

CASE REPORT

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Wolman disease presenting with hemophagocytic lymphohistiocytosis syndrome and a novel *LIPA* gene variant: a case report and review of the literature

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Abstract

Background Wolman disease is a rare disease caused by the absence of functional liposomal acid lipase due to mutations in *LIPA* gene. It presents with organomegaly, malabsorption, and adrenal calcifications. The presentations can resemble hemophagocytic lymphohistiocytosis, the life threatening hyperinflammatory disorder. Since the disease is very rare, clinicians might not think of it when a patient presents with hemophagocytic lymphohistiocytosis, and the opportunity to treat it properly can be lost, thus leading to demise of the child.

Case presentation We present a 4.5-month-old Caucasian boy with fever, icterus, and hepatosplenomegaly who was treated according to presumed hemophagocytic lymphohistiocytosis disease. Wolman disease was diagnosed after the death of the child. There are some case reports in the literature presenting patients with Wolman disease primarily diagnosed as hemophagocytic lymphohistiocytosis, which we discuss in this review. The genetic analysis revealed after his demise was compatible with Wolman disease, introducing a novel mutation in *LIPA* gene: exon 4: NM_001127605: c. G353A (p.G118D), which converts the glycine amino acid to aspartic acid.

Conclusions Considering the similarities in presentation of Wolman disease and hemophagocytic lymphohistiocytosis, the patient's life can be saved if special attention is paid to presenting features of a patient with suspected hemophagocytic lymphohistiocytosis, that is special attention to symptoms, findings on physical exams, laboratory values, and radiologic findings, and the proper treatment is urgently initiated. Reporting the novel mutations of Wolman disease can help geneticists interpret the results of their patients' genetic studies appropriately, leading to correct diagnosis and treatment.

Keywords Wolman disease, Hemophagocytic lymphohistiocytosis, HLH, *LIPA* gene

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Background

Hemophagocytic lymphohistiocytosis (HLH) is a life threatening hyperinflammatory disorder, mostly described in children, but indeed affecting all ages. The pathogenesis is rooted in deregulated immune homeostasis. Uncontrolled proliferation of activated lymphocytes and macrophages poses a dramatic hyperinflammatory response, provoking the symptoms and signs associated with the disorder [1]. Fever, hepatosplenomegaly, pancytopenia, hypertriglyceridemia and/or hypofibrinogenemia, high ferritin, large or absent natural killer (NK) cell activity, and increased amount of soluble CD25 are characteristic features of HLH [2, 3].

HLH is classified as familial and secondary. Primary, congenital, or familial type, mostly described in infants, is caused by mutations in genes such as *PRF1*, *MUNC13-4*, and *STX11*. The secondary type is found to be associated with infections, malignancies, immune deficiencies, rheumatologic diseases, and metabolic diseases, including Gaucher disease, lysinuric protein intolerance, and lysosomal enzyme deficiencies [4]. Primary HLH is basically treated by immune suppression which is provided by steroids and chemotherapy. Cure for the condition might be achieved by allogeneic hematopoietic stem cell transplantation (HSCT). Treatment for secondary HLH should primarily trigger the underlying condition, such as infection. The use of immunosuppressives and chemotherapy might also be helpful. New therapies to target immune system are suggested for both types of HLH. The condition is overall fatal and therapies should be initiated as soon as possible to rescue the patient, if possible [1, 5].

Lysosomal storage disease includes a wide array of disorders originating in a defect in lysosomal enzymes or proteins. This leads to the impotency in degradation of proteins and lipids and their accumulation in different sites, causing presentations of various diseases, such as Niemann–Pick, mucopolysaccharidosis, Pompe, cholesteryl ester storage disease (CESD), and Wolman disease (WD).

WD is rare and appears in less than 1 in 100,000 newborns. It is induced by the absence of functional liposomal acid lipase (LAL), caused by mutations in *LIPA* genes. The disease is characterized by accumulation of foamy lipid droplets in lysosomes of tissues such as liver, spleen, intestine, and lymph nodes. The patient presents with hepatosplenomegaly, failure to thrive, malabsorption, and organ specific symptoms such as hepatic damage. Adrenal calcification signifies a unique picture in WD [6]. Enzyme replacement therapy with sebelipase alfa has made a better prognosis available for patients with WD. HSCT and liver transplantation were suggested to be beneficial before the introduction of enzyme replacement therapy [7].

