Mansour J. Alwadani et al, 2019;2(2):139–142.
https://doi.org/10.24911/JBCGenetics/183-1565654717

CASE REPORT

Case report: Wolman disease in four-month infant, with pathogenic variant G87V in the Jazan region, Saudi Arabia

Mansour J. Alwadani[1*], Ahmed E. Shammakhi[1], Zainab Faraj[2], Magbol Maghfuri, Mohammed A. Mahnashi[2]

ABSTRACT

Background: Wolman disease (WD) severe lysosomal acid lipase is a rare, autosomal recessive lysosomal storage disease caused by the absence or deficiency of lysosomal acid lipase enzyme. This deficiency leads to the accumulation of cholesterol esters and triglycerides in multiple organs of the body. Jazan Region is the second smallest region of Saudi Arabia. It stretches 300 km (190 mi) along the southern Red Sea coast, just north of Yemen. It covers an area of 11,671 km² and has a population of 1,567,547 at the 2017 census. The region has the highest population density in the Kingdom and a high consanguinity marriage rate.

Case Presentation: We report a rare case of WD, misdiagnosed by a surgeon to be pyloric stenosis, treated for a while as renal tubular acidosis, found to have typical WD presentation of malabsorption, hepatosplenomegaly, and adrenal calcification.

Conclusion: This case report is the first report that described the existence of WD in the Jazan region up to date.

Keywords: Wolman disease, lysosomal acid lipase, LAL, adrenal calcification, LIPA gene, Jazan, an inborn error of metabolism, next-generation sequencing, registry.

Introduction

Wolman disease (WD) is an inherited metabolic disorder resulting from the deficiency of lysosomal acid lipase and the accumulation of cholesterol esters and triglycerides in different tissue parts. Lysosomal acid lipase is an essential enzyme that hydrolyzes triglycerides and cholesteryl esters in lysosomes. Mutations in the human Lysosomal acid lipase (LAL) gene cause two distinct phenotypes: WD, a fatal autosomal recessive form, and cholesteryl ester storage disease, which is a benign form of the disease in adults (1,2,3,4). WD usually manifests in the first year of life as failure to thrive, persistent vomiting, hepatosplenomegaly, Calcification of the adrenals, and foamy macrophages (3,5). Jazan Region is the second smallest region of Saudi Arabia. It stretches 300 km (190 mi) along the southern Red Sea coast, just north of Yemen. Surprisingly, it covers an area of 11,671 km² and has a population of 1,567,547 at the 2017 census (6). The region has the highest population density in the Kingdom and a high consanguinity marriage rate (6). We are here reporting such rare case of WD in a 4-month-old infant. She misdiagnosed as pyloric stenosis, renal tubular acidosis, and gastroesophageal reflux. Fortunately, she found to have typical WD findings with; malabsorption, failure to thrive, hepatosplenomegaly, adrenal calcification, decreased lysosomal acid lipase activity and confirmed by identification of previously reported homozygous pathogenic variant in *LIPA* gene (7). This paper is the first report that described the existence of WD in the Jazan region up to date.

Case Report

A 2-month-old full-term female baby product of normal spontaneous vertex delivery with a birth weight of 2,700 grams, length of 48 centimeters, and Apgar score of 9,9,10 at 1, 3, and 5 minutes respectively, born to a young consanguineous couple, who lost previous two daughters at the age of 5 and 3 months, respectively, without known cause or diagnosis (Figure 1. Illustrate Family Pedigree).

