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Case report

Lysosomal Acid Lipase Deficiency in Libya: A Case Report

Khalid Gashoot[1,2], Muataz Kashbour[3]*, Safa Alfegi[4], Asma Berfad[5]

[1]*Department of Diagnostic Radiology, Tripoli Central Hospital, Tripoli, Libya*
[2]*Department of Radiology, Faculty of Medicine, the University of Tripoli, Tripoli, Libya*
[3]*Department of Diagnostic Radiology, National Cancer Institute, Misrata, Libya*
[4]*Department of Internal Medicine, Tripoli Central Hospital, Tripoli, Libya*
[5]*Department of Gastroenterology, Tripoli Children Hospital, Tripoli, Libya*

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Corresponding Email. *Moutaz.om17@gmail.com*

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ABSTRACT

Lysosomal acid lipase deficiency (LAL) is a rare autosomal recessive disorder caused by mutations in the LIPA gene. Wolman disease (WD) is a severe subtype characterized by almost absence of LAL activity. Patients usually present in infancy with gastrointestinal and hepatic manifestations leading to death within the first year of life if left untreated. We report a case of a Libyan infant boy who presented at 3 months of age with persistent vomiting, diarrhea, poor feeding, and failure to thrive. Investigations revealed hypokalemia, hyponatremia, elevated liver enzymes, and abnormal fat in stool. Abdominal imaging showed hepatosplenomegaly, enlarged lymph nodes, and bilateral adrenal calcification suggestive of WD. His condition deteriorated and he succumbed to complications of hepatic failure. Genetic testing confirmed LIPA gene mutation consistent with WD. In conclusion, this study reports the first case of WD in a Libyan infant. Radiological imaging was crucial in identifying specific features of the disease. Unfortunately, the disease progresses rapidly and often results in fatal outcomes in early childhood, highlighting the limited treatment options available for this rare genetic disorder.

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INTRODUCTION

Lysosomal acid lipase (LAL) deficiency is an autosomal recessive disorder that leads to a reduction in the activity of LAL due to mutations in the LIPA gene. Wolman disease (WD) is a rare and severe subtype of LAL deficiency, characterized by nearly absent LAL activity [1]. The first three sibling cases were documented in 1956 by physician Moshe Wolman [2]. Children with this mutation accumulate cholesteryl esters and triglycerides in various tissues throughout the body resulting in a spectrum of clinical manifestations like failure to thrive and liver damage. These conditions often lead to death within the first six months of life [3].

While the genetic basis of WD is well-established, the clinical presentation can vary widely, making timely diagnosis and intervention challenging. Here we report on an infant with unique clinical features and challenges in diagnosis, with a crucial role played by radiological findings.

Case presentation

A 3-month-old infant boy was brought to the pediatric emergency room by his parents at a secondary healthcare hospital. The child was complaining of persistent vomiting, diarrhea, poor feeding, greasy stool, and failure to gain weight. The patient is the first child of healthy second-degree consanguineous parents and was born full-term via normal vaginal delivery with an unremarkable antenatal history and no family history of note. The parents report a similar symptomatic history of recurring episodes since the baby's neonatal age of 10 days. On physical examination, the patient looked pale but not acutely distressed, feverish (38^{o} C), with an abdominal exam revealing a moderately distended abdomen.

The boy was treated as a case of cow milk protein allergy and prescribed a hypoallergic milk formula. Subsequently, there was a slight improvement in symptoms but a few days later the same symptoms worsened, and the child was admitted to the hospital for dehydration and metabolic disturbance. His weight and height were both below the 0.4th growth centile, 3.600 Kg, and 60 cm, respectively. The abdomen was distended with a flat umbilicus.

The metabolic panel revealed hypokalemia (3.0), hyponatremia (133), hypocalcemia, and elevated Alkaline Phosphatase (678); full blood count showed anemia (6.9) and leukocytosis (12). Stool analysis had multiple bacteria and fat droplets. Abdominal imaging using an ultrasound showed evidence of multiple enlarged mesenteric lymph nodes of homogenous texture at the root of the mesentery, the largest being 2 x 2 cm in diameter.

During his hospital stay, he was provided with supportive management and blood transfusion. Computed tomography (CT) of the chest, abdomen, and pelvis revealed bilateral adrenal gland enlargement with punctate calcifications, hepatosplenomegaly with fatty liver, mild ascites, and enlarged hypodense mesenteric lymph nodes; such findings are suggestive of WD (Figure 1).

