Table 1 Neurological and MRI findings in 12 adult-onset Alexander disease

Case	1	2	3	4	5	6	7	8	9	10	11	12
Age of onset	53	27	–	44	–	24	51	59	64	36	51	18
Age of gene analysis	58	38	32	58	33	30	53	73	67	37	55	24
Sex	F	F	M	F	M	M	M	F	M	M	M	F
Neurological findings												
DTR UL/LL	↑/↑	↑/↑	↑/↑	↑/↑	↑/↑	↑/↑	↑/↑	N~↓/↑	↑/↑	N/N	↑/↑	↑/↑
Muscle weakness	+	+	–	–	–	+	–	–	–	–	+	+
Babinski	+/+	+/+	+/+	+/+	+/+	+/+	–/–	–/–	+/+	–/–	+/+	+/+
Sensory disturbance	+	–	–	+	–	+	–	+	+	+	+	–
Dysarthria	+	+	–	–	–	+	+	–	+	–	–	–
Dysphagia	–	–	–	+	–	–	+	–	+	–	–	+
Ataxia	+	+	–	–	–	+	–	–	+	+	–	+
Nystagmus	–	–	–	–	–	+	–	+	–	+	+	–
Palatal myoclonus	+	+	–	–	–	+	–	–	–	–	–	–
Autonomic dysfunction	+	–	–	+	–	+	–	–	+	+	–	–
Dementia	–	–	–	–	–	–	–	+	+	+	–	–
Convulsion	–	–	–	–	–	–	–	–	–	–	–	–
Muscle rigidity	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	+	+	–	n.d.	–
Other symptoms		Scoliosis						Blindness		Strabismus		Scoliosis
MRI findings												
Atrophy of medulla oblongata	+	+	+	+	+	+	+	+	+	+	+	+
Atrophy of spinal cord	+	+	+	+	+	+	+	+	+	+	+	+
Atrophy of cerebellum	–	–	–	–	–	–	–	–	–	+	+	+
White matter lesion	+	–	+	+	+	+	–	+	+	+	–	–
Periventricular rim	+	–	+	+	+	–	–	–	+	–	–	–
Abnormalities of thalamus or basal nuclei	–	–	–	–	–	–	–	–	–	+	–	+
Contrast enhancement	–	–	–	–	–	–	–	n.e	–	–	n e	–
GFAP mutation	V87G	V87G	V87G	V87G	V87G	R416W	M74T	R258C	R70W	R79H	M74T	L357P
References	(7)	(7)	(7)	This study	This study	(8)	(9)	This study	This study	This study	This study	This study

↑, increased; ↓, decreased; n.d., not described; n.e., not examined.

of which is 30 points and < 20 points is considered consistent with dementia, was 13 points. MRI showed atrophy of the medulla oblongata, spinal cord and cerebellum and showed hyperintensities and atrophy of cerebral white matter with frontal predominance. Single photon emission computed tomography (SPECT) showed a marked decrease in cerebral blood flow in the frontal and temporal lobes. She passed away at the age of 74, and autopsy findings showed numerous Rosenthal fibres, a hallmark of Alexander disease, in the subpial region, frontal white matter, substantia nigra, the dentate nucleus, etc. Therefore, the pathological findings were a clue to *GFAP* analysis. *GFAP* mutations, seen in patient 9, 10 and 12, were already known to exist in Alexander disease [(p.R70W (10, 11), p.R79H (2, 12–15), L357P (16)]. Patient 9 with an *R70W* mutation showed cognitive disorders like fronto-temporal dementia and lead-pipe rigidity in the neck and upper extremities in addition to bulbar and pyramidal signs. His cognitive dysfunction started at the age of 64. MRI showed atrophy of medulla oblongata and spinal cord (Fig. 1). In addition, small foci of age-related signal changes were present in the cerebral white matter. Patient 10 showed ataxia, autonomic dysfunction and dementia without bulbar and pyramidal signs. Atrophy of the medulla oblongata and spinal cord

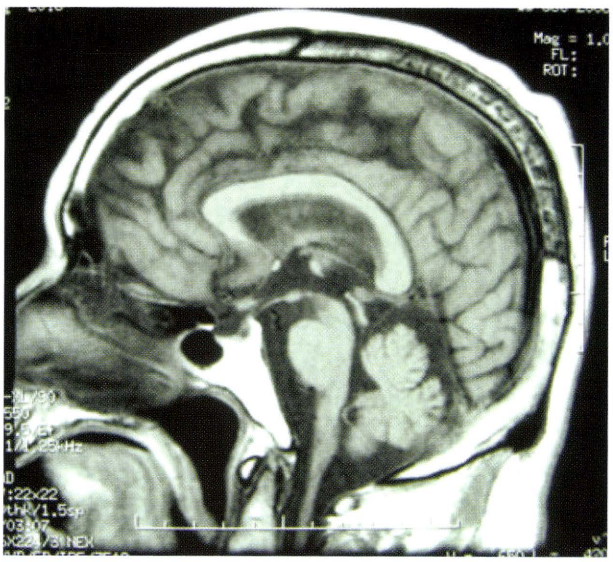

Figure 1. T1-weighted image of patient 9 with R70W mutation shows marked thinning of the medulla and upper cervical spinal cord.

were a clue to perform *GFAP* analysis. Patient 12 showed bulbar and pyramidal signs as well as scoliosis with atrophy of the medulla oblongata and spinal cord on MRI.

