Severe progressive brain atrophy in pediatric multiple sclerosis

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Title: Severe progressive brain atrophy in pediatric multiple sclerosis

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Abstract
BACKGROUND: Multiple sclerosis is an immune-mediated disease of the central nervous system. Progressive brain atrophy is a known marker of patient disability and cognitive impairment in MS patient, but limited information is available about the clinical and cognitive consequences in the pediatric population.

CASE REPORT: We present a case of aggressive pediatric-onset MS with severe rapidly progressive brain atrophy, neurological disability, and cognitive deterioration. Serial brain MRI studies demonstrate ongoing cerebral atrophy correlating with severe deficits on serial neuropsychological testing.

CONCLUSIONS: A subset of pediatric MS patient may be vulnerable to severe cognitive deterioration associated with marked brain atrophy.

Key Words: multiple sclerosis; magnetic resonance imaging; neuropsychology; childhood
Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system. Multiple studies have identified progressive brain atrophy in patients with MS, and shown it to be a marker of patient disability and cognitive impairment.\textsuperscript{1-3} Disease modifying therapy has been shown to slow progression of atrophy and short-term disability.\textsuperscript{4} There has been limited information to date about the clinical and cognitive consequences of progressive brain atrophy in MS patients in the pediatric population. We present a case of pediatric-onset MS with severe rapidly progressive brain atrophy, neurological disability, and cognitive deterioration.

Case:

In September 2002, an 11-year-old Hispanic girl developed new onset right arm weakness and was treated with intravenous immunoglobulin (IVIg), followed by a 5 day-course of intravenous steroids. Her cerebrospinal fluid was positive for oligoclonal bands and serum testing was negative for markers of Lyme, sarcoidosis, lupus, B12 deficiency, and syphilis. Her brain MRI demonstrated multiple bilateral enhancing and non-enhancing white matter lesions, including periventricular and infratentorial locations (not shown). A subsequent brain MRI in January 2003 showed at least 5 new white T2-hyperintense lesions, as well as one punctate enhancing lesion. A diagnosis of recurrent ADEM was initially entertained as clinical relapses coincided with steroid withdrawal. Further disease exacerbations prompted referral to an MS Center in 2004, whereupon she was diagnosed with MS, and started on daily subcutaneous 20 mg glatiramer acetate.
While initially relapse free during the first 2 years of therapy, she developed multiple severe relapses between 2006 and 2008 with development of fatigue, cognitive deterioration, depression, and loss of visual acuity in her right eye to 20/400, becoming essentially wheelchair-bound. She was switched to monthly cyclophosphamide 800 mg/m$^2$ infusions in collaboration with 2 Pediatric MS Centers with no further relapses. Cyclophosphamide was discontinued in June 2009 due to skin infections and multiple ulcers. The patient was then started on interferon-beta 1a 44 mcg TIW (Rebif) in October 2009, which she continues three times weekly at 50% standard dose as the full dose was associated with more than 3 fold increase of liver enzymes (AST and ALT). She has had no further relapses in the last 4 years.

She has had sudden bouts of crying and laughing, consistent with pseudobulbar affect, as well as dysphagia, dysarthria, constipation, urinary and fecal incontinence. As of January 2013, the patient could ambulate minimally with bilateral assistance (EDSS 7.0) and her examination had stabilized with remission of depressive and pseudobulbar symptoms. Her condition remains unchanged when last seen in 2015.

Overall neuropsychological testing demonstrated severe impairment (bottom 1st percentile) in verbal comprehension, perceptual reasoning, working memory, executive function, attention/concentration, memory, language, and perceptual/motor skills. The most marked change in the patient has been her change in cognitive status, beginning as developmentally appropriate in all areas by history and progressing to marked cognitive impairment in under 6
years, with an IQ of approximately 50-60 documented as of 2008. She was reportedly an honor
roll student in elementary school.

Her earliest neuropsychological evaluation in 2007 demonstrated a WASI full scale IQ of 74 in
the Borderline range (verbal 93, performance 56) in 2007, with a marked decline to 56 on full
scale IQ in 2008 (63 verbal, performance 57) mainly due to the verbal score. Her subsequent
scores were full scale IQ 55 in 2009 (verbal 64, 54 performance) and verbal comprehension 63
(1%), perceptual reasoning 52 (<1%), and working memory 60 (<1%) in 2010 on the WAIS-IV.

In 2007, verbal memory skills were impaired on the California Verbal Learning Test for Children
(CVLT-C) (list A T-score 20, mean 50, SD 10) while visual-spatial skills were impaired on the Rey
Complex Figure (standard score <52, mean 100, SD 15). Visual motor integration (VMI) was
impaired on the Beery VMI with a standard score of 46 (mean 100, SD 15) in 2007 and 47 in
2008, with Grooved Pegboard standard scores <52 (mean 100, SD 15) bilaterally in 2007, and
Delis–Kaplan Executive Function System (DKEFS) scaled scores all 1 (mean 10, SD 3) on
conditions 1 to 5. By 2009 she was no longer able to complete the Grooved Pegboard or DKEFS
testing.

Attention scores demonstrated marked impairment with Z scores of -2.8 and -2.1 (mean 0, SD
1) for digit span forward and backward respectively on the WAIS, and T scores 105 and 47
(mean 50, SD 10) for omission and commission respectively on Conners' Continuous
Performance Test-2 (CPT-2). In 2009, her attention span on Digit Span subtests was a scaled
score of 1 (<1%) for both backward and forward. By 2010, she had one or no responses during the entire Conners’ CPT-2, preventing standardized scoring.

