaneous
SP	secondary progressive

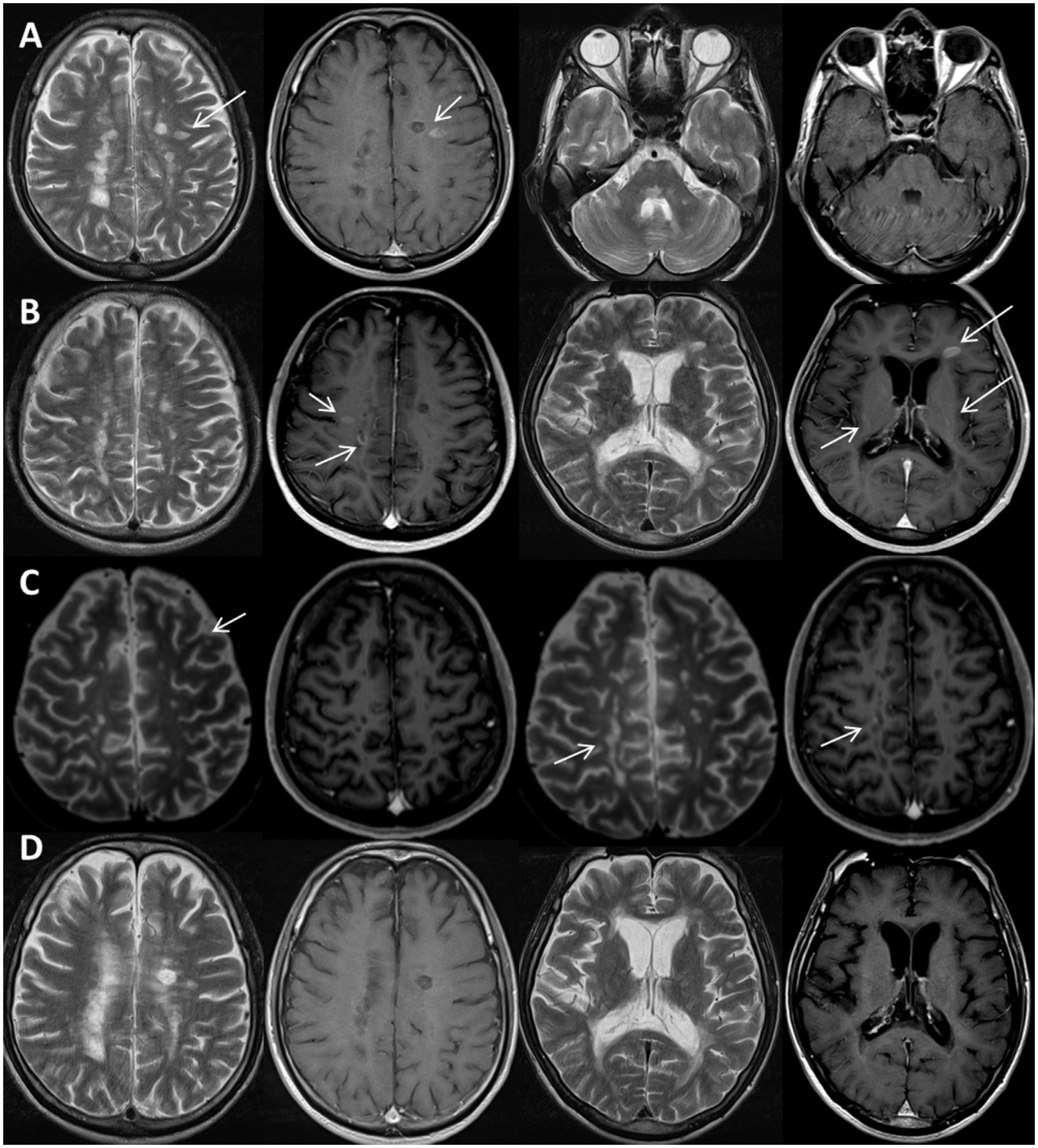

Fig. 1. Axial T_2 and post contrast T_1 weighted MRI 18 months before treatment (A), at baseline (B), 12 months after the first (C), and five months after the second cladribine treatment cycle (D). Arrows indicate areas of gadolinium enhancement.