Eleven of 12 patients (92%) with heterozygous missense mutations in GFAP presented with hyper-reflexia of the lower limbs. Babinski sign was present in 9 of 12 patients (75%). Muscle weakness, which is often asymmetric in early stages, was present in five patients (42%). Dysarthria (five patients, 42%), truncal and/or limb ataxia (six patients, 50%), nystagmus (four patients, 33%) and autonomic dysfunction, including orthostatic hypotension and bladder dysfunction (five patients, 42%), were all relatively common. Dysphagia was present in four patients (33%). Palatal myoclonus was seen in only three patients (25%). Sensations tended to be impaired in some patients – six patients had decreased vibration sense in the lower limbs (50%) and one patient presented with decreased tactile sensation in the mandibular nerve area. Parkinsonism, including lead-pipe rigidity and bradykinesia, was present in two patients. Two patients had scoliosis. Patient 8 and 9 showed abnormal behaviour, cognitive disorder and deterioration of memory. In both cases, SPECT showed a marked decrease in cerebral blood flow in the frontal and temporal lobes. Sleep disorders, including sleep apnoea and restless legs syndrome, were not observed in any patients. All patients presented with mild to severe atrophy of the medulla oblongata and upper cervical spinal cord on MRI (Fig. 1). Cerebral white matter abnormalities were observed in eight patients (67%). However, distribution of these abnormalities was not frontal dominant but was diffuse and mild. Contrast enhancement was not observed in this study. Signal abnormalities of the basal ganglia and thalami and atrophy or signal abnormalities of the cerebellum were observed in three patients and two patients, respectively.

Discussion

Because *GFAP* mutations were detected as a cause of Alexander disease, various symptoms have been reported in AOAD (3–6), such as those mimicking multiple sclerosis or brain tumour (6).

In the present study, pyramidal signs, including hyper-reflexia and/or the Babinski sign in the lower limbs (observed in 92% of the patients), could be considered characteristic neurological manifestations. Bulbar signs, including dysarthria and dysphagia, cerebellar ataxia and nystagmus were relatively frequent in Japanese patients examined and could therefore be considered cardinal symptoms of AOAD. Palatal myoclonus, which has been regarded as a frequent symptom of AOAD (6), was relatively rare in the cases examined. Symptoms of Parkinsonism, including lead-pipe rigidity and bradykinesia, were also relatively rare, but it is an important symptom in terms of mimicking PSP. Abnormal behaviour and cognitive dysfunction could be an obstacle to consideration of Alexander disease. Sleep disorders, including sleep apnoea and restless legs syndrome, which are often present in non-Japanese patients (17), were not present in any of the cases examined. However, this might not indicate that sleep disorders are a rare symptom in Japan, but that they have not been fully recognized among Japanese neurologists. Therefore, it is necessary for Japanese neurologists to have a better understanding of sleep disorders. In the present study, brainstem lesions, including atrophy of the medulla oblongata, were present in all patients examined. Cerebral white matter abnormalities were shown in 8 patients, and periventricular rim had been present in five patients; however, no case satisfied the criteria proposed for MRI diagnosis of Alexander disease (18). Farina et al. (19) described that atrophy and changes in signal intensity in the medulla oblongata and upper spinal cord are MRI diagnostic features of AOAD. A characteristic finding on MRI in our series was mild to severe atrophy of the medulla oblongata and upper cervical spinal cord, which supports the observation that signal abnormalities or atrophy of the medulla or spinal cord on MRI are a hallmark of late-onset Alexander disease with *GFAP* mutation (4, 19) rather than the MRI criteria proposed in 2001 (18).

Cerebral white matter abnormalities were observed in two-thirds of the cases examined. However, these lesions were atypical because they were symmetrical and mild and did not always show frontal predominance. These findings also support the findings of a previous study which found that cerebral white matter abnormalities observed on MRI were minimal to moderate in patients with AOAD (19). Atrophy or signal abnormalities of the cerebellum were relatively less common in the cases examined in the present study, although ataxia was a frequent clinical symptom.

In this study, three patients who showed typical symptoms of AOAD, including bulbar signs, pyramidal signs in the lower limbs and typical MRI findings indicating atrophy of the medulla oblongata and upper cervical spinal cord, did not have *GFAP* mutations. These patients also did not have any *GFAP* polymorphisms. No *GFAP* muta-

tions were observed in approximately 10% of patients with Alexander disease, in whom other genetic or as yet unknown environmental factors have been hypothesized to influence the phenotype (3, 6). These cases, therefore, require prudent diagnosis including brain biopsy.

A limitation of this study is that information about the clinical manifestations of AOAD in patients with *GFAP* mutations was based not on strict clinical criteria but on reporting by each neurologist. Sleep disorders, which are often present in non-Japanese patients, were not noted or reported in the cases examined in the present study. To clarify the clinical features in more detail, a population-based study with more detailed clinical criteria including sleep disorders is needed.

Pyramidal signs, including hyper-reflexia, Babinski sign with or without bulbar signs, autonomic failure or ataxia, could warrant *GFAP* analysis and could be useful to diagnose AOAD in Japanese patients, which has been reported in previous studies as well (6, 19). Besides, in Japan, it should be noted that abnormal behaviour and cognitive disorders including deterioration of memory could be a conspicuous symptom of AOAD.