The clinical picture and laboratory findings of HLH and WD overlap to a large extent and that is why in many cases the definite diagnosis cannot be made until genetic analysis results are announced. If WD is an option when the patient is referred with signs of secondary HLH, prompt treatment with enzyme replacement might result in a higher survival rate. We present a 4.5-month-old boy with fever, icterus, and hepatosplenomegaly, with overlapping features of both HLH and WD, and genetic analysis findings compatible with WD. A few studies are accessible in the literature introducing Wolman patients presented with secondary HLH. We review the data in hope for better understanding WD and how it can be related to or differentiated from HLH.

Case presentation

A 4.5-month-old Caucasian boy was admitted to the hospital with a 2-week history of fever following vaccination and 5 days of jaundice and drowsiness. There was no complaint of vomiting, diarrhea, convulsions or any other neurologic presentations. The parents declared that abdominal distension had been noticeable since birth. He was the only child of first cousins and was born by normal delivery after a 40-week gestation (birth weight: 3750 g, percentile: 61, z score: 0.29; birth height: 51 cm, percentile: 26, z score: -0.65; birth head circumference: 36 cm, percentile: 62, z score: 0.31). Neonatal jaundice was not announced. At 4 months, the infant had weighed 8500 g and by admission he weighed 8000 g.

There was not any significant family history except for leukemia in the patient's maternal uncle who died at the age of 17.

On examination, the patient appeared pale, icteric, and ill and had mild respiratory distress. The abdomen appeared severely distended and enlarged spleen and liver were found by palpation. No rash was observed and no lymphadenopathy could be found.

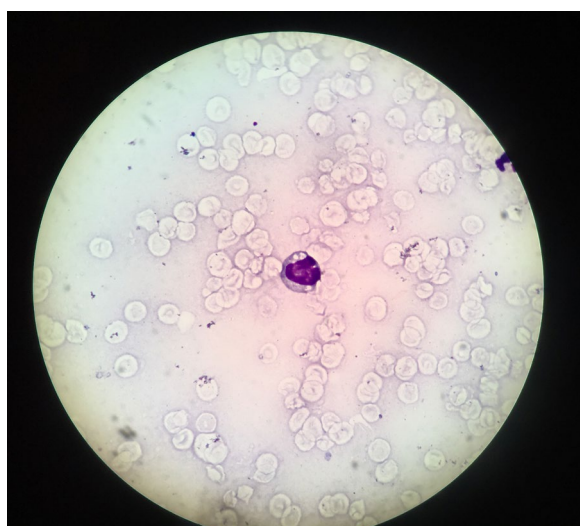
Upon admission the patient had abnormal coagulation tests, elevated liver enzymes, direct hyperbilirubinemia, low albumin, and high ferritin values (Table 1). He was anemic from the beginning, and values of platelet, neutrophils, and lymphocytes that were normal gradually decreased during admission. Figure 1 shows the peripheral blood smear of our patient stained by Romanovski method.

Attempts to find a septic source, including Epstein–Barr virus (EBV) and cytomegalovirus (CMV) polymerase chain reactions (PCRs) and blood culture were unsuccessful. Hypertension was observed and worked up; echocardiography and renal artery sonography were normal. Bone marrow aspiration was nonspecific. Due to primary suspicion of HLH, cyclosporine and dexamethasone were prescribed. Methylprednisolone pulses and

Table 1 Patient laboratory findings on admission and on last check

Laboratory values	On admission	Last check
Hemoglobin(g/l)	7.6	4.6
Platelet ($\times 10^9/l$)	65	19
WBC ($\times 10^6/l$)	7050	820
Neutrophils ($\times 10^6/l$)	3730	10
Triglyceride (mg/dl)	1110	–
Cholesterol (mg/dl)	268	–
Ferritin (ng/ml)	5370	2400
LDH (U/l)	2690	–
PT	35	20
PTT	100	36
AST (U/l)	2930	870
ALT (U/l)	603	320
ALP (U/l)	521	351
Albumin (g/dl)	2.8	2.6
NK cell activity	Not done	Not done
Soluble CD25	Not done	Not done

WBC white blood cells, PT prothrombin time, PTT partial thromboplastin time, AST aspartate transaminase, ALT alanine transaminase, ALP alkaline phosphatase

**Fig. 1** Peripheral blood smear of our patient stained by Romanovsky method showing a lymphocyte with cytoplasmic vacuolation

intravenous immunoglobulin (Ig) were also tried. This treatment is approved by ethics committee of Children's Medical Center, Tehran, Iran. Unfortunately, the patient died with a clinical picture of cardiopulmonary compromise due to hepatic failure 17 days after admission. Results of molecular analysis were ready after the patient had passed away.

