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Wolman Disease and Liver Transplantation: Case Report

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Abstract

Wolman disease (WD) is an autosomal recessive lysosomal storage disorder, caused by a deficiency of lysosomal acid lipase. Affected infants usually develop abdominal distension, hepatosplenomegaly, steatorrhea, severe malabsorption and malnutrition, and adrenal calcification. Despite treatment attempts, the clinical outcome is poor. We report a case of a 4-month-old girl with WD, presented with a rapidly progressive liver failure and a liver transplantation was performed. The graft was retrieved from her mother. The postoperative period was uneventful. The child was in a satisfactory condition about 8 weeks after surgery and the enzyme replacement therapy (ERT) was started. During the treatment weight loss and vomiting persisted and a diarrhea started. Patient died due to severe respiratory failure seven weeks after starting ERT.

Keywords: Wolman disease; liver transplantation; enzyme replacement therapy.

1. Introduction

Wolman disease is an extremely rare autosomal recessive lysosomal storage disorder, caused by mutations in the *LIPA* gene that maps to chromosome 10q23.2-q23.3 and encodes lysosomal acid lipase (LAL).

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Many mutations of *LIPA* gene have been found in Wolman disease patients and bring about an absence of LAL activity. The deficiency of LAL leads to the accumulation of cholesteryl esters and triglycerides in various tissues and organs. WD is the most severe form of LAL deficiency, a milder form is known as cholesteryl ester storage disease (CESD). A lot of mutations of *LIPA* in CESD allow the expression of significant residual LAL activity. The symptoms of WD appear during the first few months of life. Affected infants usually develop abdominal distension, hepatosplenomegaly, steatorrhea, severe malabsorption and malnutrition, and adrenal calcification. The symptoms get progressively worse and lead to life-threatening complications during infancy including severe anemia, cachexia and liver failure. Despite treatment attempts (enzyme replacement therapy, parenteral nutrition, steroids, dietary supplements, hematopoietic stem cells transplantation, liver transplantation), the clinical outcome is poor [1]. We report a case of a liver transplantation (LT) in a recipient with WD.

2. Case presentation

A female infant, first child of nonconsanguineous parents with no family history, was born at 37 weeks' gestation with birth weight of 2.4 kg and a length of 47 cm. The baby developed frequent episodes of vomiting, failure to thrive, and anemia, accompanied by gradual abdominal distension within the first few weeks of life. At 3 months of age, after consultation with a hematologist, she was referred to Department of Clinical Genetics with a suspicion of a lysosomal storage disease. On admission her weight, height, and head circumference were under the 3rd percentile for age. On physical examination there was pallor, generalized edema and hepatosplenomegaly – liver edge was palpable about 4 cm from the right costal ridge and the spleen was palpable 5 cm below the left costal margin. Initial investigations revealed evidence of liver dysfunction with elevated activity of transaminases, conjugated hyperbilirubinemia, hypoproteinemia, hypoalbuminemia, hypofibrynogenaemia and low serum levels of alpha-1 antitrypsin.

The total cholesterol and triglyceride were normal. Prothrombin time was prolonged with INR of 3.75. The complete blood count result showed microcytic and hypochromic anemia and thrombocytopenia. Serologic tests for cytomegalovirus, human immunodeficiency virus, toxoplasmosis, herpes simplex virus, rubella and hepatitis B and C virus were negative. Elevated plasma chitotriosidase activity of 1830 nmol/ml/h (5-60) was detected, indicating macrophage accumulation. The levels of sphyngomyelinase, beta-glucosidasae, beta-galactosidase and lyso-SM-509 were within normal limits. Echocardiography and transfontanellar ultrasound were unremarkable. Abdominal ultrasonography (US) showed an enlarged liver with increased parenchymal echogenicity, signs of portal hypertension, splenomegaly and mild pelvic ascites. Computed tomography (CT) of the abdomen and pelvis confirmed the previous findings at US, but calcified and symmetrically enlarged adrenal glands were also noted (Fig.1-2).

