Title
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Journal
Molecular Genetics and Metabolism, 107(1-2)

ISSN
1096-7192

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Publication Date
2012-09-01

DOI
10.1016/j.ymgme.2012.04.010

Molecular Genetics and Metabolism 107 (2012) 241–242

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Brief Communication

Mild fumarase deficiency and a trial of low protein diet

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ARTICLE INFO

Article history:
Received 26 February 2012
Received in revised form 13 April 2012
Accepted 13 April 2012
Available online 20 April 2012

Keywords:
Fumarase
Fumarate hydratase
Fumaric aciduria
Developmental delay
Hypotonia
Ventriculomegaly

ABSTRACT

We report clinical findings in a 12-year-old girl with a mild case of fumarase deficiency who continues to make progress. She has two novel mutations of the fumarase gene [c.521 C>G (p.P174R) and c.908 T>C (p.L303S)]. A trial of low protein diet did not reduce fumaric aciduria.

1. Introduction

Deficiency of fumarase (fumarate hydratase, FH 2; EC 4.2.1.2) results in fumaric aciduria (OMIM 136850), a rare inborn error of metabolism, with only 45 cases reported thus far in the literature. Fumarase exists in two isoforms: a mitochondrial isoform, which is a component of the tricarboxylic acid cycle, and a cytosolic isoform. Both isoforms are expressed in human tissues, with exception of the brain, which expresses only the mitochondrial isoenzyme. The isoforms are encoded by the fumarase hydratase gene, localized to chromosome 1q42.1 [1].

Fumaric aciduria develops early in infancy with the most common clinical findings being developmental delay, cerebral abnormalities, hypotonia, dysmorphism, convulsive disorders and microcephaly. While ventriculomegaly and cerebral atrophy are frequently reported on brain imaging in patients with fumaric aciduria, diffuse slowing of background activity with spike waves or hypsarrythmia are the common EEG findings [1]. The severity of the disorder does not appear to correlate with the level of residual enzyme activity, urinary fumarate excretion or the mutations noted.

Limited information is available on therapeutic trials in fumaric aciduria. Fumaric acid is produced as a result of many cytosolic reactions in addition to fumarase, among them: arginosuccinase (EC 4.3.2.1), adenylosuccinase (EC 4.3.2.2), and fumarylacetoacetase (EC 3.7.1.2) which are involved in protein metabolism, in addition to that synthesized in the mitochondria [1]. We thus hypothesized that a low protein diet may result in reducing fumaric acid excretion and could be used as possible dietary therapy in this disorder.

2. Methods

We describe the clinical and biochemical findings in a unique patient with fumarase deficiency. At the time of this report's commencement, the patient was a 12-year-old female who was born 3 weeks post-dates to a 26-year-old G2P1 mother. Her unrelated parents and her half-sister were healthy. Her birth weight was 3494 g and her head circumference was 35 cm (both are 60th percentile). She had her first seizure at 5 ½ months of age, followed by frequent recurrences, which prompted a complete metabolic work up.

Brain imaging revealed enlarged ventricles and cerebral atrophy and an EEG revealed diffuse slowing of the background rhythm superimposed with multifocal epileptogenic activity. Gas chromatography–

Abbreviation: EEG, (electroencephalogram).

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doi:10.1016/j.ymgme.2012.04.010

Table 1
Results of metabolites on low protein diet. There was no decrease in fumaric acid on a low protein diet (0.71 g/kg body weight). Orotic acid excretion, as an indicator of total nitrogen flux through the urea cycle, suggested compliance with this protocol.

		Orotic acid (mmol/mol Cr)	Fumaric acid (mmol/mol Cr)	Ketoglutaric acid (mmol/mol Cr)
Controls		0–3	0–5	0–210
Patient	Baseline	1.12–1.64	1883–2354	1834–2967
	On low protein	0.8–1.32	2724–3181	2990–3274
	Off diet	2.13	1754	2464

mass spectrometry analysis of organic acids [2] showed grossly increased excretion of fumaric acid (2700 mmol/mol of creatinine; controls: <5.0). Fumarase activity in lysed cultured skin fibroblasts was found to be 25% of that in controls. The diagnosis of fumarase deficiency was also confirmed by finding two mutations of the fumarase gene [c.521 C>G (p.P174R) and c.908 T>C (p.L303S)] [3].

Over the course of time, she has been hospitalized several times with seizures but otherwise is described as healthy. She is tall, and her growth parameters are in the >97th percentile. She has dysmorphic features including bitemporal narrowing, frontal bossing, depressed nasal bridge and hypotelorism. Her vision and hearing are normal. Although her motor milestones have been significantly delayed, she continues making gradual progress. She is able to walk independently with an in-toeing, wide based gait. She has severe speech impairment; however, she can communicate with the help of a picture exchange communication system and understands simple one step commands. She has been diagnosed with mental retardation and exhibits autistic behaviors.

It was hypothesized that by reducing the protein in her diet, many of the precursors of fumaric acid would be reduced, and therefore fumaric acid itself would also be reduced. Thus, while on her regular diet, urinary organic acids including orotic acid were measured for 3 days prior to initiation of the low protein diet. A low protein diet (0.71 g/kg body weight with an average of 19.3 grams per day) was then provided and she substituted carbohydrates in her diet with rice bread. This level was high enough to meet growth requirements, but not high enough to generate excess ammonia for urea cycle disposal [4]. Early morning urine samples were collected on each day for organic and orotic acid analysis. After 3 days on the low protein diet with the fumaric acid levels being consistently elevated, the diet was discontinued and urine was again collected for analysis.

3. Discussion

The results of this study are presented in Table 1 and reveal that there was no decrease in fumaric acid on this low protein diet. In fact, a slight increase, although insignificant, was noted. Alpha-ketoglutarate was also shown to increase slightly on the low-protein diet and was chosen to be monitored, not only because it is a precursor to fumarate, but its excretion in urine reflects the physiological response of kidney to an acid load [5]. Most of the reported patients with fumarase deficiency [1] have severe psychomotor retardation and are not even able to sit actively. To our knowledge, she is one of the exceptional documented patients with fumarase deficiency who has achieved enough motor development to be able to walk independently and continue to make progress. In the first ever report on fumaric aciduria, Whelan et al. (1983) described two siblings with mental retardation and speech delays, who had otherwise achieved relatively normal developmental milestones. The authors had suggested abnormal renal secretion of fumaric acid as the cause of fumaric aciduria in these cases since fumarase activity had not been measured in them [6]. The developmental progress made by our patient suggests that the motor retardation in fumarase deficiency can be mild, and perhaps the siblings reported by Whelan et al. (1983) may indeed have had true fumarase deficiency. We report results of an unsuccessful trial of a low protein diet, which may potentially exacerbate fumarase deficiency, and propose that further research into possible dietary therapies for fumarase deficiency patients be explored.

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