Cirrhosis and Liver Failure: Expanding Phenotype of Acid Sphingomyelinase-Deficient Niemann-Pick Disease in Adulthood

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Abstract Acid sphingomyelinase-deficient Niemann-Pick disease (ASMD) includes the severe neuronopathic type A, the non-neuronopathic type B, and rare intermediate cases. Here we report on such an atypical type B patient who died at 31 years of age from liver failure. This male subject was first seen in a paediatric department at the age of 3 years because of significant hepatosplenomegaly. Foam cells in bone marrow, interstitial pneumonitis, a slight facial dysmorphism and normal psychomotor development were additional findings. Acid sphingomyelinase studies in lymphocytes (and later *SMPD1* gene studies [c.151_154delGACT; c.1341-21_1341-18delAATG]) established the diagnosis of ASMD. Between the ages 6–27, he developed growth retardation, peripheral neuropathy, kyphoscoliosis, alopecia, and aortic valve insufficiency requiring valve replacement. Surgery for bilateral inguinal hernias was performed twice, when the patient was 10 and 21 years of age, respectively. At the age of 28, he was noted

to have hepatosplenomegaly and follow-up investigations revealed ascites and gastric varices. Liver biopsy showed cirrhosis without areas of necrosis (A6 in Child-Pugh classification). He developed haematemesis and worsening encephalopathy leading to his death at age 31. In conclusion, cirrhosis should be considered as a possible complication of ASMD in adult patients, even if hepatic tests are normal.

Introduction

Niemann-Pick disease (NPD) types A and B refer to an autosomal recessive lysosomal lipid storage disease caused by mutations in the *SMPD1* gene resulting in the deficient activity of the lysosomal enzyme acid sphingomyelinase (ASM, E.C. 3.1.4.12). “ASM-deficient NPD” should now be preferred, because this name allows inclusion of cases intermediate between the severe neuronopathic type A and the non-neuronopathic type B (Schuchman 2007), and also clearly differentiates this group from Niemann-Pick disease type C, a distinct entity (Vanier 2013). Most type A NPD (MIM# 257200) patients show a similar clinical course, with failure to thrive and prominent visceral involvement soon after birth, followed from 5 to 10 months of age by a progressive neurological deterioration. Death classically occurs between 1.5 and 3 years of life (McGovern et al. 2006). By contrast, typical type B NPD (MIM# 607616) is a chronic, non-neuronopathic form, with a widely variable degree of systemic involvement (McGovern et al. 2008; Hollak et al. 2012). The most typical symptoms are hepatosplenomegaly, interstitial lung disease, alteration of liver function, followed by joint/limb pain, bruising, headache, abdominal pain or diarrhoea. The age of diagnosis, typically in late infancy or childhood, may vary

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from birth until late adulthood. A majority of typical type B patients survive until late adulthood, but some patients have a severe systemic disease, eventually leading to premature death, often by liver failure or cirrhosis (Labrune et al. 1991; Wasserstein et al. 2004; Pavlu-Pereira et al. 2005; McGovern et al. 2013). Recent studies indicate that liver cirrhosis may be more frequent than previously reported in type B NPD (Tassoni et al. 1991; Thurberg et al. 2012). Respiratory insufficiency is another important cause of morbidity.

We report here on a patient with atypical ASM-deficient NPD who died from liver failure in his 32nd year of age.

Case Report

A Cambodian male patient, born at term from non-consanguineous parents, was seen at the age of 3 years with a 2-year history of hepatosplenomegaly and was noted to have facial dysmorphism, red brown colouration of the macula, and interstitial changes on a chest X-ray. The diagnosis of ASM-deficient NPD was considered and confirmed by showing deficiency of acid sphingomyelinase in lymphocytes ($0.06 \mu\text{kat/kg}$ protein; normal values 1.83 ± 0.52), using ^{14}C -sphingomyelin as the substrate (Vanier et al. 1980). ALAT and ASAT were 76 and 110 mU/L, respectively, total bilirubin 8 mmol/L. Urinary glycosaminoglycans were measured and found normal. A repeated study of urinary glycosaminoglycans and oligosaccharides performed at the age of 27 years also concluded with normal results. A skin fibroblast culture was obtained when the child was 8 years old, which confirmed the profound acid sphingomyelinase deficiency, using the same method as above. A later study of the *SMPD1* gene revealed the presence of a frameshift mutation p.Asp51Leufs*25 (c.151_154delGACT) in exon 1 and of an intronic deletion c.1341-21_1341-18delAATG (IVS4-21_IVS4-18delAATG), plus three known polymorphisms (p.Val36Ala, p.Ala48_Leu49del and p.Gly508Arg), all in a heterozygous status. Segregation of the alleles could not be studied.

