Pearson syndrome as a rare cause of liver dysfunction and malabsorption

Yasmina Dejonckheere [a], Peter Witters [b], Daisy Rymen [b]

[a] Department of Pediatrics, University Hospitals of Leuven, 3000 Leuven, Belgium.
[b] Department of Pediatrics, Center for Metabolic Diseases, University Hospitals of Leuven, 3000 Leuven, Belgium.

yasmina.dejonckheere@telenet.be

Keywords

Pearson syndrome; liver dysfunction; malabsorption; exocrine pancreatic dysfunction; lactic acidosis

Abstract

Pearson syndrome is a progressive multisystem disorder with sideroblastic anemia as its main feature. It is caused by single, large-scale deletions of the mitochondrial DNA. Most patients present in infancy with severe transfusion-dependent anemia and failure to thrive. Here, we describe a three-year-old girl with presumed liver failure during adenovirus gastroenteritis. The diagnosis of Pearson syndrome was suspected based on the co-occurrence of liver dysfunction, exocrine pancreatic insufficiency, megaloblastic anemia and lactic acidosis.This case report aims to increase general awareness for rare disorders, like Pearson syndrome, in the differential diagnosis of pediatric malabsorption and liver dysfunction.

Introduction

Acute liver failure (ALF) is a rare clinical condition in children, characterized by biochemical signs of acute hepatocellular injury and coagulopathy. The differential diagnosis of pediatric ALF is broad, including infectious and toxic etiologies, as well as underlying autoimmune or metabolic disorders (Table 1) (1). However, in the patient presenting raised transaminases, hypoalbuminemia and coagulopathy, ALF should be differentiated from a vitamin K-responsive elongation of the INR due to inadequate intake, drug interference or malabsorption (Table 2). For example severe gastrointestinal disease could also present with hypoalbuminemia, vitamin K malabsorption and elevated transaminases without ALF.

Here, we describe a three-year-old girl with presumed liver failure during adenovirus gastroenteritis. However, further investigations revealed severe malabsorption, megaloblastic anemia and lactic acidosis, fitting Pearson syndrome.

Pearson syndrome is a mitochondrial disorder caused by single, large scale mitochondrial DNA deletions (SLSMD). Sideroblastic anemia is considered to be the core feature of the disease. However, nowadays, Pearson syndrome is recognized as a multisystem disorder, demonstrating significant clinical overlap with other SLSMDs (2–4).

The aim of this case report is to increase the general awareness for rare disorders, like Pearson syndrome, in the differential diagnosis of malabsorption and liver dysfunction in the pediatric population.

Case report

A 3-year-old girl was referred to our center because of suspected nephrotic syndrome. She had been admitted for several days because of adenovirus gastroenteritis requiring intravenous rehydration. The clinical course was, complicated by hypokalemia, hypoalbuminemia, oedema of the lower extremities and episodes of somnolence.

She was the first child of non-consanguineous parents. Her medical history was unremarkable, apart from recurrent episodes of diarrhea, assumed to be due to lactose intolerance. Clinically, the patient presented a striking bronze skin tone, normal sclerae, brittle hair, a moon facies, protruding abdomen and oedema of the lower extremities. The liver was palpated 1 cm below the costal margin, there was no shifting dullness. The patient complained of persistent nausea and fatigue. Biochemically, she displayed a mild pancytopenia with macrocytic anemia and normal vitamin B12 and folate levels, normal renal function, increased transaminases (10-15 times the upper limit of normal) without cholestasis, hypoalbuminemia (23 g/L; nl: 35-52), a normal ammonia and a prolonged INR (2.1). Venous blood gas analyses revealed a normal glucose level and an increased lactate of 6 mmol/L (0,5-2,2). Screening for endocrine dysfunction was negative. Urinary analysis was normal. Abdominal ultrasound and CT of the brain were unsuspicious.

