Familial Adult-onset Alexander Disease: Clinical and Neuroradiological Findings of Three Cases

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ABSTRACT

The adult-onset Alexander disease (AOAD) dramatically differs from the early onset AD with respect to clinical and neuroradiological findings. Herein we report the detailed clinical and neuroradiological findings of a Turkish family with AOAD. In all three cases, magnetic resonance imaging revealed marked atrophy of the mesencephalon, bulbus, and cervical spinal cord accompanied with signal abnormalities in the same regions along with supratentorial white matter. Basal

ganglia were affected in two cases. Molecular genetic analysis revealed heterozygous mutation in the 8th exon of the glial fibrillary acidic protein gene M451I (c.1245G>A), leading to the diagnosis of AOAD in all cases.

Keywords: Adult-onset Alexander disease, brainstem, GFAP, leukodystrophy, M451I

INTRODUCTION

Alexander disease (AD) was first described in 1949 by Dr. W. Stewart Alexander, an Australian pathologist, as a fatal infantile leukodystrophy that is characterized by astrocytic eosinophilic inclusions containing Rosenthal fibers, mainly located in the perivascular, periventricular, and subpial spaces of the cerebral hemispheres, cerebellum, and brainstem (1,2).

Following the identification of glial fibrillary acidic protein (GFAP) mutations as the underlying genetic defect, late-onset forms are increasingly diagnosed. The disease is classified as infantile (onset before 2 years of age), juvenile (onset between 2 and 12 years of age), and adult (onset after 12 years of age) according to the age of onset.

Adult-onset AD (AOAD) has clinically and radiologically distinctive features from infantile and juvenile forms. Infantile and juvenile forms are more readily diagnosed compared with the adult-onset form because of their specific clinical and neuroradiological features. In contrast, AOAD has a wide range of presentation symptoms, which complicates its diagnosis.

Here, we describe the clinical and neuroradiological features of three patients with genetically confirmed AOAD from the same family.

CASES

Detailed physical examinations, history, and electrophysiological studies were performed by the same neurologist for all three patients. Cranial and cervical magnetic resonance imaging (MRI) studies were performed for all three patients using the 1.5 T MRI system, and the images were interpreted by the neuroradiologists. Informed consent was obtained from all three patients. Molecular analysis was performed on each patient by direct sequencing on the DNA that were extracted from peripheral blood lymphocytes.

The pedigree of the patients is shown in Figure 1. Table 1 summarizes the clinical findings of the patients, while the MRI findings are abridged in Table 2.

Case 1

A 38-year-old female patient presented with walking difficulty, unsteady gait, and speech problems since the age of 33 years. After 2 years, she fell down presumably because of gait instability, resulting in head trauma while she was pregnant. Subsequently, a tremor around her mouth and chin, dysarthric speech, and loss of strength on the right side of the body emerged, resulting in the loss of ability to take care of her daily living activities, including her personal hygiene. Two months after the delivery of her baby, she developed behavioral problems during sleep, such as meaningless vocalizations that were associated with visual hallucinations (Table 1). She has had urinary incontinence for 10 years and also has scoliosis and shortness in her right leg.

In her family history, her maternal grandmother died because of an unknown etiology. It was stated that she had developed paraplegia after repetitive head trauma.

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Table 1. Clinical findings of patients

Clinical findings	Presenting symptoms	Pyramidal	Cerebellar	Sensory	Gait	Speech	Pathological reflexes	Brainstem	Other
Case 1	Walking difficulties Imbalance Speech disturbance	Right hemiparesis		Decreased vibration	Requires a walker	Dysarthria Rhinolalia	Bilateral Babinski's sign Bilateral Hoffman's sign	Palatal myoclonus Nystagmus	Urinary incontinence* Scoliosis
Case 2	Walking difficulties	Monoparesis	Dysmetria and dysidiadochokinesia			Rhinolalia	Babinski's sign on the left		
Case 3	Walking difficulties Dizziness	Paraparesis		Decreased vibration	Flail arms	Rhinolalia	Bilateral Babinski's sign		Urinary incontinence* Scoliosis

*initial symptom

Table 2. MRI characteristics of the cases. Superscripts within the table refer to the images in Figure 2

