

DIAGNOSTIC DIFFICULTIES OF NON IMMUNOLOGICAL CONGENITAL ASCITES- CASE REPORT

Marioara Boia^{1,2}, Maria Puiu^{1,2}, Daniela Cioboata², Oana Toth², Delia Maria Nicoara², David VL^{1,2}, Aniko Manea^{1,2}

Abstract

Neonatal ascites is commonly the result of hematologic disorders that lead to hydropsfetalis; less frequently it may be caused by non-immunological disorders. One of the rare causes of non-immunological disorders aremetabolic diseases. We hereby present the case of a 5 month old infant in which 4D ultrasound performed at 24 weeks of gestation revealed increased fetal abdominal circumference by fluid accumulation in peritoneal cavity. The presence of congenital isolated ascites along with the peculiar aspect of the infant - dysmorphic features that included frontal bossing, depressed nasal bridge and broad nasal tip, large low-set ears, long philtrum, macroglossia, broad hands and feet, brachydactyly and joint contractures, coarse skin, hepatosplenomegaly, and inguinal hernia, along with biochemical analysis of β -galactosidase enzyme in leucocytes lead to the diagnosis of GM1 gangliosidosis.

Key words: congenital ascites, β -galactosidase, GM1 gangliosidosis.

Introduction

Ascites in the neonate is usually a feature of hydropsfetalis, caused by hematologic disorders. Less frequently, isolated ascites is the dominant feature. Various mechanisms have been incriminated in the pathogenesis of ascites, that include abnormal lymphatic drainage, obstruction of venous return, cardiac failure, decreased plasma oncotic pressure, as in fetal anemia, hepatic failure (storage disease) or congenital nephrosis, increased capillary permeability, urinary tract obstruction, or meconial peritonitis [1]. Far less common causes are infections such as congenital syphilis, cytomegalovirus (CMV), varicella, toxoplasmosis, and hepatitis A [2].

We report a case of GM1- gangliosidosis, in which isolated persistent ascites was the dominant clinical feature.

Case report

A 5 months old infant girl was referred to the Intensive Care Unit presenting with increasing abdominal girth.

The infant was born to a 32 year-old woman after a gestation of 35 weeks. The data gathered revealed that the

infant was the result of a second pregnancy (first ended in spontaneous abortion at 6 weeks). Routine prenatal testing revealed positive anti-Toxoplasma IgM between 8 and 20 weeks gestation, leading to oral treatment with Rovamicine. Particular prenatal phenotype detected by ultrasound prompted further evaluation; however the karyotype performed revealed no abnormalities. 4D Ultrasound performed at 24 weeks gestation revealed increased fetal abdominal circumference by fluid accumulation in peritoneal cavity.

Upon admission in our Unit the physical examination revealed an ill appearing malnourished infant with mottled, pale dark-green skin, peri-oral cyanosis during crying, facial dysmorphism with coarse features; (fig.1) low grade fever (37,9C), fed with difficulty, marked psychomotor agitation, discrete palpebral and lower limbs edema; polypnea (60 rpm), discrete intercostal retractions, no pulmonary rales upon auscultation; bradycardia, AV = 86 bpm, systolic murmur; the abdomen was distended and tense, with shifting dullness without visible collateral circulation, (fig.2) liver edge palpable at 3.5 cm below the right costal margin, spleen at 3 cm below the left costal margin; accelerated intestinal transit, with watery stools. Initial laboratory tests revealed sepsis with staphylococcus epidermidis, moderate metabolic acidosis, hypoglycemia, high levels of alkaline phosphatase, and coagulopathy. Abdominal ultrasound (fig.3) and computed tomography revealed hepatosplenomegaly and moderate amounts of ascitic fluid. Bone marrow aspirate revealed low cellularity and vacuolated lymphocytes. Biochemical analysis of β -galactosidase enzyme in leucocytes revealed very low enzyme levels consistent with a diagnosis of GM1 gangliosidosis.

Fresh frozen plasma, packed red blood cells, platelet transfusions, broad spectrum antibiotherapy, maintenance fluid with appropriate glucose and electrolytes failed to maintain normal homeostasis of the infant as the patient developed bronchopneumonia requiring mechanical ventilation and an increased requirement for inotropic support. Persistent coagulopathy and poor perfusion resulted ultimately in her demise at one month of hospital day.

