Glutaric Acidemia Type 1: A Case of Infantile Stroke

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Received: 20 November 2016 / Revised: 30 March 2017 / Accepted: 03 April 2017 / Published online: 15 April 2017
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Abstract *Background:* Glutaric acidemia Type 1 (GA-1) is an autosomal recessively inherited metabolic disorder which is associated with *GCDH* gene mutations which alters the glutaryl-CoA dehydrogenase, an enzyme playing role in the catabolic pathways of the amino acids lysine, hydroxylysine, and tryptophan. Clinical findings are often encephalopathic crises, dystonia, and extrapyramidal symptoms.

Case Report: A 9-month-old male infant referred to our department with focal tonic-clonic seizures during rotavirus infection and acute infarcts in MRI. Clinical manifestation, MRI findings, and metabolic investigations directed thoughts towards GA-I. Molecular genetic testing revealed a homozygous c.572T>C (p.M191T) mutation in *GCDH* gene which confirmed the diagnosis. Application of protein restricted diet, carnitine and riboflavin supplementations prevented the progression of Magnetic Resonance Imaging (MRI) and clinical pathologic findings during the 1 year of follow-up period.

Conclusion: This case is of great importance since it shows possibility of infantile stroke in GA-1, significance of early diagnosis and phenotypic variability of disease.

Introduction

Glutaric acidemia Type 1 (GA-1) (OMIM number #231670) is an autosomal recessively inherited, treatable disease which was to be addressed first by Goodman et al. (1975). Mutations in the glutaryl-CoA dehydrogenase (*GCDH*) gene result in glutaryl-CoA dehydrogenase (Enzyme Commission number 1.3.8.6) deficiency which is a key enzyme in the catabolic pathways of the amino acids lysine, hydroxylysine, and tryptophan. The estimated prevalence is 1 in 30,000–100,000 newborns whereas this prevalence might be much higher in some countries with high rates of consanguineous marriages (Tang et al. 2000; Strauss et al. 2003; Kölker et al. 2006, 2011; Baradaran et al. 2014). *GCDH* deficiency is characterized by increased levels of organic acid excretions; namely of glutaric acid, 3-hydroxyglutaric acid (3-OHGA), glutaconic acid in urine and glutarylcarnitine in plasma. Increased urinary concentrations of 3-OHGA is the most sensitive biochemical marker for diagnosis (Al-Dirbashi et al. 2011).

Clinical presentation with acute encephalopathic crises mostly between 6th and 18th months is triggered by febrile illness, fasting, or immunization. As for the discourse of onset, late, slowly progressive and insidious onset of cases have been defined (Fraidakis et al. 2014). Affected patients often present with dystonia and extrapyramidal symptoms such as athetosis, seizures, and intellectual disability. The macrocephaly prevalence in GA-1 is about 75% of the patients (Babu et al. 2015).

In this study, we hereby report a case with GA-1 presented with recurrent brain infarcts. Although metabolic strokes may be seen in patients with isovaleric, methyl malonic, and propionic acidemias, stroke is rarely observed in the presentation of GA-1 (Hoffmann et al. 1994).

Communicated by: Piero Rinaldo, MD, PhD

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Case

A 9-month-old male infant born out of consanguineous marriage between first cousins admitted with the complaint of focal tonic-clonic seizures during a rotavirus infection. There was no history of asphyxia or trauma. The neurologic and neuropsychological examinations were unremarkable. Biochemical investigations including serum electrolytes, blood glucose, and liver functions were within normal limits. The electroencephalography (EEG) showed normal results, so seizures were evaluated as symptomatic. Due to the focal tonic-clonic seizure episode secondary to infection, MRI of the brain was requested which revealed restricted diffusion consistent with acute infarcts in the bilateral basal ganglia, mildly dilated appearances in the lateral ventricles and an arachnoid cyst in the left Sylvian fissure (Fig. 1). Metabolic diseases screenings and coagulation anomalies were investigated and enoxaparin treatment was initiated and terminated on the 5th day due to the normal coagulation profile. On the 15th day of the hospitalization, a new MRI was ordered due to the weakness in the right-hand which showed a new infarction extending to the internal capsule genu at the level of the left globus pallidus (Fig. 2). Despite the absence of macrocephaly, characteristic presentation and neuroimaging findings along with metabolic investigations suggested the diagnosis of GA-I (Table 1). Molecular genetic testing confirmed that the patient had a homozygous and parents had heterozygous c.572T>C (p. M191T) mutation related to GA-1 which was reported in one

patient from Germany (our case is Turkish) and labeled as likely pathogenic in databases (Schwartz et al. 1998).

