DIAGNOSIS DIFFICULTIES IN SEVERE AND CHRONIC HEPATOPATHY WITH EARLY ONSET. CASE REPORT

Sorin Ioan Iurian[1], Ron Wevers[2], Bogdan Mehedintu[3]
[1]Pediatric Hospital, "Lucian Blaga" University, Sibiu
[2]Laboratory of Genetic, Endocrine and Metabolic Diseases, Radboud University Medical Centre, Nijmegen, The Netherlands
[3]Emergency Department, Pediatric Hospital, Sibiu

ABSTRACT

Authors emphasize diagnosis and treatment difficulties in a patient with severe and chronic idiopathic hepatopathy. Authors present a 5 year-old male frequently admitted for severe acute liver failure episodes with severe gastrointestinal bleedings that occurred in infancy after diet diversification. Hystory case correlated with investigations and liver function improvement after fructose-free diet initiation led to congenital fructosemia diagnosis.

Keywords: hepatic failure, congenital fructose intolerance, child

BACKGROUND

Metabolic disorders include a large spectrum of disorders due to gene defects; the genes encode enzymes that promote conversion of certain substances (substrates) into others (products). As a consequence of its accumulation, the substrate will become toxic interfering with normal hepatic cell function.

CASE PRESENTATION

The authors present a case of 5 years old male patient followed in our department since infancy.

Obstetric hystory: he was born at home in cephalic presentation at 9 months old gestational age after an unsurveilled pregnancy; authors don't have additional data regarding perinatal period (abandoned patient).

Family history: his mother diagnosed with schizophrenia; the 5th child in the family.

Patient history. The child was admitted many times in pediatric clinic from the age of 2 moths. Regarding disease severity, authors divided the case evolution in 2 periods: before dietary diversification and after initiation of mixed diet (from the age of 6 months). During first period, the case was admitted for respiratory tract infections and authors revealed mildly elevated transaminases levels (ALAT between 80-675 UI/l). For the 2nd period, authors remarked severely impairment of clinical status and liver function concomitant with diet diversification and elevated ALAT (11.000 UI/l).

Clinical exam recorded for most admittings: skin pallor, dehydration signs, impaired nutritional status; no facial dysmorphism, rickets signs, emesis, hepatomegaly, no splenomegaly; no particular odor of urine or sweat, inconstant tremor affecting both upper extremities.

In evolution, authors remarked hospitalisations justified by acute hepatic failure with dehydration, hematemesis and seizures (due to serum electrolytes imbalances and secondary encephalopathy). Authors mentioned progressive deterioration of nutritional status.

Corresponding author:
Iurian Sorin Ioan, Pediatric Hospital, "Lucian Blaga" University, 2-4 Pompeiu Onofreiu St., 550166, Sibiu
E-mail: iurian_sorsab@hotmail.com

Investigations.

- hematological evaluation: microcytic anaemia; peripheral blood smear without peculiar morphological features;
- inflammatory markers in normal range;
- glycemia, serum amylasis and functional kidney evaluation: normal range;
- liver functional tests: ASAT/ALAT ranges between 80 UI/l – 11.000 UI/l; total bilirubin, gammaGT, lactate dehydrogenase: normal values); serum creatinphosphokinase: normal range;
- blood ammonia = 82,8 mg% (normal range, NR < 60 mg%); blood electrolytes: mild hyponatremia; Astrup analysis: mildly elevated values for lactic acid;
- blood cholesterol and triglycerides: normal range (NR);
- immunological estimation: normal;
- thyroid function: NR; serum ceruloplasmin = 0,27 g/l (NR = 0,15-0,48 g/l);
- infectious diseases evaluation: negative serology for Toxoplasma gondii, lues, Epstein-Barr virus, Cytomegalovirus, hepatitis viruses A /B/C and HIV;
- sweat test: normal range.

Consultations. Neurological evaluation revealed developmental coordination disorder with spasticity; fundus eye exam without abnormalities.

Imagistics: no anomalies at transfontanellar ultrasonography; abdominal ultrasound exam has shown homogenous liver with normal echotexture and liver enlargement.

Diagnosis. Based on clinical data correlated with investigations, we considered chronic hepatopathy (see the evolution more than 6 months).

The treatment included electrolytes correction using iv infusions, procoagulant remedies, hepatoprotective therapy (iv, orally), C and E vitamins.

The evolution was characterised by liver function improvement for short periods of time. Even between hospitalisations, serum level transaminases have been maintained to mild elevation range (150-200 UI/l).