¹, „Victor Babeş” University of Medicine and Pharmacy, Timișoara

², „Louis Țurcanu” Children’s Emergency Hospital, Timișoara

E-mail: marianaboia@yahoo.com, maria_puiu@umft.ro, daniela.cioboata@yahoo.com, oana_toth@yahoo.com, delia.nicoara@gmail.com, david.vlad@umft.ro, aniko180798@yahoo.com



Fig. 1 Facial dimorphisms with coarse features



Fig. 2 Shifting dullness without visible collateral circulation

Discussion

Although inborn errors of metabolism and other single-gene defects represent merely 1 percent of cases of nonimmune fetal hydrops, their importance resides in the substantial risk of recurrence in subsequent pregnancies [2]. Most of these disorders, such as Hurler's syndrome, mucopolysaccharidosis type I, GM1 gangliosidosis type I, Gaucher's disease, Niemann–Pick disease, and β -glucuronidase deficiency are lysosomal storage diseases [2-7].

GM1 gangliosidosis is a rare lysosomal storage disorder characterized biochemically by deficient beta-galactosidase activity [8] and clinically by dysmorphic features, visceromegaly, dysostosis multiplex and neurological alteration [9].

Prevalence at birth is estimated to be approximately 1:100,000 to 200,000 live births [10].

Based on the age of onset there are three types of GM1 gangliosidosis: type I (infantile), type II (late infantile/juvenile), and type III (adult) [11]. The severe infantile phenotype (type I) is characterized by psychomotor regression by the age of 6 months, visceromegaly, cherry red spot, and facial and skeletal abnormalities [11]. Disease severity seems to be related to the level of beta-galactosidase activity [12].

It is interesting to note our patients' extremely early onset of symptoms (24 wk of gestation). GM1

gangliosidosis does not usually have a prenatal presentation, but when it happens, the most common finding is, as in our case, fetal or neonatal ascites, for reasons that remain yet unclear. Storage material in Kupffer cells, sinusoidal obstruction and subsequent portal hypertension, or hypoproteinemia due to hepatocellular dysfunction, have been hypothesized as possible explanations [13]. However, in our case, liver ultrasound and hepatic function were normal.

The clinical manifestations are the result of the accumulation of ganglioside in the lysosomes. Clinical suspicion is based on signs of storage such as facial coarsening, hypertrophic gums, cherry-red macula, visceromegaly, dysostosis and psychomotor delay [11]. Bony deformities include stubby hands, broad wrists, anterior beaking of the lumbar vertebrae, thickening of the midshaft of the humerus, and spatulate ribs [14]. There is usually rapid progression of symptoms with the development of spasticity, seizures and general neurologic deterioration with death typically occurring by age 2 [11]. In our case, the infant exhibited dysmorphic that included frontal bossing, depressed nasal bridge and broad nasal tip, large low-set ears, long philtrum, macroglossia. Additional anomalies were broad hands and feet, brachydactyly and joint contractures, coarse skin, hepatosplenomegaly, ascites and inguinal hernia. The infant exhibited no macular cherry red spot, however this feature is seldom present under the age of 6 months [15]. There was no ultrasonographic evidence of dilated and/or hypertrophic cardiomyopathy or valvulopathy. The infant developed seizures during the course of his stay in Intensive Care.



Fig. 3 Abdominal ultrasound

Peripheral blood smear (testing vacuolated lymphocytes) and urine oligosaccharides represent orientation tests [16]. Gaucher-like foam cells have been

reported on bone marrow examination [16]. Diagnosis is confirmed by biochemical assay of beta-galactosidase activity in peripheral blood leukocytes and/or by molecular genetic testing [17]. Patients with the infantile form have almost no enzyme activity, whereas patients with the adult form may have residual activity of 5-10% of reference values [11]. In our case enzyme testing for beta-galactosidase activity revealed significantly diminished activity 0,06%, consistent with classical GM1-gangliosidose.

Differential diagnosis includes mucopolysaccharidoses, sphingolipidoses and oligosaccharidoses, but the disease resembles mostly with Mucopolysaccharidosis type IVB (Morquio B). Infantile GM1 gangliosidosis shows features of mucopolisaharidosis at birth [10]. GM1 gangliosidosis and Morquio B are autosomal recessive storage disorders caused by the deficiency of β -galactosidase (GLB1), a problematic partition between Morquio B and juvenile GM1 gangliosidosis phenotypes being long discussed in literature [18].

There are currently no effective therapies for GM1 gangliosidosis, only symptomatic and supportive

treatment. A main obstacle is the blood-brain barrier, which prevents the passage of therapeutic enzymes and proteins into the brain. Substrate reduction therapy is a potential approach for clinical trials in late-onset forms [19].

Prognosis depends on the type of GM1 gangliosidosis and is extremely poor in the severe infantile form and variable in the chronic adult form of the disease [11].

Conclusions

Gangliosidosis does not usually have a prenatal presentation, but, at our patient, it is interesting to note the extremely early onset of symptoms (24 wk of gestation).

