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Case report

Glucose metabolism and diet-based prevention of liver dysfunction in *MPV17* mutant patients☆

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***Background/Aims*: To describe in detail the specific clinical and biological characteristics of three patients with *MPV17* gene mutations, a rare hepatocerebral mitochondrial DNA depletion syndrome (MDS) and the positive effects of a novel dietetic treatment based on avoidance of fasting.**

***Methods*: We describe the case histories of three members of the same family with *MPV17* mutations.**

***Results*: Two patients had a very severe and progressive liver disease: 1 died in the first year of life and the other underwent liver transplantation. The third patient, now 13 years of age, had a milder form of liver disease and developed progressive ataxia. Psychomotor involvement at onset of disease was mild or absent. No patient had severe hyperlactataemia. *In vivo* functional studies on two patients showed no hyperlactataemia even after intravenous and oral glucose loading, regular fasting hypoglycemia 3–4 h after meals and no response to glucagon. Liver function tests improved when patients received continuous iv glucose infusion or were regularly fed every 3 h.**

***Conclusions*: These clinical and biochemical features allow us to differentiate patients with *MPV17* mutations from other liver MDS and suggest that regular glucose intake at short intervals may be beneficial in slowing the progression of the disease.**

***Keywords*: MPV17; Mitochondrial diseases; Mitochondrial DNA depletion; Glucose metabolism**

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Abbreviations: MDS, mitochondrial DNA depletion syndrome; NNH, Navajo neurohepatopathy; Gamma-GT, gamma-glutamil-transpeptidase; CSF, cerebrospinal fluid; DQ, developmental quotient; IQ, intelligence quotient; MRI, magnetic resonance imaging; EEG, electroencephalogram; ERG, electroretinogram; CS, citrate synthetase; H&E, hematoxylin–eosin; CI, complex I; CII, complex II; CIII, complex III; CIV, complex IV.

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1. Introduction

MPV17 is a recently identified nuclear gene whose mutations cause an autosomal recessive hepatocerebral mitochondrial DNA depletion syndrome (MDS) [1]. This disease is identical to another disorder called Navajo neurohepatopathy (NNH, OMIM #256810) [2–4], a relatively frequent disease among Navajo people, with a prevalence of 1:1600 live births. The three different phenotypes which have been described in NNH, are in fact a "continuum" from the infantile form, showing severe liver disease in the first months of life and death before 2 years of age, to the classic form dominated by progressive neurological signs, milder liver disease and survival into adulthood [4].

A single mutation of *MPV17*, inherited from a common ancestor, is responsible for NNH. Only a few non-Navajo patients have been identified so far [1,5–7], most of whom have shown the severe phenotype dominated by liver disease in infancy. No treatment is available for this disease, besides palliative care. The only therapeutic option in selected cases, was liver transplantation when the patient showed isolated liver disease with no other organ involvement [2,4,8]. In this paper, we report the clinical and histological findings of three of the five patients initially studied by Spinazzola et al. [1] and the results of dietetic treatment aimed at stopping liver disease progression in two of them. The clinical features of the two other patients have already been reported elsewhere [9,10].

2. Patients and methods

2.1. Case reports

2.1.1. Patient 1

Born at full term from healthy first cousin parents belonging to a highly inbred family (Fig. 1a), this baby boy was mildly jaundiced in the first month of life while he was breast fed on demand. At 1 month, blood tests showed mild mixed hyperbilirubinemia (total 2.6, conjugated 1.2 mg/dL), liver cells necrosis (ALT 119, AST 153 U/L), cholestasis (gamma-GT 320 U/L) and neutropenia (neutrophils 603 mm^{-3}), which were confirmed at 3.5 months when he was hospitalized. On that occasion, severe hypoglycemia was observed after 7 h of fasting (glucose 0.38 mmol/L), which resolved with iv glucose administration; lactate was mildly elevated (3.2 mmol/L). An improvement in blood test results was observed after a few days of continuous i.v. glucose infusion and later, with regular bottle feeds every 3 h. At 5.5 months, after 2 months of a strict diet consisting of 8 feeds per day, growth was at the 50th percentile for weight and length. Hepatomegaly was still present but the infant had no jaundice (total bilirubin 0.8 mg/dL), improved liver function (ALT 47, AST 93, gamma-GT 148), normal neutrophils (4750 mm^{-3}), normal psychic development and only mild axial hypotonia. Two brief fasting tests with glucose/lactate profile, showed a fasting tolerance of 3.5 h (glucose 2.4 and 2.1 mM) without hyperlactatemia (Fig. 1b). Glucagon test at 2.5 h fasting (baseline glucose 3.8 mM) was followed by a flat curve with glucose 3.1 mM at

