following eye movement was saccadic but full. Movements of the soft palate were reduced. She had palatal tremor at 3 Hz, being synchronised with neck and vocal cord tremor. Her tongue movements appeared normal without atrophy or fasciculation. The left upper limb was plegic, and other limbs showed moderate weakness. A nose–finger–nose test showed right upper-limb ataxia. Tendon reflexes and muscle tone were normal, while the Trömner reflex and Babinski signs were positive bilaterally. There was no apparent sensory deficit or extrapyramidal signs. A urinary catheter had been inserted because of retention.

The following examinations were normal, negative or unremarkable: complete blood cell count, routine chemistry test, serum lactate acid, pyruvate acid, ACE, vitamin B_1, vitamin B_{12}, folic acid, thyroid functions, autoimmune antibodies, infection (hepatitis virus antibodies, Treponema serology, HIV antibodies, human T cell lymphotropic virus type-I antibodies), clotting studies, cerebrospinal fluid analysis, electrocardiography and transthoracic echocardiography. Urinalysis showed evidence of urinary-tract infection. Tumour markers were normal apart from elevated levels of CA19-9 (126 U/ml, normal range <37 U/ml). Enhanced body CT scan did not show any evidence of malignant tumour. A nerve-conduction study was unremarkable. Electroencephalography showed 10–12 Hz steady α waves and decreased amplitude on the left-hemispheric leads. A brain MRI revealed severe atrophy extending from the medulla to the upper cervical cord. There was T2 hyperintensity in the periventricular areas and medulla (figure 1B–D). Gadolinium enhancement was not detected. Magnetic resonance angiography was normal. Brain SPECT showed a slightly decreased perfusion of the right parietal lobe. After informed consent was obtained from the patient and her husband, genomic DNA was isolated from peripheral leucocytes. We identified novel heterozygous mutations in nucleotides 791 and 792 (791_792TG>CT), which were not found in 88 normal controls subjects. This change produced a proline for leucine in amino acid 264.

A month later, the patient was transferred to another hospital for further rehabilitation. She has not experienced exaggeration or progression since the last episode and has been stable in a general condition, but severe paresis and dysphagia have persisted without any improvement, at the time of writing 8 months afterwards.

DISCUSSION

Our patient had acute exacerbations and remissions without steady progression of the central nervus system dysfunction. Possible diagnoses included relapsing and remitting multiple sclerosis, neuro-Behçet disease, systemic lupus erythematosus and neurosarcoidosis, which were not consistent with the lack of systemic clinical features and autoimmune laboratory findings. Mitochondrial diseases were also a possible diagnosis, but normal levels of serum lactate acid and pyruvate acid did not support the diagnosis. The presence of atrophy of lower brainstem and spinal cord and mild deep white-matter lesion suggested the possibilities of spinocerebellar degeneration, leucoencephalopathy, leucodystrophy and adult polyglucosan disease, which usually do not present fluctuating clinical courses. Adult Alexander disease often shows marked atrophy of the lower brainstem and spinal cord rather than the severe white-matter abnormality with frontal predominance of infantile and juvenile Alexander disease.[1] While infantile and juvenile Alexander disease is usually progressive, adult Alexander disease has been reported to show various clinical courses.[2] They were progressive in many cases, but some cases showed acute onset.[3] The symptoms usually persists but may improve, especially at the early stage of the disease.[4] Schwankhaus and colleagues reported an autopsied case of adult Alexander disease, presenting with exacerbation and remission followed by progression, before the era of genetic comfimation.[5] This patient awoke with paralysis of his left arm and experienced recovery after 5 days but 5 years after this episode suffered from progression of disease and died. This clinical course may be similar to that of our case, although the description of this case was not enough to compare. Although symptom fluctuations were noted in adult Alexander disease, there was no report of genetically confirmed adult Alexander disease with a detailed clinical course of acute exacerbation and remission, and relapse, to our best knowledge.

Our case showed a fluctuating clinical course of adult Alexander disease. In the case of lower brainstem and spinal cord atrophy with an intermittent clinical course, a sequence analysis of *GFAP* seems warranted.

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Olfactory function in Parkinson's disease in ON versus OFF states

INTRODUCTION

Parkinson's disease (PD) patients can present deficits in all three main modalities of smell tests: odour detection threshold, discrimination and identification. Cross-sectional studies have shown no relationship between odour identification or detection threshold and disease severity, symptom duration or pharmacological treatment of PD, although odour discrimination might be worse in patients with more severe disease.[1] Few longitudinal studies have addressed the antiparkinsonian treatment effect on olfaction. Apomorphine did not change the odour detection threshold when administered to PD patients.[2] Quinn *et al*[3] applied olfactory threshold tests to PD patients with motor fluctuations and noticed no change between ON and OFF states. Nevertheless, surgical treatment for PD using deep brain stimulation (DBS) of the subthalamic nucleus may improve olfaction in PD. Hummel and colleagues[4] tested the odour detection threshold and discrimination in 11 PD patients with the DBS stimulator ON versus OFF, and noticed that discrimination improved while the stimulator was ON. Guo and colleagues[5] tested PD patients before and after subthalamic nucleus DBS surgery, in addition to stimulator ON and OFF; they found no difference in olfactory measures before and after surgery but reported an improvement in odour identification threshold (but not detection threshold) when the stimulator was ON, compared with OFF. The mechanism underlying the improvement is unclear.