Biochemical screening and therapeutic measurements for suspected acute liver failure were initiated (1). Interestingly, coagulation normalized within 24 hours of intravenous administration of 10 mg vitamin K1, suggesting either nutritional deficiency or malabsorption. Factor V and VII were not measured prior to the administration of vitamin K. While factor V is vitamin K independent and could differentiate between ALF (decreased factor V) and vitamin K malabsorption (normal levels of factor V) turn-around-time for this test is longer than correcting with vitamin K and remeasuring INR.

The hypothesis of an underlying severe malabsorption was supported by the clinical presence of steatorrhea, faltering weight and growth (Figure 1) and by the biochemical evidence of decreased levels of total protein, essential amino acids, cholesterol and fat-soluble vitamins. Exocrine pancreatic insufficiency was evidenced by an undetectable fecal elastase level, proven steatorrhea on a 3-day stool collection and an abnormal 13C-triglyceride breath test indicating low pancreatic lipase activity. The malabsorptive state was initially managed by parenteral nutrition and subsequently by tube feeding supplemented with pancreatin and fat-soluble vitamins.

Lactate remained elevated over time (4-6 mmol/L; 0,5-2,2), despite substitution with high-dose thiamine. Additional metabolic testing revealed only a slight increase of some Krebs cycle intermediates on organic acid profile.

Due to the co-occurrence of megaloblastic anemia, malabsorption due to exocrine pancreatic insufficiency, liver dysfunction and lactic acidosis, Pearson syndrome was suspected early in the course of the hospitalization. A large scale mitochondrial DNA deletion (m.10759-13990del) was demonstrated in a heteroplasmic state in the patient, but could not be detected in the mother.

Discussion

Although ALF has a low prevalence in childhood, its differential diagnosis is broad, ranging from infectious and toxic causes to a myriad of inherited

Table 1: A non-exhaustive list for the differential diagnosis of pediatric and neonatal acute liver failure

Pediatric and Neonatal Acute Liver Failure – Differential Diagnosis *- Acute liver injury, i.e. elevated transaminases* *- INR ≥ 2 without encephalopathy or ≥1,5 with encephalopathy*	
Age group	**Etiology**
Neonatal ALF	Indeterminate liver failure
	Viral infection - *Herpes simplex virus* - *Enterovirus* - *Cytomegalovirus*
	Gestational alloimmune liver disease (GALD)
	Inborn errors of metabolism - *Galactosemia* - *Tyrosinemia type 1* - *Mitochondrial disorders* - *DLD (E3) deficiency* - *Fatty acid oxidation defects* - *Urea cycle disorders* - *Niemann Pick type C* - *Transaldolase deficiency* - *Adenosine kinase deficiency*
	Neonatal hemochromatosis
	Shock or sepsis
	Intoxication
Pediatric ALF	Indeterminate liver failure
	Intoxication - *Acetaminophen* - *Other drugs and herbal medication*
	Autoimmune hepatitis
	Viral infection - *HAV, HBV, HCV, HDV* - *Herpes simplex virus* - *Enterovirus* - *Adenovirus* - *HHV6, HHV7* - *Cytomegalovirus, Epstein-Barr virus*
	Inborn errors of metabolism - *Hereditary fructose intolerance* - *Tyrosinemia type 1* - *Mitochondrial disorders* - *DLD (E3) deficiency* - *Fatty acid oxidation defects* - *Urea cycle disorders* - *Glycogen storage disease type IV* - *Wilson disease* - *Congenital disorders of glycosylation* - *Transaldolase deficiency* - *Adenosine kinase deficiency*
	Shock or sepsis Hemophagocytic lymphohistiocytosis

Table 2: A non-exhaustive list for the differential diagnosis of pediatric malabsorption.