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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

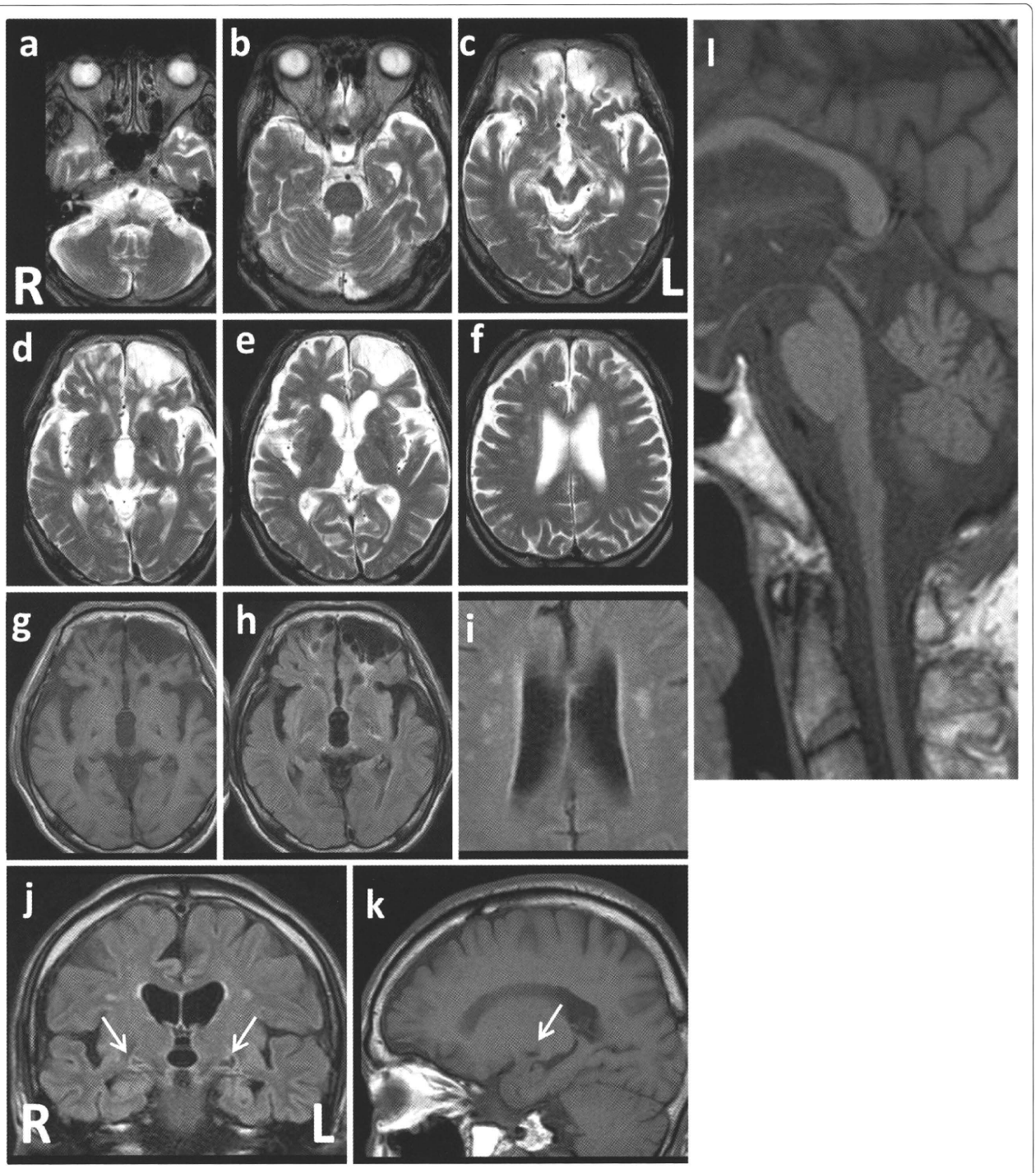

Figure 1 Brain MRI of a patient with adult-onset Alexander disease. a-f: T2-weighted axial images showing marked atrophy of the medulla oblongata (a) with slight cerebellar atrophy (a, b) but little atrophy of the pontine base (b), enlargement of the fourth ventricle (b), atrophy of the midbrain, especially 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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LETTER

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

INTRODUCTION

Adult Alexander disease is a rare leucodystrophy with severe atrophy of the lower brainstem and upper cervical cord.[1] The pathological character is the presence of Rosenthal fibres that contain aggregates of intermediate protein, GFAP, associated with mutations in *GFAP* gene.[2] Because pathogenesis is degenerative, the most typical clinical course is slowly progressive; the intermittent course has not been sufficiently described so far.[2] We show a case of genetically confirmed adult Alexander's disease with acute exaggeration and remission, and relapse.

CASE REPORT

A 33-year-old woman had been well until she suddenly fell down and lost consciousness in 2002. She had left-sided paresis and dysarthria, and was admitted to a hospital. Her medical history was unremarkable except for mild diabetes mellitus. There was no family history of neurological diseases or consanguineous marriage. Her father died of heart disease (in his 40s), her mother died of diabetes mellitus and angina pectoris (in her 50s), and her two daughters were healthy. Brain MRI showed atrophy of the upper cervical cord and T2-hyperintensity in the bilateral periventricular areas and the medulla. The patient was treated for acute ischaemic stroke with medical therapy and rehabilitation (figure1A). She gradually improved, with the ability to walk with an aid 6 months after the onset and was discharged home 1 year after the onset with left-sided weakness and slight dysarthria. There was no exacerbation or improvement of weakness and dysarthria after this episode until the age of 39, when she developed high-grade fever and respiratory failure followed by limb weakness. These symptoms worsened over 1 week, and she was admitted to another hospital and treated for pneumonia, which required mechanical ventilation, tracheostomy and percutaneous endoscopic gastrostomy (PEG). Although pneumonia improved and she was weaned from mechanical ventilation, the patient was still bed-ridden with tetraparesis, severe dysarthria and dysphagia. She was referred to our hospital 5 months later for further neurological evaluation.