Differential. In context of chronic hepatopathy, the authors have considered following possibilities:

1. Toxic substances exposures: patient hystory excluded consumption of drugs/food involved in liver damage (1,2);

2. Viral/bacterial/parasitic infections have been excluded based on negative serology tests (3);

3. Autoimmune hepatitis (4)/**primary sclerosing cholangitis** (5) were considered less likely: antinuclear antibodies negative, soluble liver antigen = 0,55 AU/ml (NR< 20), antibodies liver kidney microsomal =1,72 U/ml (NR< 3);

4. Ischemic causes (Budd-Chiari syndrome, acute circulatory failure, septic shock, acute leukemia) are less probable (normal abdominal ultrasound exam, normal range for inflammatory markers, normal hematologic parameters);

5. Biliary causes (6). Biliary atresia, biliary hipoplasia, choledocal cyst and choledocal lithiasis are unlikely (normal abdominal ultrasound exam). Authors also ruled out cystic fibrosis, sclerosing cholangitis and primitive biliary cirrhosis (antimithocondrial antibodies anti- M_2 = 0,58 AU/ml, NR < 20);

6. Inborn errors of metabolism with liver damage:

6.1. Wilson disease (7) was excluded (normal serum ceruloplasmin level);

6.2. Neonatal hemochromatosis (8) it's unlikely (normal serum iron and ferritin serum levels);

6.3. Alpha1 antitrypsin (A1AT) deficiency was excluded (A1AT = 2,83 g/l, NR = 1,11-2,97 g/l);

6.4. Disorders of carbohydrate metabolism:

6.4.1. Galactosemia (9) was excluded: late onset of disease and no clinical evidence for cataract; serum galactose = 10 mg/l (NR <100 mg/l);

6.4.2. Ereditary fructose intolerance (10,11): symptoms develop very soon after fructose ingestion; clinical features are vomiting, diaphoresis, tremor, lethargy and convulsions associated with hypoglycemia. Among complications: lactic acidosis, hyperuricemia; failure to thrive, jaundice, hepatomegaly, splenomegaly, Fanconi syndrome and hemorrhage; chronic exposure to fructose leads to progressive liver damage. Diagnosis methods include: oral fructose tolerance test, enzymatic assay of a liver biopsy or aldolase B gene mutation identification. Treatment: restrictions of fructose, sucrose and sorbitol intake; successful treatment requires detailed knowledge of the fructose content of food. Because of serum fructose value (81 mg/l, NR = 10-60 mg/l), authors weren't able to exclude this disease;

6.4.3. Glycogen storage diseases: types II, III, V and VII were excluded (normal serum values for muscular enzymes); among glycogenosis with hepatic involvement (types Ia, IV, VI) it is difficult to eliminate the type 1a;

6.4.4. Oligosaccharidosis (mannosidosis (12) and **fucosidosis)** were excluded, based on lack of oligosaccharides in patient urine;

6.4.5. Mucopolysaccharidosis (13): urinary test didn't reveal glycosaminoglycans in urine, excluding all types of mucopolysaccharidosis;

6.4.6. Congenital disorders of glycosylation (CDG) (14). Authors didn't identified any transferrin isoform anomalies, excluding CDG types I_a - I_l and types II_a, II_d, II_e, II_g, II_h;

6.5. Disorders of protein metabolism:

6.5.1. Type 1 tyrosinemia. Authors excluded type 1 tyrosinemia based on normal serum succinyl-acetone (0,7 μmol/l, NR < 4,44 μmol/l).

6.5.2. Cystinosis (15): implies muscle deterioration, blindness, kidney dysfunction, hepatomegaly/splenomegaly. We consider this disease less probable based on patient clinical exam;

6.5.3 Hereditary urea cycle abnormalities (16): primary hyperammonemia (types I and II, citrullinemia, argininosuccinic aciduria, hyperargininemia) were excluded (amonemia level close to normal range);

6.6. Disorders of lipid metabolism:

6.6.1. β-oxidation fatty acids anomalies (17). Tandem mass spectrometry revealed normal serum range for acyl-carnitin and has eliminated the majority of organic acidemias;

6.6.2. Adrenoleukodystrophy (18). Normal very-long-chain fatty acids serum levels excluded adrenoleukodystrophy (C24:0/C22:0 = 0,88 μmol/l, NR = 0,72-1,02); C26:0/C22:0 = 0,008 μmol/l, NR = 0,008-0,026);

6.6.3. Zellweger syndrome. Due to normal blood level for branched chain fatty acids and normal ratios for C_{24}/C_{22} and C_{26}/C_{22}, authors excluded Zellweger syndrome (19);

6.6.4. Sitosterolemia (20). Normal lipid pattern excludes sitosterolemia: serum cholesterol = 4528 μmol/l (NR =2600 – 5200 μmol/l), 7-dehydrocholesterol = 1 μmol/l (NR < 5 μmol/l), colestanol = 10 μmol/l (NR = 3,3 – 12,5 μmol/l);

6.6.5. Sialic acid storage disease (Boala Salla) was excluded due to normal sialic acid urinary level (21).

For diagnosis purpose, authors proceeded to **liver biopsy** that revealed chronic hepatopathy with necrotic and inflammatory lesions, moderate fibrosis and dystrophic hepatocytes suggestive for toxic or metabolic etiology.

Among all mentioned above disorders, we considered as probable congenital fructose intolerance guiding authors to test the gene. There were analysed the „hot-spot" mutations of aldolase B gene (A149P, A174D, N334K) responsible for 90% with fructose intolerance cases: no gene anomalies identified.