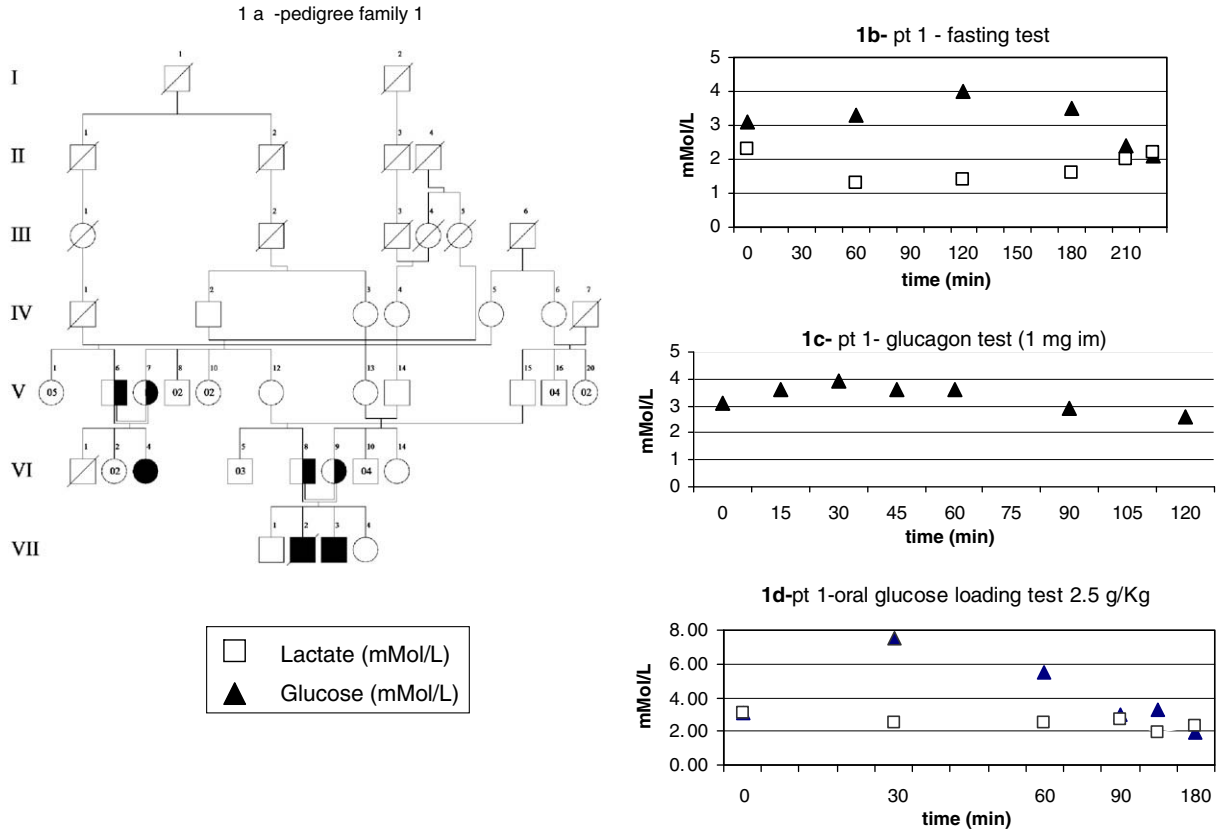

Fig. 1. (a) Family pedigree: patient 1 (VII-2), 2 (VII-3) and 3 (VI-4). (b–d) Results of functional tests in patient 1.

