Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Inborn Errors of Metabolism in Adults: Two Patients with Movement Disorders Caused by Glutaric Aciduria Type 1

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Movement disorders can be caused by many different acquired and genetic causes, including inborn errors of metabolism (IEM). Symptoms of an IEM can occur from infancy until adulthood and range from subtle to very severe symptoms. In particular, in patients that present later in life, symptoms are often less pronounced and progressive compared to the severe childhood-onset forms.[1] Late-onset IEM often present with complex phenotypes, including (multiple) movement disorders and psychiatric symptoms.[2] In clinical practice, IEM are rarely considered in adult patients presenting with a movement disorder, leading to diagnostic and treatment delay.

Glutaric aciduria type 1 (GA-1) is an example of an IEM that can present with movement disorders in adulthood. GA-1 is an autosomal recessive IEM with an estimated incidence of 1:100,000 in neonates and was first described in 1975.[3] It is caused by a deficiency of glutaryl-CoA dehydrogenase (GCDH), which is part of the catabolic pathways of the amino acids L-lysine, L-hydroxylysine, and L-tryptophan. The enzymatic defect results in elevated concentrations of specific organic acids, such as glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, and specific carnitines conjugates, such as glutaryl carnitine, in body tissues, which can all be reliably detected by biochemical analyses using gas chromatography/mass spectrometry (organic acids) and tandem mass spectrometry (acylcarnitines).

We present 2 adult patients who presented with movement disorders and were diagnosed with glutaric aciduria type 1 in adulthood.

Case Reports

Case 1

The first patient is a 45-year-old Czech woman who presented with progressive jerky movements of the limbs, gait disturbances, and speech impairment. She had a history of being a "clumsy child, slower in running than the others" and was diagnosed with cerebral palsy at the age of 3 because of movement abnormalities, although no abnormalities during pregnancy or delivery were reported. Her older brother died after seizures with cerebral bleeding when he was 20 years old (in 1986, no records available), otherwise there was no family history. No medication was used. She was married, had 2 healthy children, and worked as a cleaner at a kindergarten.

Neurological examination showed slight dysarthria, generalized chorea with possible additional myoclonus, and dystonia (Video S1). Brain magnetic resonance imaging (MRI) revealed very mild, bilaterally symmetric gliosis in the dorsal putamen without significant atrophy (Fig. 1). Metabolic testing discerned GA-1 by significantly elevated glutaric acid and 3-hydroxyglutaric acid in urine, and glutarylcarnitine in a dry blood spot. The diagnosis of GA-1 was verified by DNA analysis, confirming 2 pathogenic mutations in the *GCDH* gene (compound heterozygous mutations: c.1148G > A [p.Arg383His] and c.1262C > T [p.Ala421Val]).

A dietary treatment that consists of a low protein and high energy diet regimen and carnitine and riboflavin supplementation was introduced. Since the initiation of treatment 4 years ago, the patient has been stable without significant deterioration, and the diet is well-tolerated.

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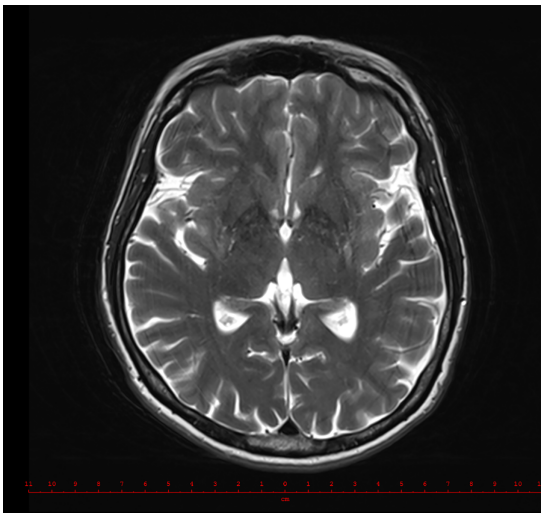

FIG. 1. Brain MRI of case 1 (T_2-weighted turbo spin-echo [T_2 TSE]) showing very mild, bilaterally symmetric gliosis in the dorsal putamen without significant atrophy.

Case 2

The second patient is a 45-year-old woman from the Netherlands who presented with generalized involuntary movements that were more pronounced on the left side of her body. Her mother noticed these involuntary movements from a very young age and they were slightly progressive over the years. She visited neurologists before and had several different diagnoses including cerebral palsy, functional movement disorder, and tics. Pregnancy and birth were normal. With the exception of delayed walking (at the age of 2 years), motor milestones were normally obtained. Family history was unremarkable, and she did not use any medication.

Neurological examination showed dystonia of the neck, mild orofacial dystonia, and slight dysarthria. Eye movement examination showed some saccadic intrusions during smooth pursuit. There were jerky, chaotic movements of the arms during rest, posture, and action, thought to be consistent with chorea and possible additional myoclonus. These movements were more pronounced on the left side. There was dystonia of the hand during writing and tapping with intermittent abnormal posture of the feet (Video S2).

Brain MRI showed abnormalities of the dorsal putamen (Fig. 2). A dystonia gene panel was performed and revealed 2 pathogenic mutations in the *GCDH* gene (compound heterozygous mutations c.482G > A [p.Arg161Gln] and c.1262C > T [p.Ala421Val]), conforming GA-1. No dietary treatment was started, but emergency treatment was advised during catabolic periods. Since her diagnosis 6 years ago, there was only slight progression of the movement disorders.