We hypothesised that in PD patients with wearing-off, odour identification would be improved in the ON state when compared with the OFF state and examined 16 PD

A case of sporadic adult Alexander disease presenting with acute onset, remission and relapse

Takashi Ayaki, Miho Shinohara, Shinsui Tatsumi, et al.

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CASE REPORT Open Access

Adult-onset Alexander disease with typical "tadpole" brainstem atrophy and unusual bilateral basal ganglia involvement: a case report and review of the literature

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Abstract

Background: Alexander disease (ALX) is a rare neurological disorder characterized by white matter degeneration and cytoplasmic inclusions in astrocytes called Rosenthal fibers, labeled by antibodies against glial fibrillary acidic protein (GFAP). Three subtypes are distinguished according to age at onset: infantile (under age 2), juvenile (age 2 to 12) and adult (over age 12). Following the identification of heterozygous mutations in *GFAP* that cause this disease, cases of adult-onset ALX have been increasingly reported.

Case Presentation: We present a 60-year-old Japanese man with an unremarkable past and no family history of ALX. After head trauma in a traffic accident at the age of 46, his character changed, and dementia and dysarthria developed, but he remained independent. Spastic paresis and dysphagia were observed at age 57 and 59, respectively, and worsened progressively. Neurological examination at the age of 60 revealed dementia, pseudobulbar palsy, left-side predominant spastic tetraparesis, axial rigidity, bradykinesia and gaze-evoked nystagmus. Brain MRI showed tadpole-like atrophy of the brainstem, caused by marked atrophy of the medulla oblongata, cervical spinal cord and midbrain tegmentum, with an intact pontine base. Analysis of the *GFAP* gene revealed a heterozygous missense mutation, c.827G>T, p.R276L, which was already shown to be pathogenic in a case of pathologically proven hereditary adult-onset ALX.

Conclusion: The typical tadpole-like appearance of the brainstem is strongly suggestive of adult-onset ALX, and should lead to a genetic investigation of the *GFAP* gene. The unusual feature of this patient is the symmetrical involvement of the basal ganglia, which is rarely observed in the adult form of the disease. More patients must be examined to confirm, clinically and neuroradiologically, extrapyramidal involvement of the basal ganglia in adult-onset ALX.

Background

Alexander disease (ALX) (OMIM #203450), originally described by Alexander in 1949 [1], is a rare and fatal disease of the central nervous system caused by astrocyte dysfunction [2,3]. The pathological hallmark of the disease is the accumulation of ubiquitinated intracytoplasmic inclusions in astrocytes, called Rosenthal fibers, which are composed of glial fibrillary acidic protein (GFAP), the main intermediate filament of astrocytes, in association with the small heat shock proteins, HSP27 and αB-crystallin [4].

The clinical features of typical infantile-onset ALX, with onset before the age of two, include megalencephaly, seizures, spastic paresis and psychomotor deterioration with leukoencephalopathy characterized by white matter abnormalities predominating in the frontal lobes. As cases accumulate, however, atypical patients have also been described. Adult-onset ALX, with onset over the age of 12, is characterized by more slowly progressive bulbar or pseudobulbar palsy, spastic paresis, ataxia, palatal myoclonus and essentially normal psychic and intellectual functions. Juvenile-onset ALX, with

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onset between age 2 and 12, bridges the gap between infantile and adult forms of the disease. However, it is not yet clear whether these three categories are the same disease. The clinical presentations are diverse; the only common feature is the presence of pathologically proven Rosenthal fibers [5,6].

Owing to the discovery of inclusion bodies indistinguishable from Rosenthal fibers in fatal GFAP transgenic mice overexpressing human GFAP in astrocytes [7], de novo heterozygous mutations in the gene encoding GFAP, the main component of Rosenthal fibers, have been identified in patients with the infantile form of ALX [8]. *GFAP* gene mutations have also been identified in the juvenile [8,9] and adult [10,11] forms. These three clinically diverse forms are now widely accepted to be part of the same spectrum [12].

Each subtype has characteristic MRI findings. Cerebral white matter abnormalities, predominating in the frontal lobes, are typical of the infantile form of ALX [13], whereas nodular brainstem lesions and a kind of "garland" along the ventricular wall are seen, with contrast enhancement, in the juvenile form [14,15]. The adult form has a unique tadpole-like feature, caused by marked atrophy of the medulla oblongata and cervical spinal cord with an intact pontine base [11].

Here we present a case of sporadic adult-onset ALX with specific MRI findings: a typical tadpole-like brainstem, but also symmetric involvement of the basal ganglia, which is unusual in the adult form of ALX.

Case Presentation

This Japanese patient, with an unremarkable past and no family history had been healthy until he was involved in a traffic accident at the age of 46. He suffered a bilateral brain contusion in the fronto-orbital areas, predominating on the left side. He did not lose his consciousness, but retrograde amnesia was seen. There was no hypoxia. After this accident, his character changed. He became querellous, could no longer manage his shop, and soon retired. He gradually became taciturn and his pronunciation became unclear, but he remained independent. At age 57, he began to drag his left foot as he walked, and this symptom gradually worsened. At the age of 59, progressive dysphagia appeared. He was referred to our hospital at the age of 60. Neurological examination revealed pseudobulbar palsy including aphonia, emotional incontinence and dysphagia, left-side predominant tetraparesis. The tone of the limb muscles was spastic, with bilateral positive Babinski signs. Axial rigidity, bradykinesia and retropulsion were observed, but no tremor or palatal myoclonus. Cerebellar ataxia was ambiguous because of spastic tetraparesis requiring use of a wheelchair, but bilateral gaze-evoked nystagmus was seen. He was clearly demented and angrily refused everything he was asked to do by shaking his head instead of speaking because of aphonia. Further evaluation of his dementia was impossible.