45 min when the test was stopped (Fig. 1c). A glucose challenge (2.5 g/kg) showed normal lactate and normal absorption of glucose which decreased progressively from 7.5 at 30′ to 1.9 mM at 180′ (Fig. 1d). The patient was re-admitted to hospital 3 weeks later with hypotonia, jaundice, ascites and melena after having had severe gastroenteritis for 6 days. Blood tests showed an abrupt worsening of liver function (total bilirubin 16.7, conjugated 9 mg/mL, ALT 185, AST 489 U/L, gamma-GT 330 U/L). Despite intensive treatment, the infant soon deteriorated and died at the age of 7 months.

2.1.2. Patient 2

Patient one's younger brother, was born at term after an uneventful pregnancy. On the basis of the beneficial effects of the diet seen in patient 1, patient two was breast fed regularly every 3 h from birth. In the third week of life a mild increase of ALT, AST and gamma-GT was first observed (51, 108, 78 U/L, respectively). Pre-feeding glucose and lactate were normal, as was cerebrospinal fluid (CSF) lactate (1659 μmol/L, n.v. 800–2100). A weekly follow-up was started and his parents were instructed to bring him to the hospital immediately, whenever he developed common childhood diseases and/or did not have regular food intake. Between 1 and 25 months of age, 65 blood samples were taken and he was hospitalized four times for common childhood complaints. On each occasion, when admitted with initial symptoms like mild anorexia or vomiting, he always had hypoglycemia (range 0.8–2.5 mmol/L), associated with biochemical signs of increased hepatocellular necrosis and cholestasis (range: ALT 150–198, AST 222–288, gamma-GT 200–350). At discharge, after 4–6 days of continuous i.v. glucose infusion, liver function tests had normalized (range: ALT 35–43, AST 50–58, gamma-GT 50–64). In those periods when he was free of infections and could be regularly fed at home, hepatocellular damage indexes increased only moderately (range: ALT 50–180, AST 35–150). Fasting tolerance was 4 h at 1 month (glucose 2.5 mmol/L) and still 4 h at 15 months (glucose 3.0 mmol/L), while treated with 5 g of raw corn-starch after each meal. He reached first year developmental milestones at a normal age and was able to walk unaided at 12 months. Weight and height were constantly at the 50th percentile. Nerve conduction studies, developmental quotient (DQ) and cerebral magnetic resonance imaging (MRI) were normal at 24 months. At 25 months, after a difficult decision taken together with the family, he underwent liver transplantation. We considered that he was at reasonable risk of sudden liver function deterioration like his brother, if he were to be affected by a more severe common illness than those he had had to date. Immediately after transplantation, he was shifted to a free diet with normal night fasting and no hypoglycemia was detected. At 30 months he began walking with an unsteady gait and was unable to climb stairs. A clinical diagnosis of ataxia was made and nerve conduction studies showed severe motor-sensory axonal polyneuropathy. Cerebral MRI and electroencephalogram (EEG) were normal. At 52 months DQ was 96 with WPPSI scale (verbal 97, performance 96).

2.1.3. Patient 3

This female patient is a relative of the first 2 patients (Fig. 1a). She had her first symptomatic hypoglycemia at 5 months with glucose 2.4 mM; ALT and AST were 165 and 237 U/L, respectively. Another three hypoglycemic crises occurred between then and 3 years of age. Repeated blood tests between 3 and 10 years of age showed normal transaminases and increased gamma-GT (range 96–163 U/L). Liver ultrasound showed fibrosis and steatosis with areas of cirrhosis. A fasting test performed at 6 years was stopped at 16 h for hypoglycemia (1.3 mmol/L) with increased plasma lactate (4.5 mmol/L). The glucagon test showed a normal increase of glucose after 6 h of fasting. From 3 to 10 years of age, she developed failure to thrive (3rd percentile for weight and height), right thoracic scoliosis, muscle hypotrophy of the lower limbs, ataxia and progressively worsening brain lesions in the cerebellar white matter and in the Substantia Nigra at MRI. Cognitive function was normal until 7 years and then worsened: Intelligence Quotient (IQ) (WISC-R) was 64 (verbal 75, performance 55) at 10 years. Slit-lamp examination showed a small corneal scarring in the left eye. Corneal sensitivity, fundus oculi and electroretinogram (ERG) were normal. Visual and somatosensory evoked potentials demonstrated abnormalities in the central transmission of the stimuli. Nerve conduction studies showed severe demyelinating damage to both motor and sensory peripheral nerves.

