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Cholesteryl Ester Storage Disease: Fatal Outcome without Causal Therapy in a Female Patient with the Preventable Sequelae of Progressive Liver Disease after Many Years of Mild Symptoms

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 13
Final Diagnosis: Multiorgan failure as a sequelae of advanced liver disease
Symptoms: A lysosomal enzyme defect • abnormal bilirubin level • abnormal lipid profile • cardiovascular complications • Child-Pugh A/B • cholestasis and/or gallbladder dysfunction • chronic and florid fibroplastic cholecystitis • frequent diarrhoea • greatly elevated hepatic content of cholesteryl esters • hepatic fibrosis • hepatomegaly • hepatosplenomegaly with thrombocytopenia • increasing jaundice • increasing transaminases • Lab-MELD 14 cirrhosis • malabsorption • oesophageal varices (Grade III) • orange-yellow liver • pressure in the right epigastrium • steatorrhoea • symptomatic gallstones • Vitamin D deficiency
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology
Objective: Rare disease
Background: Cholesteryl ester storage disease (CESD), also known as lysosomal acid lipase deficiency (LAL-D), is a rare autosomal-recessive inheritable lysosomal storage disease. Since 2015, a causal treatment with sebelipase alfa, which replaces the missing LAL enzyme, has been approved. We report a fatal course of LAL-D in a female patient.
Case Report: In 1979, CESD was first diagnosed in a 13-year-old female with marked hepatomegaly. At that time, no specific treatment for CESD was available and the spontaneous course of the disease had to be awaited. In 2013, a laparoscopic cholecystectomy for symptomatic gallstones was performed. The patient's CESD had caused a Child-Pugh A/B and Lab-MELD 14 cirrhosis with esophageal varices (grade III), a solitary fundal varix, as well as hepatosplenomegaly with thrombocytopenia. In 2016, the patient was admitted with compensated cirrhosis and splenomegaly for a ligation of esophageal varices which was complicated by vomiting of blood followed by severe coagulopathy and hemorrhagic shock. The dried blood test showed reduced acid lipase (0.03 nmol/spot*3 hours; reference range 0.2–2) and beta-galactosidase (0.08 nmol/spot*21 hours; reference range 0.5–3.2). Then 15 days after the esophageal varices bleed, the patient died due to multiorgan failure as a sequelae of advanced liver disease.
Conclusions: LAL-D should be included in the differential diagnosis of lipid metabolism disorder, hepatomegaly, and non-alcoholic fatty liver disease with fibrosis or cirrhosis. Causal treatment with sebelipase alfa should be introduced even in patients who have LAL-D and many years of clinically mild symptoms of this disease to prevent the serious sequelae of cirrhosis or cardiovascular complications.

MeSH Keywords: Fibrosis • Hypercholesterolemia • Liver Cirrhosis • Lysosomal Storage Diseases

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/907755>

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Background

With a prevalence of approximately 1: 40 000 to 1: 3000 000, cholesteryl ester storage disease (CESD) is a rare autosomal-recessive inheritable lysosomal storage disease [1]. The median age of first manifestation is about 6 years (range, 0–42 years) [2]. CESD is due to a deficiency of lysosomal acid lipase and therefore the name “lysosomal acid lipase deficiency” (LAL-D) is commonly used. The term LAL-D also covers Wolman disease, in which there is a complete lack of LAL activity, so that patients die even before the age of 2 years [3]. Without causal treatment, survival times in CESD are highly variable. In addition to fatal outcomes in childhood or adolescence, survival to over 40 years of age has been reported in 10% of published cases [4]. Symptoms observed in patients with LAL-D include abdominal and/or epigastric pain, frequent diarrhea, vomiting, malabsorption, cholestasis and/or gallbladder dysfunction, steatorrhea and cardiovascular complications [1,4,5]. Children also suffer from growth retardation.

