Approach to treatment decision making in an aggressive case of pediatric multiple sclerosis

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CASE
A 13 year old previously well female presented in April 2011 with nausea, vertigo, mild gait ataxia, diplopia and fatigue. Her initial MRI (Figure 1) showed more than 20 hyperintense lesions on T2 FLAIR that were >3 mm in size throughout the supratentorial white matter, with multiple lesions in periventricular and corpus callosal areas. Contrast enhancing lesions were found in the right frontal lobe subcortical white matter, projecting from the corpus callosum, in the optic chiasm and superior cerebellar peduncle. Multiple T1 hypointense black holes were also found. MRI features met McDonald 2010 criteria for multiple sclerosis (MS). Spinal fluid was positive for oligoclonal bands. She was treated with a 5 day course of IV solumedrol then prednisone at 50 mg/d at 10 day taper. The family was counseled for high risk of recurrent symptoms and diagnosis of MS. At the end of her course of IV steroids she had a near full neurological recovery with some mild residual sensory deficits.

In May 2011, she began to experience left sided numbness below her neck and down her leg and exhibited a positive L’Hermitte’s sign (a classic finding in MS: an electrical sensation running down the back, often elicited by bending the head forward). These new neurological symptoms localizing to the spinal cord were distinct from her initial presentation, which was more than 30 days previous to this attack. This allowed further confirmation of MS diagnosis using Poser clinical criteria. Steroid treatment was not initiated as the patient did not find these sensory symptoms bothersome. The MRI at this point showed some lesions decreased in size, and one new gadolinium enhancing lesion indicative of active inflammation. Follow up MRIs in July and August 2011 showed multiple new hyperintense lesions in the brain and spinal cord including the brainstem, some of which were gadolinium enhancing, and some older lesions increased in size.

DOES SHE HAVE MS?
There have been several iterations of the diagnostic criteria for MS. This patient meets Poser Criteria for MS: two attacks and clinical evidence of two separate lesions involving different parts of the CNS separated by a period of at least one month, and each lasting a minimum of 24 hours. She also meets McDonald 2005 Criteria: demonstrates two or more attacks and objective clinical evidence of two or more lesions (shows dissemination in space: two or more MRI-detected lesions consistent with MS, dissemination in time: two separate clinical attacks). Her initial MRI also met the 2005 criteria for lesion dissemination in space (3 of: (i) >9 T2 lesions, >3 periventricular lesions, >1 juxtacortical lesion or (iv) >1 infratentorial lesion). As well, her baseline MRI also met the newer

Figure 1: Axial and sagital T2 FLAIR images showing periventricular, corpus callosal, and juxtacortical white matter lesions.
McDonald 2010 Criteria, dissemination in space (≥1 T2 lesion in at least 2 of 4 areas of CNS (periventricular, juxtaocular, infratentorial, spinal cord)) and dissemination in time (simultaneous presence of asymmetrical gadolinium-enhancing and nonenhancing lesions). CSF oligoclonal bands were present – a finding noted in 92% of pediatric MS patients. Investigations excluded other conditions. Thus, by all criteria, she has a diagnosis of MS. Pediatric MS represents up to 10% of all cases and is characterized by a relapsing-remitting course (RRMS).

SHOULD TREATMENT BE INITIATED?
This decision can be made based on predictors of poor outcome in MS, as well as the natural history of the untreated disease. Based on data from RRMS in adults (as limited studies have been done in children), it has been found that early disease outcomes such as a) incomplete recovery from first attack and b) shorter time to second attack are strong predictors of poor prognosis and future disability (reviewed in 5), both of which this patient exhibits. The natural course of RRMS, if untreated, is as follows: in 10 years, 30-50% of patients require walking aids, and in 30 years, up to 80% require walking aids, and up to 30% are restricted to their bed with effective use of only their arms.6 Due to the certainty of her diagnosis, and likelihood of future disability, this patient would be counseled to consider treatment.

CHOICES FOR LONG TERM TREATMENT
Currently there is no cure for MS. Long-term treatment encompasses first and second-line therapies (reviewed in 7, 8).

