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Clinical Observations

Clinical Course and Images of Four Familial Cases of Allan-Herndon-Dudley Syndrome With a Novel Monocarboxylate Transporter 8 Gene Mutation

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ABSTRACT

BACKGROUND: Allan-Herndon-Dudley syndrome, an X-linked condition characterized by severe intellectual disability, dysarthria, athetoid movements, muscle hypoplasia, and spastic paraplegia, is associated with defects in the monocarboxylate transporter 8 gene (*MCT8*). The long-term prognosis of Allan-Herndon-Dudley syndrome remains uncertain. **PATIENTS:** We describe the clinical features and course of four adults in a family with Allan-Herndon-Dudley syndrome with athetoid type cerebral palsy. **RESULTS:** We identified an *MCT8* gene mutation in this family. Two of the four affected family members died at 32 and 24 years of age. **CONCLUSIONS:** Individuals with Allan-Herndon-Dudley syndrome are at increased risk for recurrent infection, such as aspiration pneumonia. These individuals require careful management with consideration for this increased risk of recurrent infection.

Keywords: Allan-Herndon-Dudley syndrome, monocarboxylate transporter 8 (MCT8) gene, brain MRI, cerebral palsy

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Introduction

Allan-Herndon-Dudley syndrome is an X-linked syndrome characterized by severe intellectual disability, dysarthria, athetoid movements, muscle hypoplasia, and spastic paraplegia.[1] It is caused by mutations in the monocarboxylate transporter 8 gene (*MCT8*).[2,3] *MCT8* encodes an active thyroid hormone transporter, which induces a greater than 10-fold increase in the uptake of triiodothyronine (T_3) into cells and to a lesser extent thyroxine (T_4), and is expressed differentially in human tissues.[4] Mutations in *MCT8* are associated with endocrine findings, including elevated bioactive T_3 and decreased T_4 levels in the presence of a normal thyrotropin (thyroid-stimulating hormone [TSH]) secretion. *MCT8* is present in many organs, such as liver, kidneys, pituitary, and thyroid gland, and is also expressed in brain.[5] Affected male patients show hypotonia and muscle weakness at birth.

Few reports document the natural history of Allan-Herndon-Dudley syndrome due to *MCT8* mutations, although a few reports describe the cause of death. Here we report a family with four adults diagnosed with athetoid type cerebral palsy. A mutation in *MCT8* was identified in one of the affected family members, two of whom died at 32 and 24 years of age.

Patient Descriptions

Patient 1

This 26-year-old man (III-3; Fig 1) is the third child in his family and was born healthy to nonconsanguineous parents after a term pregnancy without asphyxia. A male infant in the second generation died in early infancy.

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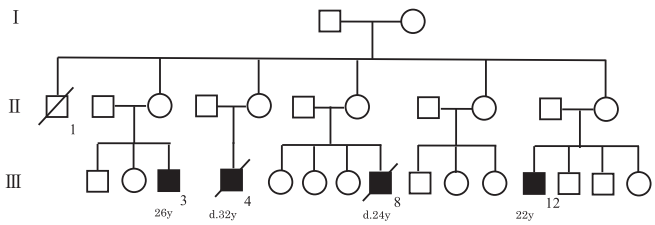

FIGURE 1.
Partial pedigree of kindred with Allan-Herndon-Dudley syndrome. Black squares indicate affected males. One boy died in early infancy and there is no information about whether he had clinical features of Allan-Herndon-Dudley syndrome (II-1). d = died; y = year.

His older brother and sister are healthy. He exhibited developmental delay with dyskinetic movements from early infancy, and he was referred to our hospital at the age of 4 months. Brain magnetic resonance imaging (MRI) revealed delayed myelination for his age; the peripheral white matter was still unmyelinated on T_2-weighted images (Fig 2). He was diagnosed with athetoid cerebral palsy and has continued rehabilitation until his current age of 26 years. Because three male cousins (III-4, III-8, and III-12; Fig 1) showed similar clinical features, Allan-Herndon-Dudley syndrome was suspected. On the latest examination at the age of 26 years, he had truncal hypotonia with limb hypertonia and hyperreflexia, muscle wasting, and dystonic posturing. He could not achieve head control, sitting, crawling, standing, or verbal communication. His face was long and narrow and scoliosis was evident. He could take some food orally with support. His body weight was 28 kg (−3.5 S.D.). He had no epilepsy.