2.2. Methods

Tissue samples: liver, muscle and skin biopsies were performed after informed parental consent. Tissues for biochemical assays were immediately frozen and stored at −80 °C until assayed. Skin biopsies and fibroblasts cultures were performed according to usual routine procedures.

3. Biochemical analysis and molecular studies

Specific activities of individual respiratory chain complexes were measured on tissue homogenates by spectrophotometric assay. Specific activities of each complex were normalized to that of citrate synthetase (CS), a mitochondrial matrix enzyme indicator of mitochondrial mass [11]. Nucleotide sequence analysis was carried out as described by Spinazzola et al. [1].

4. Morphological analyses

All liver samples were routinely formalin fixed and paraffin embedded. Sections were stained with hematoxylin–eosin (H&E), Masson trichrome for collagen tissue, PAS and PAS-diastase for glycogen, Pearl's for iron and Orcein for copper. Patients 1 and 2 both had two histological examinations over time. They were compared by means of a score from 0 to 4 attributed to 12 different histologic features (hepatocellular necrosis, ballooning, cholestasis, canalicular cholestasis, bile duct proliferation, macrovescicular and microvescicular steatosis, portal and lobular inflammation, fibrosis, Kupffer cells activation, glycogen content). Morphological analysis of skeletal muscle was carried out as previously described [12].

5. Statistical analysis

Analysis of ALT and AST was carried out every two weeks in patient 2 and the results were divided into three different sets of data according to the clinical conditions of the child: 1. well being (45 values); 2. admission to hospital for common childhood diseases (eight values); 3. discharge from hospital after at least 3 days of continuous iv glucose infusion (four values). The numbers of data were different in the three different settings and were analysed by the Kruskal–Wallis one-way analyses of variance by ranks.

6. Results

6.1. Biochemical investigations and molecular analysis

Liver respiratory chain activities and molecular analysis of the three patients are summarized in Table 1. Low activities of Complex I (CI), Complex III (CIII) and Com-

Table 1
Summary of biochemical, molecular and clinical findings of the three patients.

Patient	Liver tissue activities				Liver MtDNA depletion %	Genotype	Outcome
	CI	CII	CIII	CIV			
1	0.1	37	22	17.6	3 ± 5	p.R50Q/p.R50Q	D 7 months
2	7.6	67	55	38	11 ± 2	p.R50Q/p.R50Q	A 6 years, liver tx, ataxia
3	9.1	72	50	56	22 ± 8	p.R50Q/p.R50Q	A 13 years ataxia
Controls	19.0 ± 9.3	54 ± 17	83 ± 22	70 ± 17	100%		

Activities are expressed as nmoles of substrate/min/mg of protein and normalized to citrate synthetase. CI, CII, CIII and CIV indicate "complex I, complex II, complex III and complex IV".
D indicates "died", A "alive" and tx "transplantation".
MtDNA depletion is expressed as percentage of normal controls.

plex IV (CIV) normalized to citrate synthetase were found in liver homogenates, while they were normal in muscle homogenates and fibroblast cultures (not shown).