At the age of 6 years and 8 months, the patient's facial dysmorphism had increased, his voice was changed, the base of his thorax was enlarged. Examination showed a slight amyotrophy of the lower limbs. Neurological examination was normal except abolished tendon reflexes. Electromyography found a peripheral neuropathy. The interstitial pneumonitis was more pronounced than before.

Data between the age of 7 and 27 years are fragmentary, but the patient developed body growth delay, kyphosis, scoliosis, bowed fingers and alopecia. Surgery for bilateral inguinal hernias was performed twice, when the patient was 10 and 21 years of age, respectively.

At 20 years of age, because of aortic regurgitation, the patient underwent aortic valve replacement with mechanic prosthesis. Pathologic examination revealed severe atheroma of the aorta with calcifications. At that time, oral anticoagulant therapy was begun.

At 27 years of age, the patient had a short stature with kyphoscoliosis, dysmorphic features, and no apparent intellect alteration. Examination showed a marked hepatosplenomegaly, abolished deep tendon reflexes with minimal distal amyotrophy. His liver function tests were essentially normal, but he had a pronounced thrombocytopenia (47 G/L). Electromyography concluded with a severe demyelinating sensory-motor polyneuropathy of the four limbs, which, from a later study, remained stable for the following 3 years.

One year later, a liver biopsy was performed by transjugular procedure, revealing a 11 cm H_2O gradient in the supra-hepatic vein, a micronodular and macronodular cirrhosis without necrosis, without inflammation. Microvesicular steatosis was also found representing 70% of the total liver area (Fig. 1). Other classical factors of cirrhosis at young age – alcohol abuse, hepatitis B and C viruses, haemochromatosis and auto-immune hepatitis – were excluded.

At 30 years of age, clinical examination was unchanged. Dyspnoea on exertion was noticed; functional tests showed a mild respiratory insufficiency with FEV1/FVC at 81% and FVC at 77%. An ophthalmological examination showed a very low visual acuity (2/10 and 3/10), with absence of cataract but presence of a whitish deposit. Platelets had remained at a similar low level (49 G/L); liver tests were within normal range. Two months later, oesophageal and gastric endoscopy was performed, showing varices in the fundus, under the cardia. The patient was considered with cirrhosis (A6 in Child-Pugh classification).

When slightly over 31, the patient was referred to the hospital because of haematemesis. He also had lower limb oedema, chronic diarrhoea, abdominal pain with episodes of vomiting. Clinical examination showed short stature (1m30), liver and spleen enlargement, ascites and bowed fingers. Prothrombin level was 18%, TCA 75/34 under anticoagulant therapy, fibrinogen level 1.1 g/L (normal >2), factor V level 23%, albumin level 24.7 g/L, total bilirubin 74 $\mu\text{mol/L}$. Haematology showed a haemoglobin content of 120 g/L, platelet count 59 G/L, leucocytes 7.77 G/L (6.47 polynuclear cells, 0.77 lymphocytes). Haptoglobin level was <0.08 g/L associated with high LDH level ($\times 1.5$ normal). Liver tests were normal and lipase was mildly elevated (twice the upper normal level). A search for hepatitis B and C infection was negative. Alpha-feto protein was normal. Urinalysis found no proteinuria. No monoclonal gammopathy was present, either in serum or in urine.

Fig. 1 Trans-jugular liver biopsy. **(a)** at low magnification, the biopsy is fragmented (H&E, $\times 40$). **(b)** This staining highlights the fact that these fragments are cirrhotic nodules surrounded by fibrosis stained in

red (Picrosirius-Hemalun, $\times 40$). **(c)** Presence of hepatocytes and Kupffer cells with foamy cytoplasm probably due to the accumulation of lipids (H&E, $\times 200$)

Abdominal ultrasonography showed a dysmorphic liver with multiple punctiform hyperechogenic lesions and an important enlargement of the spleen (21 cm), and ascites. Portal hypertension was suspected because of perisplenic venous derivations. Abdominal CT scan confirmed ascites and liver and spleen enlargement, portal hypertension and pancreatitis.