Her brain imaging studies over the course of seven years demonstrated progressive severe diffuse atrophy (Figures 1 and 2). Third ventricle width, initially measured at 0.6 cm in October 2002 and 0.8 cm in September 2006, later increased to 1.3 cm by August 2009. Recently, third ventricle width has been identified as a potential correlate of cognitive impairment.\textsuperscript{5,6} MR images of a girl with epilepsy at 11 and 17 years of age are shown for comparison (Figure 3); and measurements revealed third ventricular widths of 0.1 cm in 2006 and 0.3 in 2012. Due to the MR acquisition methods, only volumetric measures for whole brain volume were possible. Whole brain volumes were measured on 2-dimensional T1-weighted images using SIENAX part of FSL.\textsuperscript{7} First, brain and skull images were extracted from the single whole-head input data. Then the brain image was affine-registered to MNI152 space and tissue-type segmentation was carried out. Normalized whole brain volumes were calculated to be 1499 mL in 2002, 1381 mL in 2006, and 1297 mL in 2012 (Supplement 1).

Discussion

Little has been described about brain atrophy in pediatric patients with MS. Prior MR studies focused on lesion distribution and diagnostic criteria, but more recent investigations have examined regional and global brain atrophy. One study in pediatric MS patients correlated thalamic gray matter volume loss with T2 lesion volume.\textsuperscript{8} Other studies demonstrated that pediatric patients with MS compared to healthy controls had significantly lower thalamic, whole
brain, and whole gray matter volumes on MRI.\textsuperscript{9,10} These measures of MRI global and thalamic volume correlated with neuropsychological test performance in patient but not control groups. A three year study supported evidence of gray matter brain atrophy in childhood onset MS when following pediatric and adult cohorts from the time of diagnosis.\textsuperscript{11} Diffusion tensor imaging in pediatric MS patients further identified deficiencies in callosal, right frontal, and right parietal white matter regions that correlated with arithmetic problems.\textsuperscript{12}

Cognitive impairment is well established in the pediatric MS population. In the largest sample studied to date, over a third of children meeting criteria for MS met criteria for cognitive impairment, defined as having at least one-third of completed test scores falling 1 standard deviation or more below published normative data.\textsuperscript{13} A subsequent longitudinal study demonstrated a dynamic process of decline, showing impairment in 31\% of a cohort of pediatric MS patients at baseline progressing to 77\% (56 of 61 patients) over 2 years.\textsuperscript{14}

Our brain imaging data was collected retrospectively from 1.5T strength MRI. Third ventricular width in our patient, already relatively large at onset, more than doubled over the course of 7 years, and whole brain volume decreased by more than 13\% over the span of a decade. This loss of brain volume is even more impressive considering that brain volume typically continues to grow in the healthy pediatric-aged population up to 16 to 18 years of age. In a similar scenario for an adult with MS where the literature reports an estimated annual 1\% loss in brain volume, the expected whole brain volume by 2012 would be roughly 1356 mL, and an additional five years would be required to attain a volume of 1297 mL.
This patient’s concomitant cognitive deterioration supports the suspicion that degenerative processes can begin early in the course of pediatric MS. There is a paucity of data about pediatric MS patients progressing to severe cognitive impairment. In one study, a notable patient with severe relapsing-remitting pediatric-onset MS was described as developing significant cognitive impairments over the course of 4 years, particularly with tasks of short-term memory, attention, executive functioning, naming, and figure reproduction.\textsuperscript{15}

In our practice, this is the worst case of rapidly progressive brain atrophy with cognitive deterioration in a patient with pediatric onset MS secondary to an aggressive disease course. While pediatric-onset cases have greater evidence of inflammatory activity and more frequent relapses, recovery is much more robust than that observed in adult counterparts and rapid decline is not the norm.\textsuperscript{16} Severe disease progression with cognitive repercussions and MRI changes is well known in the adult MS population, but has not been specifically reported together in children with MS. This case uniquely illustrates the fact that both severe brain atrophy and associated cognitive deterioration are also present in younger age cohorts and warrant studies designed to examine and correlate both aspects. Earlier treatment with more aggressive therapy may be most appropriate for such patients to improve outcomes. Future studies are needed to fully elucidate whether a subgroup of pediatric MS patients exist that are at risk of severe disease progression and rapid brain atrophy and how best to identify them prior to irreversible impairment.
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Contributions:
Vikram Bhise, MD, Composed the manuscript, performed measurements, patient care
Korhan Buyukturkoglu, PhD, Performed imaging volumetric analysis
Matilde Inglese, MD, PhD, Reviewed imaging analysis and provided feedback
Jan Wollack, MD, Reviewed manuscript and provided feedback, patient care
Konstantin Balashov, MD, Reviewed manuscript and provided feedback, patient care

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References


Figure Titles

**Figure 1. Axial FLAIR MRI at the level of the 3rd ventricle.** The year of the study is adjacent to the left lower corner of each image.

**Figure 2. Patient Axial FLAIR MRI at the level of lateral ventricles.** The year of the study is adjacent to the left lower corner of each image.

**Figure 3. Comparison Subject with Other Neurological Disease Axial FLAIR MRI at the level of the 3rd ventricle.** The year of the study is adjacent to the left lower corner of each image.