Clinical Observations

**Alternating Hemiplegia of Childhood With a de Novo Mutation in ATP1A3 and Changes in SLC2A1 Responsive to a Ketogenic Diet**

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**ABSTRACT**

**BACKGROUND:** Alternating hemiplegia of childhood (AHC) is a rare condition characterized by an early onset of hemiplegic episodes and other paroxysmal or permanent neurological dysfunctions. Recently, mutations in the ATP1A3 gene have been identified as the causal mechanism of AHC. Regarding the differential diagnosis of AHC, glucose transporter 1 deficiency syndrome may be considered because these two disorders share some paroxystic and nonparoxystic features. **PATIENT AND RESULTS:** We report a typical case of AHC harboring a de novo mutation in the ATP1A3 gene, together with a duplication and insertion in the SLC2A1 gene who exhibited marked clinical improvement following ketogenic diet. **CONCLUSION:** Because the contribution of the SLC2A1 mutation to the clinical phenotype cannot be definitely demonstrated, the remarkable clinical response after ketogenic diet led us to the hypothesis that ketogenic diet might be effective in AHC as it provides an alternative energy source for the brain.

**Keywords:** alternating hemiplegia of childhood, ATP1A3, GLUT1 deficiency syndrome, GLUT1 DS, SLC2A1, ketogenic diet

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**Introduction**

Alternating hemiplegia of childhood (AHC) is a rare disease characterized by repeated episodes of hemiplegia with onset before 18 months of age, tonic or dystonic attacks, paroxysmal features, such as abnormal eye movements, dyspnea, and other autonomic phenomena with disappearance of all symptoms in sleep, in association with developmental delay, mental retardation and other neurological abnormalities.1-5 Recently, mutations in the ATP1A3 gene have been identified as one important cause of AHC.1-8

As part of the differential diagnosis of AHC, glucose transporter 1 (GLUT1) deficiency syndrome (GLUT1 DS) may be considered since these two disorders share several peculiar paroxystic and nonparoxystic features. GLUT1 DS is a neurological disease caused by reduced transport of glucose across the blood-brain barrier due to haploinsufficiency of the SLC2A1 gene.7 The most common manifestations of GLUT1 DS include epilepsy, developmental delay, acquired microcephaly, spasticity, ataxia, dystonia and, additionally or alternatively, paroxysmal dyskinesias.8-10 Other phenotypes also have been reported, including the nonclassical phenotype of mental retardation and movement disorders without epilepsy; the spectrum of severity in this disease is really broad.8-10

We report a girl with AHC and a mutation in the ATP1A3 gene that also harbors an intronic duplication and insertion in the SLC2A1 gene. The patient exhibited a favorable,
although incomplete, response to flunarizine, followed by marked improvement with adjunctive treatment with a ketogenic diet. There is a lack of previous confirmed association between AHC and GLUT1 DS so this the first case reported.

Case report

We present a 10-year-old girl with an unremarkable family history. She was the third child of healthy, unrelated parents. Pregnancy and neonatal period were normal (gestational age: 40 weeks, weight: 3230 g, height: 49 cm, head circumference: 34 cm). At 5 months of age, she first manifested mild episodes of global hypotonia associated with clonic movements of both hands without impairment of consciousness. At 10 months of age, she developed episodes of fine tremor followed by cephalic flexion and convergent strabismus lasting up to 24 hours, all of which ceased with sleep. Microcephaly (head circumference <5th percentile) and global developmental delay became noticeable. At 12 months of age, she developed alternating hemiplegia, with a right-side predilection, lasting from minutes to hours, provoked by physical exercise and fasting and which improved with sleep. In light of the dystonic episodes, abnormal eye movements, developmental delay and alternating hemiplegia, she was diagnosed with AHC. Ancillary examinations (electroencephalogram, cerebral ultrasound, brain magnetic resonance imaging, and auditory-evoked potentials) were normal. Laboratory investigations to rule out inborn errors of metabolism (blood count, electrolytes, renal function, ammonium, lactate, creatine kinase, plasma amino acids, urinary organic acids) and karyotype also were normal.

The combination of developmental delay, microcephaly, and dystonic movements provoked by fasting suggested a neurometabolic disorder, so a lumbar puncture was performed when she was 3 years old. Cerebrospinal fluid (CSF) analysis showed a glucose concentration at the lower limit of normal range (2.6 mmol/L; reference value for age: 0.43-0.86) and lactate of 1.4 mmol/L (reference value: 2.4-3.8 mmol/L) with a CSF/blood glucose ratio of 0.54 (reference value: limit of normal range (2.6 mmol/L; reference value for age: 0.43-0.86)).

Given the AHC phenotype, at 4 years of age, treatment with flunarizine was started, leading to shortening (but not the disappearance) of the events. In light of this relative treatment failure, CSF studies, \(^{18}\)FDG-PET results and the identification of molecular changes of unknown relevance in SLC2A1, adjunctive treatment with a ketogenic diet (ratio 4:1) was initiated. The paroxysmal events almost completely disappeared, becoming milder, shorter, and less frequent. Before starting the diet, the patient had one hemiplegic attack weekly, and after starting the diet she presented hemiplegic attacks every 6 months. She also experienced improvement in motor function also was noticed: before the ketogenic diet, the patient required a wheelchair for outdoor use, but afterwards she was able to walk independently. Follow-up \(^{18}\)FDG-PET (under ketogenic diet, while the patient was asymptomatic and 1 month after the last hemiplegic attack) exhibited normal and symmetrical \(^{18}\)F-FDG uptake in the basal ganglia, as well as in the cortex (Fig B). The mechanism underlying these changes remains unknown and it probably differs from that responsible for GLUT1 DS, in which PET findings have never proven amenable to evolution (JM Pascual, unpublished observations, n = 67 and an additional n = 14). The patient has been on ketogenic diet for 4 years, and she is still receiving flunarizine.