One month later, the patient developed encephalopathy. A new episode of haematemesis led to stop anticoagulant therapy. Encephalopathy worsened. Hepatic transplantation was considered but denied because of encephalopathy, mental retardation, heart and lung involvement, and due to absence of specific therapy for ASM deficiency. Laboratory data at this stage were as follows: total protein: 47 g/L; albumin: 22 g/L; bilirubin: 182 $\mu\text{mol/L}$; haemoglobin: 102 g/L; platelets: 40 G/L; factor V: <10%; fibrinogen: 0.6 g/L with monomers of fibrin >150 $\mu\text{g/mL}$ (normal < 20), suggesting activation of coagulation.

After a new episode of haematemesis and worsening of encephalopathy, palliative therapy was considered. Ten days later, the patient died from refractory encephalopathy related to cirrhosis and hepatic failure.

Discussion

The clinical spectrum of ASM-deficient NPD (ASMD) is wide and ranges from severe infantile neurovisceral form leading to death by 3 years of age (type A) to patients with a mild form of the purely systemic form (type B) with a normal lifespan. ASMD, like Gaucher disease, shows a continuum (Schuchman 2007). An intermediate phenotype has also been described, in which some patients are closer to type A, while others are closer to type B, with a variable degree of neurologic involvement, mild developmental delay, and cherry-red maculae, along with visceral manifestations. In recent large surveys, patients with an intermediate phenotype have been included in type B by leading authors in the field (Wasserstein et al. 2004; McGovern et al. 2013)

The acid sphingomyelinase deficiency is well established in our patient, from studies in leucocytes, cultured fibroblasts and gDNA (the pathogenicity of the intronic deletion is, however, not proven). However, his clinical phenotype, although in large part compatible with a type B ASMD, is clearly atypical. Abolition of deep tendon

reflexes from the age of 6, with severe demyelinating sensory-motor polyneuritis of the 4 limbs shown in the adult age, and a possible slight mental retardation are indeed seen in a small subset of patients still considered as type B (Wasserstein et al. 2004; McGovern et al. 2013). Cardiac abnormalities of various types have also been recently described in a few, otherwise typical, type B patients (Iaselli et al. 2011). Still, cardiac involvement was particularly severe in this patient, since it required aortic valve replacement at the age of 20. Above all, the prominent dysmorphic features and skeletal deformations seen in the present patient already from early childhood are highly unusual. Because of short stature with kyphosis, hand deformities and surgery performed for bilateral inguinal hernia, search for a concomitant mucopolysaccharidosis was performed in childhood and at the adult age. Urinary excretion of glycosaminoglycans was normal in both instances. To our knowledge, this phenotype is quite unique. At least it has not been seen in a cohort of over 150 ASMD patients diagnosed in France during the past 30 years.

On the other hand, there are several reports on liver fibrosis and cirrhosis in type B patients. Liver fibrosis studied in two patients was found to occur independently of age at onset or time of the liver biopsy: it was present in a young female but absent in an adult male patient (Takahashi et al. 1997). Fatal liver failure has also been reported in two children from the French cohort (Labrune et al. 1991). Cirrhosis and portal hypertension were further reported in a 33-year-old patient with NPD (Tassoni et al. 1991). Low factor V level of coagulation could have been related not only to liver disease but also to hypersplenism with resultant expansion of plasma volume (diluting the clotting factors) and increased intrasplenic utilisation of factors which has been described in NPD (Dewhurst et al. 1979). Nevertheless, higher levels of other factors of the coagulation despite oral anticoagulant therapy suggest hepatic failure in the case reported herein.

Recent studies performed during the phase 1 trial of enzyme replacement therapy with RhASM suggest that hepatic cirrhosis may have been underestimated in type B ASMD (Thurberg et al. 2012). Among the 17 adult patients who underwent a liver biopsy during baseline screening, two had biopsy-proven full-blown cirrhosis. Another publication from the same group studied morbidity and mortality in a cohort of 103 type B patients ranging from 1 to 72 years of age (McGovern et al. 2013). Nine patients had cirrhosis or liver failure requiring liver transplantation. Of note, six patients had fulminant liver failure and three of them had evidence of cirrhosis on liver biopsy. Of those

with liver failure, two received successful orthotopic liver transplantation at 12 and 25 years of age.

The authors of the latter study propose that the massive sphingomyelin storage in lysosomes may provoke a fibrotic reaction in tissues, leading to progressive liver dysfunction, possibly compounded by inflammation. This appears somewhat in contradiction to the study by Thurberg and colleagues, where no correlation was found between sphingomyelin levels and either fibrosis grade or patient age.

