Fumarase Deficiency: A Safe and Potentially Disease Modifying Effect of High Fat/Low Carbohydrate Diet

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Abstract Fumarate hydratase deficiency (FHD) caused by biallelic alterations of the *FH* (fumarate hydratase) gene is a rare disorder of the tricarboxylic acid cycle, classically characterized by encephalopathy, profound psychomotor retardation, seizures, a spectrum of brain abnormalities and early death in childhood. Less common milder phenotypes with moderate cognitive impairment and long-term survival have been reported. In addition, heterozygous mutations of the *FH* gene are responsible for hereditary leiomyomatosis and renal cell cancer (HLRCC). There is currently no

recommended disease modifying treatment for FHD and only isolated reports of unsuccessful dietary modifications. Herein, we describe the safe and possibly disease modifying effect of a high fat, low carbohydrate diet in a 14-year-old female with severe FHD.

Introduction

Fumarate hydratase deficiency, also known as fumarase deficiency, is a rare autosomal recessive disorder of the tricarboxylic acid (TCA) cycle. Fumarate hydratase (FH) (EC 4.2.1.2) catalyses the reversible interconversion of fumarate and malate, and its deficiency leads to impaired energy production due to interruption of the TCA cycle and subsequent accumulation of various TCA intermediates including fumarate, succinate, 2-ketoglutarate and citrate. Fewer than 100 cases have been reported. The highest prevalence of FH deficiency is found in a religious community at the border of northern Arizona and southern Utah, USA, due to a founder effect (Allegri et al. 2010; Kerrigan et al. 2000).

FH deficiency has a varied clinical phenotype ranging from a fulminant course associated with fatal outcome within the first 2 years of life or a subacute encephalopathy with profound developmental delay (Morava and Carrozzo 2014). Acute metabolic crises with hypoglycemia, ketosis, hyperammonemia or acidosis are rarely observed in FH deficiency (Ewbank et al. 2013; Allegri et al. 2010). Antenatal presentations include poly- or oligohydramnios, intrauterine growth retardation, congenital hydrocephalus and other brain abnormalities (Ewbank et al. 2013, Allegri et al. 2010). Severely affected children exhibit progressive infantile encephalopathy, feeding problems, failure to

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thrive, hypotonia, lethargy, microcephaly, seizures and profound developmental delay. Most severely affected children are usually nonverbal and non-ambulatory. Epileptic seizures are common and are often treatment resistant. Age of onset and seizure type vary and may include infantile spasms with hypsarrhythmia on EEG (Ewbank et al. 2013; Loeffen et al. 2005). Neuroradiological findings include cerebral atrophy, ventriculomegaly, white matter abnormalities including delayed myelination or hypomyelination, thinning or agenesis of the corpus callosum, open opercula, choroid plexus or arachnoid cysts, small brainstem and bilateral diffuse polymicrogyria (Kerrigan et al. 2000). Visual disturbance and optic nerve hypoplasia have occasionally been described (Kerrigan et al. 2000). A spectrum of dysmorphic features has been reported to include common findings of depressed nasal bridge, frontal bossing and widely spaced eyes or less commonly cleft ala nasi or anteverted nares, ear anomalies or narrow forehead (Ewbank et al. 2013; Kerrigan et al. 2000).

Isolated increased concentration of fumaric acid on urine organic acid analysis is highly suggestive of FH deficiency. Other metabolites may also be altered in body fluids: TCA cycle intermediates (succinate, 2-ketoglutarate, citrate), dicarboxylic acids (suberic, adipic) and succinylpurine derivatives (Allegri et al. 2010). Laboratory indicators may include increased lactate, mild hyperammonemia, variable leukopenia, neutropenia and neonatal polycythemia (Allegri et al. 2010). The diagnosis is confirmed by identification of deficient FH enzyme activity in fibroblasts, leukocytes, skeletal muscle or liver and/or by molecular analysis of the *FH* gene (MIM*136850).