Laboratory tests, including hematology, routine blood chemistry, and analyses of urine and cerebrospinal fluid, were unremarkable. In addition to the bilateral contusion in the fronto-orbital areas, especially on the left side, brain MRI showed a tadpole-like brainstem, caused by marked atrophy from the medulla oblongata to the cervical spinal cord, sparing the pontine base. Marked atrophy of the midbrain tegmentum, mild cerebellar atrophy with a little enlargement of the fourth ventricle, and slight cerebral atrophy were also seen. The typical periventricular lesions (ventricular garlands [15]) and leukoencephalopathy were not seen, however, several lacunae were observed bilaterally in deep white matter. The posterior part of globus pallidus was involved bilaterally, as shown by a signal change without contrast enhancement (Figure 1).

With informed consent, the *GFAP* gene was sequenced, and a heterogeneous missense mutation was detected in exon 5 (c.827G>T), causing a change of arginine to leucine at amino acid position 276 (p.R276L). We have already described this mutation in a patient with pathologically proven hereditary adult-onset ALX [11]. There was no relationship between the present patient and the family previously reported [11]. According to an interview, however, both families originated from the same region of Japan.

Discussion

We have described here a new patient with sporadic adult-onset ALX, and have identified a heterozygous missense mutation in the *GFAP* gene, c.827G>T, p.R276L, which was already shown to be pathogenic in a case of pathologically proven hereditary adult-onset ALX [11]. This mutation has not been seen for the last 7 years. Thus, this report reconfirms the pathogenetic nature of the mutation and the clinical picture of this form of the disease. So far, the phenotype associated with the R276L mutation is adult-onset spastic ataxia with pseudobulbar symptoms.

Following identification of the *GFAP* gene as responsible for ALX [8], the adult form has been increasingly reported [10,11,15-36]. However, only a few cases have been pathologically proven [11,16,17,21,28]; the rest were diagnosed as having ALX only by molecular testing. Since missense mutations may only be polymorphisms [37], their pathogenicity must be accepted with caution. Indeed, the E223Q mutation, identified in a patient with neurological deficits and radiological findings atypical for adult-onset ALX [38], is now classified as a polymorphism [21]. Therefore, to avoid this kind of confusion, it is worthwhile defining the typical presentation of adult-onset ALX, including