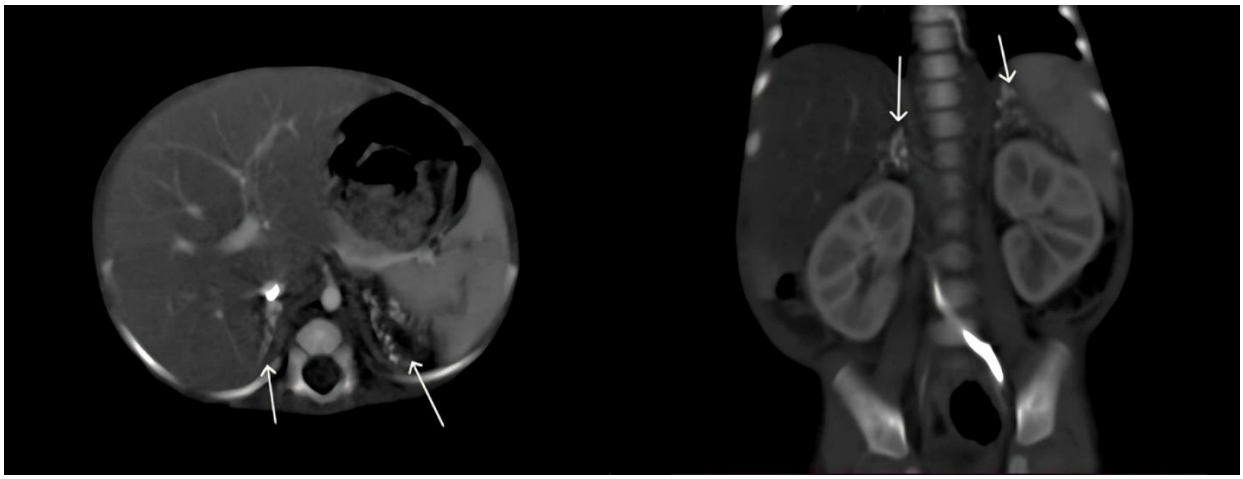

Figure 1. Coronal and axial contrast CT shows bilateral adrenal calcifications and hepatosplenomegaly.

Thereafter, the patient's clinical condition deteriorated and necessitated an immediate transfer to critical care. Upon Pediatric ICU admission he exhibited signs of respiratory distress and a marked increase in abdominal girth. Laboratory workup was in keeping with acute hepatic failure: transaminitis, elevated ALP, hyperbilirubinemia, hypercholesterolemia, and hypertriglyceridemia. Pertinent investigations are shown in table 1.

Table 1. Laboratory results. WBC: white blood cell, Hb: hemoglobin, ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; PT prothrombin time.

Laboratory test	Result
WBC	24.6 x10^{3} /µL
Hb	7 g/dL
Platelets	40 x 10^{3}/µL
PT	32 sec
ALT	182U/L
AST	295U/L
Total bilirubin	15.5 mg/dL
Direct bilirubin	11.7 mg/dL

Despite intense efforts to support the patient's critical condition he collapsed and unfortunately died. A gene expert analysis was done for the parents in search of LIPA gene mutation, the gene responsible for WD. Both parents were heterozygous carriers of the LIPA variant c.398del and genetic testing for the deceased child before his death confirmed the diagnosis of WD. The risk of couples conceiving a child with WD is 1 in 4 (25%).

DISCUSSION

WD is a rare inborn error of metabolism also known as LAL deficiency and is inherited in an autosomal recessive manner [1]. The underlying LIPA gene mutation leads to a deficiency of the enzyme LAL which is responsible for the metabolism of fats in the body. The inability of the body to break down lipids causes their abnormal build-up in various tissues and organs [4]. Specifically, cholesteryl esters and triglycerides type of fats are the metabolites that accumulate [4]. The incidence of WD is estimated to be approximately 1 in 500,000 live births [5].

In WD, lipase activity is either absent or severely deficient (<1% of normal activity), causing symptoms to appear within 2-4 months after birth [5]. Typically, it becomes evident in the first year of life when the child experiences persistent vomiting, diarrhea, failure to thrive, massive hepatosplenomegaly, and eventual hepatic failure. These symptoms are a known triad for the disorder [6]. However, as these presenting features are not unique to WD, patients are often misdiagnosed with other diseases as in our case.

Diagnosing WD is challenging due to the non-specific symptoms and lack of specific laboratory tests. High transaminase levels in the liver are frequently observed and may be accompanied by an increase in total cholesterol and triglycerides with a decrease in HDL levels [1,4]. As the disease progresses, anemia worsens and thrombocytopenia may develop [1,4]. Advanced phases of coagulation abnormalities can also develop. Detailed patient history, including family history, is essential for accurately diagnosing WD.

