Abnormalities in Glycogen Metabolism in a Patient with Alpers' Syndrome Presenting with Hypoglycemia

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Abstract Intermittent hypoglycemia has been described in association with Alpers' syndrome, a disorder caused by mutations in the mitochondrial DNA polymerase gamma gene. In some patients hypoglycemia may define the initial disease presentation well before the onset of the classical Alpers' triad of psychomotor retardation, intractable seizures, and liver failure. Correlating with the genotype, *POLG* pathogenicity is a result of increased mitochondrial DNA mutability, and mitochondrial DNA depletion resulting in energy deficient states. Hypoglycemia therefore could be secondary to any metabolic pathway affected by ATP deficiency. Although it has been speculated that hypoglycemia is due to secondary fatty acid oxidation defects or abnormal gluconeogenesis, the exact underlying etiology is still unclear. Here we present detailed studies on carbohydrate metabolism in an Alpers'

patient who presented initially exclusively with intermittent episodes of hypoglycemia and ketosis. Our results do not support a defect in gluconeogenesis or fatty acid oxidation as the cause of hypoglycemia. In contrast, studies performed on liver biopsy suggested abnormal glycogenolysis. This is shown via decreased activities of glycogen brancher and debrancher enzymes with normal glycogen structure and increased glycogen on histology of the liver specimen. To our knowledge, this is the first report documenting abnormalities in glycogen metabolism in a patient with Alpers' syndrome.

Introduction

The integrity of physiological regulation of blood glucose levels is of utmost importance to brain metabolism, with prolonged states of hypoglycemia ultimately leading to encephalopathy and death. Therefore, blood glucose levels are tightly controlled to remain within a range of 2.5 and 7.5 mmol/L (45–135 mg/dL) (Lonlay et al. 2004). Several metabolic pathways work in unison to avoid the hypoglycemic state. Mutations in genes involved in glycolysis and gluconeogenesis, glycogen synthesis and degradation, as well as fatty acid oxidation pathways and their hormonal regulators may all lead to primary hypoglycemia syndromes (Haymond 1989). To identify the defective pathway and ultimately the specific enzymatic block requires methodical analysis of various metabolic markers and tissues, which can be costly and time consuming (Mochel et al. 2005). However when hypoglycemia is a secondary finding of a known metabolic disorder, these detailed investigations are not usually performed. Mitochondrial disorders are prime candidates for secondary hypoglycemic syndromes, since their underlying energy debt may deem them unable to

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supply pathways of glucose metabolism with sufficient ATP. The Stanford Mitophenome Database is a tool generated to assist clinicians in phenotype/genotype correlations for mitochondrial disease patients (<http://www.mitophenome.org/>). Close to one third of the 174 genes in the database list hypoglycemia as a phenotypic feature (Scharfe et al. 2009). Over a decade after the initial discovery of the disease correlation between progressive external ophthalmoplegia (PEO) and mutations in the mitochondrial DNA polymerase gamma, the *POLG* gene has emerged as one of the most common causes of mitochondrial disease (van Goethem et al. 2002; Nguyen et al. 2005; Wong et al. 2008). With close to 200 pathogenic mutations described to date, the gene is associated with a wide spectrum of phenotypes and may follow autosomal dominant as well as autosomal recessive patterns of inheritance (Tang et al. 2011; Stumpf et al. 2013). As the sole polymerase responsible for mtDNA replication and repair, abnormalities in *POLG* function lead to increased mtDNA mutability and mtDNA depletion (Del Bo et al. 2003; Naviaux and Nguyen 2004). Severity of mutations correlates with the actual disease presentation, and Alpers' disease is representative of the severe end of the phenotypic spectrum (Stumpf et al. 2013). Unlike most infants with Alpers' disease, which initially present with intractable seizures and eventually progress to liver failure, our patient was ascertained due to isolated intermittent hypoglycemia. Aggressive early investigations into the underlying etiology allowed insights into the disease progression of this *POLG* patient and led us to the finding of abnormal glycogen storage in the liver, with respective absent and severely decreased activities of glycogen debrancher (GDE) and brancher enzymes (GBE) prior to the development of frank liver disease. To our knowledge, absent GDE activity has not been previously described in Alpers' patients.