7. Morphological investigations

Liver samples were analyzed in patients 1 and 2 (Fig. 2). Liver biopsy from patient 1 taken 3 days before death, showed submassive hepatic necrosis (Fig. 2A and B; score 24) with micro and macrovescicular steatosis, diffuse hepatocyte ballooning with focal giant cell formation and occasional canalicular bile plugs; liver cells necrosis was repaired by fibrosis and bile ductular proliferation, with accompanying cholangiolitis but without the formation of typical cirrhotic nodules. PAS staining showed glycogen depletion. Histology of the liver taken at autopsy, 3 days later, revealed a much more severe necrosis, with marked ballooning of residual hepatocytes, cholestasis and diffuse ductular proliferation (Fig. 2C and D; score 28). In patient 2, the first biopsy, taken at 3 weeks of age, demonstrated a normal liver structure with the exception of focal swelling of perivenular centrolobular hepatocytes, accompanied by minimal focal perivenular fibrosis, inflammation and mild Kupffer cell activation, with presence of ceroid pigment deposits. Cytoplasmic glycogen was normal with PAS staining (Fig. 2E; score 7). Explanted liver (2 years of age) showed structural alterations mostly limited to the centrolobular areas: microvescicular steatosis and few ballooned hepatocytes, with mild Kupffer cell activation; portal spaces showed mild irregular fibrous expansion, with thin and largely incomplete portal to portal septa, characterized by mild bile ductular proliferation (Fig. 2F–H; score 14).

Histopathology and electron microscopy of the muscle, performed on patient 3 was normal and no ragged red fibers were observed.

8. Statistical analysis

Patient 2's transaminases values were statistically analyzed in three different settings: well being, admissions, discharges. A significant difference was found between the three sets of data (ALT: $KW_2 = 16.71014$, $p = 0.0002$; AST: $KW_2 = 26.67904$, $p = 0.000$). Multiple comparisons showed significant differences both for ALT and AST. In particular, for ALT, between set 1 (well being) and set 2 (admissions) ($p = 0.006597$) and between set 2 (admissions) and set 3 (discharges) ($p = 0.000268$); for AST, between set 1 and 2 ($p = 0.000107$), set 2 and 3 ($p = 0.000004$) and set 1 and 3 ($p = 0.028232$) (Kruskal–Wallis one-way analyses of variance by ranks).

9. Discussion

An apparently isolated liver disease was detected in two of our three patients, very early in life. As already pointed out by Wong et al. [5], unlike other MDS [13–17], neurological involvement in this disease is very mild at onset, being limited to generalized hypotonia with preserved cognitive development. Due to this presentation, dominated by liver disease, many other metabolic disorders were ruled out before searching for a mitochondrial disorder.

A total of 34 patients [1–3,5–7] have already been described with proven *MPV17* mutation and/or NNH. Of these, 24 had severe liver failure in infancy or childhood, while 10 patients, nine of whom are Navajos, have the so called classical form with peripheral neuropathy and less liver involvement. Liver transplantation was performed in the first 2 years of life in four patients with the severe form [1–3] but also in an 11 year old patient with the classical prevalently neuropathic presentation who had developed liver carcinoma [2,3]. Other patients with the attenuated form died of liver cirrhosis in their second decade of life [2–4]. All the patients with the attenuated form are homozygous for the p.R50Q mutation (the Navajo patients and one of ours), suggesting a reduced severity of this mutation compared to the others. However, the common finding of intrafamilial variability of phenotype may also suggest extragenic influences on phenotype.

Liver histological features of our patients are similar to those reported in NNH [2,3] and other patients with