Correspondence to: Mansour J. Alwadani
*General Pediatric Department, King Fahad Central Hospital, Jazan. Saudi Arabia.
Email: dr.m.alwadani@gmail.com
Full list of author information is available at the end of the article.
Received: 23 October 2019 | **Accepted:** 27 December 2019

She was discharged the second day from the nursery in good condition. She developed frequent diarrhea and vomiting on the 23rd day; parents seek medical advice in multiple hospitals without reaching the diagnosis. She was admitted on the 30th day by the pediatric surgeon as a suspected case of hypertrophic pyloric stenosis when she presents with a pyloric-like structure palpable in her abdomen. The result of the ultrasound came unremarkable. Therefore, surgeon transfers the care to the pediatrician for diagnostic workup and management. She lost weight and have persistent metabolic acidosis, seen by a nephrologist who started her on sodium bicarbonate and oral potassium with a suspicion of renal tubular acidosis, and started by Gastroenterologist on omeprazole as clinical gastroesophageal reflux then vomiting improved and she was discharged with near outpatient follow up. Then, she missed her follow up, presented to the casualty 2 months later with progressive abdominal distension, jaundice, hepatosplenomegaly, and high-grade fever, which was a new presentation. Her examination revealed weight is 2 kg below third centile, normal length and head circumference irritable, jaundice, not dysmorphic pale, and cachectic infant is having firm and non-tender hepatosplenomegaly (Liver: 6 cm below right costal margin and spleen: 7 cm in long axis) with no lymphadenopathy. Her investigations revealed anemia: hemoglobin 7 g/dl, leukocyte count 13,97 × 10^9/l, Platelet count 188 × 10^9/l. Peripheral blood smear showed normocytic, normochromic red blood cells with reactive neutrophil and leukocytosis. (Figure 2. Histopathology slide). The liver functions were abnormal with elevated liver enzymes: AST—159 U/l (normal range: 5–40 U/l), ALT—28 U/l (normal range: 5–42 U/l). Serum Bilirubin 99 umol/dl (normal range: <21 umol/dl). Serum total protein 61 g/l (normal range: 64–82 g/l) and serum albumin 18 g/l (normal range: 38–50 g/l). Prothrombin time, partial thromboplastin time, and international normalized ratio were within the normal ranges. Lipid profile showed cholesterol 6.2 mmol/l; Triglyceride 5.3 mmol/l. Stool examination, Chest X-ray was normal. An abdominal CT scan showed bilateral adrenal calcifications (Figure 3) with hepatosplenomegaly. We as the metabolic team consulted, WD was highly suspected, enzyme assay of LAL enzyme arranged for her; which done at Hamilton lab and reported with low activity 0.02 nmol/punch/hour (reference range 0.37–2.30) confirm a diagnosis of WD. A targeted next-generation sequencing assay to an inborn error of metabolism was sent through the Saudi diagnostic lab, covering the coding sequence (CDS) and flanking regions of genes. Genomic DNA from leukocytes of this individual was used to build a PCR library of the CDS and flanking sequences of genes in the IEOM panel. Next-Generation-Sequencing resulted in >95% coverage of the targeted regions with an average depth of >150×. Following base calling and mapping variants identified and annotated relative to a reference sequence of target regions derived from GRCh37/hg19. Annotated variants were filtered to remove polymorphic, synonymous, and benign variants based upon public and private databases of sequence variants. Filtered variants were then further curated by expert opinions and reported based upon guidelines of the American College of Medical Genetics for sequence variants. A homozygous missense variant of *LIPA* (*LIPA*:NM_000235:exon4:c.260G>T:p.G87V) identified in her, a previously reported disease-causing mutation in the human gene mutation database and classified as pathogenic. The family counseled, and she was referred to a metabolic center to receive Sebelipase alfa: an enzymatic replacement treatment for lysosomal acid lipase deficiency approved for use in 2015. The patient died at the age of 6 months with secondary hemophagocytic histiocytosis, a known complication of WD.

Discussion

WD has a progressive downhill course, eventually leading to death by 3 to 6 months without treatment. WD

