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(Citation)
Brain and Development,39(9):756-762

(Issue Date)
2017-10

(Resource Type)
journal article

(Version)
Accepted Manuscript

Clinical features in very early-onset demyelinating disease with anti-MOG antibody

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Total numbers of pages: 15

Total figures: 2

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ABSTRACT

BACKGROUND: The clinical features of patients with very early-onset acquired demyelinating syndrome (ADS) with the anti-myelin oligodendrocyte glycoprotein (MOG) antibody are unknown. We investigated the clinical characteristics and described detailed treatment of weekly intramuscular interferon β-1a (IFNβ-1a) in children aged <4 years with ADS and the anti-MOG antibody.

METHODS: We conducted a retrospective chart review of patients with anti-MOG positivity who were diagnosed as having multiple sclerosis (MS) at <4 years of age.

RESULTS: Subjects comprised 2 boys and 2 girls. Initial symptoms included ataxia, facial paresis, status epilepticus, and encephalopathy. Abnormal lesions on magnetic resonance imaging scans were often detected in the brainstem and cerebellum as well as the cerebrum. All patients started receiving IFNβ-1a at age 3.1–3.5 years. The initial doses ranged from 3–6 μg, which were 1/10–1/5 doses, respectively, for adults. During 0.6–4.3 years of IFNβ-1a administration, all patients had flu-like symptoms, and 1 patient had an increased liver enzyme level. Although 1 patient discontinued IFNβ-1a therapy because of frequent relapses, no patient discontinued therapy due to severe adverse events.

CONCLUSIONS: This case series adds novel information regarding the clinical features of children <4 years old with ADS and the anti-MOG antibody.

Keywords: multiple sclerosis, beta-interferon, disease modifying therapies, children, early childhood, treatment, anti-MOG antibody

INTRODUCTION

The myelin oligodendrocyte glycoprotein (MOG) is one of the components of myelin, and it has been used to induce experimental autoimmune encephalomyelitis in an animal model of multiple sclerosis (MS) [1]. The anti-MOG-antibody has been found in patients with acquired demyelinating syndromes (ADS), such as acute disseminated encephalomyelitis (ADEM), clinically isolated syndrome (CIS), and MS [1, 2]. The anti-MOG antibody was identified in children with ADS, especially those with onset at <10 years of age, more often than in adults [1-3] because of the following reasons: 1) pediatric-onset MS before the age of 10 years is very rare, with estimated incidence rates ranging from 0.2 to 0.7% of the total population [4-7]; and 2) the anti-MOG antibody was rarely detected in patients with a final diagnosis of MS in the ADS cohort study [8, 9], in which few clinical features of patients with early-onset demyelinating disease with the anti-MOG antibody were known [1, 2]. Specifically, the clinical features of children with the anti-MOG antibody who fulfilled the criteria of MS with onset at <4 years of age are yet to be reported. Moreover, the best disease modifying therapies for patients with the anti-MOG antibody have yet to be defined, although MOG antibody-positive patients seem to respond to steroids and immunosuppressive therapy [1]. Herein, we analyzed the clinical features, including examination findings, treatment, and outcome, of four children with the anti-MOG antibody who were also diagnosed as having MS at <4 years of age. We especially described the details of treatment of interferon (IFN)-β-1a for these children, because there is no case series regarding IFNβ-1a therapy

for patients with MS in early childhood [6, 10].

SUBJECTS AND METHODS

This study was approved by the local ethical committee of Kobe University Graduate School of Medicine and Kobe Children's Hospital, which waived the need for informed consent since this was an observational study.

We retrospectively reviewed the clinical courses; examination findings, including Magnetic resonance imaging (MRI) and Cerebrospinal fluid (CSF); treatments; and outcomes recorded in the medical records of 4 patients at Kobe Children's Hospital between January 2010 and December 2015 who were definitively diagnosed as having MS in early childhood, according to the revised McDonald criteria [11]. The criteria of immune-mediated CNS demyelinating disorders, including ADEM and CIS, were used, according to the International Pediatric MS Study Group [12]. A relapse was defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS lasting >24 h in the absence of a fever or infection [11]. Anti-aquaporin4 (AQP4) and anti-MOG antibodies were assayed by cell-based assays using living HEK-293 transfected cells with human AQP4 M23-isoform or full-length human MOG as previously described [13].