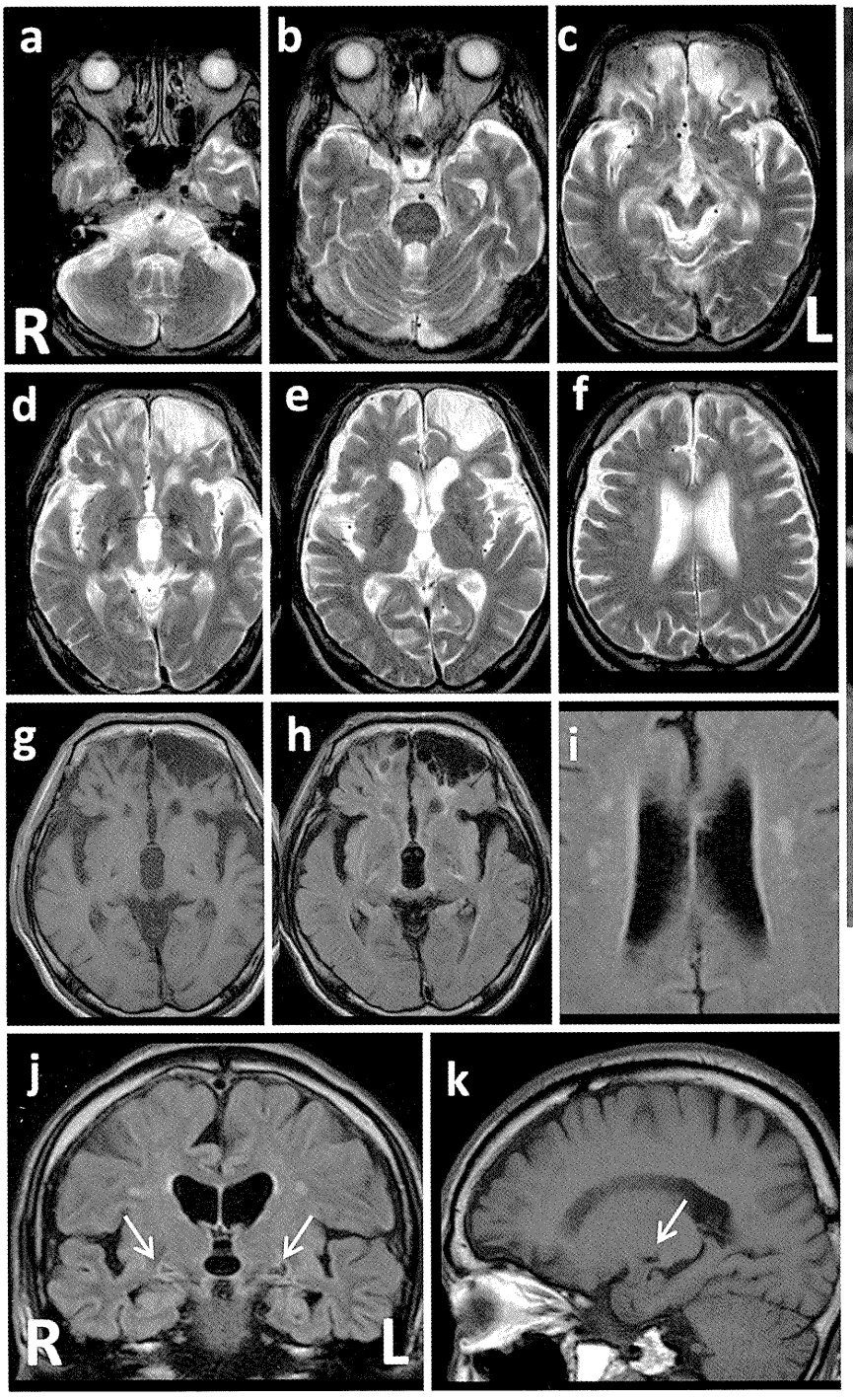

Figure 1 Brain MRI of a patient with adult-onset Alexander disease. a-f: T2-weighted axial images showing marked atrophy of the medulla oblongata (a) with slight cerebellar atrophy (a, b) but little atrophy of the pontine base (b), enlargement of the fourth ventricle (b), atrophy of the midbrain, especially the dorsal part (c), bilateral changes in the posterior part of globus pallidus (d), bilateral lesions of the fronto-orbital areas, predominating on the left, caused by brain contusion (d, e, g, h), moderate cortical atrophy with ventricular enlargement (e, f), and bilateral lacunae in the deep white matter, but no leukoencephalopathy (f). g and k: T1-weighted images of the lesions on axial (g) and sagittal (k) sections. h, i and j: FLAIR images of the lesions on axial (h, i) and coronal (j) sections. The lesions on coronal (j) and sagittal (k) sections are indicated by arrows. Note the absence of ventricular garlands [15]. l: T1-weighted sagittal section showing typical tadpole-like brainstem atrophy, consisting of marked cervico-medullary atrophy with an intact pontine base; note that atrophy of the midbrain tegmentum also contributes to the formation of the tadpole.

age at onset, cardinal clinical symptoms, neuroradiological findings and clinical course, as described in published reports [see review article, ref [33]].

To date, at least 24 reports of adult onset ALX, including over 40 patients, with 22 different missense mutations in the *GFAP* gene, have been published (Table 1) [10,11,15-36]. There are no sex differences, and half of the cases are familial, consistent with autosomal dominant transmission. The mean age at onset is in the late thirties, although an asymptomatic carrier over age 60 has been described [30]. The cardinal triad of the clinical presentation is pseudobulbar or bulbar palsy, spastic paresis (usually hemiparesis, not paraparesis, at onset), and ataxia, each of which is observed in approximately 70% of patients. Palatal myoclonus is observed in only one third, although it is specific to ALX, and the key finding for a diagnosis, especially in hereditary cases [10]. Mental function is usually preserved, although our patient was obviously demented. Dementia cannot, however, be considered a symptom of adult-onset ALX in this patient, because of his cerebral contusion.

As for the MRI findings [see review article, ref [34]], most of the cases had medullary abnormalities (either signal abnormalities or atrophy), and the marked tadpole-like atrophy of the medulla oblongata and cervical spinal cord with an intact pontine base [11]. We would like to emphasize that not only cervicomedullary atrophy with an intact pontine base, but also severe atrophy of the midbrain tegmentum contributes to the formation of the tadpole. This unusual atrophy is quite specific to adult-onset ALX, and 88% of the patients with adult-onset ALX in the literature showed marked medullary atrophy (Table 1). Thus, awareness of this MRI pattern allows effective selection of the patients who need genetic investigations for mutations in the *GFAP* gene [34]. Indeed, we could have diagnosed adult-onset ALX in the present patient on the basis of this form of brainstem atrophy.

Table 1 Summary of the clinical features and MRI features of adult-onset Alexander disease reported in the literature [10,11,15-36].

Sex Difference	M/F = 23/22
Average age at onset	37.0 ± 17.9 (n = 36), Range: 12.5-62
Clinical features	
Bulbar symptom	35/45 (78%)
Pyramidal tract signs	33/45 (73%)
Ataxia	31/44 (71%)
Palatal myoclonus	15/38 (39%)
MRI findings	
Marked medullary atrophy	37/42 (88%)
Deep white matter abnormalities	21/43 (49%)
Brainstem signal change (including nodular lesions)	16/36 (44%)

Approximately half of the patients had deep white matter lesions or periventricular rims, although not always with frontal predominance as in infantile-onset ALX; the absence of these abnormalities is significantly associated with older age at onset (average age at onset; negative 43.7 ± 14.1 (n = 18) vs. positive 30.9 ± 12.8 (n = 18), $p = 0.008$), consistent with previous study [34]. Similarly, nodular lesions in the brainstem are observed in about half of the patients, and are significantly associated with a younger age at onset (average age at onset; positive 28.2 ± 11.8 (n = 13) vs. negative 43.6 ± 13.9 (n = 18), $p = 0.003$).