Case Report

The patient was delivered by cesarean section due to breech presentation; postnatal course was only significant for transient neonatal jaundice. At 4 months of age, she had two episodes of difficult arousal in the morning following uneventful nights, resulting in emergency room visits. Review of outside medical records showed that isolated glucosuria was present, without documented abnormal blood glucose values. This raised the suspicion of a renal tubular defect, but repeated urine glucose and biochemical studies did not confirm this possibility. Neurological consultation, including EEG, was unrevealing. At 10 months of age, fasting morning blood glucose was 2.4 mmol/L while the patient was asymptomatic. This prompted admission to our

hospital for further studies. Physical exam, including developmental milestones, was normal and there was no clinical or laboratory evidence of muscle or liver involvement. A fasting study was performed at night, after the patient had been feeding regularly during the day. After 8 h of fast, a finger stick blood glucose level was 2.7 mmol/L and venous blood samples for critical labs were obtained (Table 1).

Results were consistent with ketotic hypoglycemia. The normal lactic acid and low alanine suggested intact gluconeogenesis. The response of growth hormone and insulin at the time of hypoglycemia were appropriate. Although serum cortisol level was within the normal reference range, it was considered inappropriately low for a child with hypoglycemia. The initial diagnosis of hypocortisolism was made, and the patient was discharged on treatment with hydrocortisone and frequent feeds. MRI of the brain and pituitary gland was normal. Two days before her first birthday, the patient had early morning lethargy, with a blood sugar of 1.7 mmol/L. She had missed her 2 am feed which resulted in an 11-h fast. The patient fully recovered after formula and orange juice were given. On the day of her birthday, she was asymptomatic and medications and meals were given as scheduled. However in the middle of the night, the patient had a seizure. Blood sugar was normal at 96 mg/dL and she was taken to the emergency room where repeat blood sugar was 3.7 mmol/L. She was admitted to intensive care unit due to lethargy, seizures, and apnea requiring intubation and mechanical ventilation. Sepsis work up and ammonia were normal, cortisol (after stress dose in ER) was high at 5,904 nmol/L (214 µg/dL), and comprehensive metabolic panel was normal, except for elevated AST and ALT of 173 and 141 U/L, respectively.

Due to hypoglycemia while on steroids and mildly elevated LFTs, repeat metabolic testing was obtained. Organic acids once more showed ketosis, whereas lactic acid, acylcarnitines, and CK were normal and alanine was again low at 163 µmol/L. MRI of brain (2nd) showed bilateral symmetric diffusion abnormalities in both occipital lobes (Fig. 1 #2) and subtle T2 prolongation in the same areas, which, in view of the normal MRI two weeks prior, was interpreted to be secondary to the recent hypoglycemic episode. A new fasting study was done while on hydrocortisone, after the patient was on frequent feedings for a few days (Table 2). The patient developed again hypoglycemia and increased ketone body production; however, postprandial samples revealed high blood sugar and lactic acid. Glycogen storage disease (GSD) type 0 was suspected, but no mutation was found after full sequencing of *GYS2* (Prevention Genetics, Marshfield, WI). The patient did not have further hypoglycemia or seizures while on scheduled feeds and steroid therapy. Repeat MRI of brain (3rd, 18 days following 2nd MRI) showed resolution of previous diffusion abnormalities, but persistent abnormal T2 prolongation in the medial aspects of both occipital lobes

Table 1 Fasting study #1

	Glucose (3.6–6.1 mmol/L)	CO2 (15–28 mmol/L)	ALT (10–32 U/L)	Cortisol (77.3–634.6 nmol/L)	GH(2–10 ng/mL)	Insulin (0–90.3 pmol/L)	Lactic acid (0.5–2.2 mmol/L)	β -OH- Butyrate (0.05–0.19 mmol/L)	Alanine (246–486 μ mol/L)	CK (24–206 U/L)
Results	1.5 mmol/L	21 mmol/L	151 U/L	331.08 nmol/L	29 ng/mL	<6.95 pmol/L	1.6 mmol/L	1.32 mmol/L	175 μmol/L	36 U/L

All reference laboratory ranges are in parentheses. All out of range values are in bold. Reference laboratory ranges were developed for the normal population with normal blood glucose values.