RESULTS

Patients comprised 2 boys and 2 girls ranging in age from 1.7–3.1 years at the moment of the first demyelinating symptoms. The mean age at diagnosis of MS was 3.0 years (range: 2.5–3.3 years), and the mean time from the first symptoms until diagnosis was 0.7 years (range: 0.2–1.3 years). A summary of the patients' clinical courses is shown in Table 1 and Figure 1. Three of 4 patients were diagnosed as having CIS at the moment of the first demyelinating symptoms. Among those patients, we could not exclude the possibility of a cerebellar tumor in patient 2 who had a limited obscure lesion in the cerebellum on MRI with initially normal CSF findings. Her symptoms, including a walking difficulty and ataxia, recovered after treatment with dexamethasone; however, she experienced a relapse of symptoms with multiple abnormal lesions on MRI and abnormal CSF findings. She was diagnosed as having MS after 2 months (Figure 2). Another patient (patient 3) was diagnosed as having ADEM with initial symptoms of fever, unconsciousness, and status epilepticus. He had a recurrent symptom of ataxia with abnormal lesions on MRI after 6 and 9 months. Then he was diagnosed as having multiphasic ADEM, and prednisone was prescribed. After 16 months from the first demyelinating event, he was finally diagnosed as having MS because of the presence of an asymptomatic gadolinium-enhanced lesion on MRI (Figure 2). All patients had obvious increases in the myelin basic protein level in CSF one or more times during the course of their diseases, although only 2 patients (patients 1 and 4) showed abnormalities at the moment of the first demyelinating symptoms. An oligoclonal band (OCB) in the CSF was detected in 1 patient (patient 2) during the follow-up periods. The anti-AQP4 antibody was not detected in any patients,

but the anti-MOG antibody was detected in all patients. The anti-MOG antibody was confirmed as positive after initiating disease modifying therapies, specifically, IFN-β-1a in all patients. Findings of spinal MRI were normal in all patients during the follow-up periods. The final expanded disability status scale score was 0.0 in all patients, except patient 1.

All patients were treated with Avonex® (Biogen), a weekly intramuscular IFNβ-1a, as first-line therapy after they were diagnosed as having MS. The mean duration between the time of diagnosis of MS and IFNβ-1a initiation was 0.3 years (range: 0.2–0.7 years). A summary of the patients' clinical courses is shown in Table 2. The initial doses ranged from 3–6 μg, whereas the usual dose in an adult patient is 30 μg. After several months from treatment initiation, the doses were increased to 9–15 μg at the attending physician's discretion. The dose of patient 1 was increased after a gadolinium-enhanced lesion was detected on MRI. The dose of patient 4 was increased after a relapse. Patients 1 and 3 showed no relapse after starting IFNβ-1a therapy. Conversely, patient 2 experienced two relapses during the 7 months of IFNβ-1a treatment, and she stopped taking IFNβ-1a and was switched to prednisolone. The neutralizing antibody of IFNβ-1a was negative in patient 2. After adding azathioprine because of an additional relapse, patient 2 experienced no more relapses, and the prednisolone was tapered off. All patients had flu-like symptoms after several hours from the injection at initiation and during the follow-up periods. During the maintenance doses, 1 patient had an injection site reaction, and 3 patients had increased liver enzyme levels; however, these adverse events recovered without intervention. No patient

discontinued IFNβ-1a therapy due to adverse events.

DISCUSSION

This study showed the clinical features of four patients with the anti-MOG antibody who presented with an MS phenotype at <4 years of age. There is no previously reported case series of this kind because this condition is a rare entity. However, similarly, eight patients with a median age of 3 years at onset (range: 1–7 years) of multiphasic disseminated encephalomyelitis and MOG antibodies have been reported recently [14]. When we compared the reported toddlers with MOG antibodies to our cases, we found similar clinical symptoms; ataxia was predominantly identified, otherwise other symptoms, including fever, were sporadic [14]. Neuroimaging and CSF findings were also similar between the reported cases and our patients; the brainstem and cerebellum were often involved, and an OCB was rarely identified [14]. Alternatively, our findings were consistent with those of previous patients with very early-onset MS with an untested anti-MOG antibody; ataxia (57%) was predominant in symptoms at onset, and the brainstem and cerebellum were often involved, according to MRI [6, 15]. These findings indicated that it is difficult to predict a positive anti-MOG antibody by clinical features at very early-onset ADS; therefore, routine testing for the MOG antibody may be recommended for these patients. However, school-aged children with ADS and the MOG antibody dominantly presented with visual symptoms and abnormal lesions in the optic nerve on an MRI scan [16, 17]. School-aged children with ADS with the MOG antibody

presented with less ataxia and abnormal lesions in the brainstem or cerebellum compared with our patients[16, 17]. In summary, we presumed that affected lesions by the MOG antibody may change from the brainstem and cerebellum to the optic nerve during the years of growing up. A prospective large cohort study will be needed to assess this hypothesis.

The fact that all patients with the MS phenotype at <4 years of age had a positive anti-MOG antibody seemed surprising, because MOG antibody positivity can predict a non-MS disease course at the onset of first demyelinating symptoms [8, 9]. We presumed this discrepancy resulted from the study design. We checked the MOG antibody only in patients with the MS phenotype; we did not assess the MOG antibody in patients with the onset of first demyelinating symptoms. The prevalence of the MOG antibody in patients with the MS phenotype at onset <4 years of age remains unclear, although the prevalence of the MOG antibody was 16.9% (43/255) with pediatric MS and 2.8% (17/597) with adult MS [2]. Our findings indicated that very young-onset cases with the MS phenotype showed more MOG antibody positivity than older pediatric cases.

