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Case Report

Diagnosis, treatment, and follow-up of a case of Wolman disease with hemophagocytic lymphohistiocytosis

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ABSTRACT

Wolman Disease (WD) is a severe multi-system metabolic disease due to lysosomal acid lipase (LAL) deficiency. We report on a WD infant who developed an unusual hemophagocytic lymphohistiocytosis (HLH) phenotype related to WD treated with sebelipase alfa. A male baby came to our attention at six months of life for respiratory insufficiency and sepsis, abdominal distension, severe hepatosplenomegaly, diarrhea, and severe growth retardation. HLH was diagnosed and treated with intravenous immunoglobulin, steroids, cyclosporine, broad-spectrum antimicrobial therapy, and finally with the anti-IL-6 drug tocilizumab. WD was suspected for the presence of adrenal calcifications and it was confirmed by LAL enzyme activity and by molecular analysis of *LIPA*. Plasma oxysterols cholestan-3β,5α,6β-triol (C-triol), and 7-ketocholesterol (7-KC) were markedly increased. Sebelipase alfa was started with progressive amelioration of biochemical and clinical features. The child died from sepsis, 2 months after sebelipase discontinuation requested by parents. Our case shows the importance of an early diagnosis of WD and confirms the difficulty to reach a diagnosis in the HLH phenotype. Sebelipase alpha is an effective treatment for LAL deficiency, also in children affected by WD. Further data are necessary to confirm the utility of measuring plasma c-triol as a biochemical marker of the disease.

1. Introduction

Lysosomal acid lipase (LAL) (GenBank: NP_ 000226.2) deficiency (LAL-D) (MIM #278000) is a rare (1:40,000 to 1:300,000 live births) autosomal recessive lysosomal storage disorder (LSD) caused by a significant reduction of LAL activity due to biallelic variations of *LIPA* (Chr. 8 10q23.31) (GenBank: NG _008194.1) [1]. LAL is an essential enzyme that plays a crucial role in LDL metabolism as it hydrolyzes triglycerides and cholesteryl esters in lysosomes. LAL-D leads to exaggerated cholesterol synthesis and dyslipidemia despite the extremely high lysosomal accumulation of cholesterol esters in tissues such as the liver, spleen, adrenals, lymph nodes, and small-bowel [1].

Wolman Disease (WD) is a severe multi-system disease that usually manifests in the first two or three months of life due to the rapid accumulation of cholesterol esters and triglycerides in tissues. The majority of symptoms of WD are rather unspecific, whereas, besides hepatosplenomegaly, the hallmarks of the disease are: 1) triangular symmetrically enlarged and calcific adrenal glands; 2) high total serum concentrations of cholesterol, LDL, triglycerides, and low serum concentration of HDL; 3) lymphocytosis in peripheral smear and vacuolated macrophages in bone marrow [1]; 4) elevated serum levels of the oxysterols cholestan-3β,5α,6β-triol (C-triol) and 7-ketocholesterol (7-KC) [2]. Hemophagocytic lymphohistiocytosis (HLH) associated with WD has so far been reported in 15 cases [3–11].

WD's prognosis has always been considered extremely poor because, in past years, the only available treatments were supportive care, and

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liver and/or hematopoietic stem cell transplantation: most children died within the first year of life, and survivors are considered exceptional cases. Since 2015, the use of sebelipase alfa for the treatment of WD has been approved by the authorities by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) [12]. Few reports on the efficacy of sebelipase alfa in WD are available and show promising results in terms of biochemical parameters of liver function improvement, weight gain, and life expectancy [13–15]. To the best of our knowledge, the effect of sebelipase alfa in patients with WD and HLH has been described in only four cases. Here we report on a WD infant presenting splenomegaly at birth, who developed an unusual HLH phenotype related to WD at 6 months of age, that was treated with sebelipase alfa, the recently available enzyme replacement therapy.

2. Case presentation

A male baby, the third son of non-consanguineous parents from Ghana, was born at 38 weeks of gestational age from cesarean section, after a pregnancy complicated by polyhydramnios and gestational diabetes; the family history was unremarkable. Birth weight was 3910 g (97° pc), length 51 cm (78° pc), cranial circumference 35 cm (72° pc). At the first clinical evaluation, splenomegaly was noticed while the baby did not show malformations or dysmorphic features.

