Molecular Genetics and Metabolism xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

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

Review article

Long-term liver disease in methylmalonic and propionic acidemias

Apolline Imbard[a,b,1], Nuria Garcia Segarra[c,d,1], Marine Tardieu[e], Pierre Broué[f], Juliette Bouchereau[c], Samia Pichard[c], Hélène Ogier de Baulny[c], Abdelhamid Slama[g], Charlotte Mussini[h], Guy Touati[f], Marie Danjoux[f], Pauline Gaignard[g], Hannes Vogel[i], François Labarthe[e], Manuel Schiff[c,j,1], Jean-François Benoist[a,b,*,1]

[a] Biochemistry Laboratory, APHP, Robert Debré University Hospital, Paris, France
[b] Paris Sud University, Chatenay Malabry, France
[c] Reference Center for Inborn Errors of Metabolism, APHP, Robert Debré University Hospital, Paris, France
[d] Center for Molecular Diseases, CHUV, Lausanne, Switzerland
[e] Pediatric Unit, CHRU, Tours, France
[f] Hepatology and IEM Unit, Children Hospital, Toulouse, France
[g] Biochemistry Laboratory, APHP, CHU Bicêtre, Le Kremlin Bicêtre, France
[h] Department of Pathology, APHP, CHU Bicêtre, Le Kremlin Bicêtre, France
[i] Neuropathology, Stanford University Medical Center, Palo Alto, CA, USA
[j] UMR1141, PROTECT, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

ARTICLE INFO

Keywords:
Organic acidemias
Alpha-fetoprotein
Hepatomegaly
Liver disease
Liver fibrosis
OXPHOS deficiency
MMA
PA

ABSTRACT

Background and objectives: Patients affected with methylmalonic acidemia (MMA) and propionic acidemia (PA) exhibit diverse long-term complications and poor outcome. Liver disease is not a reported complication. The aim of this study was to characterize and extensively evaluate long-term liver involvement in MMA and PA patients.
Patients and methods: We first describe four patients who had severe liver involvement during the course of their disease. Histology showed fibrosis and/or cirrhosis in 3 patients. Such liver involvement led us to retrospectively collect liver (clinical, laboratory and ultrasound) data of MMA (N = 12) or PA patients (N = 16) from 2003 to 2016.
Results: Alpha-fetoprotein (αFP) levels were increased in 8/16 and 3/12 PA and MMA patients, respectively, and tended to increase with age. Moderate and recurrent increase of GGT was observed in 4/16 PA patients and 4/12 MMA patients. Abnormal liver ultrasound with either hepatomegaly and/or hyperechoic liver was observed in 7/9 PA patients and 3/9 MMA patients.
Conclusions: These data demonstrate that approximately half of the patients affected by MMA or PA had signs of liver abnormalities. The increase of αFP with age suggests progressive toxicity, which might be due to the metabolites accumulated in PA and MMA. These metabolites (e.g., methylmalonic acid and propionic acid derivatives) have previously been reported to have mitochondrial toxicity; this toxicity is confirmed by the results of histological and biochemical mitochondrial analyses of the liver in two of our MMA patients. In contrast to the moderate clinical, laboratory or ultrasound expression, severe pathological expression was found for three of the 4 patients who underwent liver biopsy, ranging from fibrosis to cirrhosis. These results emphasize the need for detailed liver function evaluation in organic aciduria patients, including liver biopsy when liver disease is suspected.
Take home message: MMA and PA patients exhibit long-term liver abnormalities.