Another novel finding in this study was the description of IFNβ-1a in very young children. IFNβ-1a is widely used in the pediatric population with MS, and it has been evaluated in several non-randomized studies that have shown the class III or IV evidences for reducing the annualized relapse rate and safety of the drug [18-21]. However, subjects of all previous studies were school children and adolescents. The present study described the specific administration methods,

including the initial and maintenance doses and adverse events, of weekly intramuscular IFNβ-1a therapy in early childhood. The fact that no patients had severe adverse events suggests that 1/5–1/2 of full doses of weekly IFNβ-1a were tolerated in children with MS aged at <4 years old. The doses we used were likely to be slightly lower compared to reported doses for school children, as most patients received full doses and a few patients received 1/2 doses, if the difference in ages and weights was subtracted between our study and previous reports [10, 18-20]. Determining the effectiveness of IFNβ-1a therapy for this population was impossible because of a lack of patients or follow-up periods. However, IFNβ-1a therapy may be an option for patients with very early onset MS, because this therapy seemed to prevent relapses for patients 1 and 3. Moreover, the fact that "children experience 2–3 times more frequent relapses than adults early in the disease course, with annualized relapse rates of 1.12–2.76 compared with 0.3–1.78 seen in adults" [6] and "a longitudinal study found that 75% of patients demonstrated worsening cognitive function on follow-up testing at 2 years" [6] may support the early initiation of IFNβ-1a therapy. However, our results indicated that some patients such as patient 2 may be refractory to IFNβ-1a therapy, but they respond to other therapy. We administered IFNβ-1a irrespective of the MOG antibody because of the lack of evidence and identification of the MOG antibody at the time of administering IFNβ-1a therapy. However, the therapeutic strategy could be affected by MOG antibody positivity [1]. MOG antibody-positive patients appear to respond to steroids and immunosuppressive therapy, but the effect of IFN is yet to be known [1]. Therefore, we considered that IFNβ-1a therapy should be

cautiously selected in patients with the MOG antibody. The therapeutic strategies need to be optimized in patients with pediatric inflammatory demyelination with the MOG antibody in the future.

Our study was limited by the small number of patients and its retrospective, single-center design, however, our results add novel information regarding the clinical features of patients with very early-onset demyelination with the anti-MOG antibody. Moreover, although the data should be interpreted cautiously, a reduced dose of the weekly intramuscular injection of IFNβ-1a was tolerated in our study population. Large-scale study will be needed to verify our results in patients with the anti-MOG antibody.

Acknowledgments

This work was partly supported by a Grant-in-Aid for Young Scientists (B) (15K19614). The authors thank all participating physicians, nurses and patients. We thank Dr. Ai Unzaki and Dr. Masashi Nagai at Kobe University Graduate School of Medicine for technical assistant of this study.

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Figure legends

Figure 1. Patients' clinical courses and treatment

★: first demyelinating symptoms; ✕: time of the definite diagnosis of MS; ■: relapse; □: radiologic evidence of new disease activity (a gadolinium-enhanced lesion was detected on MRI without new symptoms or worsening of pre-existing symptoms); mPSL: methylprednisolone pulse therapy; IVIg: intravenous immunoglobulin; DEX: intravenous dexamethasone; IFN: interferon ß-1a; PSL: oral prednisone; AZP: azathioprine

Figure 2. Patients' MRI findings

Brain MRI scans of patient 2 (a, b) and patient 3 (c–e). (a) At onset, a hyperintense area with an obscure border in the cerebellum was detected on a T2-weighted image (WI). (b) After 2 months, multiple hyperintensities of the cerebellum, white matter, and brainstem (in order from left to right) on a T2WI were detected. (c) Multiple hyperintensities were observed in the white matter at symptom onset, and (d) white matter and basal ganglia were detected on T2WI 9 months after symptom onset. (e) After 16 months, an additional white matter hyperintensity was detected on a T2WI (left), and gadolinium-enhanced lesions were found in the left temporal robe (right).