He came to our attention at six months of life, transferred from another hospital because of respiratory insufficiency and sepsis associated with abdominal distension due to severe hepatosplenomegaly. The medical history revealed protracted fever (>39 °C), progressive abdominal distension, with hepatomegaly, and worsening splenomegaly (spleen diameter was 7 cm at 2 months of life and increased in the following 30 days to 8.9 cm), failure to thrive (weight below −4 SDS according to WHO Growth charts), and diarrhea. Blood examination revealed marked elevation of AST (1210 U/L; n.v. <60) and ALT (404 U/L; n.v. <45), C reactive protein (CRP), ferritin (>7500 ng/mL; n.v. 24–336) and severe anemia with normal serum bilirubin levels. Interleukin (IL)-6 (38.8 g/mL; n.v. <5.9) and IL-8 (204 pg/mL, n.v. <70) resulted elevated, while tumor necrosis factor (TNF)-alpha, beta IL-1, IL-12p70 and IL-10 were all in normal range. Diagnostic criteria of HLH (5/8 criteria) were fulfilled, according to the diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis published in 2007 [16]. Bone marrow aspirate showed a normal cellular immunophenotype compatible with erythroid hyperplasia. HLH was treated with intravenous immunoglobulin, methylprednisolone, prednisone, cyclosporine, and broad-spectrum antimicrobial therapy. Several platelets and red blood cell transfusions were performed, total parenteral nutrition with vitamin supplementation was early started and maintained due to clinical severe conditions and malnutrition.

After a transient amelioration of general conditions CRP (28.9 mg/dL) and IL-6 (1493 pg/mL) levels remarkably increased and an off-label treatment attempt with the anti-IL-6 drug tocilizumab, at 8 mg/kg, was performed once, resulting in a significant reduction of the inflammatory state. Further diagnostic evaluations were performed including intestinal ultrasonography which showed sufferance with thickening of the valves and cerebroid aspect at the jejunal and ileal level.

During the diagnostic workup, Niemann-Pick disease type A and Gaucher's disease were excluded based on normal sphingomyelinase and beta-glucocerebrosidase activities. Severe primary immunodeficiencies (fHLH, SCID, IPEX, XLP1, XLP2) were excluded through extensive immunological workup, functional immunological tests (perforin expression on NK cells and degranulation test, TRECs, KRECs, T proliferation assay), and molecular analysis (FOXP3, SH2D1A, XIAP genes). Juvenile myelomonocytic leukemia was ruled out by performing GM-CSF hypersensitivity assay. Array – Comparative Genomic Hybridization (CGH-Array) was performed and showed a supernumerary chromosome derived from chromosome 9, inherited from the healthy father, apparently without any clinical significance.

To exclude a hepatic storage disorder, the patient finally underwent an ultrasound-guided needle biopsy of the liver. The histology revealed an ultrastructural framework compatible with non-complex lipid accumulation associated with cholesterol crystals (Fig. 1).

The diagnostic journey came to an end when, in addition to the results of the biopsy of the liver, the direct abdominal X-ray revealed adrenal calcifications (Fig. 2) confirmed by the abdominal US and magnetic resonance imaging (MRI). WD was suspected and confirmed by severely reduced LAL enzyme activity in lymphocytes (< 1%; 1.4 nmoL/mg / 30 min; n.v. 760–1100) and by molecular analysis of *LIPA*, showing a compound heterozygous genotype composed of a novel variation, likely pathogenic and absent in GnomAD database, c.358A > C (pSer120Arg), inherited from the mother and of the known variant c.428 + 1G > T, inherited from the father. Further metabolic investigations showed a marked increase of plasma oxysterols cholestan-3β,5α,6β-triol (C-triol) (665 ng/mL, n.v. <23.6) and of 7-ketocholesterol (7-KC) (536 ng/mL, n.v. <40.1), while at lysosphingolipid analysis, Lyso-SM-509 was only slightly increased 4.78 MoM (multiples of the median; n.v. <4.50).