The treatment with protein restricted diet (1.4 g/kg/day natural protein, 1 g/kg/day protein with amino acid supplements), carnitine (100 mg/kg/day), and riboflavin (100 mg/day) supplementations was initiated. During the follow-up while patient was on diet, there were no observed metabolic crises even if he had infections, but delayed motor and language development were significant in comparison with his peers. He started to walk without support when he was 24-month-old and currently (38-month-old) speaks only few words and there is still mild right hemiparesis. Because of normal control EEG tests and a seizure-free period antiepileptic treatment was withdrawn after 2 years. Control brain MRI after 29 months from first evaluation showed loss of volume and a T2 signal increase in the left putamen and caudate nucleus, and minimal volume loss and a slight T2 signal increase in the right putamen, and an arachnoid cyst in the left anterior temporal lobe and left anterior frontal lobe (Fig. 3).

Discussion

GA-1 is a treatable neurometabolic disease of autosomal recessive trait which develops due to the mutations of *GCDH* gene on chromosome 19p13. It might prevail more frequently in some populations with high rates of consanguinity and first cousin marriages as in our case. The usual

Fig. 1 A1 (diffusion weighted sequences) and A2 (apparent diffusion coefficient); MRI of the brain: restricted diffusion consistent with acute infarcts in the bilateral basal ganglia, mildly dilated appearances in the lateral ventricles and an arachnoid cyst in the left Sylvian fissure

Fig. 2 B1 (diffusion weighted sequences) and B2 (apparent diffusion coefficient); 15 days after from the first brain MRI; A new infarction in the internal capsule genus at the level of the left globus pallidus

Table 1 Blood and urine biochemistry results of case

Metabolite	Result ($\mu\text{mol/L}$)	Normal ($\mu\text{mol/L}$)
<i>Tandem MS</i>		
Free carnitine (C0)	3.07	7.00–80.00
Total carnitine	37	25.0–75.0
Glutaryl carnitine	0.6	0.35–20.0
C5DC/C8	2.87	0.0–1.8
C5DC/C16	0.48	0.0–0.06
<i>GC-MS</i>		
Glutaric acid (GA)	0	00.0–3.8
3-Hydroxyglutaric	0	00.0–4.6

age of presentation varies from 6 months to 2 years of age; often triggered by an infection, fasting, or immunization with acute metabolic encephalopathy. There may also be acute neuroregression and extrapyramidal symptoms following an initial phase of normal or almost normal development by striatal necrosis with stroke like characteristics. As the disease exhibits a slow progression, late onset presentations or asymptomatic cases in elderly ages were rarely reported (Fraidakis et al. 2014; Wang et al. 2014). Our case is compatible with typical age of presentation with 9 months of age, he was the first child of the family with consanguineous marriage and presented with stroke associated seizure during an acute gastroenteritis.

Due to the bilateral symmetric striatum involvement, impairment of perfusion in both infarcted watershed areas and the absence of the distribution of blood flow derived

from the affected blood vessels and clinically silent clinical manifestation in comparison with ischemic stroke patient was with diagnosed metabolic infarction due to glutaric aciduria (Strauss et al. 2007).

Macrocephaly, acute encephalitis like crises, dystonia due to bilateral striatal injury, and characteristic frontotemporal atrophy are the hallmarks of the disease. Generalized dystonia superimposed on axial hypotonia is predominantly occurred following an acute encephalitis crisis. Dystonia and hypotonia were not existed in our case at the time of diagnosis. Macrocephaly is a constant feature and can be present at birth or a rapid increase of head circumference can take place after birth with an estimated frequency of 65–75% reported in patients with GA-1, however microcephaly can be observed in patients with GA-1 during the first 8 months of life and besides there were cases reported

Fig. 3 C1 (diffusion weighted sequences) and C2 (apparent diffusion coefficient); 29 months after from the first MRI; loss of volume and a T2 signal increase in the left putamen and caudate nucleus, and

minimal volume loss and a slight T2 signal increase in the right putamen, and an arachnoid cyst in the left anterior temporal lobe and left anterior frontal lobe

without macrocephaly (Baradaran et al. 2014; Gupta et al. 2014; Wang et al. 2014). There is no association between macrocephaly and outcome whereas in some cases the frequency of macrocephaly was higher in mild impairment group than severe one, leading to an early diagnosis by macrocephaly (Mushimoto et al. 2011). In our case the above stated symptoms were all absent except encephalitis like crises, he was normocephalic with occipitofrontal circumference of 50–75th percentile for chronologic age.