Table 1. Summary of Patients' Clinical Courses and Examination Findings

Case	1	2	3	4	Summary
Sex	M	F	M	F	M: 2 (50%)
Age at onset (years)	2.0	3.1	1.7	2.3	
Symptoms at onset	Facial paresis	Ataxia	Fever	Ataxia	Ataxia: 2 (50%)
	Hemiparesis	Vomiting	Encephalopathy	External	Others: 1 (25%)
		Walking difficulty	Status epilepticus	ophthalmoplegia	
Initial diagnosis	CIS	CIS (Brain tumor)	ADEM (acute	CIS	CIS: 3 (75%)
			encephalitis)		
CSF findings					
Pleocytosis (>5/μL)	- (4/μL)	- (5/μL)	+ (34/μL)	+ (111/μL)	2 (50%)
Protain elevation (>40mg/dL)	- (35mg/dL)	- (23mg/dL)	+ (45mg/dL)	+ (44mg/dL)	2 (50%)
OCB	-	+	-	-	1 (25%)
IgG index[a] elevation (>0.7)	- (0.65)	+ (0.89)	+ (0.72)	- (0.56)	2 (50%)
MBP[a] elevation (>100pg/mL)	+ (306pg/mL)	+ (285pg/mL)	+ (775pg/mL)	+ (472pg/mL)	4 (100%)
AQP4-Ab	-	-	-	-	0 (0%)
MOG-Ab	+	+	+	+	4 (100%)
Abnormal findings on MRI at onset [b, c]					
Deep white matter	+	-	+	+	3 (75%)
Thalamus or basal ganglia	+	-	-	+	2 (50%)
Brain stem	-	-	-	+	1 (25%)

Cerebellum	-	+	-	-	1 (25%)
During the follow-up periods [b, c]					
Subcortical white matter	+	+	+	+	4 (100%)
Deep white matter	+	+	+	+	4 (100%)
Basal ganglia or thalamus	+	+	+	+	4 (100%)
Brain stem	+	+	-	+	3 (75%)
Cerebellum	+	+	-	-	2 (50%)
Optic nerve	-	-	-	-	0 (0%)
Spinal cord	-	-	-	-	0 (0%)
Final diagnosis	RRMS	RRMS	RRMS	RRMS	
Follow-up periods (years)	5.4	2.3	3.4	2.8	
Final EDSS score	1.0 (FS1, mental, ADHD)	0.0	0.0	0.0	

M: male; F: female; no.: number; CIS: clinically isolated syndrome; ADEM: acute disseminated encephalomyelitis; CSF: cerebrospinal fluid; OCB: oligoclonal band; MBP: myelin basic protein; AQP4-Ab: Aquaporin-4 antibody; MOG-Ab: myelin oligodendrocyte glycoprotein antibody; MRI: magnetic resonance imaging; RRMS: relapsing-remitting MS; EDSS: Expanded Disability Status Scale; FS: functional system; ADHD: attention deficit hyperactivity disorder

[a]The maximum values of all examinations are presented.

[b]Abnormal findings were defined as a high intensity area on a T2-weighted image.

[c]Abnormal lesions were categorized as subcortical white matter, deep white matter, basal ganglia, thalamus, brain stem, cerebellum, optic nerve, or spinal cord.

Table 2. Summary of IFNβ-1a Therapy

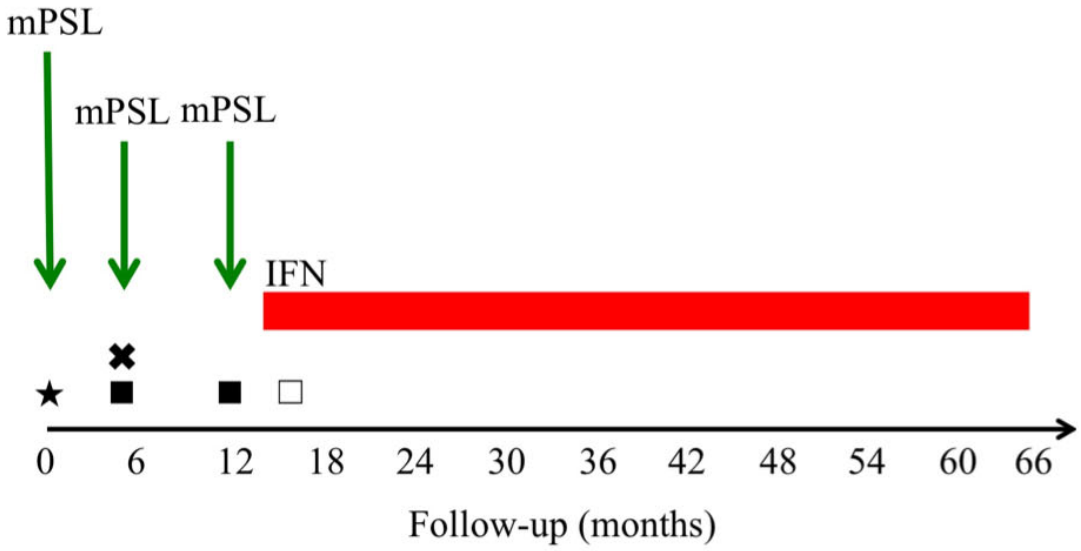
Case	Conditions at IFN initiation				Number of months on IFN per dosage						Total duration of IFN (years)	Adverse events			Annualized relapse rate (times/year)	
	Age (years)	Preceding treatment	Weight (kg)	Height (cm)	3 μg	6 μg	7.5 μg	9 μg	12 μg	15 μg		Flu-like symptoms	Increased liver enzyme	Injection site reaction	Before IFN therapy	During IFN therapy
1	3.1	None	19.2	102.1		1.5		5.5	4	40[a]	4.3	Fever (38.6°C) Headache	ALT (50IU/L)[b]	Pain in leg	1.8	0
2	3.5	None	11.5	86.0	0.25	4.5		2→off			0.6	Fever (38.9°C)	ALT (296IU/L)[b]	None	2.5	3.3
3	3.2	PSL	15.7	99.3		7		4.5	12[a]		1.9	Fever (38.6°C)	ALT (49IU/L)[b]	None	1.3	0
4	3.5	None	16.2	98.9		0.75	6.5	13[a]			1.7	Fever (39.0°C) Headache	None	None	0	0.6