According to the Italian medicines and healthcare products regulatory agency (AIFA), the patient was eligible for starting enzymatic replacement therapy with sebelipase alfa, which was started at the dose of 1 mg/kg, increased to 2 mg/kg after the first month of therapy. Each infusion was preceded by premedication with methylprednisolone and chlorphenamine. The patient was closely monitored during the infusion, and no side effects were observed. In the first month of therapy with sebelipase alfa, transaminase levels significantly reduced.

During the following months, the patient showed a constant and progressive improvement of clinical, hematological, and biochemical parameters of liver function. Unfortunately, the prolonged hospitalizations at the local facility due to several catheter-related bloodstream infections prompted the parents to request the interruption of sebelipase treatment. We made the parents aware of the deleterious consequences of interrupting sebelipase alfa and finally consented to their request. Since then, the child underwent only supportive treatment and died within two months due to intercurrent sepsis.

3. Discussion

Our case shows that WD, along with other treatable metabolic diseases, should be considered in the diagnostic workup of splenomegaly diagnosed at birth for an early diagnosis and treatment. HLH features could have been misleading in suspecting WD, that was not immediately considered due to the extreme rarity of the disease association (15 WD cases with HLH have been reported at today) (Table 2), the relatively slight elevation of total cholesterol levels, the negative bone marrow aspirate, and the lack of visualization of the adrenal calcification at the abdominal US [3–11]. Most probably due to the diagnostic delay, our patient developed severe HLH features.

The oxysterols measurement represented in our case a useful diagnostic tool, with an interesting application during the follow-up. We are aware that this biochemical evaluation is not always feasible and in our case, it was obtained only thanks to the collaboration with a research laboratory. An alternative strategy for suspected lysosomal storage disorders, starting with targeted Next-Generation Sequencing panels or Whole-Exome Sequencing followed by a complete biochemical characterization could have accelerated the diagnosis and shortened the period between the onset of symptoms and diagnosis [17,18].

The pathophysiology of secondary HLH in WD has not been fully elucidated, and some authors suggested that cholesteryl ester crystals may induce inflammasome activation in macrophages playing a causative role [7]. It has recently highlighted the significant contribution of oxysterols as an easy and cost-saving screening tool in the differential diagnosis of the inherited errors of cholesterol metabolism that cause infantile cholestasis similar to WD, as Niemann Pick C, acid sphingomyelinase deficiency (Niemann-Pick disease type A/B), Smith-Lemli-Opitz syndrome, and cerebrotendineous xanthomatosis [20]. Our WD