Abbreviations: *ALT* Alanine aminotransferase, *GH* Growth hormone, *CK* Creatine kinase

Age 10 months; post 8-h fast. Organic acid: significant ketosis, mild increase in dicarboxylic acids. Acylcarnitine: slight elevations of C2 and several other acylcarnitines from C12:1 to C18:1 with no diagnostic pattern

was interpreted as evolution of prior insult. By the time of discharge (20 days stay), the patient had returned to baseline except for cortical visual impairment with expected resolution given improved MRI findings and normal visual evoked potentials. Two months later, the patient had new seizures and developed respiratory failure despite being compliant with every 4-h feeding regimen and hydrocortisone treatment. Blood sugar was normal at home as well as in the emergency room. MRI of the brain (4th) showed further improvement of T2 prolongation in occipital lobes without new lesions. The patient recovered fully within a few days and was playful and interactive. No hypoglycemia was documented during this admission, but lactic acid and ALT were persistently elevated and were as high as 17.7 mmol/L (0.5–2.2 mmol/L) and 103 U/L (10–32 U/L), respectively. A muscle biopsy was ordered, and skin and liver biopsies were obtained at 15 months of age. Muscle biopsy was studied on cryostat sections by H&E, modified trichrome stain, ATPase, NADH-TR, PAS, PAS diastase, Oil red O, phosphorylase A, B kinase, cytochrome oxidase, and acid phosphatase (Bonilla et al. 1992). Results showed <1 % COX negative fibers, but were otherwise normal (no ragged red fibers). Muscle electron microscopy also showed normal results (Long Beach Memorial Medical Center). Electron transport chain studies performed on muscle were at the low end of the control range for NADH cytochrome C reductase (complex I/III) and cytochrome c oxidase (complex IV) (CIDEM, Cleveland, OH). An in vitro fatty acid oxidation probe assay performed in skin fibroblasts showed normal results (Mayo Clinic, Rochester MN) (Blau et al. 2008).

Liver pathology showed relatively uniform nodules divided by fibrous bands with ductular proliferation. The majority of the hepatocytes exhibited cytoplasmic fine vacuolization containing abundant glycogen (confirmed by PAS with and without diastase). The overall histology was reported as consistent with a glycogen storage disease. Liver enzyme activities and glycogen content were measured on frozen liver biopsy tissue using standard spectrophotometric methods that have already been published (Wapnir 1985; Brown and Brown 1989). The residual enzyme activity was measured indirectly by measuring the amount of glucose or phosphate released using glucose or phosphate reagent. Liver glycogen content was borderline elevated at 7.1 % (normal 3.3 ± 1.7); glucose-6-phosphatase, glycogen phosphorylase, and glycogen phosphorylase kinase activities were all repeatedly normal with a G-1P/Glu ratio of 50 % indicating normal glycogen structure. Branching enzyme activity was low at 20 μ mol/min/g of tissue (normal 85 ± 31), and glycogen debrancher enzyme (GDE) activity assessed in liver tissue was undetectable (performed twice at Duke University Medical Center).

Sequence of the debrancher (*AGL*) gene was normal (Prevention Genetics, Marshfield, WI).

Fig. 1 Diffusion-weighted images (MRI #2 and #5). MRI #2 shows bilateral symmetric diffusion abnormalities in both occipital lobes. MRI #5 shows brain atrophy with periventricular and subcortical white matter signal abnormality and full resolution of occipital lesions

Table 2 Fasting study #2

Fasting time	4 h	5 h	6 h	7 h	8 h	8.5 h	9 h	9.5 h	1 h*	2 h*	3 h*
Glucose (3.6–6.1 mmol/L)	5.2	5.8	4.2	3.3	3.4	4.9	3.9	3.1	8.9	6.8	6.7
Alanine (246–486 µmol/L)								281			
Lactate (0.5–2.2 mmol/L)								2	3.3	4.3	4.3
β-OH-Butyrate(0.05–0.19 mmol/L)								0.64	0.26	0.18	0.21
Cortisol (77.3–634.6 nmol/L)			129.7**								
FFA (0.5–0.9 mmol/L)								1.2			

All reference laboratory ranges are in parentheses. All out of range values are in bold. Reference laboratory ranges were developed for the normal population with normal blood glucose values.

Abbreviations: *FFA* Free fatty acids, *β-OH-Butyrate* Beta-hydroxybutyrate

**Although cortisol value is within normal range it is considered low for a child with hypoglycemia

*Postprandial studies; all specimens are from central line

Age 24 months: during hydrocortisone treatment + after frequent feedings for +2 days

Two weeks after discharge from her third hospitalization, the patient presented with refractory myoclonic seizures. MRI of brain (5th, 1 month apart from 4th) revealed, for the first time, mild brain atrophy with periventricular and subcortical white matter signal abnormality and full resolution of the occipital lesions (Fig. 1 #5). The patient progressed rapidly to encephalopathy, lactic acidosis, and hepatic failure. *POLG* sequencing revealed compound heterozygous mutations c.1399G>A, p.[A467T]+c.2542G>A, p.[G848S], as underlying cause of the disease.