PSL: prednisolone; IFN: interferon β-1a; ALT: alanine aminotransferase; no., number

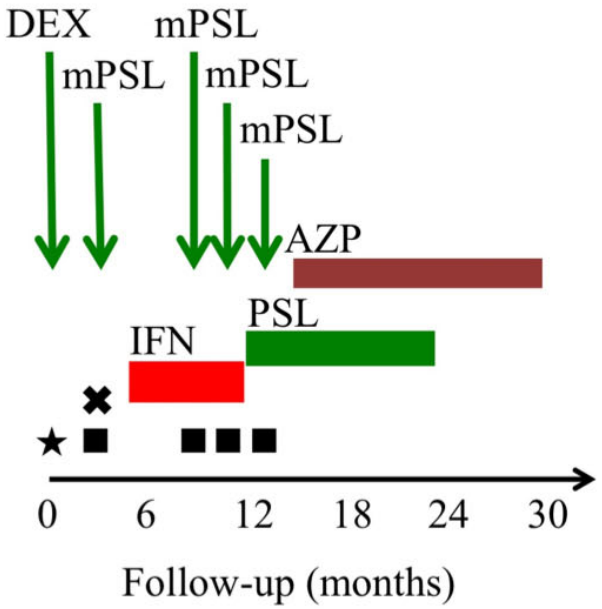
[a]Maintenance doses are shown at the last moment of the follow-up periods.

[b]Maximum values are shown during the follow-up periods.

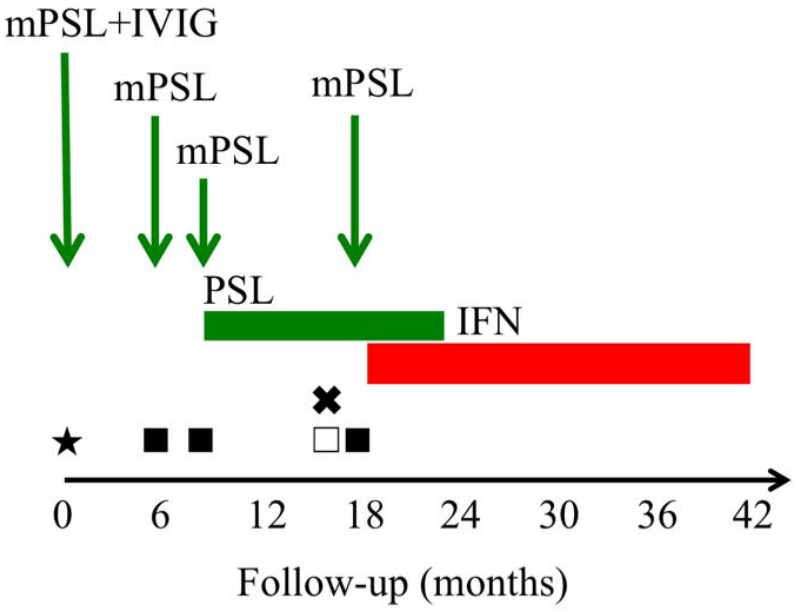
Patient 1
Onset: 2 years, 0 months; Diagnosis: 2 years, 6 months



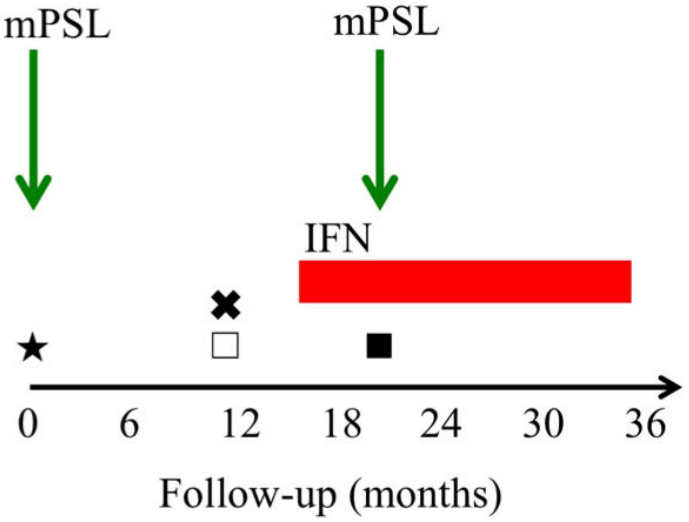
Patient 2
Onset: 3 years, 2 months; Diagnosis: 3 years, 4 months