At the age of 26 years, the brain MRI obtained at 5 years of age was reviewed, and the thyroid hormones were checked. This revealed a pattern of abnormalities suggestive of Allan-Herndon-Dudley syndrome: TSH 1.3 μIU/mL (normal 0.4-4.0), T_3 2.4 ng/mL (normal 0.7-1.76), and T_4 5.9 μg/dL (normal 4.8-10.5). Because an *MCT8* mutation in exon 5, c.1621G>T (G541C), was identified (Fig 3), he was diagnosed with Allan-Herndon-Dudley syndrome.

Patients 2-4

Patient 2 (III-4) was referred to our hospital for delayed development at the age of 23 months and diagnosed with dyskinetic quadriplegia with dystonic spontaneous movements. He never achieved head control, sitting, crawling, standing, or verbal communication. At the age of 20 years, he was 133.0 cm (−6.5 S.D.) tall and weighed 17 kg (−4.4 S.D.). Brain MRI performed at age 13 years indicated delayed myelination, whereas MRI at age 18 years had progressed but still showed immature myelination of the white matter and atrophy of the cerebral white matter. He also had intractable epilepsy, although no recurrent infection was evident. He died at 32 years, after eating and taking his medicine; there was evidence of vomiting.

Patient 3 (III-8) was referred to our hospital for developmental delay and diagnosed with dyskinetic quadriplegia with dystonic spontaneous movements at the age of 5 months. He failed to achieve head control, sitting, crawling, standing, or verbal communication. At the age of 22 years he weighed 20.6 kg (−4.1 S.D.). No convulsions were observed. MRI performed at the age of 3 years indicated delayed myelination. He required a tracheotomy and gastrostomy at the age of 23 years for chronic respiratory distress associated with recurrent aspiration pneumonia and gastroesophageal reflux. He died at the age of 24 years after a respiratory tract infection that led to a cough requiring frequent oral suction.

Patient 4 (III-12) was born with a cleft lip and palate that was surgically repaired at age 18 months. He was referred to our hospital at the age of 5 months for developmental delay and was diagnosed with dyskinetic quadriplegia with dystonic spontaneous movements. He did not achieve head control, sitting, crawling, standing, or verbal communication. At the age of 22 years he was 146.5 cm (−4.2 S.D.) tall and weighed 24 kg (−3.7 S.D.). Although he has had recurrent bronchitis and pneumonia since the age of 2 years, his family refused a tracheotomy and gastrostomy. At the age of 11 years, brain MRI revealed delayed myelination for his age. At the age of 22 years, his TSH, T_3, and T_4 levels were 1.5 μIU/mL (normal 0.4-4.0), 2.31 ng/mL (normal 0.7-1.76), and 5.7 μg/dL (normal 4.8-10.5), respectively.

Discussion

We identified an *MCT8* mutation in a patient with athetoid cerebral palsy for over 20 years, leading to a final diagnosis of Allan-Herndon-Dudley syndrome. The clinical features, family history, MRI findings, and thyroid hormone levels were all compatible with Allan-Herndon-Dudley syndrome (Table).

MCT8 mutations have been identified in previously genetically unresolved patients with radiological features suggestive of a Pelizaeus-Merzbacher–like disease, a type of leukodystrophy, and with progression of myelination.[6]

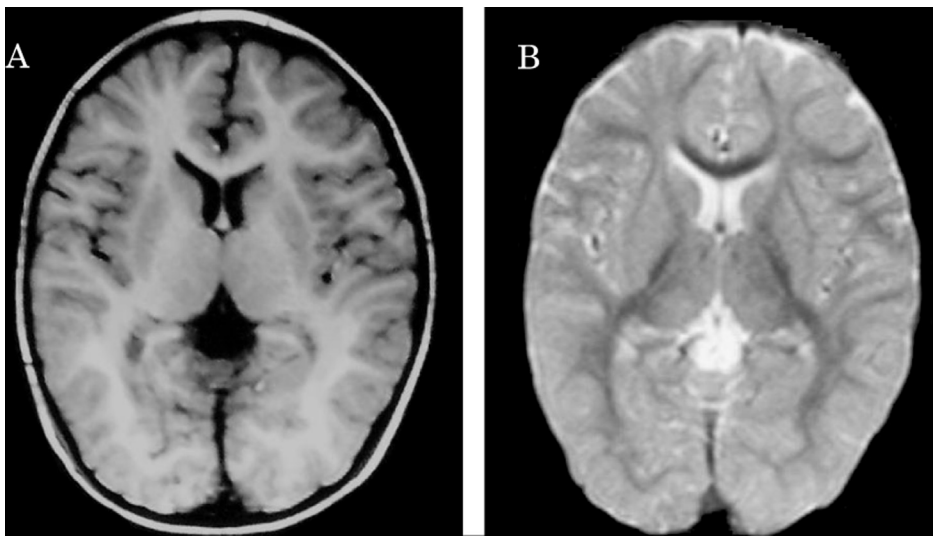

FIGURE 2.
(A) T_1-weighted image (repetition time (TR) 400, echo time (TE) 14) and (B) T_2-weighted image (TR 2000, TE 120) reveal delayed myelination at age 5 years (Patient 1).