The accumulation of the potentially toxic compound sphingosylphosphorylcholine, which shows a large increase in liver and spleen of ASMD patients (Rodriguez-Lafresse and Vanier 1999), along with sphingomyelin, cholesterol and bis(monoacylglycero)phosphate, could also be contributing to liver dysfunction. Furthermore, ASM deficiency is associated with elevation in cytokines, which could also play a role in the development of liver fibrosis and cirrhosis. In a study in the ASM-deficient mouse model, it was also suggested that liver fibrosis could be related to cathepsin B overexpression (Moles et al. 2012).

In conclusion, our observation further demonstrates that liver failure and cirrhosis can occur in adult patients with ASMD. Thus, regular monitoring of liver status by biochemical tests, i.e. hepatic tests, haemostasis, hepatic ultrasonography and eventual subsequent histological study should be part of the follow-up for patients with type B ASMD. Because of liver failure or low platelet count, transjugular procedure should be considered. Histological study should be discussed on an individual basis, but probably included as a tool in the care of patients from the perspective of future enzyme replacement therapy.

Synopsis

Liver failure and cirrhosis are possible complications of acid sphingomyelinase deficiency in adult patients.

Conflict of Interest

All the authors declare that they have no conflicts of interest.

Ethics Approval

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.

References

- Dewhurst N, Besley GT, Finlayson ND, Parker AC (1979) Sea blue histiocytosis in a patient with chronic non-neuropathic Niemann–Pick disease. *J Clin Pathol* 32:1121–1127
- Hollak CE, de Sonnaville ES, Cassiman D et al (2012) Acid sphingomyelinase (Asm) deficiency patients in The Netherlands and Belgium: disease spectrum and natural course in attenuated patients. *Mol Genet Metab* 107:526–533
- Iaselli F, Rea G, Cappabianca S, Fabozzi G et al (2011) Adult-onset pulmonary involvement in Niemann–Pick disease type B. *Monaldi Arch Chest Dis* 75:235–240
- Labrune P, Bedossa P, Huguet P et al (1991) Fatal liver failure in two children with Niemann–Pick disease type B. *J Pediatr Gastroenterol Nutr* 13:104–109
- McGovern MM, Aron A, Brodie SE et al (2006) Natural history of type A Niemann–Pick disease: possible endpoints for therapeutic trials. *Neurology* 66:228–232
- McGovern MM, Wasserstein MP, Giugliani R et al (2008) A prospective, cross-sectional survey study of the natural history of Niemann–Pick disease type B. *Pediatrics* 122:e341–e349
- McGovern MM, Lippa N, Bagiella E et al (2013) Morbidity and mortality in type B Niemann–Pick disease. *Genet Med* 15:618–623
- Moles A, Tarrats N, Fernandez-Checa JC, Mari M (2012) Cathepsin B overexpression due to acid sphingomyelinase ablation promotes liver fibrosis in Niemann–Pick disease. *J Biol Chem* 287:1178–1188
- Pavlu-Pereira H, Asfaw B, Poupctova H et al (2005) Acid sphingomyelinase deficiency. Phenotype variability with prevalence of intermediate phenotype in a series of twenty-five Czech and Slovak patients. A multi-approach study. *J Inher Metab Dis* 28:203–227
- Rodriguez-Lafrasse C, Vanier MT (1999) Sphingosylphosphorylcholine in Niemann–Pick disease brain: accumulation in type A but not in type B. *Neurochem Res* 24:199–205
- Schuchman EH (2007) The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann–Pick disease. *J Inher Metab Dis* 30:654–663
- Takahashi T, Akiyama K, Tomihara M et al (1997) Heterogeneity of liver disorder in type B Niemann–Pick disease. *Hum Pathol* 28:385–388
- Tassoni JP Jr, Fawaz KA, Johnston DE (1991) Cirrhosis and portal hypertension in a patient with adult Niemann–Pick disease. *Gastroenterology* 100:567–569
- Thurberg BL, Wasserstein MP, Schiano T et al (2012) Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann–Pick disease type B). *Am J Surg Pathol* 36:1234–1246
- Vanier MT (2013) Niemann–Pick diseases. *Handb Clin Neurol* 113:1717–1721
- Vanier MT, Revol A, Fichet M (1980) Sphingomyelinase activities of various human tissues in control subjects and in Niemann–Pick disease – development and evaluation of a microprocedure. *Clin Chim Acta* 106:257–267
- Wasserstein MP, Desnick RJ, Schuchman EH et al (2004) The natural history of type B Niemann–Pick disease: results from a 10-year longitudinal study. *Pediatrics* 114:e672–e677