Discussion

Since the initial discovery of the causal relationship between *POLG* mutations and Alpers' syndrome, an enormous body of literature elucidating this disease mechanism has accumulated. Large studies exploring phenotype/genotype correlations are mostly focused on the primary clinical features involving

liver pathology, encephalopathy, neuropathy, and dysphagia (Horvath et al. 2006; Wong et al. 2008; Tang et al. 2011). Although multiple reports have associated hypoglycemia with Alpers' disease, the underlying etiologies have not been delineated, or remain speculative (Naviaux et al. 1999; Ferrari et al. 2005; Nguyen et al. 2005; Bortot et al. 2009). In a recent article by Scalais et al., an Alpers' patient with the same p.[A467T]+p.[G848S] genotype presented with hypoglycemia and hyperlactatemia as the prominent initial findings. In contrast to our patient who initially presented with isolated ketotic hypoglycemia, normal lactic acid level, and normal physical exam at 10 months of age, this infant had already developed severe liver dysfunction at 3.5 months of age with jaundice, ascites, and hepatomegaly. A liver biopsy at ~9 months of age showed micronodular cirrhosis and bile ductular proliferation (Scalais et al. 2012). At 18 months a second liver biopsy showed Kupffer cells with PAS positive large granules and glycogen rosettes, a finding usually considered secondary to glycogen storage

(Roels et al. 2009). Enzymatic studies for glucose 6-phosphatase activities were normal in both biopsy samples and fructose 1 phosphate aldolase/fructose 1,6 biphosphate activities were normal in the first biopsy. Unfortunately, there is no mention whether liver glycogen content or glycogen brancher and debrancher enzyme activities were measured. Interestingly the authors describe that their patient did not respond to glucagon, a response that could be consistent with GDE deficiency depending on the fasting time. Due to the many similarities between our patient and the one previously published (Roels et al. 2009; Scalais et al. 2012), one may speculate whether our findings are genotype specific. A search of the Human DNA Polymerase Gamma Mutation Database (<http://tools.niehs.nih.gov/polg>) for p.[A467T]+p.[G848S] revealed 18 additional published cases. Of these, only two publications mention hypoglycemia and neither of them address glycogen metabolism (Ferrari et al. 2005; Nguyen et al. 2005). The relatively high numbers of this particular genotype and the lack of prior pursuit of glycogen studies may encourage retrospective chart review and enzymatic analyses on stored liver samples for this patient population.

To further broaden our search for derangement in glycogen metabolism in mitochondrial disease, we took a close look at other mtDNA depletion syndromes which can be associated with hypoglycemia. Insights derived from studies on *MPV17*, a gene of unknown function leading to progressive liver failure in infancy, prove particularly interesting (Karadimas et al. 2006). Patients with mutations in *MPV17* have shown an exceptionally high rate of secondary hypoglycemia. In a recent publication on *MPV17* deficiency, Uusimaa reports on 12 different families with *MPV17*-related mtDNA depletion syndrome and 50 % of them had hypoglycemia (Uusimaa et al. 2013). Furthermore detailed metabolic studies on 2 *MPV17* patients revealed early fasting intolerance (3–4 h postprandially) with physiological parameters resembling glycogen synthesis and glycogenolysis defects. Unfortunately, enzymatic tests in liver elucidating the precise etiology of disrupted glycogen metabolism were not done in these patients (Parini et al. 2009). Interestingly a study exploring the potential function of *MPV17* via the yeast homologue Sym1 showed that Sym1 deficiency induces disturbed glycogen metabolism. The authors speculate that this finding may likely be secondary to abnormal levels of mitochondria-derived TCA cycle intermediates (Dallabona et al. 2010). Patients with mutations in another mtDNA depletion syndrome associated with hypoglycemia, deoxyguanosine kinase (*DGUOK*), also showed increased glycogen in liver tissues in multiple cases (Dimmock et al. 2008). A lack of enzymatic glycogen metabolism studies in this publication again did not allow further insights into the exact mechanisms of hypoglycemia secondary to liver failure.