Patient 3
Onset: 1 year, 8 months; Diagnosis: 3 years, 0 months



Patient 4
Onset: 2 years, 4 months; Diagnosis: 3 years, 4 months



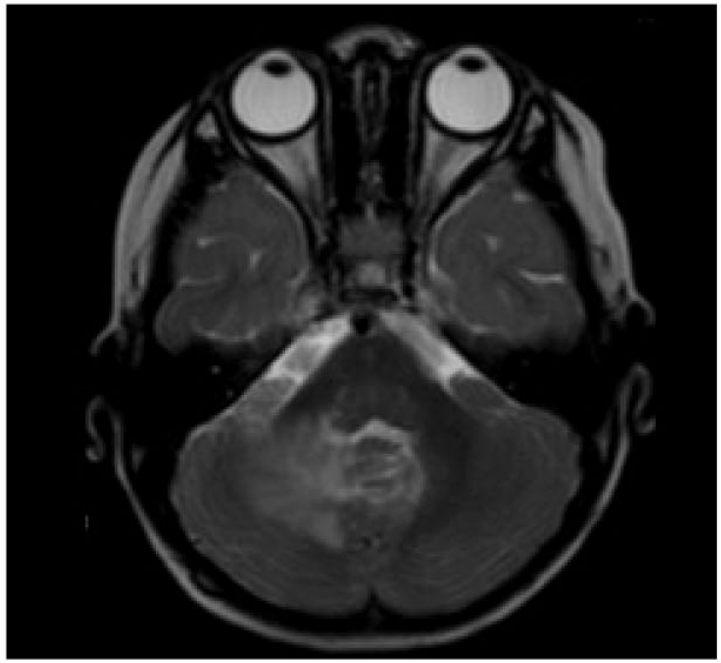


Figure 2a

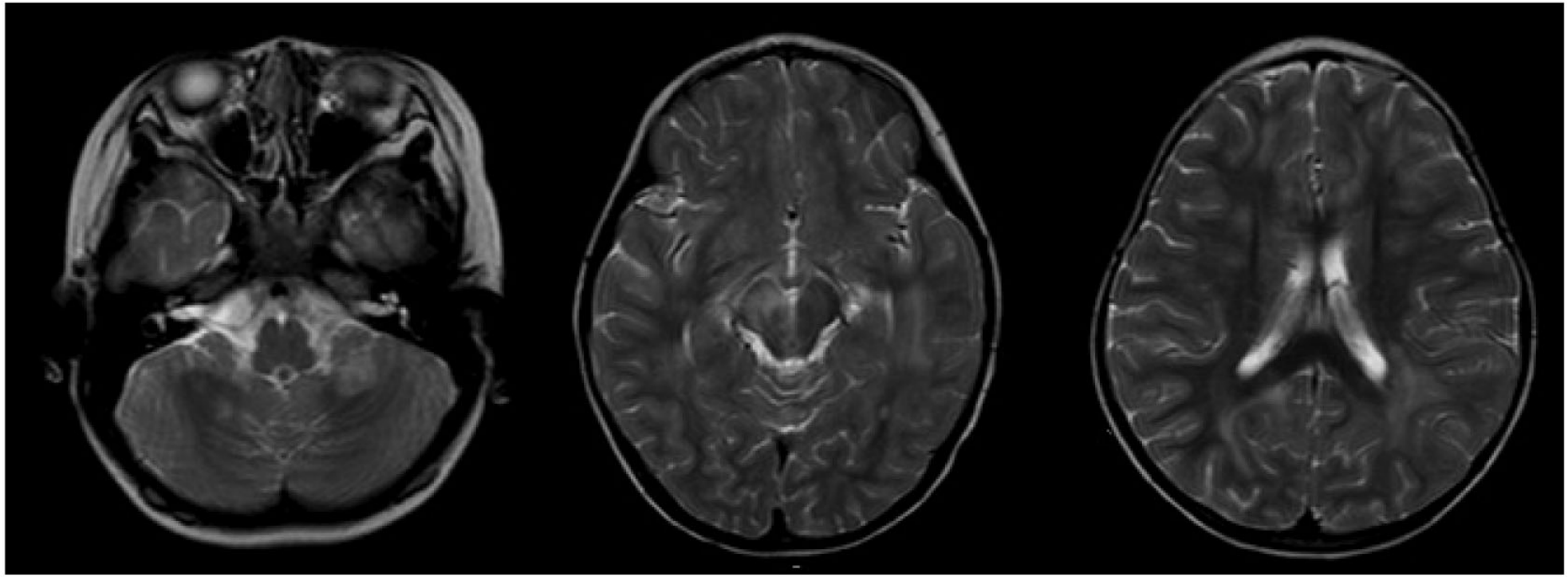


Figure 2b

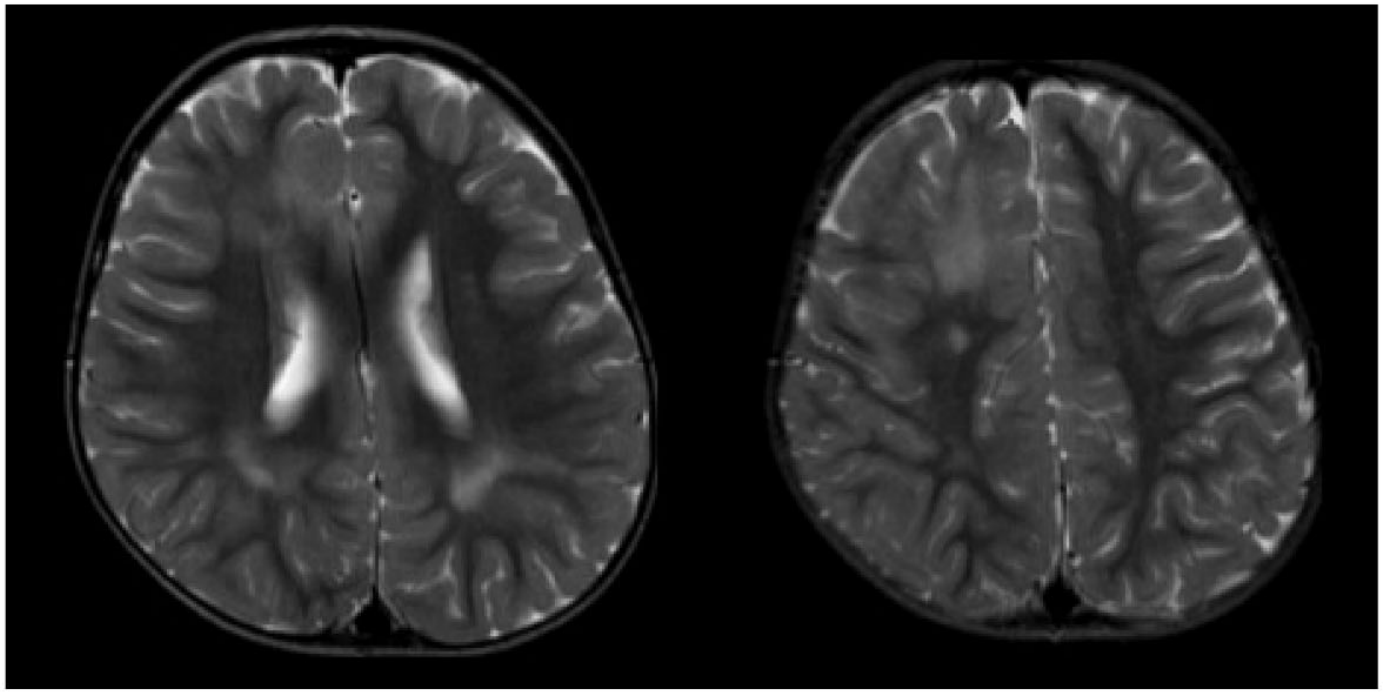