Abbreviations: MMA, Methylmalonic acidemia; PA, Propionic acidemia; αFP, alpha-fetoprotein; ID, intellectual disability; IQ, intelligence quotient; GH, growth hormone; GGT, gamma-glutamyltranspeptidase; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; AST, aspartate transaminase; ALT, alanine transaminase; WISC IV, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; *IDH1*, Isocitrate dehydrogenase 1; *IDH2*, Isocitrate dehydrogenase 2; *PCCA*, Propionyl CoAcarboxylase; cblA, Cobalamin A

* Corresponding author at: Reference Center for Inborn Errors of Metabolism, Robert Debré University Hospital, APHP, 48, Boulevard Sérurier, 75019 Paris, France.
E-mail address: jean-francois.benoist@aphp.fr (J.-F. Benoist).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.ymgme.2018.01.009
Received 19 September 2017; Received in revised form 29 January 2018; Accepted 30 January 2018

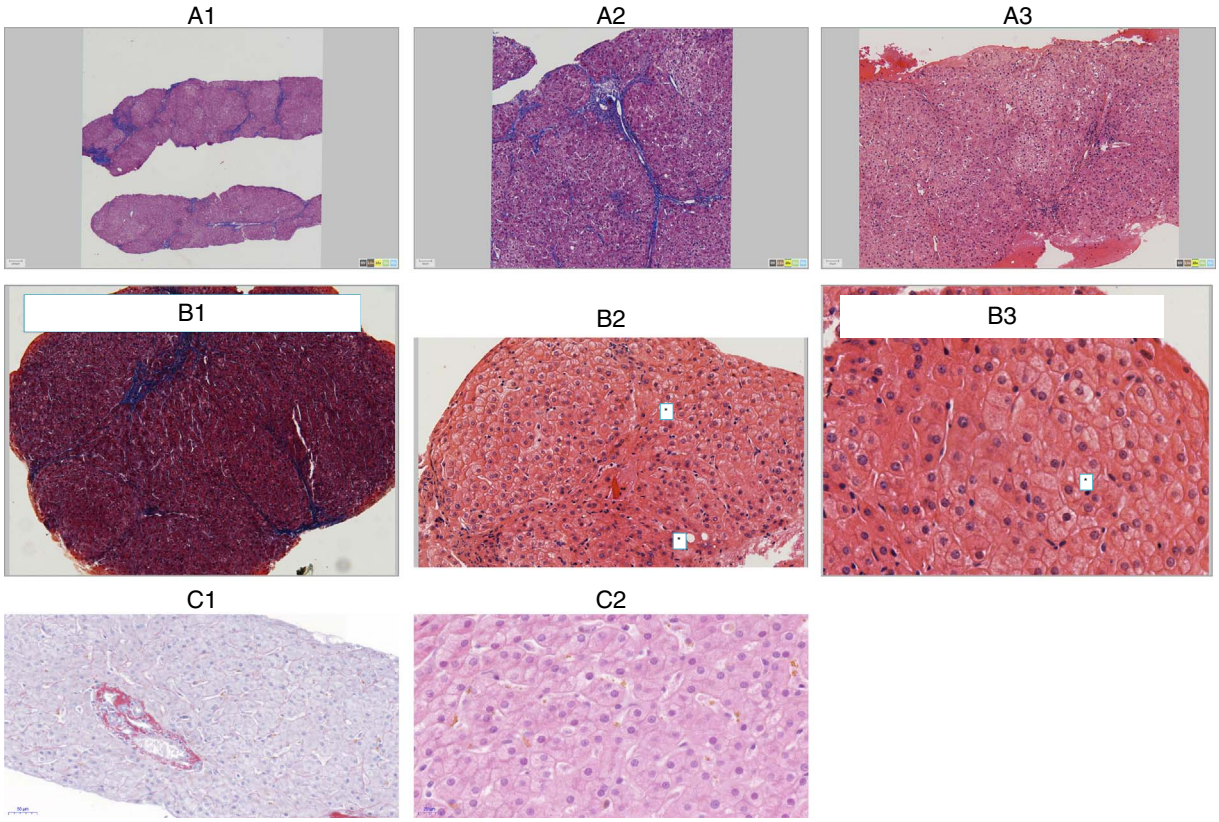

Fig. 1. Liver biopsy histology in patient #1 an #4.
Panels A: Patient #1 at the age of 8. A1 Hepatic parenchyma shows irregular nodulation with some portal fibrosis and porto-portal septa, without cirrhosis (Masson's trichome, original magnification ×25). A2 Portal spaces exhibit fibrosis with porto-portal extension, involved with scanty and irregular perisunoïdal fibrosis (Masson's trichome, original magnification ×100). A3 Hepatocytes were subnormal with rare pericellular rehancement, without any steatosis (hematoxylin, eosin and saffron, original magnification ×100).
Panels B: Patient #1 at the age of 13. B1 Hepatic parenchyma shows micronodular cirrhosis with portal fibrosis, and scanty perisunoïdal fibrosis (Masson's trichome, original magnification ×200). B2 Hepatocytes were subnormal, with rare micro and macrosteatosis (*). (hematoxylin, eosin and saffron, original magnification ×200). B3 Normal hepatocytes, with rare microvascular steatosis (*). (hematoxylin, eosin and saffron, original magnification ×400).
Panels C: C1 Liver parenchyma was normal apart, no portal fibrosis nor central, scanty perisunoïdal fibrosis (Picro sirius, original magnification ×200). C2 On histologic examination, hepatocytes were normal, without any steatosis nor megamitochondries. NB: iron overload in Küpffer's cells, (hematoxylin, eosin and saffron, original magnification ×400).

1. Introduction