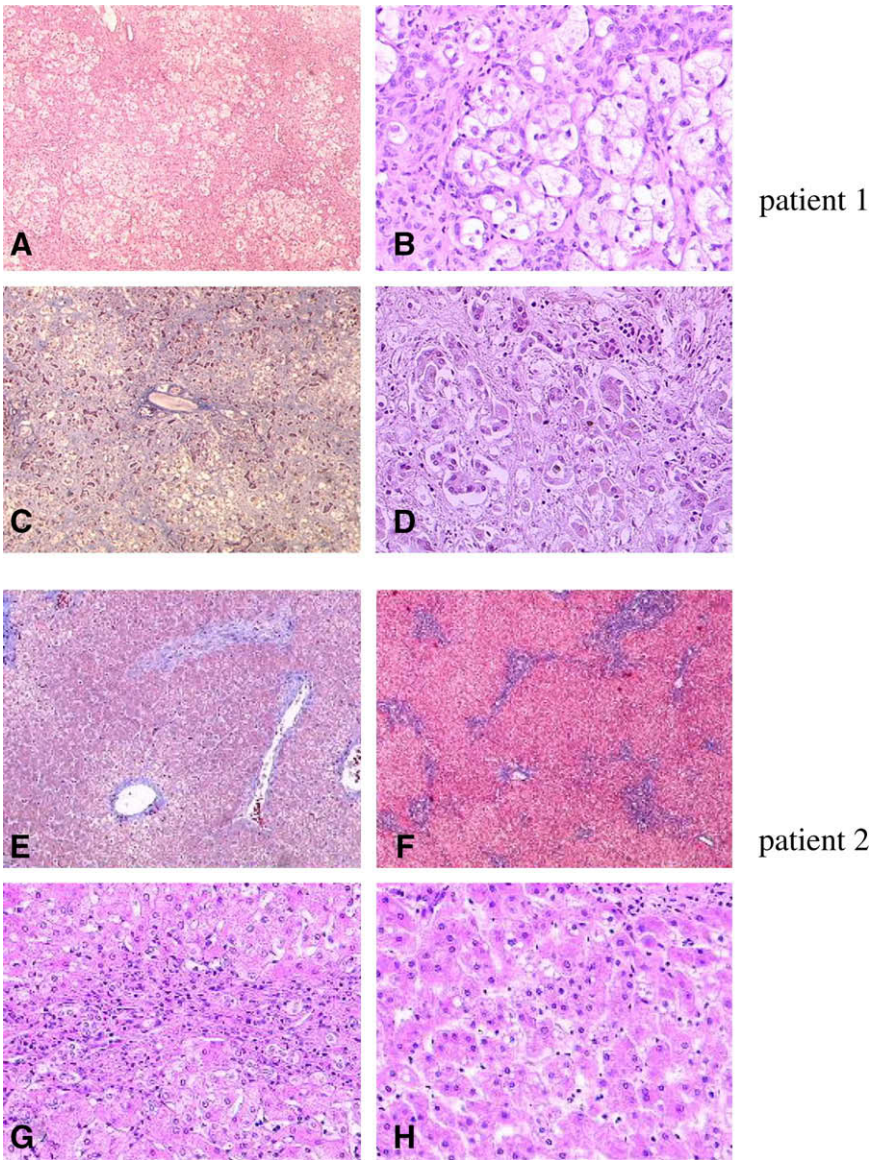

Fig. 2. Patient 1: Biopsy taken 3 days before the death demonstrating large areas of confluent necrosis (A, H&E 40×) replaced by fibrosis and ductular proliferation, with diffuse ballooning of speared hepatocytes (B, H&E 400×). Liver from autopsy showed complete lobular derangement due to massive necrosis (C, Masson trichrome 40×), replaced by bile duct proliferation and canalicular cholestasis of residual hepatocytes (D, H&E 400×). Patient 2: Biopsy taken at 3 weeks demonstrating a structurally normal liver, with light cytoplasmic swelling of perivenular hepatocytes (E, Masson 40×). The explanted liver showed moderate structural alteration, with preserved centrolobular veins and portal to portal fibrous septa (F, Masson 40×). Higher magnifications demonstrate moderate septal proliferation of bile ducts (G, H&E 400×) and lobular micro vescicular steatosis (H, H&E 400×).

MPV17 mutations [5–7]. They are also similar to those reported for other MDS [17]. We had the opportunity to study liver specimens of patients 1 and 2, at different ages. The histological findings of patient 2 at 3 weeks and at 25 months of age and those of his older brother at 8 months of age, 3 days before death, well illustrates the progression of liver disease in *MPV17* patients. Accordingly, we could say that the first histological signs of this liver disease consist of focal vacuolization in perivenular centrolobular hepatocytes, accompanied by Kupffer cell activation. Liver cell necrosis in this disease is fluctuating, also depending on concomitant diseases. Evolution to prevalent fibrosis and/or cirrhosis is likely dependent on the entity of recurrent episodes of hepatocellular damage.