The complete absence of GDE activity in our patient's liver sample was confirmed by repeat assay. Additionally

control enzymes that run in parallel were normal, ruling out the possibility of technical problems. Since the *AGL* gene had been sequenced previously with normal result, it is possible that the absence of GDE activity was secondary to decreased mRNA and protein levels or due to decreased enzyme activity secondary to a damaged, misfolded protein. We were not able to address this question directly due to the lack of remaining liver sample. Changes in gene expression secondary to *POLG* mutations have been observed previously in fibroblast cell lines derived from *POLG* patients (Voets et al. 2012) as well as in the *POLG* mutator mouse skeletal muscle (Hiona et al. 2010). We accessed the mRNA data deposited in the gene expression omnibus repository (GEO <http://www.ncbi.nlm.nih.gov/geo/>) (GSE21189) and did not find evidence of altered mRNA levels for the glycogen debrancher enzyme in mouse skeletal muscle (Edgar 2002; Hiona et al. 2010; Barrett et al. 2012). Since the *POLG* mutator mouse is a model for premature aging rather than for Alpers' disease, we also reviewed another recently submitted GEO dataset by Falk et al.: "Transcriptome profiling in primary human mitochondrial respiratory disease" (GSE 42986). Here we compared mRNA data collected on human skeletal muscle from three mtDNA depletion syndrome patients (*POLG*, *MPV17*, *RRM2B*) to three control patients with abnormalities in the pyruvate dehydrogenase complex and normal mitochondrial electron transport. The comparison suggested robust and unaltered expression levels for the *AGL* gene, in human skeletal muscle (data not shown) which may not be representative of expression levels in the liver.

AGL is a large protein comprised of 1,532 amino acids (NP_000019.2). It is unusual insofar that it is a monomer with two active sites, catalyzing two different enzymatic reactions (4- α -glucotransferase and amylo-1,6-glucosidase) (Nakayama et al. 2001). Its large size and structure may deem the protein more vulnerable to the effects of free radical damage and low levels of ATP both of which have been observed in *POLG*-related phenotypes (Vries et al. 2007; Voets et al. 2012). Potential increased production of free radicals in our patient may have been further compounded by conditions of low glucose and hypoxia which may add to the unfolded protein response and free radical damage (Elanchezhian et al. 2012). Abnormalities in glycogen metabolism secondary to *POLG* mutations may also translate to other organs involved in glycogen metabolism. Particularly a closer look at astrocytes may prove to be interesting since it has recently been shown that polyglucosan polar bodies confined to this tissue are able to cause a mitochondrial disease phenocopy with leukodystrophy and diaphragmatic failure (Dainese et al. 2013) and that cultured astrocytes derived from mice deficient in glutathione activity and increased free radicals have altered glycogen metabolism (Lavoie et al. 2011).

Ultimately hypoglycemia associated with mitochondrial DNA depletion syndromes may have different etiologies depending on the function of the gene involved, the patient's specific genotype, mutations in modifier genes as well as disease stage, progression, and degree of liver involvement.

To our knowledge, this is the first report on a child with Alpers' syndrome in which the underlying cause for intermittent hypoglycemia has been linked to abnormal glycogen metabolism. This may not only carry significance for Alpers' patients or patients with other *POLG*-related syndromes but may hold interesting information for mitochondrial disease in general.

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Competing Interest

The authors have no competing interests.

Synopsis

Hypoglycemia associated with mitochondrial disease mimicking glycogen storage disease may be underrecognized or underreported and may manifest prior to the onset of typical mitochondrial disease symptoms like seizures or liver failure.

Compliance with Ethics Guidelines

Conflict of Interest

Mariella Simon declares that she has been partially supported by Hailey's wish foundation, a charitable foundation interested in supporting causes concerning mitochondrial disease.

Richard Chang declares that he has no conflict of interest.

Deeksha Bali declares that she has no conflict of interest.

Lee-Jun Wong declares that she has no conflict of interest.

Ying Peng declares that she has no conflict of interest.

Jose Abdenur declares that he has no conflict of interest.

Informed Consent

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 (5). The study does not qualify as human subject research since the patient is deceased and there are no subject identifiers.

Animal Rights

This article does not contain any studies with animal subjects performed by the any of the authors.

Contributions of Individual Authors

Mariella Simon wrote the abstract, introduction, and discussion.

Richard Chang wrote the case report and cared for the patient.

Deeksha Bali was in charge of enzyme studies for glycogen storage disease.

Lee-Jun Wong was in charge of *POLG* testing.

Ying Peng oversaw neurological testing and cared for the patient.

Jose E. Abdenur designed clinical and laboratory testing strategy and planned and edited the manuscript.

All authors have reviewed the final version of the manuscript.

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