MRI characteristics	Case 1	Case 2	Case 3
Supratentorial periventricular white matter abnormalities	+ ^{A1}	+ ^{B1}	+ ^{C1}
Increased white matter signal in ADC weighted images	+	+	+
Dilated ventricles	+ ^{A1}	+ ^{B1}	+ ^{C1}
Signal increase in the medial part of corpus callosum in T2 and FLAIR weighted sequences	+ ^{A1}	+ ^{B1}	+ ^{C1}
Signal changes in putamen and globus pallidus	+ ^{A1}	-	Right + ^{C1}
Hyperintensity of pyramidal tractus in the mesencephalon	+ ^{A2}	+ ^{B2}	+ ^{C2}
Hyperintense rim in pons and mesencephalon in FLAIR weighted sequences	+ ^{A2}	+ ^{B2}	+ ^{C2}
Atrophy of cerebellar peduncles	+ ^{A3}	+ ^{B3}	+ ^{C3}
Signal changes in cerebellar dentate nuclei	+ ^{A3}	+ ^{B3}	+ ^{C3}
Cerebellar atrophy	+ ^{A3}	+ ^{B3}	+ ^{C3}
Atrophy and signal changes in brain stem	+ ^{A4}	+ ^{B4}	+ ^{C4}
Atrophy and signal changes in the C1-C2 spinal cord	+ ^{A4}	+ ^{B4}	+ ^{C4}
Gd enhancement	-	-	-

ADC: apparent diffusion coefficient; C1-C2: cervical 1 and 2; FLAIR: fluid-attenuated inversion recovery; Gd: gadolinium

On neurological examination, her speech was markedly dysarthric and rhinolalic. She had horizontal nystagmus and oromandibulolingopalatal myoclonus. Muscle tone was globally normal, but muscle strength was 3/5 on the right upper extremity and 4/5 on the right lower extremity. Deep tendon reflex (DTR) was globally brisk. Babinski's sign was bilaterally positive. Vibration sensation was decreased, and she had ataxia and could walk with support.

Laboratory tests, including complete blood count, electrolyte panel, liver and kidney function tests, blood chemistry, HIV and hepatitis serology,

antinuclear antibody (ANA), anti-dsDNA, and extractable nuclear antigen antibodies (ENA) panels, were normal. Elevated thyroid-stimulating hormone (TSH) and anti-thyroid autoantibody levels along with normal T3 and T4 levels were consistent with Hashimoto's thyroiditis.

Electrophysiological studies revealed oromandibular myoclonic tremor.

Cranial MRI revealed striking atrophy of the brainstem that was accompanied with ventricular dilation without a significant dilation of the cerebral sulci. On the T2W images, periventricular white matter appeared to show ill-defined hypointensities. Fluid attenuation inversion recovery (FLAIR) images confirmed the abovementioned prominent white matter changes and a hyperintense rim around the pons and bulbous.

Dentate nuclei appear to be atrophic and coupled with an increased signal on T2W sequences.

In addition to these findings, the cervical spinal cord was atrophic, although no prominent signal abnormalities were noted on T2W images (Figure 2a).

Molecular genetic analysis revealed heterozygous mutation in the 8th exon of the GFAP gene M451I (c.1245G>A), leading to the diagnosis of AOAD.

Case 2

A 35-year-old male patient, who is the brother of the first case, presented with difficulty in walking and loss of strength in the left leg. His symptoms started abruptly 8 months ago, following a psychological stress.

On neurological examination, his speech was mildly rhinolalic. He also had mild paresis in his left lower extremity. DTR was globally normoactive with a positive Babinski's sign on the left side. Mild dysmetria and dysidiadochokinesia were present on the left side. Laboratory tests, including complete blood count, electrolyte panel, liver, kidney and thyroid function tests, blood chemistry, HIV and hepatitis serology, ANA, anti-dsDNA, and ENA panel, were normal.

His cranial MRI displayed similar but milder findings compared with case 1, including an hyperintense rim around the pons and bulbous (Figure 2b).

He also had heterozygous mutation in the 8th exon of the GFAP gene M451I (c.1245G>A), leading to the diagnosis of AOAD.

Case 3

A 60-year-old female patient, who is the mother of the other two cases, presented with a burning sensation on her head and vertigo for 5 years.

Figure 2. a-c. MRI findings of the cases. A1-4 belongs to case 1, B1-4 belongs to case 2, and C1-4 belongs to case 3. Axial FLAIR-weighted MRI in A1, A2, B1, B2, C1, C2. Axial T1-weighted MRI in A-C3. Sagittal T1-weighted MRI in A4, Sagittal T2-weighted in B-C4. Refer to table 2 for details

She had had difficulty in walking and standing for 2 years because of the loss of strength in both lower extremities, which was more prominent on the right side, leading to the inability to work in a standing position for a long time or to walk long distances.

She had had urinary incontinence for 7 years.

