ATP1A3 variants and slowly progressive cerebellar ataxia without paroxysmal or episodic symptoms in children

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The disease causing missense variants in ATP1A3 was first identified in families with rapid-onset dystonia parkinsonism in 2004, and since then several ATP1A3-related disorders have been recognized.1,2 Classic phenotypes include alternating hemiplegia of childhood (AHC) and rapid-onset dystonia parkinsonism.3 More recently other phenotypes have been associated with variants in ATP1A3, such as cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensory motor hearing loss (CAPOS syndrome),4 relapsing encephalopathy with cerebellar ataxia5/fever-induced paroxysmal weakness encephalopathy,6 early-onset epileptic encephalopathy,7 rapid-onset ataxia in childhood8 or adulthood,9 childhood-onset schizophrenia,10 and autism spectrum disorders.11

Paroxysmal episodic symptoms such as transient tonic or flaccid hemiplegia, dystonia, tonic seizures, episodic cerebellar ataxia, and abnormal ocular movements are the most common symptoms in patients with ATP1A3-related disorders1-12 (Table 1), except for childhood-onset schizophrenia or autism spectrum disorders. Thus, identifying these symptoms can be helpful in clinical practice to aid in the early diagnosis of ATP1A3-related disorders. However, in intermittent periods between these paroxysmal symptoms, most patients with ATP1A3-related disorders present with persistent neurological deficits such as hypotonia, motor delay, ataxia, nystagmus, cognitive and behavioural dysfunction, or involuntary movements such as dystonia or choreoathetosis.1 Interestingly, less severe ATP1A3 phenotypes have not been reported to date. Here we report two cases of infantile-onset cerebellar ataxia, due to two different ATP1A3 variants. Both patients showed slowly progressive cerebellar ataxia without paroxysmal or episodic symptoms. Brain magnetic resonance imaging revealed mild cerebellar cortical atrophy in both patients. Whole exome sequencing revealed a de novo heterozygous variant in ATP1A3 in both patients. One patient had the c.460A>G (p.Met154Val) variant, while the other carried the c.1050C>A (p.Asp350Lys) variant. This phenotype was characterized by a slowly progressive cerebellar ataxia since the infantile period, which has not been previously described in association with ATP1A3 variants or in ATP1A3-related clinical conditions. Our report contributes to extend the phenotypic spectrum of ATP1A3 mutations, showing paediatric slowly progressive cerebellar ataxia with mild cerebellar atrophy alone as an additional clinical presentation of ATP1A3-related neurological disorders.

A heterogeneous spectrum of clinical manifestations caused by mutations in ATP1A3 have been previously described. Here we report two cases of infantile-onset cerebellar ataxia, due to two different ATP1A3 variants. Both patients showed slowly progressive cerebellar ataxia without paroxysmal or episodic symptoms. Brain magnetic resonance imaging revealed mild cerebellar cortical atrophy in both patients. Whole exome sequencing revealed a de novo heterozygous variant in ATP1A3 in both patients. One patient had the c.460A>G (p.Met154Val) variant, while the other carried the c.1050C>A (p.Asp350Lys) variant. This phenotype was characterized by a slowly progressive cerebellar ataxia since the infantile period, which has not been previously described in association with ATP1A3 variants or in ATP1A3-related clinical conditions. Our report contributes to extend the phenotypic spectrum of ATP1A3 mutations, showing paediatric slowly progressive cerebellar ataxia with mild cerebellar atrophy alone as an additional clinical presentation of ATP1A3-related neurological disorders.

CASE REPORT

Two adolescent (case 1: male, 15y; case 2: female, 12y) patients from the National Center of Neurology and Psychiatry in Tokyo were studied. Ataxia was assessed using the Scale for the Assessment and Rating of Ataxia (0–40). This study was approved by the ethical committee of the National Center of Neurology and Psychiatry. Written informed consent was obtained from the parents.