Besides the typical clinical and neuroradiological features, this case of adult-onset ALX is instructive because of the bilateral involvement of the basal ganglia. This is not uncommon in infantile or juvenile-onset ALX, and is one of the radiological criteria for the diagnosis [13], but has rarely been observed in the adult form of the disease. Symmetrical striatal lesions were observed in one patient, however, with hypointensity on T2-weighted MRI [22]. Basal ganglia lesions with hyperintensity on T2-weighted MRI, such as spotty lesions [19] and bilateral lesions in the lateral putamen [30], have occasionally been reported; both of these signs are ambiguous, however, and do not resemble those of our patient. Thus, the symmetrical lesions in our patient are interesting findings in adult-onset ALX, and might be related to a rigid-bradykinesia type parkinsonism, although this is uncertain because spastic paresis masks the parkinsonism. The clinical signs and symptoms of basal ganglia involvement, such as parkinsonism [patient 1 of ref [21]], diffuse bradykinesia [22], and rigidity of the arms [29] are rarely reported. The obvious parkinsonism reported in one patient was induced by valproate [32].

Conclusion

We described here a new sporadic case of genetically confirmed adult-onset ALX. The tadpole-like brainstem atrophy is quite specific for adult-onset ALX. Thus, faced with a patient with progressive spastic ataxia, bulbar or pseudobulbar signs, and the typical tadpole on MRI, a genetic investigation of the *GFAP* gene is strongly recommended. The unusual feature of our patient is the obvious symmetrical involvement of the basal ganglia, which presumably caused a rigid-bradykinesia type parkinsonism. More cases must be studied to completely elucidate the characteristics of adult-onset ALX.

Consent

Written informed consent was obtained from the patient and his wife for publication of this case report and

accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

ALX: Alexander disease; GFAP: glial fibrillary acidic protein; FLAIR: fluid attenuated inversion recovery;

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Authors' contributions

This manuscript was drafted by MN. YT and IN contributed to the references and helped to write the manuscript. JH, HS and KS sequenced the *GFAP* gene. All authors contributed to the critical review and approval of the final draft.

Competing interests

The authors declare that they have no competing interests.

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Original article

Diffuse cerebral hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum

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Abstract

Three unrelated Japanese patients who presented with ataxia and mild mental retardation were examined in this study. Early development was normal in two patients and slightly delayed in one. All could walk independently, but were unstable due to cerebellar ataxia. They had mild intellectual retardation and displayed slow, progressive, and mild clinical courses. Two patients lost the ability to walk at 12 and 25 years of age. Brain MRI of the three patients revealed diffuse cerebral hypomyelination, moderate cerebellar cortical atrophy, and hypoplasia of the corpus callosum, which were seen in other diffuse hypomyelination syndrome. No known abnormalities were found in biochemical and genetic studies. Auditory brainstem responses and nerve conduction studies were normal. A definite diagnosis could not be made because of the lack of hypodontia, hypogonadism, cataracts, or basal ganglia atrophy. Based on common MRI findings and the relatively mild clinical courses, we believe that these patients may have another subset form of diffuse hypomyelination syndrome involving the cerebral white matter and cerebellum.

Keywords: Hypomyelination; Cerebellar atrophy; Atrophy of the corpus callosum; Slow progressive; MRI

1. Introduction

Recent advances in magnetic resonance imaging (MRI) have made it easy to recognize the presence of cerebral white matter disorders. However, despite extensive investigations, more than half of young patients with cerebral white matter disorders cannot be diagnosed correctly [1]. van der Knaap et al. [1] successfully divided abnormalities of cerebral white matter into several categories using MRI. Several new syndromes involving cerebral white matter have been described recently. Childhood ataxia with diffuse central nervous system hypomyelination was consistent with vanishing white matter leukoencephalopathy [2,3]. Leukoencephalopathy with swelling and a discrepantly mild clinical course was named megalencephalic leukoencephalopathy with subcortical cysts [4]. Genetic abnormalities were discovered in both disorders [5,6]. A new syndrome characterized by hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) was also proposed by van der Knaap et al. [7]; the underlying genetic abnormality responsible for this entity has not been identified [8–10]. Other new syndromes involving diffuse hypomyelination with systemic abnormalities such as cataracts, hypogonadism, and/or hypodontia have also been reported [11–15].

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We describe three unrelated cases with common brain MRI findings including supratentorial diffuse hypomyelination, cerebellar atrophy, and hypoplasia of the corpus callosum, and relatively mild clinical courses.

2. Patients and methods

Clinical histories for each patient are presented in Table 1.

Patient 1 was an 11-years-old female. She was born to healthy and unrelated parents after an uneventful delivery, and had a healthy younger brother. Early developmental milestones were normal. She obtained head control at 3 months, sat without support at 6 months, and walked without support at 11 months. She started to speak words at 18 months and sentences at 2 years of age. Her parents noted that she walked unsteadily from the time she began to walk, and that she fell down easily. The patient came to our hospital at 4 years of age. She had ataxic gait, dysarthria, intention tremor, and dysmetria. She also had a mild intellectual disability. At 11 years of age, she showed no further deterioration. She had a short stature (119 cm; −3 SD), normal head circumference, and cerebral symptoms (mild spasticity and intellectual disability). Teeth were normal, and blood examination revealed normal gonadotropin levels.