The patient was normotensive, alert and well oriented, which was evident by her response with preserved facial expressions. Optic fundi and nerves were normal. Her

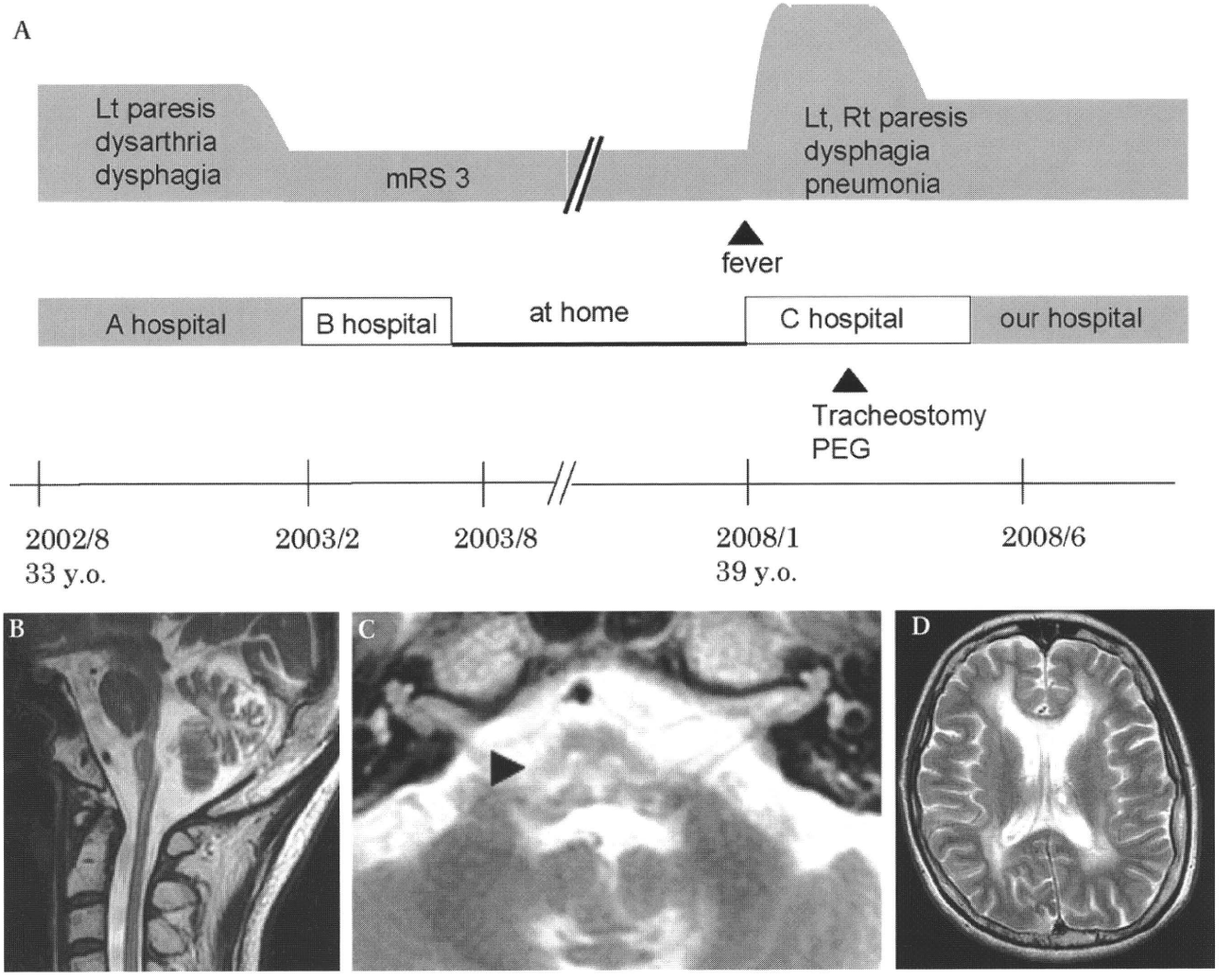

Figure 1 (A) Clinical course. mRS, modified Rankin Scale; PEG, percutaneous endoscopic gastrostomy. (B) Sagittal and (C), (D) axial T2 weighted MRI of brain. Severe atrophy extends from the medulla to the upper cervical cord (B). There is hyperintensity in the medulla (C arrowhead) and the periventricular area (D).

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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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Competing interests None.

Patient consent Obtained.