Cranial radiologic imaging is generally useful and specific but still lacks high rates of success about diagnosis. Frontotemporal atrophy is the earliest feature, even in the asymptomatic period. Structural changes of basal ganglia, incomplete opercularization of the insular cortex, widening of the Sylvian fissures, and cerebrospinal fluid spaces are the characteristic of GA-1. Deep white matter and diffuse periventricular involvement can be existed for early or late onset subtypes and they seem to be correlated with duration of the disease and are not clinically subtype specific (Bähr et al. 2002). Published data reveals that MRI abnormalities have been defined for all patients with or without clinical signs; the severity of striatal lesions on MRI correlates with severity of the movement disorder and extra-striatal MRI findings do not correlate with the movement disorder (Harting et al. 2009; Garbade et al. 2014; Pusti et al. 2014; Wang et al. 2014). In our case, there was existed striatal injury but no movement disorders such as dystonia.

Up to now, more than 200 mutations have been detected in the *GCDH* gene. R402W and E181Q mutations are more prevalent than the other types (Baradaran et al. 2014; Gupta et al. 2014). There is no data about the types of common genetic mutations responsible for GA-1 in Turkey. Homozygous mutation of c.572T>C (p.M191T) as in our case

first was reported in 1998 in a male patient with German origin with <0.5% residual enzyme activity (Schwartz et al. 1998). The disease exhibits clinical variability which has a correlation with differently altered enzymatic activities due to the different positions of pathogenic variants in *GCDH* gene (Gupta et al. 2014). We weren't able to analyze the residual enzyme activity for our case due to financial problems.

Because of parents are heterozygous carriers, during genetic counseling preimplantation genetic diagnosis was explained to family in case of planned pregnancy due to the 25% chance of child to be affected.

In compliance with the findings of previous studies, there is no correlation between phenotype and genotype, but some of the mutations are correlated with the excretion of glutaric acid and residual enzyme activity (Goodman et al. 1975; Baradaran et al. 2014; Gupta et al. 2014). As for our case, there was no urinary excretion of glutaric (GA) and hydroxyglutaric acids (3-OHGA). As the sustained Tandem Mass Spectrometry, high level of C5DC in the repeated tests suggested the existence of GA-1, genetic molecular analysis was recommended out of suspicion for GA-1, even though the outcomes of analysis for organic acids in urine were all normal.

The newborn screening will be beneficial for a better outcome as the diagnostic delay may also lead to irreversible damage. Although it is the case that 10–20% of the patients still develop some level of motor and intellectual impairment (Boy et al. 2016) even with an appropriate treatment, excellent outcomes can be obtained thanks to early diagnosis and dietary therapy nevertheless. Our patient was asymptomatic at 9 months of age; such symptoms as macrocephaly, movement disorder, feeding

problems, or psychomotor delay were absent. In contrast to the fact reported by the previous data that patients with early onset suffer worse neurological outcome when compared to patients with late onset, our case with early onset happened to involve mildly good neurological outcome (Wang et al. 2014). The neurological development of the patient was close to the normal and there were no recurrent seizures. This clinical case has been reported herein to highlight the phenotypic variability of neuro-metabolic disorders such as GA-I, and emphasize the importance of a high index of suspicion.

Details of the Contributions of Individual Authors

Gül Demet Kaya Ozcora, Mustafa Kendirci, Sefer Kumandaş: collected the data, conducted the analyses and interpretation of the data, and prepared early drafts of the paper.

Gül Demet Kaya Ozcora, Mustafa Kendirci, Sefer Kumandaş: conceptualized and supervised development of the research, assisted with analysis and interpretation of the data and contributed to writing the manuscript.

Gül Demet Kaya Ozcora, Songül Gökay: participated in the collection of the data and helped manuscript preparation.

Mehmet Canpolat, Fatih Kardaş: helped in recruitment and provide testing facilities.

All authors read and approved the final manuscript.

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A Competing Interest Statement

The authors declare that there is no conflict of interest regarding this work.

Conflict of Interest

Gül Demet Kaya Ozcora, Songul Gokay, Mehmet Canpolat, Fatih Kardaş, Mustafa Kendirci, Sefer Kumandaş declare that they have no conflict of interest.

Details of Funding

This work received no specific grant from any funding organization.

Ethics Statements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Parents provided informed consent prior to use their child's history information, genetic test results, photographs, and video images. Signed consent form for publication was obtained.

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