Discussion

AHC is a rare disorder (with an estimated prevalence of 1 in 1 million children) first described by Verret and Steele in 1971. Krakelog and Aicardi established the clinical diagnostic criteria currently in use in 1980. AHC is characterized by hemiplegic, tonic, or dystonic episodes and abnormalities of ocular movements with onset before 18 months of age, as well as global neurological dysfunction. Hemiplegic events often can be related to environmental triggers such as physical activity, insufficient food intake or certain foods, whereas symptoms are usually relieved by sleep. The diagnosis of AHC relied on clinical

| A | PET images show high \(^{18}\)F-FDG uptake in the basal ganglia, particularly in putamen and caudate, clearly greater than the normal cortex. (B) PET images after starting ketogenic diet show normal and symmetrical \(^{18}\)F-FDG uptake in basal ganglia as well as in the cortex. \(^{18}\)F-FDG, \(^{18}\)F-deoxyglucose proton emission tomography; PET, positron emission tomography. |
grounds until de novo mutations in ATP1A3 were identified as a primary cause of AHC.1-6 This gene encodes the α-3 subunit of the sodium-potassium ATPase, which is preferentially expressed in the basal ganglia, hippocampus and cerebellum.5 Flunarizine, a calcium channel blocker, decreases frequency, severity and duration of attacks, demonstrating partial efficacy in at least 70% of patients.2 as was observed in our patient.

First described in 1991, GLUT1 DS is a disorder of brain energy metabolism caused by diminished brain glucose entry.13,14 Severe epilepsy, developmental delay, acquired microcephaly, spasticity, and dystonia are common manifestations.8,9 Among the epileptic and early events, apnea decreases frequency, severity and duration of attacks, hypoglycorrhachia in CSF in the context of a normal serum mitigation and improvement in other neurological symptoms that it causes have been divided as a primary cause of AHC.4-6 This gene encodes the GLUT1 transporter structure, although effects on mRNA expression or stability have not been investigated. This mutation is overrepresented in GLUT1 DS, but it can occur in nonaffected relatives, making the potential contribution of this additional mutation to the pathogenesis of AHC undetermined (5 of 55 GLUT1 DS cases, only the proband described in this report exhibited an AHC phenotype, and 2 of 104 related asymptomatic controls; JM Pascual, unpublished observation). In support of a co-causal role of this variant,18FDG-PET studies, biochemical analysis of CSF, and the response to a ketogenic diet support the involvement of impaired glucose transport as a phenotypic modifier in our patient. In this regard, our patient suggests novel hypotheses. In the presence of potentially impaired sodium homeostasis in the basal ganglia caused by a mutation at the ATP1A3 gene, subtle changes in brain glucose transport might cause additional deleterious effects. However, studies in Spanish and French cohorts have failed to detect mutations in SLC2A1 in a total of 53 AHC patients,5,8 such that this matter will deserve further investigation since it is evident that these two diseases share symptoms, including movement disorders. In the French cohort (23 patients),14 exhibited normal glucose CSF levels, whereas 9 remained undetermined.8

Our patient harbored a duplication and insertion in an intron of the SLC2A1 gene, which is not expected to alter GLUT1 transporter structure, although effects on mRNA expression or stability have not been investigated. This mutation is overrepresented in GLUT1 DS, but it can occur in nonaffected relatives, making the potential contribution of this additional mutation to the pathogenesis of AHC undetermined (5 of 55 GLUT1 DS cases, only the proband described in this report exhibited an AHC phenotype, and 2 of 104 related asymptomatic controls; JM Pascual, unpublished observation). In support of a co-causal role of this variant,18FDG-PET studies, biochemical analysis of CSF, and the response to a ketogenic diet support the involvement of impaired glucose transport as a phenotypic modifier in our patient. In this regard, our patient suggests novel hypotheses. In the presence of potentially impaired sodium homeostasis in the basal ganglia caused by a mutation at the ATP1A3 gene, subtle changes in brain glucose transport might cause additional deleterious effects. However, studies in Spanish and French cohorts have failed to detect mutations in SLC2A1 in a total of 53 AHC patients,5,8 such that this matter will deserve further investigation since it is evident that these two diseases share symptoms, including movement disorders. In the French cohort (23 patients),14 exhibited normal glucose CSF levels, whereas 9 remained undetermined.8

Our patient fulfilled all criteria for AHC and improved with flunarizine treatment. She also displayed clinical and analytical features overlapping with those of GLUT1 DS and, although the contribution of SLC2A1 mutation to the clinical phenotype cannot be definitely demonstrated,18FDG-PET data and a favorable clinical outcome after a ketogenic diet could support the potential implication of GLUT1 DS in the phenotype of our AHC patient. But because the implication of the SLC2A1 mutation is not clear, there is also a possibility that AHC itself might benefit from a ketogenic diet. The ketogenic diet might work as ketones provide an alternative energy source for the brain. Also ketogenic diet might reduce neuronal excitability, present in AHC because of the increased intracellular sodium concentration, and in this way reduce the paroxysmal symptoms. Therefore, investigation of the interrelation between sodium, ATP and glucose homeostasis in the brain is expected to shed light on potentially synergistic disease mechanisms.

References