Even the neonatal ascites may have as a possible explanation the storage material in Kupffer cells, sinusoidal obstruction and subsequent portal hypertension, or hypoproteinemia due to hepatocellular dysfunction, in our case liver ultrasound and hepatic function were normal.

There are currently no effective therapies for GM1 gangliosidosis, only symptomatic and supportive treatment, as it has an extremely poor prognosis in the severe infantile form.

References

- Norton ME. Nonimmune hydrops fetalis. *Semin Perinatol* 1994;18:321-332
- Gillan JE, Lowden JA, Gaskin K, Cutz E. Congenital ascites as a presenting sign of lysosomal storage disease. *J Pediatr* 1984;104:225-231
- Beck M, Bender SW, Reiter H-L, et al. Neuraminidase deficiency presenting as non-immune hydrops fetalis. *Eur J Pediatr* 1984;143:135-139
- Applegarth DA, Toone JR, Wilson RD, Yong SL, Baldwin VJ. Morquio disease presenting as hydrops fetalis and enzyme analysis of chorionic villus tissue in a subsequent pregnancy. *Pediatr Pathol* 1987;7:593-599
- Nelson J, Kenny B, O'Hara D, Harper A, Broadhead D. Foamy changes of placental cells in probable beta glucuronidase deficiency associated with hydrops fetalis. *J Clin Pathol* 1993;46:370-371
- Lissens W, Dedobbeleer G, Foulon W, et al. Beta-glucuronidase deficiency as a cause of prenatally diagnosed non-immune hydrops fetalis. *Prenat Diagn* 1991;11:405-410
- Meizner I, Levy A, Carmi R, Robinsin C. Niemann-Pick disease associated with nonimmune hydrops fetalis. *Am J Obstet Gynecol* 1990;163:128-129
- Singer HS, Schafer IA. Clinical and Enzymatic Variations in GM1 Generalized Gangliosidosis. *Amer J Hum Genet* 24:454-463, 1972
- Abu-Dalu KI, Tamary H, Livni N, Rivkind AI, Yatziv S. GM1 gangliosidosis presenting as neonatal ascites. *J Pediatr*. 1982 Jun;100(6):940-3.
- Brunetti-Pierri N, Scaglia F. GM1 gangliosidosis: review of clinical, molecular, and therapeutic aspects. *Mol Genet Metab*. 2008 Aug. 94(4):391-6
- Y. Suzuki, A. Oshima, E. Namba. β -Galactosidase deficiency (β -galactosidosis) GM1 gangliosidosis and Morquio B disease. C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle (Eds.), *The Metabolic and Molecular Bases of Inherited Disease*, McGraw-Hill, New York (2001), pp. 3775–3809
- Yamamoto Y, Hake CA, Martin BM, Kretz KA, Ahern-Rindell AJ, Naylor SL, Mudd M, O'Brien JS: Isolation, characterization, and mapping of a human acid beta-galactosidase cDNA. *DNA Cell Biol* 1990, 9:119-127.
- Stocker JT, Dehner LP, Husain AN. Stocker and Dehner's Pediatric Pathology
- Textbook of Clinical Pediatrics Authors: Elzouki, A.Y., Harfi, H.A., Nazer, H., Oh, W., Stapleton, F.B., Whitley, R.
- Fernandes J, Saudubray JM, van den Berghe G, Walter JH (Editors) *Inborn Metabolic Diseases Diagnosis and Treatment Fourth, Revised Edition*
- Muthane U1, Chickabasaviah Y, Kaneski C, Shankar SK, Narayanappa G, Christopher R, Govindappa SS. Clinical features of adult GM1 gangliosidosis: report of three Indian patients and review of 40 cases. *Mov Disord*. 2004 Nov;19(11):1334-41.

17. Warner TG, Robertson AD, Mock AK, Johnson WG, O'Brien JS. Prenatal Diagnosis of GM1 Gangliosidosis by Detection of Galactosyl-Oligosaccharides in Amniotic Fluid with High Performance Liquid Chromatography Am J Hum Genet 35:1034-1041, 1983
18. Caciotti A, Donati MA, Bardelli T, d'Azzo A, Massai G, Luciani L, Zammarchi E, Morrone A. Primary and Secondary Elastin-Binding Protein Defect Leads to Impaired Elastogenesis in Fibroblasts from GM1-Gangliosidosis Patients. Am. J. Pathol. 2005;167:1689–1698
19. Van Gelder CM, Vollebregt AA, Plug I, van der Ploeg AT, Reuser AJ (2012) Treatment options for lysosomal storage disorders: developing insights. Expert OpinPharmacother 13:2281–2299.

Correspondence to:

Marioara Boia
“Victor Babes” University of Medicine and Pharmacy
2 Eftimie Murgu Timisoara, Romania
E-mail: marianoaia@yahoo.com