Figure 2c

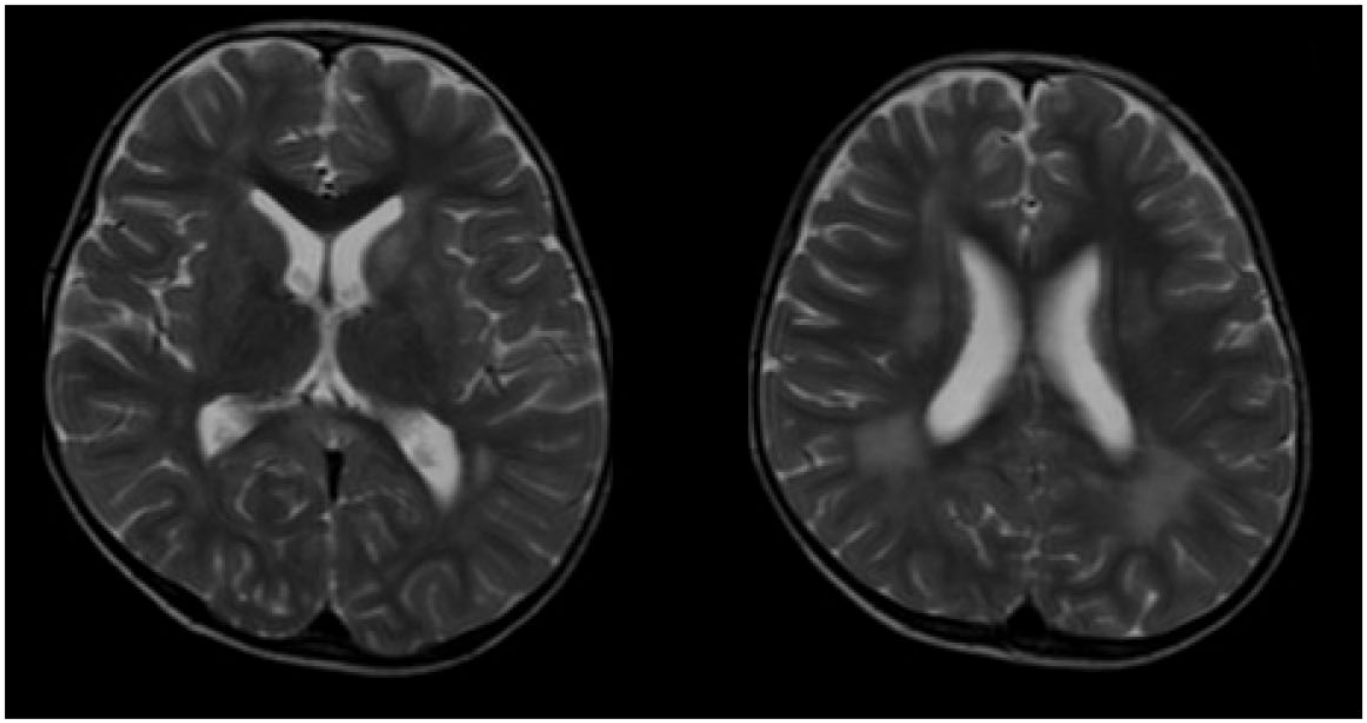


Figure 2d

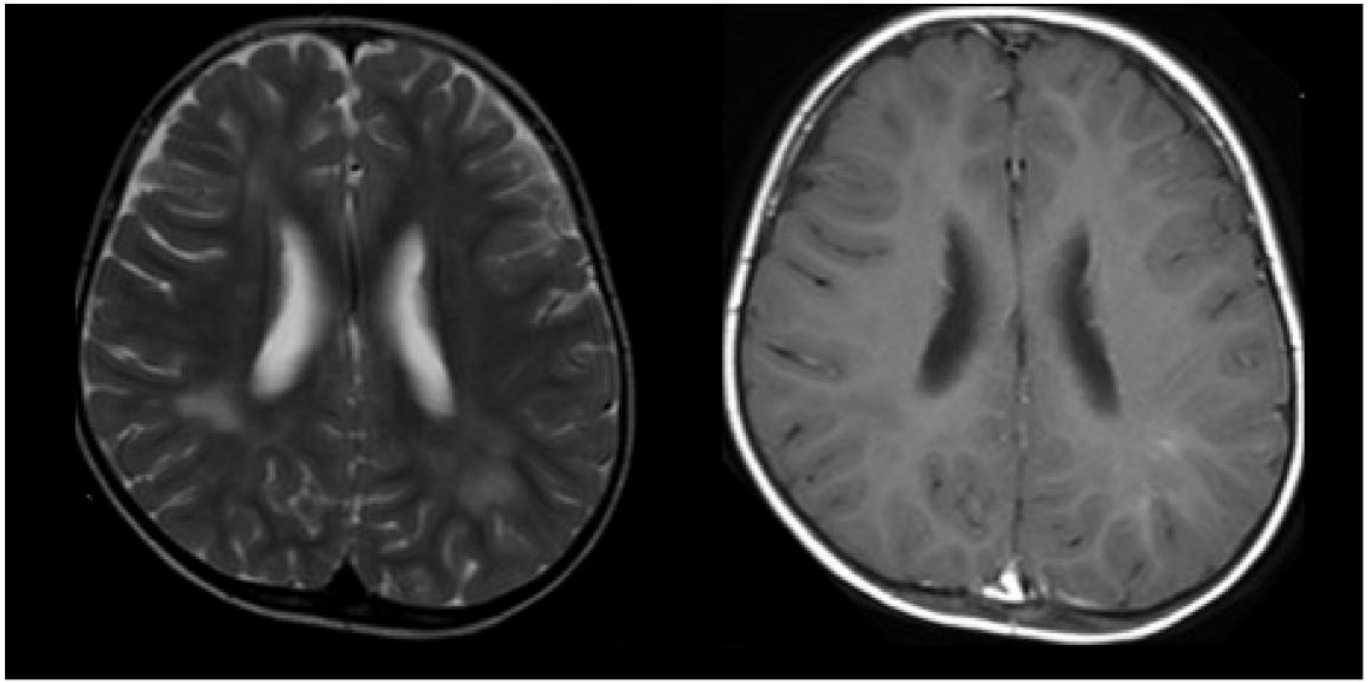


Figure 2e