First line therapy: Immunomodulation
First line therapy for MS includes interferon β (Rebif, Avonex, Betaseron) and glatiramer acetate (Copaxone). The clinical benefit of interferon β is thought to be mediated through several mechanisms: inhibition of proinflammatory cytokines, induction of anti-inflammatory mediators, reduction of lymphocyte migration across the blood brain barrier, and inhibition of T-cell activation, among others. In Phase III pivotal trials in adult MS, interferon treatment demonstrated a 30% reduction in relapse rate compared with placebo for periods of 2-3 years.8 Formal trials have yet to include patients under 18 years old, but retrospective reviews show benefit and suggest safety and tolerability (reviewed in 7, 8).

Glatiramer acetate is an acetate salt mixture of synthetic polypeptides designed to mimic human myelin basic protein (MBP). It is postulated to induce regulatory and/or suppressor T cells, shift T helper response from Th1 to Th2, and shift antigen presenting cell function to type II. It was found to reduce relapse number of relapses by 29% in adults with RRMS over 2 years.10 Studies in children are limited but it seems to be effective (reviewed in 8).

First-line treatment failure can occur due to inadequate effectiveness (failure to reduce relapse rate), intolerable adverse effects or presence of unacceptable level of breakthrough disease (severity or frequency of attacks).11 It is difficult to define treatment failure and consensus criteria for children have not been established. However, one paper showed that 1/4 of children experience breakthrough disease and switched to second-line therapy an average of 1.5 years after starting first-line therapy.11

Second line therapy
Second line MS therapy includes cyclophosphamide and natalizumab. Cyclophosphamide acts to induce a general state of immunosuppression. Its mechanism is presumably through lymphocytotoxicity and decreasing lymphocyte subsets (reviewed in 8). It is used in adult patients with severe active MS, and a retrospective study in pediatric patients with severe MS revealed a reduction in the mean annualized relapse rate, although 75% of patients acquired new lesions on MRI over 12-24 months of treatment.12 The risk of infertitility, infection and long-term malignancy increases with total dose and strategies for fertility preservation should be considered (reviewed in 8). It is an option for aggressive MS refractory to first-line therapies.

Natalizumab (Tysabri) inhibits VLA4 through binding to a subunit of α4β integrin, inhibiting lymphocyte migration across blood brain barrier and also resulting in T-cell apoptosis. In adult MS trials, it has been shown to decrease relapse rates by 68% and reduce the formation of new enhancing lesions by >90% relative to placebo.13 Open label case series in adolescents described a marked relapse-rate reduction and favorable safety profile (reviewed in 8). However, it has been associated with increased risk of opportunistic infection. Of particular concern, Tysabri has been associated with a 1/1000 incidence of active infection with JC virus, leading to progressive multifocal leukoencephalopathy (PML), an infection almost exclusively associated with immunosuppressed patients including AIDS. Careful monitoring strategies including prior determination of JC virus serology are now in place and protocols for treatment of PML are being optimized (reviewed in 14). Nonetheless, PML is a major deterrent for widespread use of Tysabri.

TWO MODELS OF CARE
The nature of MS as a chronic disease and its onset in childhood lend careful consideration to the intensity of initial therapy. Two potential models of care (as discussed in 8) can be considered: 1) ‘Start low and escalate if necessary’ and 2) ‘Start strong and maintain.’ Approach #1 is currently the standard of practice for most pediatric MS patients. It emphasizes greater safety with reduced potency and may be valuable to consider in multiple sclerosis, a disease with lifelong exposure to medication. Approach #2 involves powerful immunosuppression followed by maintenance of remission by less potent medications, which is similar to care of pediatric patients with severe rheumatological disease. It is considered for newer therapies and more aggressive disease, as it provides greater early disease suppression, which is important to consider in the context of limiting inflammation-mediated brain injury in the context of a developing pediatric CNS. However, it carries greater risk of toxicity, significant risk of opportunistic infection (e.g. PML in the case of Tysabri) and consideration of potentially life-altering decisions (e.g. fertility implications in the case of cyclophosphamide), which is especially pertinent in the care of pediatric patients. In this case of our patient: should the treatment decision reflect the current standard of care for pediatric MS patients or does her highly aggressive disease indicate that second line therapy should be pursued?

EPILOGUE
The family decided to pursue cyclophosphamide as their choice of treatment. Though the role of the physician is to guide patients and their families towards appropriate treatment, it is pertinent to keep in mind that the family has the final decision.
REFERENCES