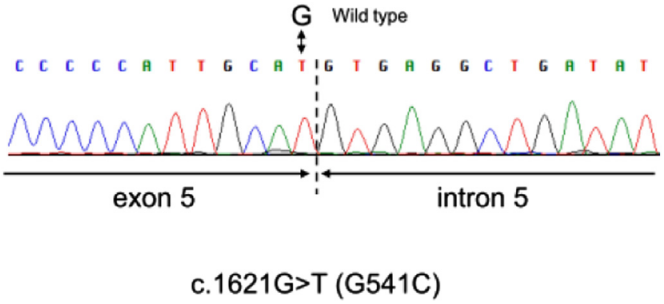

FIGURE 3.
Electropherograms showing the mutation found in exon 5 of *MCT8* in the propositus.

Therefore Allan-Herndon-Dudley syndrome is likely underrecognized, and a diagnosis of athetoid type cerebral palsy is made, unless specific white matter abnormalities are documented.[7] Altered T_3 and T_4 levels or MRI findings may be a useful screen for Allan-Herndon-Dudley syndrome.

Reports of a normal myelination pattern in the later life of patients with Allan-Herndon-Dudley syndrome suggest either that myelination, although delayed, will occur eventually, or that the residual *MCT8* activity associated with *MCT8* mutations is sufficient for normal myelination to progress.[8] The MRIs of all four of our patients suggested delayed myelination. Conversely, the MRI of Patient 2 still indicated delayed myelination at the age of 18 years, although there was improvement compared with the previous images. A previous study reported that myelination remained abnormal, suggesting a persistent myelination defect, while there was some improvement on T_2-weighted images.[7] Although the cerebral white matter atrophy compared with that performed before in Patient 2, cortical and subcortical atrophy have been reported in patients with Allan-Herndon-Dudley syndrome.[3,9]

The prognosis of patients with Allan-Herndon-Dudley syndrome has not been reported in detail. In one study of 32 patients, eight lived beyond 70 years, indicating relative longevity.[3] In the same series, however, three affected male patients died before age 10 years; one died in his teens, two died during their twenties, and four died during their thirties. Of these, the causes of death were described in only three patients: aspiration pneumonia at the age of 22 years, leukemia at 9 months, and pneumonia at 32 years.[3] Aspiration pneumonia was reported in another patient as a cause of death at age 10 years.[10] These findings suggest that prognosis of Allan-Herndon-Dudley syndrome is variable. Two of our patients died unexpectedly, at 32 and 24 years of age, possibly because of aspiration pneumonia. All four of our patients had severe motor and intellectual disabilities, and recurrent infections occurred in two, one of whom died. Therefore individuals with Allan-Herndon-Dudley syndrome might have a higher risk of recurrent infection, such as aspiration pneumonia. Because three of our patients have difficulty with aspiration during feeding, early application of gastrostomy with a Nissen fundoplication may be recommended for prevention of aspiration pneumonia. In people with severe motor and intellectual disabilities in addition to Allan-Herndon-Dudley syndrome, respiratory disease is a major cause of death.[11] In this population, the reported survival rate at age 20 and 30 years is 73% and 64%, respectively.[11] Accordingly, recurrent infection might be part of the clinical course of patients with severe motor and intellectual disabilities and not specifically Allan-Herndon-Dudley syndrome. Further studies should elucidate factors related to the prognosis of patients with *MCT8* mutations.

TABLE.
Clinical and Radiographic Findings of Allan-Herndon-Dudley Syndrome

- X-linked syndrome
- Clinical features:
  - Childhood hypotonia, dysarthria, athetoid or other distal limb movements, muscle hypoplasia, and severe intellectual disability.
- Diagnosis/testing:
  - Brain MRI during the first few years with markedly delayed myelination.
  - Thyroid function tests reveal high serum T_3. Serum T_4 concentration is often reduced but may be within the normal range. Serum TSH concentrations are normal or slightly elevated.
  - Mutations in the monocarboxylate transporter 8 gene (*MCT8*) are associated with this disorder.

Abbreviations:
MRI = Magnetic resonance imaging
T_3 = Triiodothyronine
T_4 = Thyroxine
TSH = Thyroid-stimulating hormone

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