CONCLUSION

Even though the gene testing didn't identified any hot-spot mutation, authors weren't able to eliminate hereditary fructose intolerance because disease started after administration of food containing fructose, justifying initiation of fructose-free diet. After implementation of restrictive diet, authors noticed promptly improvement of liver function.

Nowadays, the patient follows a severe diet allowing food containing lactose and glucose. The diet restrictions include avoidance of food comprising saccharose, fructose and sorbitol: fruits (apples, pears, bananas, grapes, peaches, pineapples, apricots), fruit juices, honey, vegetables (beet, carrot, yellow corn, potatoes, rice, anion, pepper), chocolate, marmelade, cereals, wallnut, cocos, peanuts and sweet drinks. We mention the difficulty to follow this diet because of severe restrictions.

This presentation can also be used as a diagnosis algorythm for chronic hepatopathy due to inbon errors of metabolism.

Aknowledgements

We kindly thank to Professor Ron Wevers and his team from Laboratory of Genetic, Endocrine and Metabolic Diseases, Radboud University Medical Centre, Nijmegen, The Netherlands – for given support in case investigation.

REFERENCES

1. **Bernal W., Donaldson N., Wyncoll D., Wendon J.** Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. *Lancet*. Feb 16 2002; 359(9306):558-63.
2. **Bass N.M.** Drug-Induced Liver Disease. In: Friedman S, McQuaid K, Grendell, J, eds. Current Diagnosis and Treatment in Gastroenterology. 2nd ed. New York, NY: McGraw-Hill Professional; 2003. 664-79.
3. **Wasley A., Grytdal S., Gallagher K.** Surveillance for acute viral hepatitis--United States, 2006. MMWR Surveill Summ. Mar 21 2008; 57(2):1-24.
4. **Krawitt E.L.** Autoimmune hepatitis: classification, heterogeneity, and treatment. *Am J Med. Jan* 17 1994; 96(1A):23S-26S.
5. **Gotthardt D., Chahoud F., Sauer P.** Primary sclerosing cholangitis: diagnostic and therapeutic problems. *Dig Dis*. 2011; 29 Suppl 1:41-5.
6. **Drebber U., Mueller J.J., Klein E., Kasper H.U., Schulze F., Schardt K., et al.** Liver biopsy in primary biliary cirrhosis: clinicopathological data and stage. *Pathol Int. Aug* 2009; 59(8):546-54.
7. **Schilsky M.L.** Wilson disease: Current status and the future. Biochimie. Jul 30 2009.

8. **Adams P.C,. Searle J.** Neonatal hemochromatosis: a case and review of the literature. *Am J Gastroenterol.* Apr 1988; 83(4):422-5.
9. **Segal S.** Galactosemia unsolved. *Eur J Pediatr.* 1995; 154 (7 Suppl 2):S97-102.
10. **Gomara R.E., Halata M.S. et al.** Fructose intolerance in children presenting with abdominal pain. *J Pediatr Gastroenterol Nutr.* Sep 2008; 47(3):303-8.
11. **Tsampalieros A., Beauchamp J. et al.** Dietary fructose intolerance in children and adolescents. *Arch Dis Child.* Dec 2008; 93(12):1078.
12. **Sun H., Wolfe J.H.** Recent progress in lysosomal alpha-mannosidase and its deficiency. *Exp Mol Med.* Mar 31 2001; 33(1):1-7.
13. **Ashworth J.L., Biswas S. et al.** Mucopolysaccharidoses and the eye. *Surv Ophthalmol.* Jan-Feb 2006; 51(1):1-17.
14. **Clayton P.T., Grunewald S.** Comprehensive description of the phenotype of the first case of congenital disorder of glycosylation due to RFT1 deficiency (CDG In). *J Inherit Metab Dis.* 2009; 32 Suppl 1:S137-9.
15. **Nesterova G., Gahl W.** Nephropathic cystinosis: late complications of a multisystemic disease. *Pediatr Nephrol.* Jun 2008; 23(6):863-78.
16. **Haeberle J., Boddaert N., Burlina et al.** Suggested Guidelines for the Diagnosis and Management of Urea Cycle Disorders. *Orphanet J Rare Dis.* May 29 2012; 7(1):32.
17. **Gregersen N., Wintzensen H. et al**. C6-C10-dicarboxylic aciduria: investigations of a patient with riboflavin responsive multiple acyl-CoA dehydrogenation defects. *Pediatr Res.* Oct 1982; 16(10):861-8.
18. **Wanders R.J.** Peroxisomes, lipid metabolism, and human disease. *Cell Biochem Biophys.* 2000; 32 Spring:89-106.
19. **al-Essa M., Dhaunsi G.S. et al.** Zellweger syndrome in Saudi Arabia and its distinct features. *Clin Pediatr (Phila).* Feb 1999; 38(2):77-86.
20. **Vecka M., Zak A. et al.** Noncholesterol sterols. *Acta Univ Carol Med Monogr.* 2008; 154:5-101.
21. **Lemyre E., Russo P. et al.** Clinical spectrum of infantile free sialic acid storage disease. *Am J Med Genet.* 1999 Feb 19; 82(5):385-91. Review.