Molecular genetics

The whole exome sequencing (WES) process was performed with NovaSeq6000 Paired-end sequencing platform and read length of 150 bp paired-end (PE). The library type was SureSelect V6-Post and the coverage was 100 \times . The analysis of the WES data revealed a novel homozygous mutation in *LIPA* gene exon 4: NM_001127605:c. G353A (p.G118D), which converts the glycine amino acid to aspartic acid (Table 2). The parents' heterozygous status for this variant was confirmed by Sanger sequencing method (Fig. 2).

The sequence analysis by in silico tool Polymorphism Phenotyping (PolyPhen) predicted that this missense mutation is probably damaging with a score of 1.000 (specificity of 100%). The same analysis with Protein Variation Effect Analyzer tools (PROVEAN) predicted a deleterious effect with PROVEAN score of -5.515 (cutoff: -2.5) [8–10].

Search method

We searched PUBMED and SCOPUS for English language sources in April 2020, using the keywords HLH OR hemophagocytic lymphohistiocytosis and Wolman. All the found articles were read and the relevant ones were included. The search was repeated in July 2021 before final edition, and two articles were added to the main reviewed articles.

Discussion and conclusions

In the light of our research in PubMed and SCOPUS for any case presentation of WD resembling manifestations of HLH, we found eight reports (see Tables 3 and 4). Perry *et al.* described three infants in 2001; a brother and sister presented at 49 and 26 days with hepatosplenomegaly, anemia, and elevated liver transaminases and

Table 2 Features of the likely pathogenic variant found in our patient with Wolman disease presenting with HLH

	Gene	Zygoty	Variant	Inheritance	Outcome	MAF	OMIM	dbSNPrsID
Affected child	<i>LIPA</i>	Homozygous	G118D	AR	Likely pathogenic	<0.01	613,497	–
Father	<i>LIPA</i>	Heterozygous	G118D					
Mother	<i>LIPA</i>	Heterozygous	G118D					

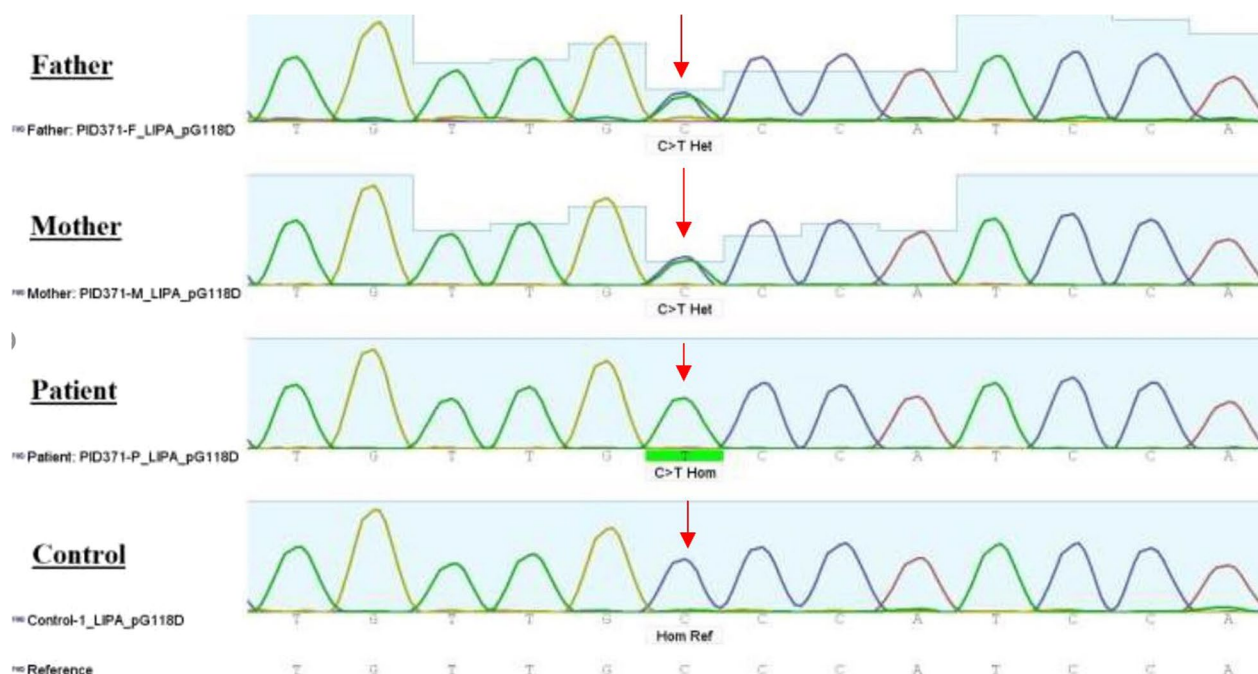


Fig. 2 An electropherogram of father (top), mother (second), patient (third), and control (bottom), demonstrates a mutation (arrow) in exon 4 that results in conversion of amino acid glycine at position 118 to aspartic acid. On the top, the arrow indicates the paternally inherited c.482delA and the arrow in the second row approximates the location of the maternally inherited deletion