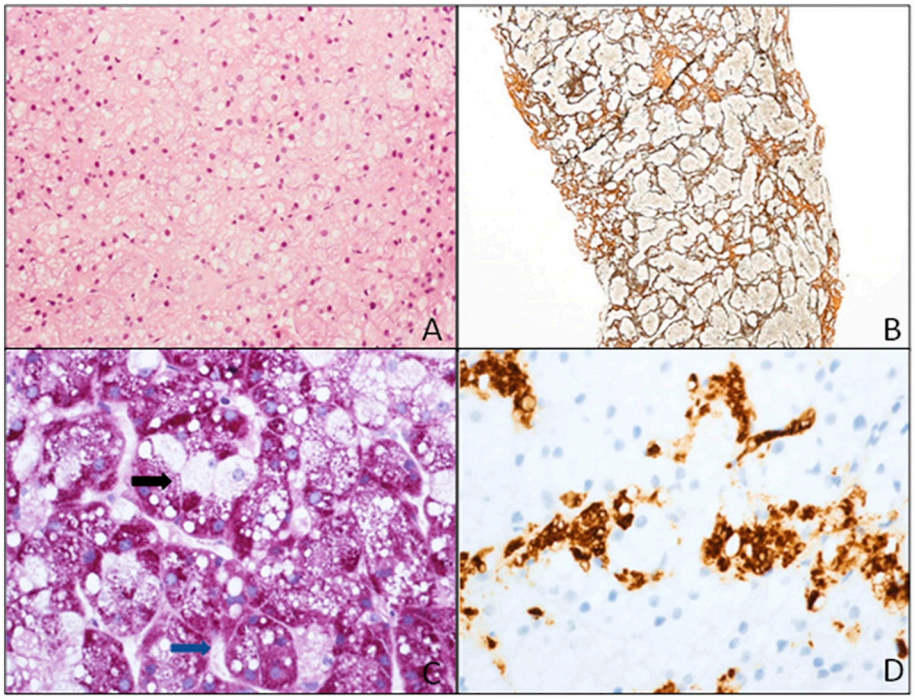

Fig. 1. Liver histology results: non-complex lipid accumulation associated with cholesterol crystals. (A) Hematoxylin and eosin staining illustrate a mixed pattern of hepatocytes with microvesicular steatosis and foamy Kupffer cells (histiocytes) (20×). (B) Reticulin stain showing the lobular and portal tract fibrosis (10×). (C) Periodic acid–Schiff staining showing pale Kupffer cells with vacuolated cytoplasm (black arrow) and hepatocytes containing lipid vacuoles (blue arrow) (40×). (D) CD68 immunohistochemical staining demonstrating Kupffer cells with lipid deposits and needle-shaped crystals of cholesterol (40×).

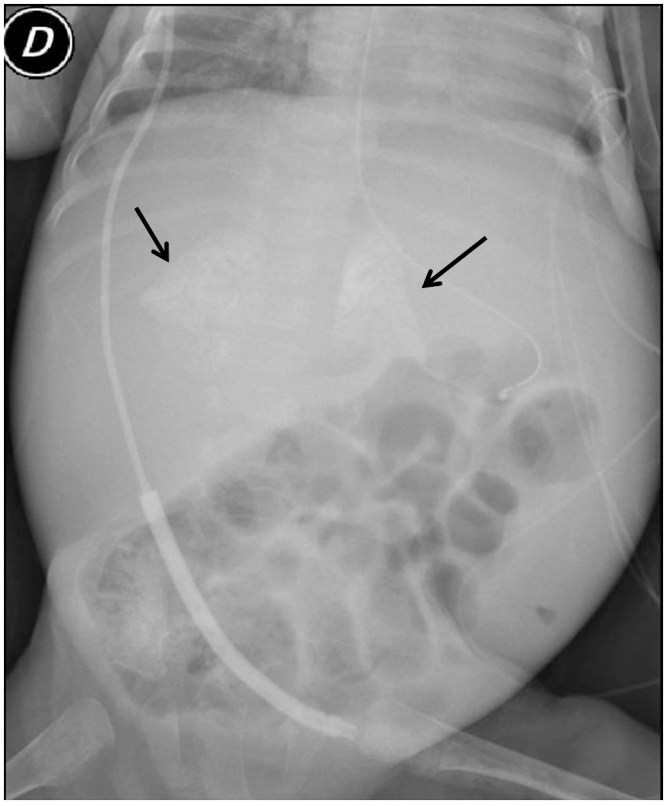

Fig. 2. Abdominal X-ray with calcific adrenal glands (arrows).

patient's oxysterol levels were markedly higher than in the reported LAL-D patients with CESD, probably as a result of a more severe disease phenotype [2]. We are convinced that our patient significantly reduced the oxysterol levels after several sebelipase alfa infusions. This substantially contributed to the persistent reduction and normalization of the CRP levels. This concept is in line with the hypothesis of Taurisano et al. that postulated the possible correlation of cholesterol esters with the exaggerated immune response and an interleukine storm of HLH in WD patients [7]. This is also in line with the results of Potter et al. who recently described five WD patients, two out of them with HLH phenotype, who showed elevated C-triol levels at diagnosis that reduced within a few months after the start of sebelipase alfa [19].

The pro-inflammatory role of oxysterols has been confirmed in recent studies showing their potential pathogenic role in intestinal inflammatory diseases [20]. Oxysterols may play a key role in WD's pathogenesis, at least in determining the onset of hyper inflammation and intestinal damage. Accordingly, they could be used to monitor the treatment with sebelipase alfa. In our case, the evaluation of oxysterols represented an interesting and helpful opportunity that was made possible only thanks to the collaboration with a specialized laboratory of inborn errors of metabolism.