There are currently no recognized therapies to ameliorate or reverse the metabolic abnormalities resulting from decreased activity of FH (Morava and Carrozzo 2014). Management remains supportive, with regular multisystem surveillance. We report here a female with fumarase deficiency, predicted to be severe on enzyme and mutational analysis, who has had a milder course, possibly due to early institution of a high fat/low carbohydrate diet.

Case History

The proband was the first-born child to non-consanguineous parents of Italian and Caucasian Australian background. Delivery was by emergency caesarean section at 35 weeks gestation, for maternal hypertension and deranged liver function tests. The pregnancy was otherwise uncomplicated. Birth growth parameters were all above the 90th percentile and Apgar scores were 8 and 9 at 1 and 5 min, respectively. She required tube feeding for the first 4 days, and 24 h of phototherapy for jaundice on day 3. She was discharged on day 10 on a combination of breast and bottle feeds, but continued to have feeding difficulties. By

7 months of age her weight had fallen to the 3rd centile and she was hypotonic with delayed early developmental milestones. A urine metabolic screen at 9 months of age found increased fumaric acid, prompting referral to the metabolic service. On examination at 9 months of age, she had relative macrocephaly with a head circumference on the 75–90th percentile. Her weight was less than the 3rd percentile and length on the 10–25th percentile. She was non-dysmorphic but had eczema and nasal obstruction. She was thin with minimal fat stores and reduced muscle bulk. She was generally hypotonic and unable to sit unsupported. Cardiovascular, respiratory and abdominal examinations were normal. Blood and urine lactates were normal and there were no other urinary tricarboxylic acid cycle (TCA) intermediates present to suggest a mitochondrial disorder. Plasma amino acids and plasma acylcarnitines were normal. The diagnosis was confirmed with cultured skin fibroblast enzyme analysis: fumarate hydratase (FH) activity was 9% of normal controls (patient enzyme activity 9 nmol/min/mg protein, normal reference range 78–119 nmol/min/mg protein) (Mitochondrial Laboratory, Victoria Clinical Genetics Service and Murdoch Children's Research Institute). Molecular analysis revealed compound heterozygous mutations in the *FH* gene (c.521C>G, p.Pro174Arg; c.1204C>T, p.His402Tyr). (Dr V Shih, Neurochemistry Laboratory, Massachusetts General Hospital, Boston MA, USA.) Her parents were found to be heterozygous for one or other of these mutations.

At 14 months of age she was started on a high fat/low carbohydrate diet, with the diet goals of 60% energy from fat, 30% from carbohydrate and 10% from protein. Initiating the diet was complicated by allergy to milk and soy, and increased rate of weight gain (85–97th centile for BMI), but there was a gradual change over the first year from a baseline intake of 36% energy from fat, 48% from carbohydrate and 16% from protein. The diet has been adhered to lifelong with a minimum of 50% fat at times of lesser compliance. She has grown well with close monitoring and dietetic review. Monitored bloods have been generally within normal range, including full blood counts, liver and renal function tests, plasma lactate, plasma amino acids, essential fatty acids, plasma lipids and micronutrient levels. Supplementation of calcium intake has been required. Urine organic acid analysis has never detected lactate or other TCA cycle intermediates and her fumaric acid excretion has reduced to moderate levels. At most recent diet analysis at age 13 years, fat made up 58%, carbohydrate 25% and protein 14%, providing 1.7 g/kg/day protein (RDI 0.87 g/kg). Twenty-two percent of fat was saturated due to dietary preferences and BMI was on the 82nd percentile. Her energy intake was 128% EERM; however, BMI has been consistently been between the 75th and 85th centile since 6 years of age. Her home sick day

plan comprises 50:50 lipid:carbohydrate with a target of 2,200 kcal/day (basal EER $\times$ 1.2 for illness), and an inpatient emergency plan for illness and surgical procedures advises maintenance intravenous fluids of 0.45% saline with 5% dextrose and 20% intralipid at 2–3 g/kg/day.