Case 1

Case 1 was born after an uneventful pregnancy from non-consanguineous parents. He was able to smile at 2 months, hold his neck up at 3 months, sit without support at 8 months, walk unassisted at 24 months, and vocalize words at 22 months. He presented unsteadiness at 12 months in his sitting position. Walking was always unsteady with wide-based gait. He communicated using several words slowly and unclearly. At 15 years, his ataxic symptoms gradually became worse and he often fell while walking; he was referred to our hospital at this stage. Based on the

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Wechsler Intelligence Scale for Children, his IQ was 40 and the neurological examination performed at 15 years indicated cerebellar ataxia including saccadic eye movement, ocular motor apraxia, dysarthria, dysdiadochokinesis, dysmetria, intention tremor, decomposition of movements, and wide-based gait. Deep tendon reflexes were within the normal range. His Scale for the Assessment and Rating of Ataxia score was 12. She had no telangiectasia, pes cavus, or visual/hearing disabilities. There were no signs of episodic abnormal ocular movement, seizures, dystonic events, bulbar symptoms, autonomic dysfunction, or respiratory disturbances. Brain magnetic resonance imaging (MRI) revealed pure cerebellar cortical atrophy dominantly in the vermis (Fig. 1a).

Case 2
Case 2 was born after an uneventful pregnancy from non-consanguineous parents. She was able to hold her neck up at 5 months, sit without support at 15 months, walk unassisted at 2 years 11 months, and vocalize a word at 3 years. Her walking was always unsteady. At 7 years, she went to a hospital for unsteady walking, and brain MRI revealed a slight cerebellar cortical atrophy (Fig. 1b). Increased unsteadiness was reported when she had fever by viral infection. The unsteadiness gradually increased, and she was then referred to our hospital. Neurological examination revealed mild intellectual disability, saccadic eye movement, and wide-based gait, dysdiadochokinesis, dysmetria, and intention tremor. Normal deep tendon reflexes, visual acuity, and hearing ability were attested. Her Scale for the Assessment and Rating of Ataxia score was 12. She had no positive family history. He resisted at 2 years 11 months, and vocalize a word at 3 years.

RESULTS
Blood tests including alpha-fetoprotein, albumin, cholester, lactate/pyruvate, and cytosine-thymine-guanine repeats in spinocerebellar ataxia 1, 2, 3, and dentatorubral pallidolysian atrophy disclosed no abnormalities in both patients. From the clinical and examination findings, ataxia telangiectasia, mitochondrial encephalopathies, neuronal ceroid lipofuscinosis, infantile neuroaxonal dystrophy, congenital disorders of glycosylation, spinocerebellar ataxia 1, 2, 3, and dentatorubral pallidolysian atrophy were ruled out. Then, trio whole exome sequencing was carried out using previously described methodology.13

Variants in ATP1A3 (NM. 152296.5) were identified by whole exome sequencing: c.460A>G: p.(Met154Val) in case 1 and c.1050C>A: p.(Asp350Lys) in case 2. These variants were confirmed by Sanger sequencing in the patients and their parents, and were found to be heterozygous de novo variants. These variants have not been reported previously, and computed analysis tools (SIFT, Polyphen2) predicted

### Table 1: Main features reported in ATP1A3-related disorders

| Main symptoms | RDP1,2,4 | CAPOS5 | RECA6/FIPWE7 | Present cases |
|---------------|----------|--------|--------------|---------------|
| **AHC1,2,3**  | Repeated attacks of hemiplegia that alternate in laterality | Rapid-onset of dystonia and parkinsonism | Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss | Relapsing cerebellar ataxia and/or weakness | Slowly progressive cerebellar ataxia |
| **Paroxysmal or episodic symptoms** | | | | | |
| **Frequency** | | | | | |
| Seizure-like spells | Prominent bulbar findings | Rarely repeated | Episodic cerebellar ataxia | Less than once a year | No paroxysmal or episodic symptoms |
| Several times a month | Rapid-onset dystonia | | | | |
| Rapid-onset ataxia | | | | | |
| **Cerebellar symptoms** | Ataxia (slowly progressive in some cases) | Ataxia | Ataxia (recover or persistent) | Ataxia (stepwise progressive) | Ataxia (insidious onset) |
| **Brain MRI findings** | Cerebellar cortical atrophy (in some cases) | Normal | Normal | Cerebellar cortical atrophy | Cerebellar cortical atrophy |

AHC, alternating hemiplegia of childhood; RDP, rapid-onset dystonia parkinsonism; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss; RECA, relapsing encephalopathy with cerebellar ataxia; FIPWE, fever-induced paroxysmal weakness and encephalopathy; ROA, rapid-onset ataxia; MRI, magnetic resonance imaging.
Figure 1: Brain magnetic resonance imaging (MRI) in case 1 (a) and Case 2 (b). (a) Brain MRI findings (axial; T2-weighted images, coronal; short-T1 inversion recovery, sagittal; T1) of case 1 (age 15y). Diffuse cerebellar cortical atrophy is seen predominantly in the vermis. No abnormal signal intensity is seen. (b) Brain MRI findings (axial; T2-weighted images, sagittal; fluid-attenuated inversion recovery) of case 2 (age 7y). Diffuse mild cerebellar cortical atrophy is seen. No abnormal signal intensity is seen.