It has been demonstrated that enzymatic activity does not fully predict WD's phenotype, and a strict genotype/phenotype correlation is possible only in most severe cases with homozygosity for loss of function mutations [1].

Whether WD with HLH could represent an expression of a more severe *LIPA* genotype is challenging to evaluate. The 15 previously reported cases affected by WD with HLH come from different geographical areas (Saudi Arabia, Egypt, Canada, Oman, Italy, Turkey, Portugal, Poland, and Tunisia) (Table 1).

The genotype of our patient (c.358A > C / c.428 + 1G > T) is different from the other reports of WD with associated HLH in which *LIPA* molecular analysis was performed. In Table 1 we reported all described cases with HLH-WD with *LIPA* genotype, treatments, and outcome. In the past years, the only treatments available for children with WD were limited to supportive care and, in some cases, to the liver or hematopoietic stem cell transplantation [21]. Few publications are available on the therapeutic outcome of sebelipase alfa on patients HLH-WD. Santos Silva et al. [10] reported two cases who died after one and six weeks of treatment, respectively. Potter et al. described two patients that received hematopoietic stem cell transplantation (HSCT) after 4 and 3 months from the first infusion of sebelipase alfa respectively: one patient died 5 months after HSCT, the other is still alive and on treatment with sebelipase alfa at the time of the report publication [19]. Our

Table 1
Diagnostic criteria of HLH [16]compared to features of our patient and other 15 HLH-WD cases.

		Our patient	1 [5]	2 [5]	3 [5]	4 [6]	5 [7]	6 [8]	7 [3]	8 [10]	9 [10]	10 [9]	11 [11]	12 [11]	13 [11]	14 [19]	15 [19]
1	Fever	+	+	NA	NA	+	+	+	+	+	−	NA	+	+	+	NA	+
2	Splenomegaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	Cytopenias (≥2 of 3 lineages)	+	+	NA	NA	+	+	+	+	−	+	+	+	+	+	NA	+
	Hemoglobin <90 g/L	+	+	+	+	+	+	+	+	+	+	+	+	+	+	NA	+
	Platelets $<100 \times 10^9$/L	+	+	NA	NA	+	+	+	+	−	+	+	+	+	+	NA	+
	Neutrophils $<1.0 \times 10^9$/L	+	No	NA	NA	−	NA	−	−	−	−	−	−	−	−	NA	+
4	Hypertriglyceridemia or	+	+	+	+	+	+	+	+	+	+	+	+	+	+	NA	NA
	Fibrinogen ≤1.5 g/L	−	NA	NA	NA	+	+	NA	+	−	−	+	NA	+	+	NA	NA
5	Ferritin ≥500 μg/L	+	+	NA	NA	+	+	+	+	+	+	+	+	+	+	NA	NA
6	Low or absent NK cell activity	NA	NA	NA	NA	NA	NA	NA	+	NA	−	NA	NA	NA	NA	NA	NA
7	Soluble CD25 > 2400 U/mL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8	Hemophagocytosis found in bone marrow, lymph nodes or spleen	−	+	NA	NA	+	+	+	−	+	+	NA	+	+	NA	NA	NA

(NA, Not Available)

Table 2
Ethnicity, parents' consanguinity, *LIPA* genotypes, treatments, and outcome of our patient and other HLH-WD cases.