The pathophysiology of LAL-D leads to the lysosomal accumulation of cholesteryl esters and triglycerides because their hydrolysis to cholesterol and free fatty acids is impaired [4]. LAL-D often becomes apparent through elevated levels of total cholesterol and LDL cholesterol. In addition, HDL cholesterol can be decreased and triglycerides increased [5]. Another characteristic early sign of LAL-D is the increase in transaminases as a sign of liver involvement [2]. The diagnosis of LAL-D can be confirmed or excluded by an enzyme-based blood test (peripheral leukocytes or dried blood).

The treatment approaches tried for LAL-D in former times included parenteral nutrition for malabsorption in infants and a low-cholesterol and low-triglyceride diet. Cholestyramine has been used as drug treatment in an attempt to improve metabolism [5]. On the other hand, statins are considered potentially damaging in patients with LAL-D because, although they reduce plasma LDL cholesterol and triglycerides, they can also potentiate the hepatic production of cholesteryl esters, in that the number of LDL receptors on hepatocytes is increased [4]. Since cirrhosis can develop in the natural course of LAL-D, liver transplantation is a treatment option, which in 2 published cases were undertaken relatively late, i.e., at the age of 43 years [2]. However, the LAL-D persisted after this operation, so that damage to the transplanted organ appears likely [6]. Although hematopoietic stem cell transplantation is potentially curative in patients with LAL-D, the high risks involved, including fatal complications, do not make this a good option [7].

Causal treatment consists of enzyme replacement using sebelipase alfa (KANUMA®), which was approved in 2015. Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) that replaces the missing LAL enzyme activity and thereby

reduces the hepatic fat content and the elevated transaminases usually seen in LAL-D [8,9]. Alanine aminotransferase (ALT) was permanently reduced in 60 out of 61 treated patients (98%) over the course of 78 weeks and normalized in 31 patients (51%) [10]. Due to the mechanism of action, levels of cholesterol and triglycerides can initially increase without further symptoms in the first 2 to 4 weeks of treatment with 1 mg/kg sebelipase alfa every 2 weeks, until normalization of the parameters of lipid metabolism is achieved within another 8 weeks. Reversibility of some of the manifestations of the LAL-D disease (e.g., hepatic fibrosis) by sebelipase alfa is within the realm of possibilities [11]. However, sometimes enzyme replacement therapy or liver transplantation cannot be carried out early enough to prevent a “point of no return”. This is illustrated by the fatal course of a female patient who had suffered from mild symptoms of LAL-D for many years.

Case Report

CESD was first diagnosed in a 13-year-old female in 1979 during the workup for marked hepatomegaly. Laparoscopy and liver biopsy revealed a large and typically orange-yellow liver, greatly elevated hepatic content of cholesteryl esters and a lysosomal enzyme defect in the fibroblast culture. According to the case report on this patient published in 1981, she also suffered from headaches, a feeling of pressure in the right epigastrium and increasing jaundice [12]. Laboratory findings were abnormal for bilirubin (6.0 mg/dL), lipid profile (total cholesterol 316 mg/dL, HDL cholesterol 26 mg/dL, triglycerides 178 mg/dL), α_1 -antitrypsin (363 mg/dL). At that time, as no specific treatment for CESD was available, the spontaneous course of the disease had to be awaited.

In 2013 the patient was hospitalized and underwent a successful laparoscopic cholecystectomy for symptomatic gallstones. Histological examination revealed chronic and florid fibroplastic cholecystitis. By this time, the CESD had led to the development of Child-Pugh A/B and Lab-MELD 14 cirrhosis. There were associated esophageal varices (grade III), a solitary fundal varix and hepatosplenomegaly with thrombocytopenia. Vitamin D deficiency and calcium deficiency were also present. The patient was discharged without medication. In view of the Child-Pugh A/B stage, liver transplantation was not yet an option at this point.

Three years later, in July 2016, the 49-year-old patient was readmitted due to a subjective increase in abdominal circumference, tiredness, scleral jaundice, nausea, pruritus, and lack of appetite. Cirrhosis had now progressed to Child-Pugh C, Lab-MELD score 18. The patient had previously taken increased NSAIDs because of axillary herpes zoster. In addition, hepatic encephalopathy had occurred twice in the preceding months. For 4 months, the patient had been given rifaximin. Esophageal

Table 1. Course of laboratory values.