In view of adrenal calcification and clinical symptoms the diagnosis was narrowed down to WD. For the confirmation of diagnosis, LAL activity in peripheral leukocytes was measured and was found to be 38 nmolMU/h/mg (135-530). DNA sequencing of the *LIPA* gene demonstrated that the patient was homozygous for a known splice site mutation c.822+1G>A. Both parents were heterozygous carriers of the mutation.

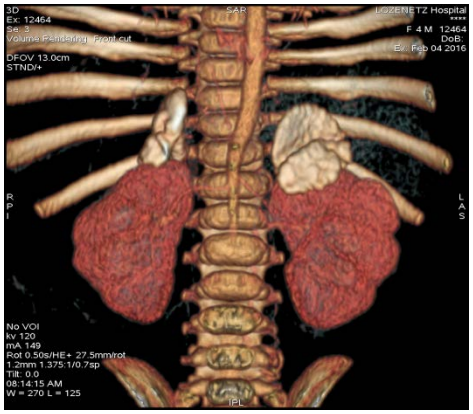

Figure 1: Enlarged adrenal glands with calcificationon CT

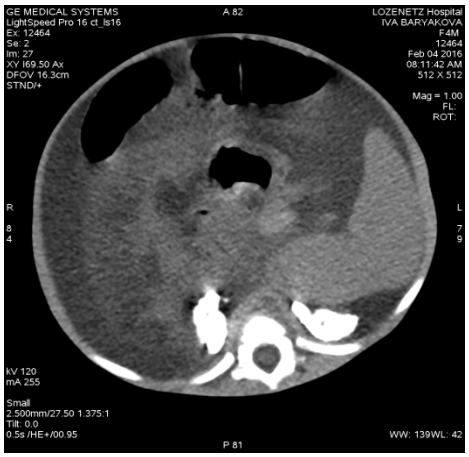

Figure 2: Hepatomegaly and adrenal gland calcification on CT

At 4 month's age the baby had severerapidly progressive hepatic dysfunction and was referred to a transplantation center, where an emergency living donor liver transplantation was performed.

The child received a segment II and III hepatic graft weighing 320 grams from the left lobe of his mother's liver. She was extubated 8 hours later in the intensive care unit. During an uneventful postoperative period, the hepatic function normalized (Table 1). The immunosuppressive regimen was based on Tacrolimus and Methylprednisolone.

Gradually the child improved clinically and was discharged in a satisfactory condition about 8 weeks after surgery and was transferred to Department of Clinical Genetics, where the enzyme replacement therapy with Sebelipase alpha (Kanuma, SynagevaBioPharma Corporation, Lexington, Massachusetts, USA) was started. The starting dose was 1 mg/kg weekly intravenously and was gradually increased to 3 mg/kg weekly due to the lack of a clinical response. During the treatment weight loss and vomiting persisted and a diarrhoea started. Patient died due to severe respiratory failure seven weeks after starting ERT.

Table 1: Chronological changes in laboratory test results

	Before LT	After LT 1st day	After LT 10st day	At discharge
Hemoglobin (g/L)	95	97	92	111
White cell count (/mm³)	4.6	1.0	10.8	9.6
Platelet (/mm³)	82	60	227	312
ALT (IU/L)124	124	268	22	34
AST (IU/L)	222	290	20	42
Alkaline phosphatase (IU/L)	291	46	40	105
T- Bil (mg/dL)	156	47	14	5
D- Bil (mg/dL)	97	26.2	6.4	2.8
GGT (IU/L)	45	30	19	20
Total Protein (g/L)	62.5	40	45	43
Albumin (g/L)	32	25	33	24
PT (sec)	41.3	19	16	25.7
INR	3.63	1.86	1.37	2.1

ALT alanine transaminase, *AST* aspartate transaminase, *T-Bil* total bilirubin, *D-Bil* direct bilirubin, *GGT* gamma-glutamyl transferase, *PT* prothrombin time, *INR* international normalized ratio

3. Discussion

WD is a progressive disorder and usually it is fatal. It leads to a death before 1 year of age. The symptoms are apparent within the first months postpartum. Current management of LAL deficiency (LALD) focuses on lipid control and improvement of liver complications. The nutritional support and the blood transfusions are included in the supportive intervention. Corticosteroid and mineralocorticoid replacement is indicated in the presence of adrenal insufficiency.