Figure 2: ATP1A3 protein and phenotypic spectrum. AHC, alternating hemiplegia of childhood; RDP, rapid-onset dystonia-parkinsonism; EOEE, early-onset epileptic encephalopathy; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss; RECA/FIPWE, relapsing encephalopathy with cerebellar ataxia/fever-induced paroxysmal weakness and encephalopathy; COS, childhood-onset schizophrenia; ROA, rapid-onset ataxia.
the likely pathogenic in each. Both variants are located on the intracellular region of Na\(^+\)/K\(^-\)-ATPase \(\alpha3\) subunit (Fig. 2).

Whole exome sequencing excluded ataxia telangiectasia, ataxia-oculomotor apraxia 1/2, spinocerebellar ataxia 5/13/29, and many other autosomal dominant or recessive cerebellar ataxia disorders in childhood.

**DISCUSSION**

The purpose of this study was to advance the understanding of phenotypes associated with variants in \(ATP1A3\). Specifically, we reported two cases with symptoms that have not been previously associated with variants in \(ATP1A3\). These symptoms include infantile-onset of slowly progressive pure cerebellar ataxia and mild to moderate intellectual disability, which have not been previously reported in patients with \(ATP1A3\)-related disorders (Table 1). Thus, these two cases did not show any characteristic symptoms of CAPOS syndrome, relapsing encephalopathy with cerebellar ataxia\(^9\)/fever-induced paroxysmal weakness encephalopathy\(^7\), nor any paroxysmal symptoms usually seen in AHC\(^3\) and rapid-onset dystonia parkinsonism.\(^4\)

Brain MRI in both patients revealed pure mild cerebellar cortical atrophy. In \(ATP1A3\)-related disorders, brain MRI abnormalities are not generally detected. However, as we previously reported,\(^14\) some patients with typical AHC show mild cerebellar cortical atrophy in adulthood. The cerebellar atrophy detected by brain MRI in both cases of the current study is similar to the atrophy previously reported in typical patients with AHC and the c.2401G>A (p.Aspl601Asn) variant or c.2423C>T (p.Pro808Leu) variant in \(ATP1A3\).\(^4\) Therefore, pure mild cerebellar cortical atrophy may be a trait that can help to identify progressive cerebellar ataxia cases of \(ATP1A3\)-related neurological disorders. The mechanisms of underlying this relation are unknown, as the Na\(^+\)/K\(^-\)-ATPase \(\alpha3\) subunit is ubiquitously expressed in the brain, including the cerebellar cortex,\(^15\) which does not explain our current finding of pure cerebellar atrophy.

Recently, some adult patients with rapid-onset ataxia were reported,\(^10\) and patients with childhood-onset ataxia-dominant with \(ATP1A3\) variants were also reported.\(^9\) However, patients with infantile-onset and pure slowly progressive cerebellar ataxia caused by \(ATP1A3\) variants without any paroxysmal symptoms have not been reported. Currently, some phenotype/genotype correlations have been described. For instance, CAPOS syndrome is caused by p.Glu818Lys mutation\(^9\) and relapsing encephalopathy with cerebellar ataxia\(^9\)/fever-induced paroxysmal weakness encephalopathy\(^7\) is caused by p.Arg756Ser/His/Cys mutation. The mutations which cause AHC are mostly different from those causing rapid-onset dystonia parkinsonism. In AHC, a correlation between a relatively severe phenotype with the genotype of p.Glu815Lys, and a moderate phenotype with the genotype of p.Asp801Asn and p.Gln947Arg has been reported.\(^3\) In the present report, we describe for the first time two \(ATP1A3\) variants, namely p.Met154Val (case 1) and p.Asp350Lys (case 2). These are both located in the intracellular cytoplasmic region of the Na\(^+\)/K\(^-\)-ATPase, but further research is needed to clarify the potential modifications affecting the regulation of Na\(^+\)/K\(^-\)-ATPase.

Although based on only two patients, we believe that the symptoms reported, namely infantile-onset and slowly progressive cerebellar ataxia, could be a new subtype of \(ATP1A3\)-related neurological disorders. Overall, the findings have important implications for the diagnosis of spinocerebellar ataxia.

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