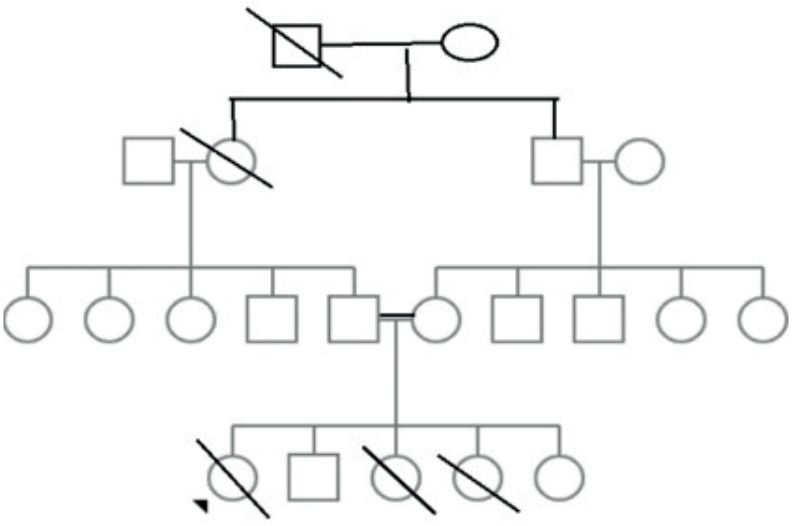

Figure 1. *Pedigree of the patient showing an autosomal recessive pattern.*

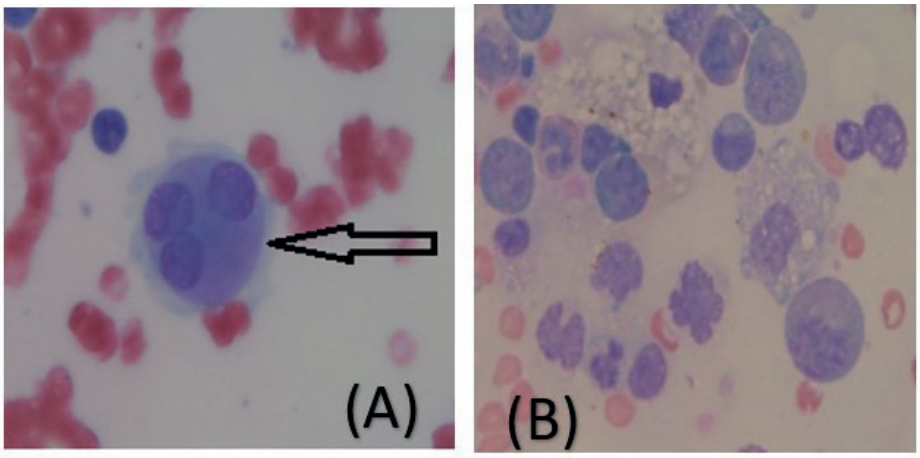

Figure 2. *Bone marrow aspirate revealed foamy macrophages. (A) Showed a single macrophage cell with multiple lipid deposits (arrow), (B) showed many foamy macrophages.*