	First Admission to Hospital (2016)				Transfer to University Hospital (2016)			
	Reference range	July 20	July 29/31	Sept. 5	Reference range	Sept. 6	Sept. 9	Sept 21
White blood cells (nL ⁻¹)	4.4–11.3	2.1	1.6	2.3	3.6–9.2	6.64	2.77	12.55
Hb (g/dL)	12.3–15.3	11.6	10.1	11.3	12.0–15.2	7.5	7.2	8.2
Platelets (nL ⁻¹)	201–379	23	31	26	180–380	47	18	32
INR	0.90–1.25	1.61	2.16	1.67		2.20	1.67	2.56
aPTT (sec)	26.0–40.0	50.9	46.6	49.8	24.4–32.4	78.9	80.8	57.9
Creatinine (mg/dL)	0.5–0.9	0.9	0.7	0.5	0.6–1.1	0.5	0.89	1.74
AST (U/L)	10–35	88	66	91	<35	48	42	105
ALT (U/L)	10–35	72	58	68	<35	38	22	76
AP (U/L)	35–104	117	89	109	25–100	51		
GGT (U/L)	5–39	113	112	96	<35	41	25	47
LDH (U/L)	135–214	244	194	263	120–247	128	145	
Cholinesterase (KU/L)	5.3–12.9		1.7		4.9–11.9	1.0		
Total bilirubin (mg/dL)	0.1–1.2	5.24	3.73	5.09	0.3–1.2	3.6	11.1	20.9
Albumin (g/dL)	3.4–4.8	2.5	2.0	2.6	3.4–4.8	1.0	3.4	2.1
CK (U/L)	26–140	101	61	146*	26–140	35	238	236
Troponin I (ng/L)					≤40	<6	6	129
Myoglobin (μg/L)					<110	48	1.036	2.175
CRP (mg/dL)	<0.5	1.7	6.5	0.9	<0.5	0.5	6.9	8.1

* CK-MB 43 U/L (reference range: 7–25 U/L).

varices and fundal varices were present (in each case treated with Histoacryl®). As well as elevated transaminases and pancytopenia, clotting tests were abnormal (Table 1).

Only 5 days after early discharge at the patient's request, she was readmitted for acute onset of epigastric pain. Due to the rapid improvement in symptoms, she wanted a prompt discharge. Two days later, she was re-hospitalized with a febrile urinary tract infection with *E. coli* (*Escherichia coli*) sepsis that could be treated with parenteral antibiotics.

At the beginning of September 2016, the patient was admitted with compensated cirrhosis and splenomegaly for a currently planned repeat ligature of esophageal varices. The exclusion of relevant fundal varices was initially successful. However, on the following day she vomited blood. The emergency endoscopy with Histoacryl treatment of an esophageal varix in the region of the Z-line stopped the bleeding, at least temporarily. After transfer of the intubated and ventilated

patient to the intensive care ward, she was given an emergency transfusion of erythrocytes and rotational thromboelastometry (ROTEM)-based clotting factor replacement. Although the bleeding could be arrested by the insertion of an esophageal stent and clipping of an acute Forrest Ia bleed in the cardia, severe coagulopathy and hemorrhagic shock developed. Laboratory abnormalities indicated an infection for which antibiotics were given. Appropriate replacement treatment was given for severe hypoalbuminemia. In the context of the coagulopathy, a diffuse nosebleed developed, which was treated by tamponade. Despite clotting factor replacement, it was not possible to stabilize the patient in the further course, and an Hb-relevant diffuse bleeding tendency persisted. The dried blood test on September 9, 2016 showed reduced acid lipase (0.03 nmol/spot*3 hours; reference range 0.2–2) and beta-galactosidase (0.08 nmol/spot*21 hours; reference range 0.5–3.2).