	Geographic origin	Parents consanguinity	*LIPA* genotype	*LIPA* variation(s) pathogenicity	Treatments	Outcome
Present case	Ghana	No	c.358A > C / c.428 + 1G > T	Likely pathogenic/ pathogenic	Tocilizumab 8 mg/kg one infusion only Sebelipase alpha 1 mg/kg/wk. IV for one month then 2 mg/kg /week IV	Died at 17 months
Santos Silva et al. [10]	Poland	Not reported	c.509C > A(p.S103R)/ c.796G > T(p.G266X)	Both pathogenic	Sebelipase alpha 1 mg/kg IV (two weeks), 3 mg/kg IV (two weeks), and 5 mg/kg IV	Died at 6 months
Santos Silva et al. [10]	Portuguese (Roma ethnicity)	Yes (first cousins)	Homozygous c.966 + 2 T > G-intron 9	Likely pathogenic (splice site)	Sebelipase alpha 1 mg/kg (one dose)	Died at 5 months
Küçükçongar Yavaş et al. [8]	Turkey	Yes	Homozygous c.260G > T (p.Gly87Val)	Pathogenic	Supportive treatments	Died at 3 months
Tinsa et al. [3]	Tunisia	Yes	Homozygous c.153C > A (p.Tyr51*)	Likely pathogenic (premature stop codon)	Supportive treatments	Died at 4 months
Alabbas et al. [9]	Saudi Arabia	Yes (first degree)	Homozygous c.(428 + 1_967–1)_(*1_?)del	Deletion of exons 9 and 10, likely pathogenic	Anakinra 10 mg/kg twice per day for 7 days Etoposide 150 mg/m2 (3 doses)	Died at 5 months
Al Essa M et al. [4]	Saudi Arabia	Yes (first cousins)	ND	–	Supportive treatments	Died at 4 months
Perry R et al. [5]	Canada	ND	ND	–	Chemotherapy	NA
Perry R et al. [5]	Canada	ND	ND	–	Allogeneic BMT	NA
Rabah F et al. [6]	Saudi Arabia	Yes (first cousins)	No variations detected	–	Chemotherapy, immunosuppressive	Died at 4 months
Taurisano R et al. [7]	Italy	No	ND	–	Supportive therapy	Died at 5 months
Elsayed et al. [11]	Egypt	Yes (double cousins)	Homozygous G969A (W130X)	Likely pathogenic	NA	Died
Elsayed et al. [11]	Egypt	Yes (double cousins)	Homozygous c.438delC (p.S112X)	Likely pathogenic	NA	NA
Elsayed et al. [11]	Egypt	Yes (first cousins)	Homozygous c.G969A (p. W289X)	Likely pathogenic	NA	NA
Potter et al. [19]	NA	NA	Missense variant. Homozygous	Likely pathogenic	Sebelipase alfa, HCT	Died at 13 months
Potter et al. [19]	NA	NA	c.684delT [p. (Phe22Leufs*13)]/ exon 4 deletion (frameshift)	Likely pathogenic	Sebelipase alfa, omalizumab, HCT	Alive—2 years 8 months old

(NA, Not Available; ND, Not Done)

experience showed that sebelipase alfa treatment was very effective in a young WD child with HLH, highlighting promising results on biochemical parameters of inflammation, on liver function, on disease-associated biomarkers as well as on weight gain, and on life expectancy. To our knowledge, our patient represents the first case of WD with associated HLH who has not been transplanted with hematopoietic stem cells and survived after the first year of life on sebelipase alfa treatment. However our case showed also that the management of a child with WD is extremely complex and as recently reported by Potter et al. [19] the enzymatic replacement therapy (ERT) alone could not be sufficient to allow prolonged survivor for these patients. The combination of ERT with HSCT could represent a more efficacious treatment in WD,however

in our opinion this option still raises some concerns, mainly related to the risks related to HSCT procedures in infants with highly deteriorated clinical conditions and adrenal insufficiency.

4. Conclusions

In conclusion, our case shows the difficulty to reach a correct prompt diagnosis when WD exhibits the HLH phenotype. It seems to confirm that ERT in WD with HLH patients could be considered a life-saving treatment, that probably won't allow "per se" prolonged survivor due to the high complexity of patient's management. It confirms the need to explore the possibility of other therapies associated with ERT able to further improve life expectancy, reduce the need for intensive care and ameliorate the quality of life of WD patients. Further data are necessary to confirm the utility of measuring plasma c-triol as a biochemical marker of the disease in monitoring the efficacy of ERT during follow-up, to more precisely tailor sebelipase alfa treatment. For these reasons WD patients should be early referred to specialized centers where it is possible to start an highly recommended multidisciplinary approach.

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Informed consent statement

Written informed consent has been obtained from the patient's parents to publish this paper.

Declaration of Competing Interest

The authors declare no conflict of interest.

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