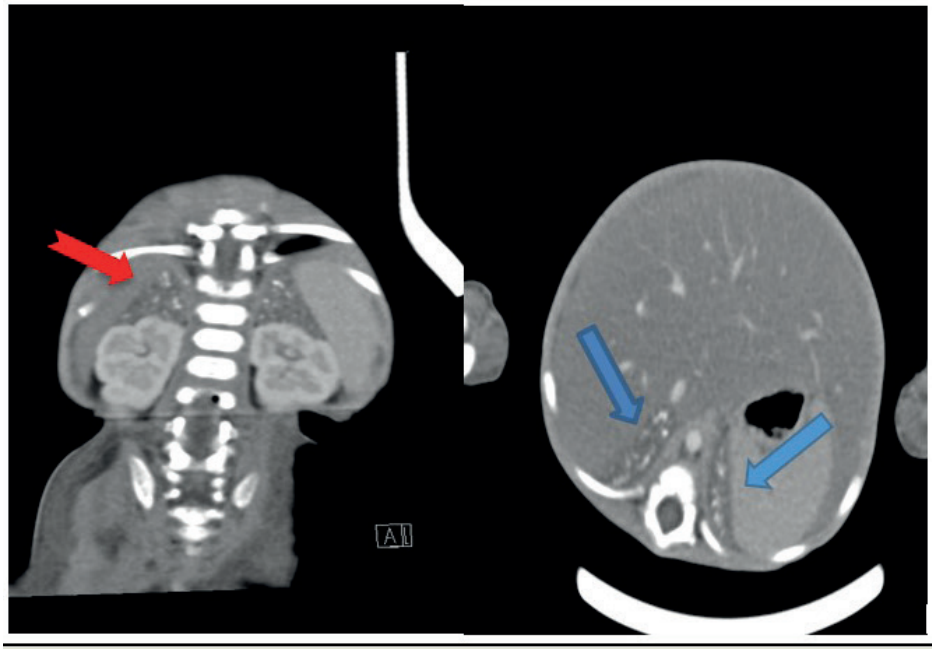

Figure 3. *Coronal and axial view of the abdominal CT scan showing multiple adrenal calcifications (red and blue arrows).*

is one of the rarest diseases with prevalence worldwide has estimated at one in 40,000 to 300,000 (5). Jazan is a southwest region among the government of Saudi Arabia sharing a border with Yemen and with an estimated population to approximately 1,567,547 in 2017 (6), and the high delivery rate yearly reaches 20,000 to 25,000 delivery per year. Consanguineous marriage in the Jazan region is a tradition among tribes. Thus the inborn error of metabolism and recessive disorders is highly prevalent but under-diagnosed due to lack of biochemical and molecular genetic investigational facilities and unavailable disease registry. We believe in the existence of a lot of missed cases resembling our patient's story, and symptomatology awareness needed for rare diseases like our case report.

Conclusion

We have highlighted the hallmark clinical presentations of WD. However, a diagnosis should consider in the evaluation of any child with a significant family history of deaths among young infants with massive splenomegaly. Cautiously, any infant present with either failure to thrive, hepatosplenomegaly, foamy histiocytes, adrenal calcification, or secondary hemophagocytic lymphohistiocytosis considers WD (4).

Funding
None.

Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication
Informed consent was obtained from the parents.

Author details
Mansour J. Alwadani[1], Ahmed E. Shammakhi[1], Zainab Faraj[2], Magbol Maghfuri, Mohammed A. Mahnashi[2]
1. General Pediatric Department, King Fahad Central Hospital, Jazan. Saudi Arabia
2. Clinical Genetic and Metabolic division of General Pediatric Department, King Fahad Central Hospital, Gizan, Saudi Arabia

References

1. Al Essa M, Nounou R, Sakati N, Le Quesne G, Joshi S, Archibald A, et al. Wolman's disease: the King Faisal Specialist Hospital and Research Centre experience. Ann Saudi Med 1998; 18(2):120–4. https://doi.org/10.5144/0256-4947.1998.120
2. Hoffman EP. Barr ML, Giovanni MA, Murray MF. Lysosomal acid lipase deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993 [cited 2019 Nov 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK305870/
3. Ługowska A, Tylki-Szymańska A. Lysosomal acid lipase deficiency: Wolman Disease and Cholesteryl Ester Storage Disease. Int J Clin Rev. 2012; 10. https://doi.org/10.5275/ijcr.2011.11.05
4. Tylki-Szymańska A, Jurecka A. Lysosomal acid lipase deficiency: wolman disease and cholesteryl ester storage disease. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2014; 35(1):99–106.
5. Pericleous M, Kelly C, Wang T, Livingstone C, Ala A. Wolman's disease and cholesteryl ester storage disorder: the phenotypic spectrum of lysosomal acid lipase deficiency. Lancet Gastroenterol Hepatol. 2017; 2(9):670–9. https://doi.org/10.1016/S2468-1253(17)30052-3
6. General Authority for Statistics. Population_characteristics_surveysar.Pdf [cited 2019 Dec 17]. Available from: https://www.stats.gov.sa/sites/default/files/population_characteristics_surveysar.pdf
7. Valles-Ayoub Y, Esfandiarifard S, No D, Sinai P, Khokher Z, Kohan M, et al. Wolman disease (LIPA p.G87V) genotype frequency in people of Iranian-Jewish ancestry. Genet Test Mol Biomarkers. 2011; 15(6):395–8. https://doi.org/10.1089/gtmb.2010.0203