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Case report

Serial MRI changes in a patient with infantile Alexander disease and prolonged survival

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Abstract

Alexander disease is a major entity of leukodystrophy; magnetic resonance imaging (MRI) studies of the brain typically show extensive changes in the cerebral white matter with frontal predominance. Heterozygous missense mutations of *GFAP* are thought to be sufficient for the molecular diagnosis, which has widened the Alexander disease entity beyond the classical one. We report the patient, a 16-year-old Japanese boy, with infantile-onset Alexander disease, showing striking MRI findings; extreme white matter loss of cerebrum through cerebellum, severe atrophy of basal ganglia, cerebellum, brain stem, and cervical spinal cord. Molecular analysis showed a heterozygous mutation R239L (c.730G > T) in *GFAP*. A relative long disease course, over 15 years, with the help of mechanical ventilation revealed the striking MRI progression.
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Keywords: Infantile Alexander disease; *GFAP*; R239L; White matter; Cerebellum

1. Introduction

Alexander disease (OMIM #203450), a major entity of leukodystrophy, was originally defined pathologically by an accumulation of rod-shaped eosinophilic deposits, recognized as Rosenthal fibers within astrocytes, and demyelination of the white matter [1,2]. Magnetic resonance imaging (MRI) studies of the brain typically show extensive changes in the cerebral white matter with frontal predominance [3]. Since Brenner et al. revealed that heterozygous missense mutations of glial fibrillary acidic protein (GFAP) gene were associated with Alexander disease, showing a heterozygous mutation in *GFAP* is thought to be sufficient for the molecular diagnosis [1,4]. This relative ease for the diagnosis has widened the Alexander disease entity beyond the classical one [1,5]. Here, we report on an Alexander disease patient with a heterozygous mutation R239L (c.730G > T) in *GFAP*, showing a striking MRI progression over 15 years.

2. Case report

The patient (a 16-year-old boy) was the first child of non-consanguineous parents. There was no history of neurological illness in previous generations. He was born at 38 weeks of gestation by normal delivery after an uncomplicated pregnancy. At the time of birth, he weighed 2940 g (−0.24, standard deviation (SD)), his

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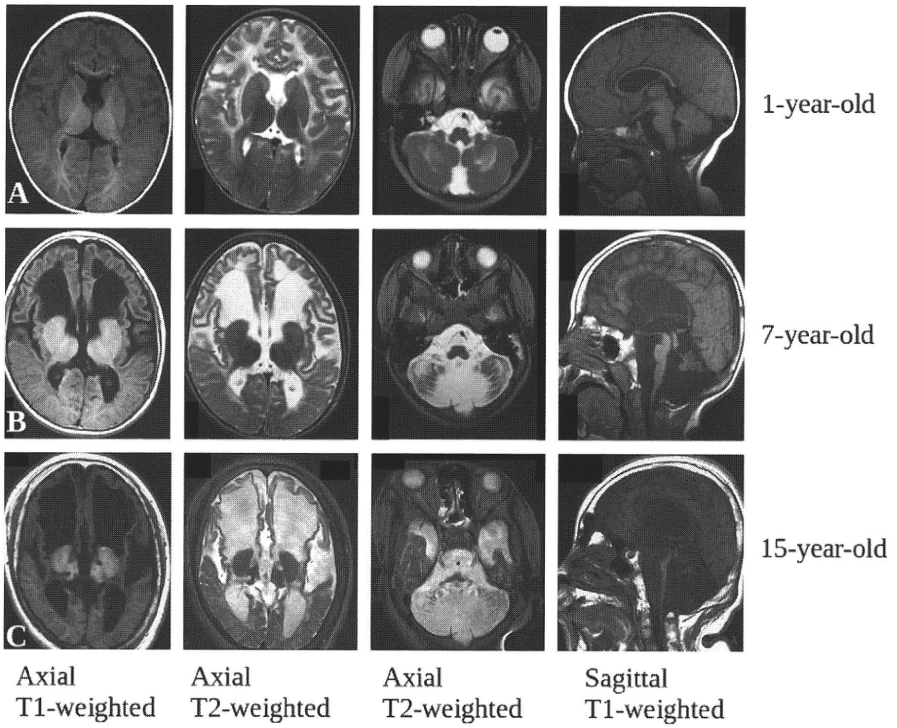

Fig. 1. The rows A–C show MRI studies of our patient (axial T1-weighted image at the level of basal ganglia, axial T2-weighted image at the level of basal ganglia, axial T2-weighted image at the level of cerebellum, and mid-sagittal T1- weighted image), performed at age 1 year-6 months, 7 years-2 months, and 15 years-11 months. Cerebral white matter signal-intensity abnormalities (low T1-weighted and high T2-weighted) with frontal predominance involving the arcuate fibers, the external and the extreme capsule, and basal ganglia symmetric signal-intensity abnormalities involving mainly the caudate and putamen, are already apparent in A. Cerebellar white matter signal-intensity abnormalities are also noted in A. Frontal dominant cerebral white matter cavitation, cerebral and cerebellar white matter volume loss, and brain-stem and cerebellar atrophy are apparent in B. Cerebral and cerebellar white matter have almost vanished in C. Severe brain-stem, cerebellar, and cervical spinal cord atrophy are also noted in C.

length was 51.5 cm (+1.19, SD), and his head circumference (HC) was 32.0 cm (−0.93, SD); serial HC measurements through age 4 years were all within normal limits (i.e., 48.6 cm (+0.27, SD), 48.8 cm (−0.25, SD), and 50.0 cm (−0.29, SD) at age 18 months, 2 years-8 months, and 4 years-5 months, respectively). His developmental milestones were delayed during infancy (i.e., visual tracking at age 2 months, head control at 5 months, sitting unsupported at 8 months, walking with aid at 1 year-7 months and speaking at 1 year-3 months). At 1 year-6 months, after a bout of convulsion, he came to our hospital. Brain computed tomography showed symmetric low density areas in the white matter of the frontal lobe extending into the parietal lobes (figure not shown). Thorough examinations, such as brain magnetic resonance imaging (MRI), electrophysiologic studies, cerebro-spinal-fluid examination, and lysozomal enzyme assays, were done, remained inconclusive. The treatment with anticonvulsants was not successful. Subsequently, he showed psychomotor regression. Around age 6 years, he became bedridden and gradually respiratory insufficiency was evident. At age 8 years, he received a tracheotomy, becoming ventilator dependent.