Pediatric malabsorption – Differential Diagnosis
Coeliac disease
Pancreatic disorders - *Cystic fibrosis* - *Exocrine pancreatic insufficiency* - *Chronic pancreatitis* - *Johanson-Blizzard syndrome* - *Schwachman-Diamond syndrome*
Crohn's disease
Infectious diarrhea - *Giardia lamblia* - *Cryptosporidium* - *Hookworm*
Hepatobiliary dysfunction with cholestasis
Short bowel syndrome
Congenital disorders of the brush border enzymes - *Glucose-galactose transporter deficiency* - *Sucrase-isomaltase deficiency* - *Microvillus inclusion disease* - *Trichohepatoenteric syndrome*
Inborn errors of metabolism - *Abetalipoproteinemia* - *Mitochondrial disorders, including MNGIE and Pearson syndrome* - *Congenital disorders of glycosylation*
Acrodermatitis enterohepatica
Intestinal lymphangiectasia

metabolic disorders (Table 1). Pediatric ALF is defined by the biochemical evidence of severe liver injury, i.e. increased transaminases and/or biliary dysfunction, and a vitamin K-unresponsive coagulopathy (INR ≥ 1,5 with encephalopathy or INR ≥ 2 without encephalopathy) (1). Important in this definition is the response to vitamin K, which will differentiate a tentative diagnosis of ALF from disorders associated with severe vitamin K deficiency such as inadequate intake, drug interference or malabsorption. Hence, intravenous administration of high dose vitamin K1 (1 mg for infants and 10 mg for children) should be pursued in any patient demonstrating new onset biochemical evidence of hepatocellular injury and coagulopathy (Figure 2) (1). In case of vitamin K deficiency, complete normalization of the coagulopathy is generally observed within hours of parenteral vitamin K administration. In liver failure, on the other hand, vitamin K will at best improve but never normalize the coagulopathy, making the resulting prothrombin time/INR a fairly good marker for the severity of liver damage. In addition, dosage of coagulation factors V and VII prior to vitamin K administration can further support the diagnosis, since the synthesis of factor V is independent of vitamin K.

Also in our case report, the presumed diagnosis of adenovirus-associated ALF was overruled by the prompt correction of the INR upon administration of vitamin K1. The alternative hypothesis of malabsorption was further supported by faltering weight and growth (Figure 1), as well as biochemical markers suggestive of both protein and fat malnutrition. In addition, steatorrhea was observed during hospitalization and also accounted in retrospect for the recurrent episodes of diarrhea in the last 1,5 year.

Pediatricians are regularly facing failure to thrive or malabsorption, and are therefore familiar with its differential diagnosis. Nevertheless, more rare disorders should also be considered, especially when biochemical or clinical findings are inconsistent with the usual suspects (Table 2) (5,6). Also in our case report, it were some peculiar lab results that directed us towards the final diagnosis. For example, a mild pancytopenia was observed that did not improve upon recovery from adenovirus gastroenteritis. In addition, red blood cells were macrocytic in the absence of vitamin B12 or folic acid deficiency or a high reticulocyte count. Also, lactic acid remained elevated despite thiamine substitution, and could thus not be accounted for by the malabsorption per se. Hence, the diagnosis of Pearson syndrome was already assumed early in the course of the hospitalization, based on