Patient 2 was a 16-years-old male. He was born to healthy and unrelated parents after an uneventful delivery. Early development was normal. He began to walk when he was 12 months old, but his walking remained unstable from the time he began walking. He spoke several words from 1 year of age, and simple sentences from 3 years of age. He lost the ability to walk at 12 years of age. At 16 years of age, he showed increasing muscle tone and exaggerated deep tendon reflexes. Pathological reflexes were positive. He could not maintain an upright position, and had tremors and dysmetria in the upper extremities. Motor deterioration was prominent, but intellectual disability was not progressive.

Patient 3 was a 33-years-old male. He was born to healthy and unrelated parents after an uneventful delivery. He achieved steady head control at 4 months of age, and could roll over at 7 months. He could walk without support at 2 years and 4 months of age, but tended to walk unsteadily. The patient was diagnosed with ataxic cerebral palsy at 3 years of age. He was able to speak several words from the age of 2 years, and could construct sentences from 6 years of age. He attended a school for physically handicapped children for 12 years. Motor and intellectual deterioration started after 20 years of age. He lost the ability to walk by 25 years of age, and gradually lost the ability to speak words. He developed tonic seizures at 27 years of age, and was

Table 1
Clinical history and present findings in the patients

	Patient 1	Patient 2	Patient 3
Current age (Y)	11	16	33
Sex	Female	Male	Male
Consanguinity	No	No	No
Initial motor development	Normal	Normal	Delayed
Unsupported walking	11 months unsteady	12 months unsteady	2 year 4 months unsteady
Onset of motor deterioration	No deterioration	10 Years	20 Years
Loss of walking	Still able to walk	12 Years	25 Years
Motor signs			
Ataxia	Yes	Yes	Yes
Tremor	Yes	Yes	Yes
Choreoathetosis	No	No	No
Dystonia	No	Yes	Yes
Spasticity	Yes	Yes	Yes
Rigidity	No	Yes	Yes
Dysarthria	Yes	Yes	Yes
Nystagmus	No	No	No
Intelligence	MR (mild)	MR (mild)	MR (moderate)
Cognitive decline	No	Yes	Yes
Epilepsy	No	No	Yes: Few seizures
Vision	Normal	Normal	Normal
Hearing	Normal	Normal	Normal
HC	Normal	Normal	Normal
Stature	<2SD	Normal	Normal
Hypogonadism	No	No	No
Hypodontia	No	No	No
Cataract	No	No	No

HC, head circumference; MR, mental retardation.

successfully treated with carbamazepine. At 33 years of age, he showed increasing muscle tone and exaggerated deep tendon reflexes. Pathological reflexes were positive. He could sit, but not move, by himself, and had tremors and dysmetria in the upper extremities. The patient also exhibited spasticity and mild dystonia.

All patients underwent biochemical studies of blood and urine, genetic analysis, neurophysiological examination. MRI and proton magnetic resonance spectroscopy (MRS) were performed with 1.5T. Conventional T1- and T2-weighted images were obtained in axial and coronal section. Sagittal section was done only in T1-weighted image. MRS of the cerebral white matter was performed.

3. Results

3.1. Laboratory findings

Patients underwent the following tests: blood gas analysis; blood lactate/pyruvate analysis; sialic acid analysis; protein-C and protein-S tests; very long-chain fatty acid analysis (blood); lymphocyte lysosomal enzyme activities (arylsulfatase A, beta galactosidase, and hexosaminidase A); amino acid analysis (plasma); and organic acid analysis (urine). No abnormal results were obtained.

Genetic analyses of the proteolipid protein (*PLP*) and gap junction protein (*GJP12*) for Pelizaeus-Merzbacher disease did not reveal abnormalities. Karyotypic analysis of blood cells did not reveal abnormalities, and showed that there were no deletions in chromosome 18.

Brainstem auditory evoked potentials were recorded, and the latencies of waves I–V were found to be normal in all patients. Nerve conduction velocities and the amplitudes of compound muscle action potentials were also within normal limits.

3.2. MRI

A complete lack of myelin throughout the supratentorial cerebral white matter was observed in all cases in T2-weighted images (Fig. 1a–c). In T1-weighted images, myelin in the cerebral white matter in patients 2 and 3 seemed almost normal (data not shown). The brainstem and cerebellar white matter contained some myelin in T2-weighted images. The corpus callosum was very thin, and was normally myelinated in T1-weighted images in all patients (Fig. 1d–f). Diffuse cerebellar atrophy, particularly in the cortex, was observed in all patients (Figs. 1 and 2). Pons was slightly atrophic in all (Fig. 2). T2-weighted and fluid-attenuated inversion-recovery images did not reveal abnormal intensities in the cerebellum and pons.

In patient 1, T2-weighted images revealed diffuse high-intensity areas in cerebral white matter (Fig. 3a, d), but the T1-weighted images revealed a slow progressive loss of myelin (Fig. 3b, c, e, f). The volume of basal ganglia was preserved in all patients. Mild diffuse cerebral atrophy was observed only in patient 3.