Methylmalonic acidemia (MMA) and propionic acidemia (PA) are inborn errors of the catabolism of branched-chain amino acids and odd-numbered chain fatty acids. Acute or chronic symptoms are caused by the accumulation of toxic compounds proximal to the metabolic block. Clinical phenotypes vary from severe neonatal-onset forms with poor outcome to milder late-onset presentations. Neonatal-onset patients present after an initial symptom-free interval with acute and severe neurological deterioration with metabolic ketoacidosis, hyperammonemia and sometimes pancytopenia. In most cases, there is no liver dysfunction. Late-onset forms may present with acute life-threatening encephalopathy or intermittent or chronic symptoms such as ataxia, behavioral disturbances, recurrent vomiting, anorexia, failure to thrive, aversion to protein-rich foods and developmental delay. During these attacks, patients typically exhibit metabolic ketoacidosis with hyperammonemia. Pancytopenia, particularly neutropenia, is frequently associated [1–3].

MMA and PA patients may develop various complications throughout the course of the disease, and the overall outcome is poor despite improvements in therapeutic management [4]. Chronic complications include poor nutritional status with growth retardation, anorexia, osteopenia, and hematological abnormalities (anemia, neutropenia, thrombocytopenia or pancytopenia) [5]. Visceral complications include cardiomyopathy, arrhythmia (especially a prolonged QTc interval in PA) and acute pancreatitis [6]. Patients with MMA typically develop tubulo-interstitial nephropathy with chronic renal failure by late childhood or adolescence [3]. Neurological outcome is poor, with both acute and chronic basal ganglia involvement potentially causing movement disorder of variable severity. Other symptoms include intellectual disability (ID), epilepsy, chronic muscular weakness, sensorineural deafness, psychiatric disorders and optic nerve atrophy [1,4,7]. Neurocognitive outcome is poor and tends to be worse in PA than in MMA [4,8,9].

To date, liver disease has not described as a visceral complication in MMA or PA patients. We report herein 4 patients with MMA who exhibited liver complications. This finding was an incentive to retrospectively review clinical, laboratory and liver ultrasound data of patients with either MMA or PA followed in our center to evaluate the frequency of liver complications in MMA and PA patients.

2. Patients and methods

2.1. Case # 1

The first patient is a 17-year-old girl who was diagnosed with mut° MMA at the age of 4.5 months after presenting with coma and ketoacidosis. Molecular analysis revealed a homozygous splice mutation (c.2124 + 1G > A) in the *MUT* gene.

After initial management of the acute deterioration with i.v. glucose and L-carnitine, she was further treated with a protein-restricted diet, L-carnitine and metronidazole. She was not fully compliant, and