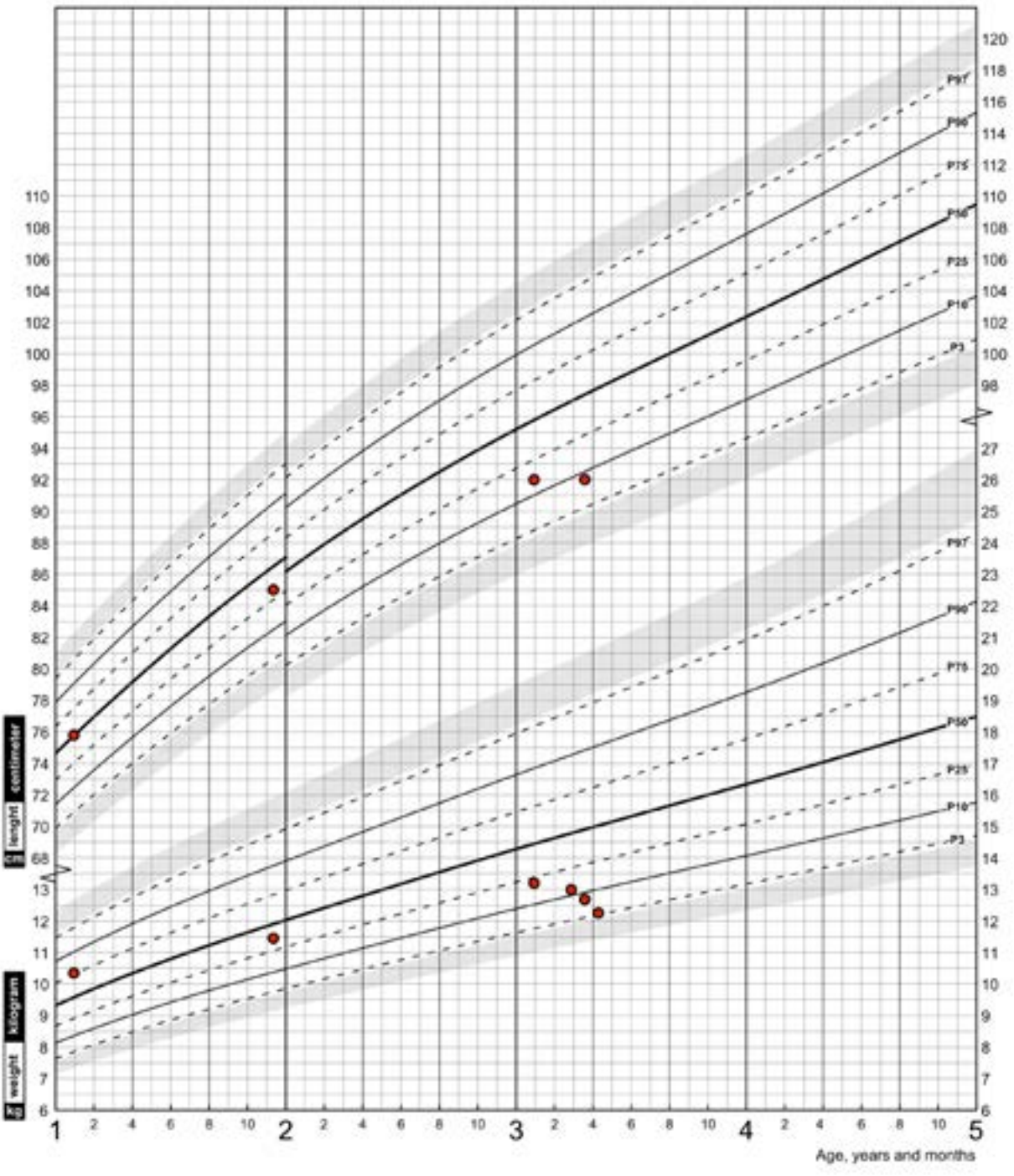
the co-occurrence of pancytopenia with macrocytosis, lactic acidosis, liver dysfunction and exocrine pancreatic insufficiency.

Pearson syndrome is a multisystem mitochondrial disorder originally defined by the presence of sideroblastic anemia and to a lesser extent exocrine pancreatic insufficiency. Together with Kearns-Sayre Syndrome (KSS) and Progressive External Ophthalmoplegia (PEO), Pearson syndrome constitutes one of the three overlapping phenotypes of SLSMDs (2). These large mitochondrial DNA (mtDNA) deletions usually occur spontaneously, either through improper mtDNA repair or replication. Therefore, germline transmission, i.e. inheritance through the maternal line, is only observed in a small proportion of patients with SLSMDs (7).