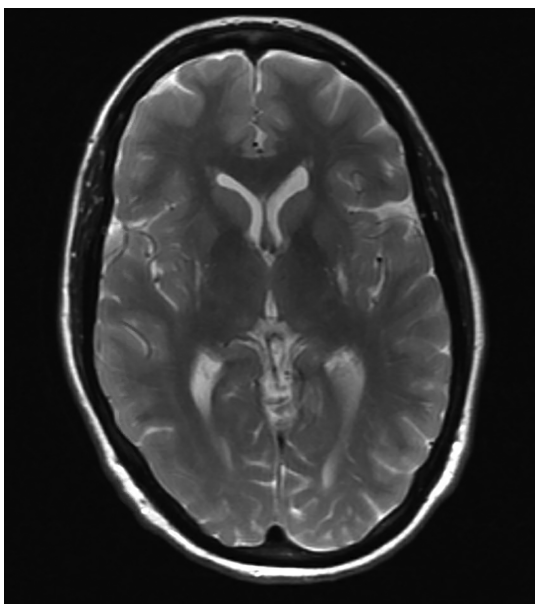

FIG. 2. Brain MRI of case 2 (T_2 TSE) showing abnormalities of the dorsal putamen.

Discussion

Here, we describe 2 adult patients presenting with lifelong movement disorders because of GA-1. These 2 cases illustrate that in patients with complex movement disorders, especially when they start with a mild phenotype at young age, GA-1 should be considered. Both patients were considered to have cerebral palsy despite the absence of a history of perinatal problems. Because of progression of symptoms later in life, a genetic disorder was suspected.

As in our cases, the diagnosis of GA-1 can be made by biochemical screening with findings of the specific metabolites in urine and dry blood spot or by molecular genetic testing revealing disease-causing mutations on both *GCDH* alleles. It is important to note that newborn screening for GA-1 is possible since the late 1990s, but is still not implemented in every country.[4] Our cases show clearly that there are adults with GA-1 who have not suffered from acute crises and have not been screened for GA-1 before.

Newborns with GA-1 may be asymptomatic, although they often develop macrocephaly, subdural or retinal bleedings, hypotonia, and motor developmental delay. Most pediatric-onset and untreated patients with GA-1 experience acute encephalopathic crises during the first 6 years of life, triggered by infectious diseases, febrile reactions to vaccinations, surgery, or catabolic episodes. These crises result in striatal injury, leading to severe generalized dystonia.[1,5] However, not all patients have this acute-onset dystonia, because some patients develop a more insidious onset of dystonia without evident triggers.[1] A recent study presented 8 late-onset patients: 3 were asymptomatic, 3 had non-specific general symptoms, and 2 presented with dementia, tremor, and epilepsy.[6] A wide range of MRI abnormalities can be found in GA-1, including T_2/FLAIR hyperintensity and/or volume loss in the striatum, which typically occur after acute encephalopathy. The pallidum

may be affected as well. In some cases, isolated signal changes of the globus pallidus are observed. Other changes include white matter changes, temporal or frontal hypertrophy, and transient subependymal nodules.[5] The latter are characteristic for late-onset GA-1 patients, although they were not found in our 2 cases.[6]

In childhood, the identification of patients with GA-1 at the earliest stage of disease is important, because emergency treatment may prevent or lessen brain damage. Furthermore, dietary treatment, consisting of low lysine, high energy diet, and carnitine supplementation, may improve neurologic outcome in these early-onset GA-1 patients, with a reduction of acute encephalopathic crises and movement disorders from 80–90% to 10–20%.[5] After adolescence, the risk of developing an acute crisis is much lower, and hardly any acute crises occur during intercurrent illness after the age of 12.[7]

There are no systematic studies on effectiveness of dietary treatment after the age of 6 years, and the therapeutic impact is limited when the diagnosis is made after manifestation of neurological disease. At present, it remains to be elucidated whether treatment efficacy varies among the different patient groups, including the insidious-onset forms and late-onset forms.[8] Emergency treatment during catabolic states should be advised to all patients with GA-1, however, only case reports on emergency treatment in adults have been published.[5]

With the implementation of next-generation sequencing, unexpected diagnoses are made in adult patients with movement disorders, showing that the spectrum of symptoms of IEM is broader than previously assumed. Unfortunately, there is a lack of adult neurologists who are familiar with these disorders, leading to incorrect diagnoses and delay of treatment. Some of these patients are, like the patients described above, incorrectly diagnosed with cerebral palsy.[9,10] Furthermore, many patients who are diagnosed during GA-1 screening programs develop movement disorders with an insidious course (despite early treatment) and will be transferred to adult neurology services in the coming years. This also underscores the need for adult neurologists who are familiar with IEM and their neurological symptoms.

In summary, we describe 2 adult patients with movement disorders who were diagnosed with a treatable IEM at the age of 45. These cases emphasize the importance of considering an IEM in the differential diagnosis in adult neurology. Until now, little attention is given to these disorders in neurological training and daily clinical practice, leading to considerable diagnostic delays.

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Author Roles

(1) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Disclosures

Ethical Compliance Statement: The patients were informed and a signed consent was obtained. The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Video S1. Neurological examination of case 1, showing a combination of chorea, dystonia, and myoclonus.

Video S2. Neurological examination of case 2, showing a combination of chorea, dystonia, and myoclonus.