On neurological examination, her speech was mildly rhinolalic. Muscle strength was only mildly decreased at the distal parts of the lower extremities, resulting in -5/5 muscle power on the toes and ankles bilaterally. DTR was globally normoactive with a bilateral positive Babinski's sign. During walking, her arms' positions and movements resembled flail arms; she could not walk on her toes but performed better while walking on her heels. Her Romberg test was positive, while she could not walk for more than four steps on a tandem walk. Superficial sensory examination revealed no pathologies but vibration was markedly decreased on the lower extremities.

Laboratory tests, including complete blood count, electrolyte panel, liver, kidney and thyroid function tests, blood chemistry, HIV and hepatitis serology, ANA, anti-dsDNA, and ENA panel, were normal. Electroneuromyography revealed motor axonal neuropathy prominent on the lower extremities.

Her cranial MRI revealed similar findings with cases 1 and 2, although the dilation of the ventricles was less prominent and the basal ganglia were more prominently affected (Figure 2c).

Lumbar MRI revealed mild scoliosis and minimal bulging in multiple disks without any compression to the medulla spinalis or neural roots.

She also had an heterozygous mutation in the 8th exon of the GFAP gene M451I (c.1245G>A), leading to the diagnosis of AOAD.

DISCUSSION

The causative agent of AOAD is the mutation of the GFAP gene that is located on the long arm of the 17th chromosome and is inherited as an autosomal dominant trait. Disease can greatly vary in the clinical presentation and age of onset, even within the same family with the exact same mutations, thus complicating the diagnosis and genotype-phenotype correlation further (3). The disease course can range from an asymptomatic course to severe disablement. Incomplete penetrance of the mutation, environmental factors, and triggering events may contribute to this variability. As for triggering factors, head trauma has been reported to be an initiating factor in adrenoleukodystrophies, vanishing white matter disease, and has also been described in an AOAD case right before the initiation of the symptoms (4,5,6). As noted above, the initiation of the symptoms in case 1 following a severe multitrauma, including head injuries, raises the question whether head trauma is actually a triggering factor in such cases.

All the members of the family were heterozygous carriers of M451I (c.1245G>A) mutation, which has been previously reported in the literature (7). The signs and symptoms of our cases reveal some similarities with gait instability as the presenting symptom in all three patients. In addition, they all had pyramidal signs, rhinolalia, and Babinski's sign. Scoliosis, decreased vibration sense, and urinary incontinence were present in cases 1 and 3. Urinary incontinence was dated from before the presenting symptoms were described by the patients, raising the question of whether it is one of the initial symptoms in cases 1 and 3.

Diagnosing patients only on the basis of clinical findings is a challenge, and some patients have been misdiagnosed as multiple sclerosis, primary lateral sclerosis, amyotrophic lateral sclerosis, myasthenia gravis, multisystem atrophy, spinocerebellar ataxia, and cervical myelopathy (8). Palatal myoclonus is a rather specific finding for AOAD; however, it is only observed in one-third of patients (9).

White matter abnormalities are reported to be less common in patients older than 40 years of age (10). Nonetheless, MRI revealed prominent periventricular white matter abnormalities in all our cases despite the fact that the age of onset was 56 years in case 3.

Basal ganglia involvement is a diagnostic feature for infantile and juvenile forms of the disease but it is an uncommon finding in the adult-onset form of the disease, although it has been reported occasionally in the literature (6,11,12,13,14,15,16). Signal changes in the putamen and globus pallidus were observed bilaterally and unilaterally in the MRI of cases 1 and 3, respectively. Detailed examination did not reveal any clinical findings regarding the extrapyramidal system involvement, although it has been occasionally reported in the literature (6,13,17,18,19).

Another striking MRI finding is the hyperintense rim seen around the pons and bulbous, and especially visible on the FLAIR images. This imaging finding aligns very well with the diagnostic pathological feature of the disease that inclusion bodies are located in the subpial spaces around the brainstem (2).

Although contrast enhancement has been reported to be more frequent in patients younger than 40 years, none of our patients showed contrast enhancement, including the two patients with relatively younger onset (10). AOAD has a wide range of clinical presentation, therefore MRI plays a key role in raising the suspicion for diagnosis in the presence of typical findings, such as medullary abnormalities and tadpole-like atrophy of the brainstem (20), and may guide the clinician in identifying the candidates for genetic testing (10).

In conclusion, AOAD shows great variations regarding the clinical findings and age of onset; therefore, recognition of the radiological findings plays an essential role in identifying the candidates for genetic testing, leading to earlier diagnosis and more effective counseling for the patients and their families.

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