Global developmental delay was evident in infancy: she sat unsupported at 11 months, walked at 18 months and had delayed expressive language. Hearing and ophthalmology assessments were normal. A pre-school developmental assessment at 4 years and 7 months found mild to moderate intellectual disability and schooling has been in a special unit. Initial MRI brain at 1 year of age showed mild cerebral atrophy, predominantly affecting the frontal lobes bilaterally. There was a generalised reduction in white matter bulk with prominent lateral ventricles and a slight increase in posterior periventricular white matter signal bilaterally. Myelination was appropriate. The frontal lobe grey matter appearance was suspicious for polymicrogyria. There was onset of seizures with status epilepticus at 22 months of age. Seizures have been relatively well controlled on monotherapy with carbamazepine, apart from a brief period of seizure recurrence in early adolescence of unknown cause. Her most recent EEG at the age of 11 years showed background abnormalities with intermittent slow-

ing and bilateral, focal epileptiform discharges without clinical correlation. Serial MRI scans of the brain have shown asymmetrical cerebral sulcal and gyral patterns consistent with polymicrogyria, particularly in the anterior frontal, posterior parietal and temporal lobes. Ventriculomegaly is thought to reflect parenchymal white matter volume loss (Fig. 1). The Cho/Cr ratio was markedly reduced on MRS in both white matter and basal ganglia; however, the NAA/Cr ratio was normal. No lactate peaks were identified. At age 10 years, she underwent repair of a large multi-fenestrated atrial septal defect with left-to-right shunt and right ventricular dilatation. Consistent with published literature, she has not had any acute metabolic decompensation with illness. Currently, at the age of 14 years she is in a special unit at her school and has a mild-to-moderate intellectual disability. She is an active member of her community and is involved in Girl Guides. She has been seizure free on carbamazepine for more than 1 year and is growing well on the 85th centile for weight, 70th centile for height and 98th centile for head circumference. Her general health is good, other than hay fever and constipation.

Having reached her teenage years, we have recommended annual abdominal MRI surveillance due to the risk of

Fig. 1 (a) MRI brain aged 12 months. Generalized white matter loss with mild prominence of the ventricular system in keeping with white matter loss. Slight prominence to the grey matter within the mildly atrophied frontal lobes without definite migrational abnormality. (b) MRI brain aged 14 years. Asymmetrical mild enlargement of the

lateral ventricles likely secondary to parenchymal white matter volume loss. Asymmetrical cerebral sulcal and gyral patterns, particularly of the anterior frontal, posterior parietal and the temporal lobes, are suspicious for polymicrogyria or other cortical malformation

HLRCC and there is, as yet, no evidence of HLRCC. The same screening has been recommended to her parents who have been reviewed by a familial cancer service.

Discussion

Our patient presented before 6 months of age, with typical features of FHD: hypotonia, poor weight gain and developmental delay. Aside from relative macrocephaly there were no overt dysmorphic features. Her MRI findings of diffuse bilateral polymicrogyria, enlarged lateral ventricles and decreased white matter with seizure disorder are characteristic. Her seizure control is much better than reported despite the structural brain abnormalities. Relative macrocephaly has been reported in FHD in association with cerebral atrophy and enlarged extra-axial CSF spaces (Kerrigan et al. 2000). Cardiac involvement in FHD is rare, but ventricular septal defects and patent ductus arteriosus have been reported (Mroch et al. 2012).

A clear genotype–phenotype correlation has not been shown for FHD or HLRCC (Deschauer et al. 2006; Bayley et al. 2008). The FH gene, located at 1q42.1, consists of ten exons encoding 510 amino acids of both mitochondrial and cytosolic isoforms of FH. Most mutations are concentrated at the C-terminus of the FH enzyme (Allegri et al. 2010). There are currently 172 unique variants reported in the Leiden Open Variation Database (LOVD 3.0), many of which are private mutations (<http://databases.lovd.nl/shared/genes/FH>). Our patient's c.1204C>T (p.His402Tyr) variant in exon 8 has been previously reported in a case of severely affected monozygotic twins, one dying aged 1 year (Phillips et al. 2006). The c.521C>G (p.Pro174Arg) variant in exon 4 has been reported in both HLRCC and severe, fatal FHD (Mroch et al. 2012).