We would like to highlight some particular biochemical findings in our patients that are different from other MDS. First, lactic acidosis was not a major finding, as also described by Navarro-Sastre et al. [7], with maximum values of 4–6 mmol/L only when the patients were already very compromised. Second, hypoglycemia in the two patients who were thoroughly investigated, consistently ensued 3–4 h after the meal, while in other liver MDS, hypoglycemia usually develops after a more prolonged fasting (personal observation). Furthermore, oral glucose challenge or continuous iv glucose adminis-

tration did not increase the levels of blood lactate, as is otherwise commonly seen in other respiratory chain disorders [18]. These physiological features are similar to those of glycogen storage disease type I where both glycogenolysis and gluconeogenesis are impaired and energy production is only based on glycolysis. Unfortunately an enzymatic assessment in liver tissue for glycogenolysis or gluconeogenic pathway was not done in our patients. Since patient 1 improved both clinically and biochemically when strictly fed every 3 h, we started feeding his younger brother every 3 h from birth. Like his sibling, this patient had signs of hepatocellular necrosis and cholestasis very early in life. His fasting tolerance lasted for a maximum of 4 h and his liver function tests severely worsened whenever he had an even mild deviation from his usual caloric intake. Taken together, these observations strongly suggest that glucose and regular caloric intake have a role in protecting liver from hepatocyte necrosis and preserving liver architecture in *MPV17* mutant patients.

From a functional point of view, the liver disease in patient 3 was less severe than that of her cousins. To date, she is in fact the only non- Navajo patient who may be classified as having the classical form. She had biochemical signs of hepatocellular necrosis only during the hypoglycemic episodes and, unlike her cousins, she had better fasting tolerance and a clear response to glucagon.

With the exception of liver transplantation which has only been performed in a few cases [2,3,7], no other treatment for this disease has been reported to date. At least two patients died suddenly after an abrupt worsening of their liver disease [2,5]. Dietetic treatment could be helpful in similar cases as supportive care, while waiting for liver transplantation to be performed. No clear response to dietetic treatment has been observed in the past for liver MDS [13,14]. We report here that in two patients with *MPV17* related MDS, diet based feeding every 3 h was useful in slowing progression of liver damage. The glucose challenge test in patient 1 and the blood tests during glucose infusions in patient 2 showed that both patients were able to properly use glucose as a fuel without producing lactate, suggesting that dietetic treatment may be beneficial in other *MPV17* mutant cases. Physicians may be reluctant to perform stress and challenge tests in very sick patients or to shift them to a rigid diet without a proven benefit. However, our data suggest trying continuous glucose infusion for a few days in any MDS patient with liver involvement, even before having reached a specific diagnosis: if a reduction of transaminases is obtained, the same patient should start strict feeding every 3 h.

Results from patient 2 and those reported among the other transplanted patients [2,4,7] indicate that liver transplantation did not prevent the evolution of peripheral and central neuropathy. Therefore, the decision to pursue this procedure remains controversial, particularly considering the risks of the surgical procedure and the lifelong dependence on immunosuppressive treatment. However, patient 2 underwent liver transplantation, in consideration of the impending risk of developing acute fatal liver failure like his older brother, prior to knowing the natural history and the specific genetic cause of the disease.

In conclusion, our *MPV17* patients were characterized, as other previously reported patients [2–5], by mild or absent neurological involvement at onset, absent or mild hyperlactatemia, consistently severe hypoglycemia 3–4 h after meals, no hyperlactatemia after glucose loading, beneficial effect of i.v. glucose and frequent feeding on liver function tests. The peculiar clinical and laboratory features of *MPV17*-related MDS can help differentiate it from other MDS forms. Our experience suggests that the impairment of liver function in *MPV17*-related MDS may be treated, or its progression slowed down, by a strict diet based on frequent meals. It will be of interest to confirm this observation in a larger series of patients. A more thorough understanding of the function of the *MPV17* protein is also needed to devise better therapeutic strategies for this disease.

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