Since age 1 year-6 months, brain MRIs were done at various intervals until age 7, which showed broad symmetrical white matter involvements, extending from the cerebrum through the cerebellum, with progressive white matter cavitation or loss (Fig. 1A and B). Cerebral frontal lobe dominant white matter abnormalities, symmetrical basal ganglia involvements, periventricular rims, and cerebellar atrophy were also noted.

At age 15 years, he showed macrocephaly; his HC was 59.5 cm (+3.2, SD), repetitive facial myoclonus, poor visual fixation or tracking, auditory startle response, severe muscle atrophy of all extremities, and the loss of deep-tendon reflexes. He had a sleep wake cycle and could show some vague facial expressions, indicating comfort or discomfort. Brain MRI revealed extreme white matter loss of the cerebrum through the cerebellum, severe atrophy of basal ganglia, cerebellum, brain stem, and cervical spinal cord (Fig. 1C). Table 1 summarizes serial MRI changes in this patient (Table 1). After obtaining parental informed consent, gene analysis revealed a heterozygous mutation R239L (c.730G > T) in *GFAP* (Fig. 2).

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Table 1
Serial MR1 changes in our patient.

Age	Main findings	
	Signal-intensity abnormalities	Volume abnormalities
1-year-6-month	Cerebral white matter (frontal dominant), basal ganglia (symmetrical), cerebellar white matter and periventricular rims	
2-year-8-month		Cerebral white matter atrophy and glimpse of cerebral white matter cavitation (frontal lobe)
3-year-1-month		Glimpse of basal ganglia atrophy
4-year-1-month		White matter cavitation and atrophy progressed (frontal lobe)
5-year-0-month	Cerebellar white matter abnormally progressed	White matter cavitation and atrophy progressed (frontal lobe) and glimpse of cerebellar and brain-stem atrophy
7-year-2-month		Cerebral white matter cavitation (extending to parietal lobe), cerebral, basal ganglia, cerebellar and brain-stem atrophy progressed
15-year-11-month	White matter signal abnormalities less visible (due to extensive cavitation or atrophy)	Almost vanished cerebral and cerebellar white matter, severe brain-stem, cerebellar, and cervical spinal cord atrophy

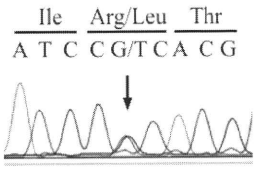

Fig. 2. Direct sequencing analysis of the patient shows a heterozygous mutation R239L due to a G to T transversion (c.730G > T; arrow) of *GFAP*.

3. Discussion

The clinical presentation of Alexander disease can be divided into three groups, infantile, juvenile, and adult [2]. van der Knaap et al. defined the five MRI criteria for infantile or juvenile Alexander disease, such as extensive cerebral white matter changes with frontal predominance, a periventricular rim with high signal on T1-weighted images and low signal on T2-weighted images, abnormalities of basal ganglia and thalami, brain stem abnormalities, and contrast enhancement of particular gray and white matter structures [3]. We did not employ gadolinium enhancement, however; the four MRI criteria out of five, other than the contrast enhancement, were fulfilled on his early MRI. Although, some of infantile Alexander disease patients did not manifest macrocephaly and others manifested it after infancy, the lack of macrocephaly, progressive white matter cavitation and volume loss led us to almost disregard his diagnostic possibility of Alexander disease, and vanishing white matter became a tentative diagnosis [6,7]. R239 is one of hotspots of *GFAP* mutations and an infantile Alexander disease patient with R239L mutation was previously reported [1,4,8]. Thus, the heterozygous R239L mutation in our patient made the Alexander disease diagnosis certain.

Although there are some reports of Alexander disease patients with cerebral white matter cavitation, as far as we know, the extensive cavitation, as though almost all white matter has vanished not only in the cerebrum but also in the cerebellum, seen in our patient, has not been reported [6,9]. Brain-stem and cervical spinal cord involvements, seen in our patient, are common findings in adult-onset Alexander disease [10]. In his early MRI, the supratentorial lesions progressed diffusely preserving the basic characteristics of infantile Alexander disease; a frontal predominance of the white matter abnormalities relatively sparing the frontal cortex and the occipital lobe [2,3]. After infancy, subtentorial lesions gradually developed in the whole rhombencephalon, finally ending in the twiggy brain-stem and the nearly vanishing cerebellum, representing the possible extreme end stage of adult type Alexander disease [10]. So, it would be said that he had serially demonstrated the extreme characteristics of each type Alexander disease in a period of 15 years, with the help of mechanical ventilation (and, of course, his parents' love and dedication). Toxic gain-of-function of GFAP has a pivotal role in Alexander disease pathogenesis [1,2]. The lesional distribution difference in each Alexander disease subtype might result from not only the disease severity but also an age-dependent astrocyte activity in a particular part of brain. Until now the precise data are lacking, therefore, it is a mere speculation, awaiting data from further studies'.