Classical Pearson syndrome presents in infancy with bone marrow failure and transfusion-dependent sideroblastic anemia. Exocrine pancreatic dysfunction is a variable finding, only seen in about 30% of patients (2,3,8). In addition, liver dysfunction, lactic acidosis and failure to thrive are some of the more prevalent clinical features. Pearson syndrome is often fatal at young age, due to septicemia, overwhelming lactic acidosis or hepatocellular insufficiency (9). Although patients surviving infancy typically demonstrate hematological improvement, they develop features compatible with KSS over time (2). This phenotypical shift is assumed to result from mitotic segregation with a gradual clearance of mtDNA deletions from rapidly dividing cells, and their accumulation in non-dividing tissues, e.g. the endocrinological organs and the central nervous system (7). As such, patients may develop pigmentary retinopathy, external ophthalmoplegia, progressive neurological impairment, sensorineural hearing loss, endocrinological issues (e.g. adrenal insufficiency and diabetes mellitus), renal tubulopathy and cardiac conduction defects (2,4).

Our case report relates to the phenotypic heterogeneity of Pearson syndrome. Although our patient demonstrated several features associated with

Figure 1: Growth charts (http://www.vub.ac.be/groeicurven) of the patient upon presentation, demonstrating a decline of both weight and height centiles with a more pronounced decline for weight compared to height.



Pearson syndrome, the hematological findings, which are considered as the chief hallmark, were only present to a limited extent.

At this point, no curative treatment exists for patients with Pearson syndrome. Therefore, symptomatic management and awareness of possible complications are critical to minimize disease-associated mortality and morbidity (7).

Conclusion

This case report highlights the importance of a comprehensive differential diagnosis in the patient with malabsorption and/or exocrine pancreatic insufficiency. Additional features such as liver dysfunction, elevated lactate or refractory megaloblastic anemia should trigger further genetic and metabolic investigations. Because of the phenotypic variability, Pearson syndrome should be considered in any patient with suggestive clinical features, even in the absence of the full clinical spectrum.

The authors have no conflict of interest to declare. Informed consent was obtained. This case report is approved by the ethical committee of University Hospitals of Leuven (S66706).

REFERENCES:

1. Squires JE, Alonso EM, Ibrahim SH, Kasper V, Kehar M, Martinez M, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure. J Pediatr Gastroenterol Nutr. 2022;74(1):138–158.
2. Björkman K, Vissing J, Østergaard E, Bindoff LA, de Coo IFM, Engvall M, et al. Phenotypic spectrum and clinical course of single large-scale mitochondrial DNA deletion disease in the paediatric population: a multicentre study. J Med Genet. 2021.doi: 10.1136/jmedgenet-2021-108006.
3. Wild KT, Goldstein AC, Muraresku C, Ganetzky RD. Broadening the phenotypic spectrum of Pearson syndrome: Five new cases and a review of the literature. Am J Med Genet. 2020;182(2):365–373.
4. Broomfield A, Sweeney MG, Woodward CE, Fratter C, Morris AM, Leonard J V., et al. Paediatric single mitochondrial DNA deletion disorders: an overlapping spectrum of disease. J Inherit Metab Dis. 2015;38(3):445–457.
5. Pietzak MM, Thomas DW. Childhood malabsorption. Pediatr Rev. 2003;24(6):195–204.
6. Rahman S. Gastrointestinal and hepatic manifestations of mitochondrial disorders. J Inherit Metab Dis. 2013;36(4):659–673.
7. Pitceathly RDS, Rahman S, Hanna MG. Single deletions in mitochondrial DNA: Molecular mechanisms and disease phenotypes in clinical practice. Neuromuscul Disord. 2012;22(7):577–586.
8. Pronman L, Rondinelli M, Burkardt DD, Velayuthan S, Khalili AS, Bedoyan JK. Pearson Syndrome: A Rare Cause of Failure to Thrive in Infants. Clin Pediatr. 2019;58(7):819–824.
9. Crippa BL, Leon E, Calhoun A, Lowichik A, Pasquali M, Longo N. Biochemical abnormalities in Pearson syndrome. Am J Med Genet 2015;167(3):621–628.

Figure 2: Administration of vitamin K in patients with hepatocellular injury and coagulopathy.
*In addition dosage of factor V and VII can be performed prior to the administration of vitamin K. Both factor V and VII will be decreased in case of acute liver failure, whereas only factor VII will be decreased in case of vitamin K deficiency.