ERT has proven effective and now is the treatment of choice for patients with lysosomal storage disorders without central nervous system involvement [2]. The orphan drug Kanuma (sebelipase alfa) was approved by the U.S. Food and Drug Administration (FDA) in December, 2015 for the treatment of LALD (WD and CESD). Data from clinical trials showed that the recombinant human LAL enzyme significantly reduced liver volume, lipid and transaminase levels [3]. Hematopoietic stem cell transplantation (HSCT) has had mixed results [4]. The LT can be considered for individuals who progress to cirrhosis and liver failure and requires further study. There are only several reports of LT in patients with LALD [1,5,6,7,8]. Ambler and his colleagues present the first published case of successful LT in an adult with CESD, with excellent liver function and a normal lipid profile 2 years later [9]. Simon J. and his colleagues confirm that the clinical outcome is poor for infants with LALD, despite variations in treatment attempts (HSCT and LT) [1].

In our case, because of the rapidly progressive, life-threatening liver failure and an impossibility to start ERT

immediately after diagnosis establishment (for administrative and financial reasons), living donor liver transplantation has been performed. It was successful, but LALD persisted in other tissues after the procedure and the outcome was poor. The cause of death was the progression of WD. It is incorrectly to comment the results from ERT in our patient because the laboratory markers (lipids and transaminases) were in normal range at the beginning of ERT and because the period of treatment was very short. Very early onset within the first few weeks of life and an aggressive course of disease in our case were additional unfavorable factors. All patients included in clinical trials were with milder presentation [3].

4. Conclusion

LT was a life-saving treatment rather than a cure for WD. WD is a progressive disorder and perhaps the response to ERT is influenced by the severity of the phenotype at treatment initiation.

Conflict of Interest

The authors declare no conflict of interest

References

[1]. S. Jones, V. Valayannopoulos, E. Schneider, S. Eckert, M. Banikazemi, M. Bialer et al**. "**Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants" Genetics in Medicine, vol. 18, pp. 452-458, 2016

[2]. R. Desnick, E. Schuchman "Enzyme replacement therapy for lysosomal diseases: lessons from 20 years of experience and remaining challenges" Annual Review of Genomics and Human Genetics, vol. 13, pp. 307-335, 2012

[3]. V. Valayannopoulos, V. Malinova, T. Honzík, M. Balwani, C. Breen, P. Deegan et al. "Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency" *Journal of Hepatology*, vol. 61, pp. 1135-1142, 2014

[4]. A. Yanir, M. Allatif, M. Weintraub, P. Stepensky "Unfavorable outcome of hematopoietic stem cell transplantation in two siblings with Wolman disease due to graft failure and hepatic complications" Molecular Genetics and Metabolism, vol. 109, pp. 224-226, 2013

[5]. B. Burton, N. Silliman, S. Marulkar "Progression of liver disease in children and adults with lysosomal acid lipase deficiency" Current Medical Research and Opinion, vol. 33, pp. 1211-1214, 2017

[6]. J. Arterburn, W. Lee, R. Wood, B. Shaw, R. Markin "Orthotopic liver transplantation for cholesteryl ester storage disease" Journal of *Clinical Gastroenterology*, vol. 3, pp. 482-485, 1991

[7]. G. Ferry, H. Whisennand, M. Finegold, E. Alpert, A. Glombicki "Liver transplantation for cholesteryl ester storage disease" Journal of *Pediatric Gastroenterology* and *Nutrition*, vol. 12, pp. 376-378, 1991

[8]. L. Leone, P. Ippoliti, R. Antonicelli, F. Balli, B. Gridelli "Treatment and liver transplantation for cholesterol ester storage disease" Journal of *Pediatrics*, vol. 127, pp. 509-510, 1995

[9]. G. Ambler, M. Hoare, R. Brais, A. Shaw, A. Butler, P. Flynn, et al. "Orthotopic Liver Transplantation in an Adult with Cholesterol Ester Storage Disease" Journal of Inherited Metabolic Disease, vol. 8, pp. 41-46, 2013.