More severe clinical symptoms usually correlate with lower levels of enzyme activity (Ottolenghi et al. 2011), although this relationship has not been clear and consistent in all studies (Morava and Carrozzo 2014). FH enzyme activity less than 10% of the control mean generally results in a severe phenotype (Ottolenghi et al. 2011), although the most profoundly affected individuals have enzyme activity of 1–2% or unrecordable. Residual FH enzyme activity can be 0–35% of the control mean in affected individuals, overlapping with that of obligate heterozygotes (Morava and Carrozzo 2014). Milder cases of FHD are less common and those reported still have moderate developmental delay, often without expressive language (Ezgu et al. 2013; Maradin et al. 2006; Kimonis et al. 2012). A severe phenotype was predicted for our patient based on her presentation with hypotonia and developmental delay by 6 months, her structural brain abnormalities and seizures, and fibroblast enzyme activity 9% of normal controls. In

addition, she is compound heterozygous for two mutations previously reported in severe cases with early fatality.

FH functions as a tumour suppressor, rare for an enzyme involved in intermediary metabolism (Bayley et al. 2008). Individuals with germline heterozygous mutations in the FH gene are predisposed to multiple cutaneous and uterine leiomyomas (MCUL) and hereditary leiomyomatosis with renal cell cancer (HLRCC). The gene alteration in HLRCC was identified in 2002 by Tomlinson et al. Pathogenic germline FH mutations have been detected in 76–100% of families with suggestive features (Lehtonen 2011). The estimated lifetime risk of renal cancer in HLRCC is 15% (Menko et al. 2014). Based on the youngest case reported at 10 years of age, predictive FH mutation testing and annual abdominal MRI surveillance with 1–3 mm slices through the kidneys in order to detect very small tumours are recommended from 8 to 10 years of age (Menko et al. 2014). Other syndromic features of cutaneous piloleiomyomas and early uterine fibroids may not be obvious and the aggressive papillary cancers may metastasize when less than 1 cm in diameter (Menko et al. 2014). Renal ultrasound is not recommended due to the low sensitivity in detecting such small lesions. Heterozygote parents of patients with FHD have been reported with HLRCC (Ezgu et al. 2013; Maradin et al. 2006). Early detection is important because of the aggressive nature of renal cancers associated with HLRCC and high death rates of 74% from metastatic disease (Gardie et al. 2011). Treatment should be prompt and generally consists of wide-margin surgical excision and consideration of retroperitoneal lymph node dissection for even small unilateral tumours. The precise risk of HLRCC to individuals affected with FHD is not known, as very few survive to adulthood.

Several mechanisms of tumorigenesis in HLRCC have been proposed. There is decreased oxidative phosphorylation due to disruption of the TCA cycle and impairment of the oxidative function of the electron transport chain. Accumulated fumarate competitively inhibits the function of hypoxia inducible factor (HIF) prolyl hydroxylase (HPH), resulting in HIF accumulation. This in turn leads to an increase in the expression of anti-apoptotic and proliferative genes such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and transforming growth factor- α (TGF- α), all of which enhance angiogenesis and support tumour growth and survival (Sudarshan et al. 2007; Yang et al. 2012). This in turn results in epigenomic modifications (Xiao et al. 2012).

There are few published reports of dietary interventions in FHD. Fumaric acid is a by-product of protein catabolism; however, a brief therapeutic trial of low protein diet (0.71 g/kg/day for 3 days) proved unsuccessful in altering urinary excretion of fumaric acid or improving clinical signs (Kimonis et al. 2012). Similarly, protein restriction of

0.8 g/kg/day in a 45-day-old infant failed to demonstrate any improvement in the urinary excretion of fumaric acid (Baştuğ et al. 2014). Smith and Robinson used a metabolic model of FHD to assess the ability of various metabolites to increase ATP production in a state of 0% fumarase activity. Supplementation with aspartate appeared most effective in increasing ATP production, perhaps bypassing the enzymatic block by replenishing oxaloacetate (Smith and Robinson 2011). An increase in glucose caused minimal increase in ATP production, but a large increase in lactate. Fatty acid metabolism was reported to be relatively restricted by the block to acetyl CoA entering the TCA cycle, and it has been recommended to avoid the ketogenic diet in FHD (Ewbank et al. 2013).