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Case Report

Multiple Sclerosis

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A case of cerebral aquaporinopathy

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Abstract

A 35-year-old woman was hospitalized due to impaired consciousness. Magnetic resonance imaging (MRI) revealed multiple parenchymal lesions in supra and infratentorial brain regions, which were considered responsible for her declining consciousness level. She was treated with intravenous methylprednisolone. Neurological symptoms improved and she was discharged. She was readmitted 14 months later due to intractable hiccups. A follow-up brain MRI revealed an abnormal signal near the area postrema in the dorsal medulla. Serum aquaporin-4 antibody levels were positive, but there were no visual manifestations or myelitis. Spinal MRI was negative for longitudinally extended transverse myelitis throughout the clinical course.

Keywords

aquaporin-4, longitudinally extended transverse myelitis, magnetic resonance imaging, neuromyelitis optica, optic neuritis, prednisolone

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Introduction

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system (CNS). The cardinal features of NMO include severe optic neuritis and longitudinally extended transverse myelitis (LETM). Whether NMO is a variant of multiple sclerosis (MS) or a separate disease altogether has long been debated. Currently, with the advent of the aquaporin-4 (AQP4) antibody, NMO has been recognized as a discrete disease.[1,2] Here we describe the case of a patient who showed recurrent brain lesions on magnetic resonance imaging (MRI) and who had detectable AQP4 antibody levels. Interestingly, there were no features of optic neuritis or LETM present on the patient's spinal MRI.

Case report

A 35-year-old woman was admitted to our hospital with a high fever, headache and impaired consciousness. A neurological examination revealed left medial longitudinal fasciculus syndrome, left facial palsy and impairment of consciousness. The complete blood count as well as serum electrolyte and glucose levels were normal. Serum antinuclear antibodies were absent. The erythrocyte sedimentation rate was 18 mm/h and the C-reactive protein concentration was 0.13 mg/l. The antibody concentration for double-stranded DNA was below 10 IU/ml. Antibody tests for proteinase-3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) and myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) were negative. A cerebrospinal fluid examination revealed a normal cell count (3/mm^3, mononuclear cells 3/mm^3, polymorphonuclear cells 0/mm^3), and elevated protein (56 mg/dl) and myelin basic protein concentrations (504 pg/ml; normal range <102 pg/ml). The patient was negative for IgG (7mg/dl), IgG index (0.44), soluble-interleukin-2 receptor (<85 IU/ml) and oligoclonal IgG.

Upon admission, MRI revealed multiple parenchymal lesions in both the supra and infratentorial regions

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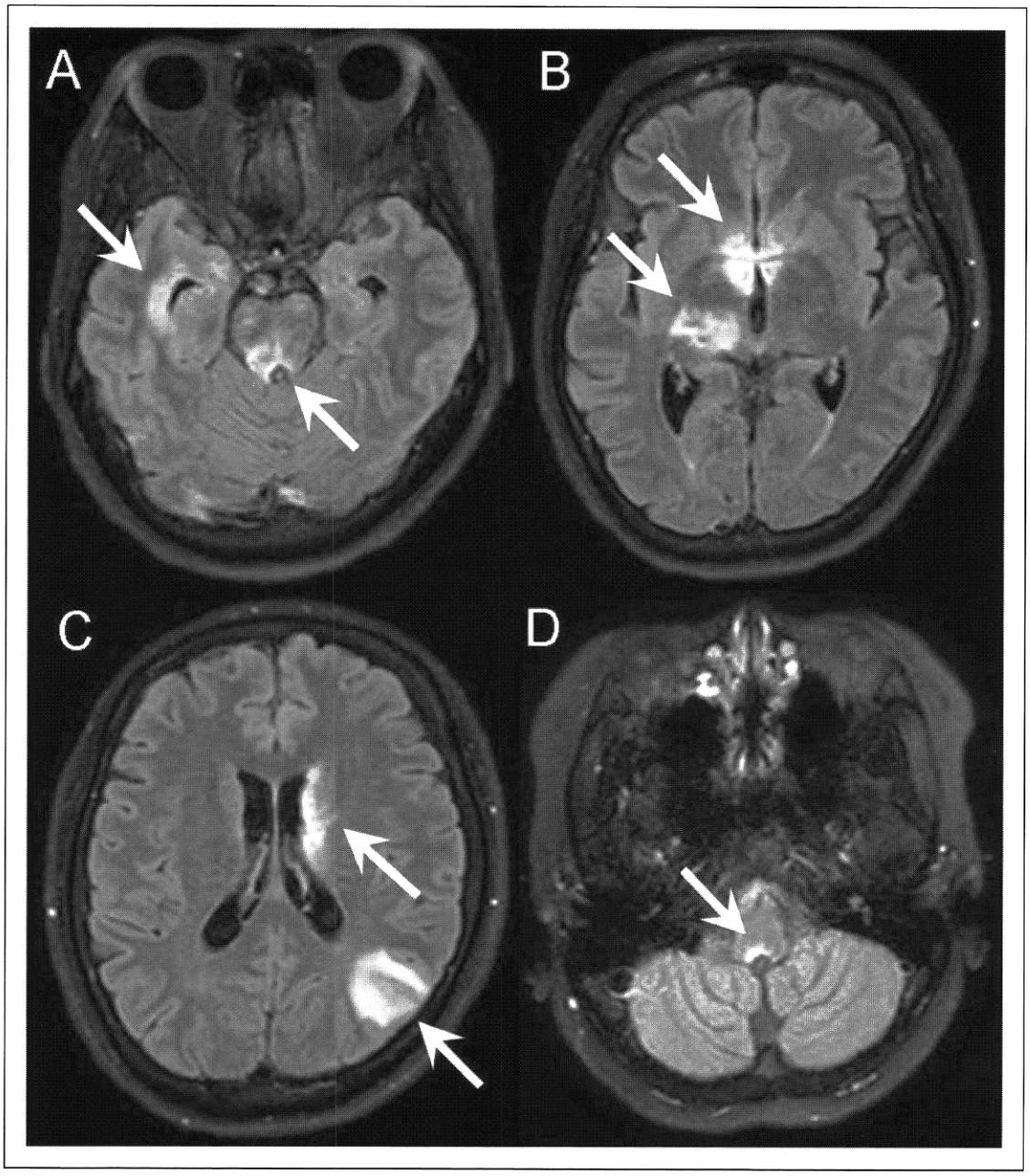