As signs of the death of remaining hepatic tissue, the apoptosis marker M30 and the overall cell death marker M65 [13]

Figure 1. (A) Increasing bilirubin values and (B) cell death markers (M30/M65).

rose on Day 6 (Figure 1). Because of the progressive hepatic decompensation without the possibility of stabilizing the clotting situation, and multiorgan failure, the patient was no longer suitable for a liver transplant. Therefore, after detailed discussion with the relatives, no further escalation of the intensive medical therapy was undertaken. Fifteen days after the esophageal varices bleed, the patient died due to multiorgan failure as a sequelae of advanced liver disease.

Discussion

The 49-year-old female patient with LAL-D died of progressive cirrhosis of the liver. No causal treatment for LAL-D had been given. The LAL-D disease had been stable for a long time. Up to her 5th decade, apart from some residual activity of the LAL-D, the patient was able to lead an almost normal life. However, the fact that over a long period of time the disease caused only a few symptoms, the patient did not recognize the seriousness of the disease and the need for treatment. In the end, liver transplantation was no longer possible and sebelipase alfa treatment at this stage of the disease had no prospect of success.

The cell death markers (M30 and M65) rose slightly due to the death of the few remaining hepatocytes to values of approximately 500 U/L and approximately 1000 U/L, respectively. In contrast, an average of 10 times higher values of these parameters have been measured in acute liver failure [13], which suggests previously intact liver parenchyma, without pre-existing disease in case of an acute liver damage.

In principle, stabilization of the disease picture is possible if sebelipase alfa is given at the stage of hepatic fibrosis. In a placebo-controlled phase 3 study on sebelipase alfa, 32 out of 66 patients underwent a liver biopsy at the start of the study [8]. All these patients had at least fibrosis (Ishak stage ≥ 1) and in

10 patients the biopsy confirmed cirrhosis (Ishak stage 5 or 6). The hepatic fat content was significantly reduced in a group of 36 patients after treatment with sebelipase alfa for 20 weeks (age 4 to 54 years) compared to a placebo group ($n=30$; age 4 to 58 years). After 52 weeks of sebelipase alfa therapy, the fibrosis stage (Ishak score) had improved by 1 ($n=2$) or 2 points ($n=6$) in 8 out of the 12 patients in whom a follow-up biopsy was undertaken [11]. Treatment with sebelipase alfa appears still worthwhile even in patients at the cirrhosis stage.

However, as in the case reported here, a timely causal treatment is sometimes not initiated. On the one hand, this can be due to misdiagnosis (e.g., cryptogenic cirrhosis) and on the other hand there may be a lack of patient compliance or adherence, especially if symptoms are only slight over a long period. In a case of cryptogenic cirrhosis, LAL-D should be considered as a possible cause in both children and adults. A simple enzymatic blood test can confirm or exclude the diagnosis [1,5]. If the suspected diagnosis is confirmed, follow-up investigations can be directed towards known risks and causal treatment and sebelipase alfa can be introduced.

The course of LAL-D is progressive and unforeseeable, but it is probably dependent on residual LAL activity. Clinical and biochemical changes are subtle and generally cause no medical concerns. However, as in the case reported here, clinical deterioration can occur rapidly, rendering prompt management by causal therapy with sebelipase alfa or liver transplantation impossible. In addition, the cardiovascular complications often seen in LAL-D can develop unpredictably. Our patient showed increases in troponin I and myoglobin during the course of intensive medical therapy which, in addition to the sequelae of cirrhosis, suggested that pathological cardiovascular changes were present. Previous evidence showed that even steatosis without elevated liver enzymes has some impact on the development cardiovascular disease [14]. This is because the liver plays a significant role in the development of coronary heart

disease due to essential liver functions involving lipid and glucose metabolism which are mainly regulated by the liver [15].

Conclusions

In summary, fatal outcomes of LAL-D can be avoided by inclusion of this rare inherited disease in the differential diagnosis of lipid metabolism disorder, hepatomegaly, non-alcoholic fatty liver disease with fibrosis or cirrhosis, as well as by the promotion of treatment adherence. Sebelipase alfa should also be introduced in patients with many years of clinically mild

symptoms of LAL-D to prevent the serious sequelae of cirrhosis or cardiovascular complications.

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Conflicts of interest

Ali Canbay has received lecture fees and consultancy fees from Shire, Alexion, Falk-Foundation and Gilead.

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