Contrary to predictions, our patient's clinical progression has followed a milder phenotype with well-controlled

seizures and mild-to-moderate intellectual disability, possibly due to the high fat/low carbohydrate dietary intervention commenced at 14 months of age. We propose that a high fat diet may increase the amount of reduced high-energy NADH and FADH₂ molecules, allowing adequate ATP generation through the mitochondrial electron transport chain irrespective of reduced TCA cycle activity. As a long chain of reduced carbon atoms, fatty acids fuel more cycles of the TCA cycle than glycolysis, and additionally generate one molecule each of NADH and FADH₂ for each cycle of beta-oxidation. Complete beta-oxidation of palmitate requires seven cycles of beta oxidation thereby generating 7 NADH and 7 FADH₂ and 8 molecules of acetyl-CoA. Each molecule of acetyl-CoA then releases 2 molecules of NADH and 1 of FADH₂, prior to the fumarate block in the TCA cycle (see Fig. 2). Contrary to

Fig. 2 Tricarboxylic acid cycle: each molecule of acetyl-CoA releases 2 molecules of NADH (reactions 1 and 2) and 1 of FADH₂ (reaction 3) prior to the fumarate block in the TCA cycle

Table 1 Semi-quantification of urinary fumaric acid excretion over time

Date	Fumarate ($\mu\text{mol}/\text{mmol}$ creatinine)	Comments
24/03/2004	1,262	Diet was commenced in November 2004
21/05/2004	650	
01/06/2004	1,104	
27/06/2005	679	Ketonuria detected in this sample collected during an intercurrent illness
22/11/2016	344	
26/05/2017	429	

Smith and Robinson's findings we have not observed a block to fatty acid beta-oxidation.

Our patient has never had elevated plasma or urinary lactate. We propose that a low carbohydrate diet reduces flux through glycolysis, thereby limiting lactate production. We have observed a semi-quantitative reduction in urinary fumaric acid to one-third of levels prior to dietary intervention (see Table 1). Patients with FHD have occasionally been reported with normal urinary fumaric acid excretion (Ottolenghi et al. 2011) and elevations do not correlate reliably with phenotype severity (Prasad et al. 2017). Nonetheless the reduction in her urinary fumarate excretion and the absence of other TCA intermediates may reflect anaplerosis and continuation of the TCA cycle, perhaps through aspartate. Previous attempts at a low protein diet may have reduced anaplerosis. Our patient has not been protein restricted and at last review her protein intake of 1.7 g/kg/day was well above the recommended daily intake for age of 0.87 g/kg/day. Plasma amino acids remain normal.

In summary, our patient had a typical clinical presentation for severe FHD with significant developmental delay by 9 months of age, seizures and structural brain malformations. In addition, her residual fumarase enzyme activity was only 9% of normal and she is compound heterozygous for two mutations previously reported in cases of early fatality. Despite this her development appears to have surpassed any other reported cases of FH. This case is important as it demonstrates after 12 years of follow-up that a high fat/low carbohydrate diet is safe and may be potentially disease modifying.

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Key Synopsis

Long-term use of a high fat, low carbohydrate diet in severe fumarate hydratase deficiency is safe and may result in a milder outcome.

Details of the Contributions of Individual Authors

Bryony Ryder, John Christodoulou and Shanti Balasubramaniam were involved in the clinical management of the patient. Sue Thompson and Ashleigh Mitchell provided dietary advice in the management. Francesca Moore performed and interpreted metabolic laboratory investigations. John Christodoulou advised on the diagnostic work-up and initiating dietary management. Bryony Ryder and Shanti Balasubramaniam drafted the manuscript. All authors have read/critically revised the manuscript.

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Compliance with Ethics Guidelines

Conflict of Interest

Bryony Ryder, Francesca Moore, Ashleigh Mitchell, Sue Thompson and Shanti Balasubramaniam declare that they have no conflict of interest. John Christodoulou is a communicating editor of the *Journal of Inherited Metabolic Disease*.

Ethics Approval

Ethics approval was not required for publication of this case report.

Informed Consent

Parental consent was obtained for the publication of this chapter.

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