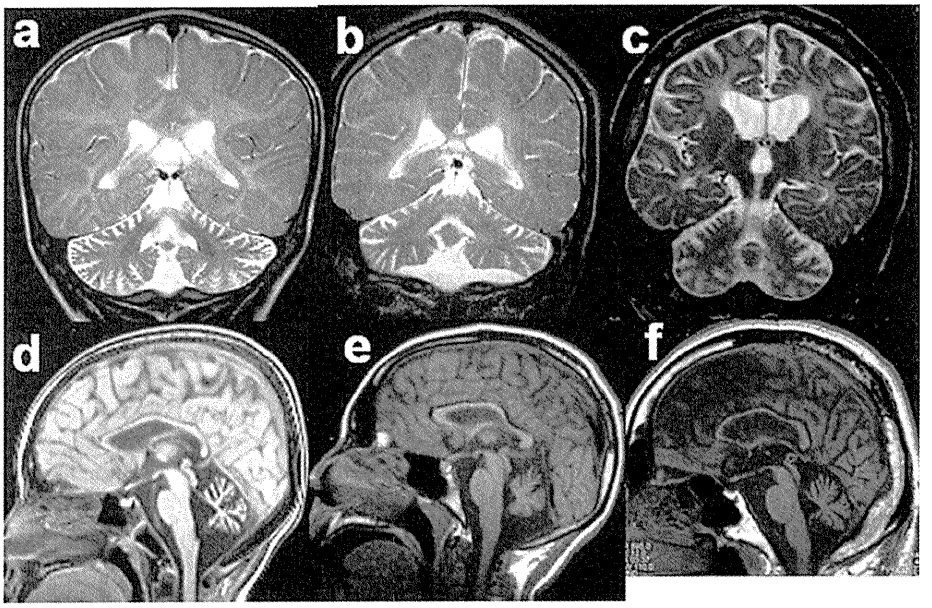

Fig. 1. T2-weighted coronal MRI (a, b, c) revealing high-intensity areas in the cerebral white matter and diffuse cerebellar cortical atrophy. Cerebral atrophy can be observed only in patient 3. T1-weighted sagittal MRI (d, e, f) reveals atrophy of the cerebellar vermis and hypoplasia of the myelinated corpus callosum in all cases (a, d: patient 1; b, e: patient 2; c, d: patient 3).

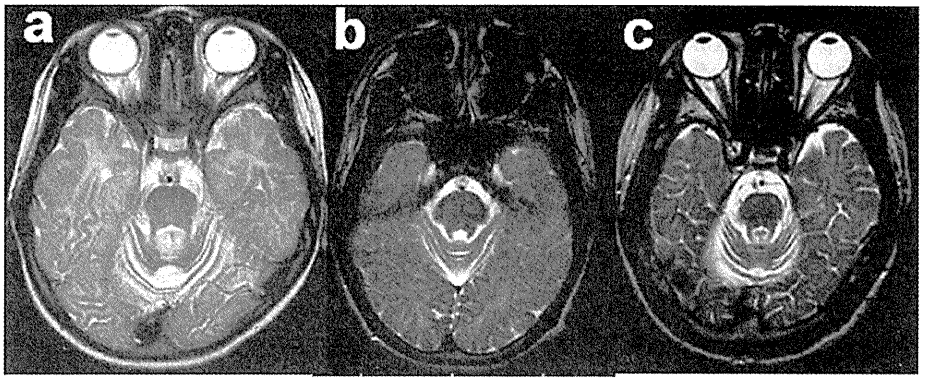

Fig. 2. T2-weighted axial MRI at the cerebellopontine level (a: patient 1; b: patient 2; c: patient 3). The cerebellar cortex is atrophic, and normal signal intensity can be seen in all three cases. Pons is slightly atrophic, but myelination appears normal in all cases.