Figure 1. Axial fluid-attenuated inversion recovery (FLAIR) brain magnetic resonance images. (A), (B), (C) Brain MRI on first admission. Transaxial FLAIR images showed multiple brain parenchymal lesions in both supra and infratentorial regions. (D) Brain MRI taken 14 months later. A new small focus of hyperintensity near the area postrema in the dorsal medulla was identified.

of the brain, which were thought to be responsible for the patient's declining consciousness level (Figure 1A–C). The lesions were located in the pons, periaqueductal region, periventricular white matter adjacent to the right temporal horn, hypothalamus, central gray matter and the left parietal cortex. These lesions were hyperintense on fluid-attenuated inversion recovery (FLAIR) images. Some of these lesions were revealed by contrast enhancement after the administration of a gadolinium-based contrast agent. Differential diagnoses considered from the imaging findings were MS, intravascular lymphoma and angiitis. Biopsies of the bone marrow, skin and muscle were normal. A diagnosis of angiitis was not supported by the laboratory findings. Brain biopsy was considered but was not carried out because of a failure in agreements.

The patient was treated with intravenous methylprednisolone at a daily dosage of 1.0 g for 3 days, followed by a reducing dose of oral prednisolone. The neurological symptoms improved gradually, and after

getting discharged in a couple of months she was able to ambulate independently. The signal abnormalities were significantly improved on a follow-up brain MRI.

Fourteen months after initial admission, the patient was readmitted due to intractable hiccups, at which point she was on a daily dosage of 4.0 mg prednisolone. Laboratory findings were within normal limits. A follow-up brain MRI with subtle contrast enhancements revealed signal abnormalities near the area postrema in the dorsal medulla (Figure 1D).

Spinal MRI was unremarkable. Both visually evoked potentials and auditory brainstem responses were normal. Serum AQP4 antibody levels were positive, and the stored serum from her first hospital admission was also positive for AQP4 antibodies.

Discussion

NMO is an inflammatory disorder of the CNS, and tends to affect the optic nerves and spinal cord. In general, NMO follows a relapsing course and clinically begins with either optic neuritis or myelitis, and can manifest as isolated myelitis or optic neuritis.[2] However, the patient described here had neither visual symptoms nor LETM throughout the clinical course. The brain lesions depicted on MRI were the only indications of NMO in this patient. However, the lesions in the right central gray matter and the left parietal cortex had an atypical location and appearance for NMO, which made the prospective diagnosis of NMO more difficult.

A recent neuroimaging study revealed that brain lesions can occur in a fraction of patients with NMO, and that the vulnerable areas often reside adjacent to the ventricular system.[3] Lesions around the third or fourth ventricles or the aqueduct of Sylvius area are more common than those adjacent to the lateral ventricles.[3] In this case, hyperintense areas on FLAIR images were noted in the periaqueductal region and hypothalamus during the first episode. Subsequently, a new area of signal abnormalities emerged in the area postrema of the medulla, which is known to be another area affected by NMO. The characteristic distribution of these lesions prompted investigations into serum AQP4 antibody levels, despite the fact that the patient lacked clinical evidence of optic neuritis or LETM, both cardinal features of NMO.

AQP4 is a ubiquitous protein in the CNS; however, it is most heavily distributed in the spinal cord and tegmental medulla extending into the area postrema. These are the areas where there is typically a striking loss of AQP4 in patients with NMO.[4]

The AQP4 antibody has 73% sensitivity and 91% specificity for diagnosing NMO and is considered to be a specific autoantibody marker for NMO.[5] The brain lesions in this case were conceivably caused by astrocytic impairment associated with NMO. However, neither clinical manifestations of myelitis nor LETM on spinal MRI were revealed throughout the clinical course. To the best of our knowledge, this is the first AQP4 antibody-positive case showing lesions restricted to the brain. It is possible that this patient may experience a relapse of NMO in the future with a more typical constellation of symptoms. However, this case poses a diagnostic dilemma for NMO. Therefore, it is proposed that such patients should be diagnosed with 'AQP4-autoimmune syndrome' rather than NMO.

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Conflict of interest statement

None declared.

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