Imaging plays a crucial in diagnosing WD. Various imaging techniques such as ultrasound, abdominal radiographs, contrast-enhanced abdominal CT scans, and MRI are commonly used. An abdominal x-ray can show calcification of the adrenal glands and an enlarged hepatic shadow [7,8]. The contrast-enhanced abdominal CT scan is the preferred imaging technique for diagnosing the disease as it can reveal an enlarged fatty liver, splenomegaly, and enlarged adrenals with calcification. In our case, the CT scan findings indicated hepatosplenomegaly and bilateral adrenal calcification, which are typical for the disease. [7,9,10].

Currently, there are no clear guidelines for managing patients with WD. Palliative care has been the only available treatment option, which typically involves blood transfusions to address anemia and compensate for adrenal insufficiency [1]. While some cases have been reported where bone marrow transplant has been used to treat the disease, four out of five patients experienced complications related to the treatment, leading to death [1,11].

However, some ongoing studies are currently being conducted to test the effectiveness of recombinant human LAL and enzymatic replacement therapy for LAL deficiency. Sebelipase alfa, one of these therapies, has shown promising results with a 100% survival rate of five WD patients who were followed up for up to ten years. These studies may provide an effective future treatment option. [2,12,13].

CONCLUSION

This report documents the first case of WD in an infant from Libya. WD is a rare genetic disorder that affects the metabolism of fatty substances. It can be difficult to diagnose promptly due to the various symptoms it exhibits. Radiological imaging helped identify hepatosplenomegaly with bilateral adrenal enlargement and cortical calcifications, which are pathognomonic. Unfortunately, the disease progresses rapidly and often proves fatal in early childhood. Treatment options are limited.

Conflict of interest

There are no competing interests of any of the authors, and they have no connection to the industry or organizations.

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نقص في حمض الليباز الليزوزوم في ليبيا: تقرير حالة

خالد قشوط[1،2]، معتز كشبور[3]*، صفاء الفقي[4]، أسماء برفاد[5]

[1]قسم الأشعة التشخيصية، مستشفى طرابلس المركزي، طرابلس، ليبيا
[2]قسم الأشعة، كلية الطب، جامعة طرابلس، طرابلس، ليبيا
[3]قسم الأشعة التشخيصية، المعهد القومي للأورام، مصراتة، ليبيا
[4]قسم الطب الباطني، مستشفى طرابلس المركزي، طرابلس، ليبيا
[5]قسم أمراض الجهاز الهضمي، مستشفى طرابلس للأطفال، طرابلس، ليبيا

المستخلص

نقص الليباز حمض الليزوزومي هو اضطراب جسدي متنحي نادر ناجم عن طفرات في جين. نقص الليباز حمض الليزوزومي مرض ولمان هو نوع فرعي حاد يتميز بغياب نشاط الليباز حمض الليزوزومي تقريبًا. عادة ما يصاب المرضى في مرحلة الطفولة بمظاهر معوية وكبدية تؤدي إلى الوفاة خلال السنة الأولى من العمر إذا تركت دون علاج. قمنا بالإبلاغ عن حالة طفل ليبي رضيع ظهر عند عمر 3 أشهر وهو يعاني من القيء المستمر والإسهال وسوء التغذية وفشل النمو. كشفت التحقيقات عن نقص بوتاسيوم الدم ونقص صوديوم الدم وارتفاع إنزيمات الكبد والدهون غير الطبيعية في البراز. أظهر تصوير البطن تضخم الكبد الطحال، وتضخم الغدد الليمفاوية، وتكلس الغدة الكظرية الثنائي مما يوحي بوجود مرض ولمان .تدهورت حالته وتعرض لمضاعفات الفشل الكبدي. أكدت الاختبارات الجينية طفرة جين نقص الليباز حمض الليزوزومي المتوافقة مع مرض ولمان .في الختام، تشير هذه الدراسة إلى الحالة الأولى لمرض ولمان لدى رضيع ليبي. كان التصوير الإشعاعي حاسما في تحديد السمات المحددة للمرض. ولسوء الحظ، يتطور المرض بسرعة وغالباً ما يؤدي إلى نتائج مميتة في مرحلة الطفولة المبكرة، مما يسلط الضوء على خيارات العلاج المحدودة المتاحة لهذا الاضطراب الوراثي النادر.

الكلمات الدالة. مرض ولمان، نقص الليباز حمض الليزوزومي، التصوير المقطعي بالكمبيوتر، تضخم الكبد الطحال، تقرير الحالة.