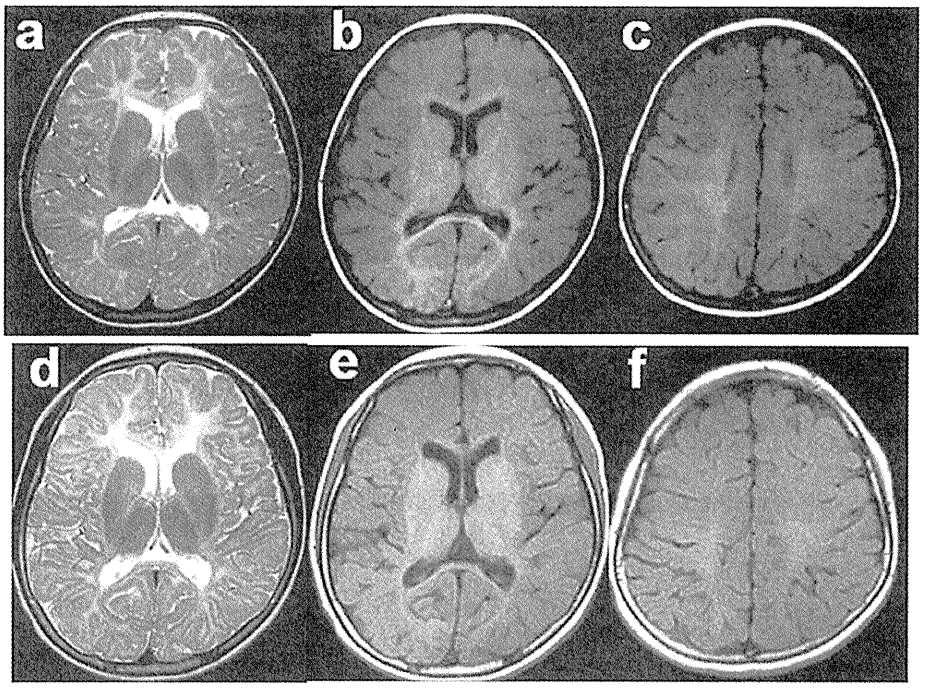

Fig. 3. Axial MRI of patient 1. At 4 years of age (above), diffuse high-intensity areas can be seen throughout the white matter in T2-weighted image (a) and high-intensity areas are evident in the central white matter in T1-weighted images (b, c), indicating diffuse hypomyelination. At 11 years of age (below), T2-weighted image shows findings (d) identical to that seen at 4 years of age. T1-weighted images show that the area of myelinated white matter is reduced (e, f) compared with that seen at 4 years of age, indicating a progressive disorder. The volume of basal ganglia is normal.

3.3. MRS

MRS of the cerebral white matter revealed that the lactate/lipid peak, the *N*-acetylaspartate (NAA)/creatine (Cr) ratio, and the choline/Cr ratio were normal in all patients.

4. Discussion

The common symptoms in the patients described in this study were ataxic gait, mild or moderate intellectual deterioration, and a very mild progressive clinical course. Common MRI findings included diffuse high-intensity areas in the cerebral white matter in T2-weighted images, mild cerebellar atrophy, and hypoplasia of the corpus callosum. MRI findings in all patients indicated hypomyelination due to the diffuse high-intensity signal throughout the abnormal area in the cerebral white matter in T2-weighted images, and the relatively high-intensity area in T1-weighted images. Biochemical and/or genetic studies excluded disorders characterized by diffuse hypomyelination such as Peliza-

Table 2
MRI findings in various diffuse hypomyelination syndromes

Syndrome	Cerebral white matter	Atrophy of the basal ganglia	Atrophy of the cerebellum	Atrophy of the corpus callosum	Specific features
H-ABC	Diffuse hypomyelination	(+)	(+)	(+) or (−)	Atrophy of the basal ganglia
4H	Diffuse hypomyelination	(−)	(+) or (−)	(+)	Hypogonadism Hypodontia Peripheral neuropathy
HH	Diffuse hypomyelination	(−)	(−)	(+) or (−)	Hypodontia
HCC	Diffuse hypomyelination	(−)	(−)	(+) or (−)	Cataract Peripheral neuropathy Hyccin deficiency
Present cases	Diffuse hypomyelination	(−)	(+)	(+)	Mild clinical course

H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum.
4H, hypomyelination with hypogonadotropic hypogonadism and hypodontia.
HH, hypomyelination and hypodontia.
HCC, hypomyelination and congenital cataract.

eus-Merzbacher disease, Salla disease, or Pelizaeus-Merzbacher-like syndrome [16,17].

MRI findings of diffuse cerebral hypomyelination have been described in other syndromes, including hypomyelination and congenital cataracts (HCC), hypomyelination with hypogonadotropic hypogonadism and hypodontia (4H), hypomyelination and hypodontia (HH), and hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). These syndromes have characteristic findings that occur along with diffuse cerebral hypomyelination, such as congenital cataracts and peripheral neuropathy in HCC (no cerebellar atrophy); hypogonadotropic hypogonadism, hypodontia and peripheral neuropathy in 4H; hypodontia in HH; and cerebellar and basal ganglia atrophy in H-ABC.

MRI findings of the cerebral white matter in the patients described here were similar to the four syndromes listed above (Table 2), but further myelin loss was observed in T1-weighted images in patient 1 during follow-up. Identical MRI changes have been reported in some patients with H-ABC [10]. The patients in this study also had slow progressive clinical courses. Some patients with H-ABC have rapid progressive clinical courses [7,10]. Progression of clinical courses in the three patients was slower than that reported in patients with H-ABC. Changes in motor ability in our patients were similar to those seen in HCC patients. Except for one case, all HCC patients lost the ability to walk with support by 20 years of age [14].

The genetic abnormality responsible for HCC is caused by defects in a gene that encodes a new protein named "hyccin" [13]. The function of hyccin has not been identified, although it has putative transmembrane segments suggesting membrane localization. RNA blot analysis shows that hyccin is expressed ubiquitously in the adult brain and lens. Genetic abnormalities have not been identified for H-ABC, 4H, or HH. It is possible that these disorders are caused by a similar protein deficiency, and that genes expressed in the cerebral white matter and/or peripheral nerve (at least in the cases of 4H [15] and HCC [14]) are involved.

Although a genetic abnormality was not found in our patients, we believe that they have another subset form of diffuse hypomyelination syndrome involving the cerebrum and cerebellum because of common MRI findings and clinical symptoms. The common MRI findings were diffuse cerebral hypomyelination, cerebellar atrophy, and corpus callosum atrophy without basal ganglia atrophy. The underlying genetic abnormalities responsible for the various diffuse cerebral hypomyelination syndromes have been discovered only for HCC; hence, the pathogenesis of these syndromes must be pursued at a genetic level to ascertain if these syndromes are independent.

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