Table 3 Comparisons of signs and symptoms in reviewed patients

Author	Sex	Age	Consanguinity	FTT	Fever	Diarrhea	Organomegaly	Death	Genetic variant
Perry et al. (2001) [11]	M (s)	49 days	Yes	-	-	-	Yes	67 days	-
	F (s)	26 days	Yes	-	-	-	Yes	67 days	-
	M	25 days	Yes	-	-	-	Yes	67 days	-
Santos et al. (2018) [4]	M	60 days	Yes	Yes	Yes	-	Yes	5 months	[LIPA] c.966 + 2T > G-intron 9 (in homozygosity)
	F	4 months	-	Yes	No	-	Yes	6 months	LIPA gene (c.509C > A (p.S103R)/c.796G > T (p.G266X),)
Taurisano et al. (2014) [3]	F	4 months	No	Yes	Yes	Yes	Yes	5 months	
Yavas et al. (2015) [13]	F	2 months	-	Yes	Yes	Yes	Yes	3 months	Exon 4 heterozygous location c:260G > T (GGC > GTC), p.Gly87Val
Elsayed et al. (2015) [14]	M	2.5 months	Yes	Yes	Yes	-	Yes	Not known	homozygous G969A (W130X) mutation
	F	3 months	Yes	Yes	Yes	-	Yes	Not known	homozygous c.438delC (p.S112X)
	M	3 months	Yes	Yes	Yes	-	Yes	Not known	c.G969A (p.W289X)
Tinsa et al. [15] (2018)	F	3 months	Yes	Yes	Yes	No	Yes	4 months	exon 3: NM_000235.3: c.153 C > A (p.Tyr51*)
Rabah et al. [16] (2014)	M	2 months	Yes		Yes	-	Yes	3 months	Not found
Alabbas et al. [17] (2021)	M	4 months	Yes	Yes	Yes	-	Yes	4 months	(428 + 1_967-1)(*1_?) del in the LIPA gene (NM_000235.3; chr.10):
Present case (2021)	M	4.5 months	Yes	No	Yes	Yes	Yes	5 months	exon4:c.G353A;p.G118D, CADD: 32

Table 4 Comparisons of laboratory findings in reviewed patients

Author	Ferritin ng/ml	Coagulopathy	Hb (g/l)	platelet ($\times 10^9/l$)	WBC ($\times 10^6/l$)	Neutrophil ($\times 10^6/l$)	BiliT (mg/ dl)	Bili D (mg/dl)	AST (U/l)	ALT (U/l)	LDH (U/l)	Albumin (g/dl)	Fibrinogen (mg/dl)	TG (mg/ dl)	BM Hemophagocytosis
Perry et al. [11]	-	-	Low	-	-	-	-	-	Elevated	Elevated	-	-	-	Elevated	Yes
	-	-	Low	-	-	-	-	-	Elevated	Elevated	-	-	-	Elevated	Yes
Santos et al. [4]	19,867	-	6.3	318,000	-	6120	Elevated	Elevated	299	68	3140	2.9	2.5	785	Yes
	21,577	Yes	8.4	117,000	-	8500	Elevated	Elevated	540	130	3300	1.9	3.18	539	Yes
Taurisano et al. [3]	8900	Yes	7.1	53,000	-	-	19.58	17.32	258	114	2302	2.4	1.24	450	Yes
Yavas et al. [13]	> 1650	-	7.6	92,000	12,000	-	-	-	-	-	-	-	-	361	Yes
Elbayed et al. [14]	2363	-	5	98,000	3800	-	-	-	-	-	1612	-	-	528	Yes
	1664	-	6.9	95,000	5600	-	-	-	78	17	1612	2.2	1.5	-	No
	2543	-	7.8	80,000	10,500	-	-	-	-	-	-	-	2	947	not done
Tinsa et al. [15]	4876	Yes	7.7	51,000	10,200	-	17	-	120	190	1107	-	1.8	308	Yes
Rabah et al. [16]	5600	Yes	6.9	73,000	11,900	-	19	13	38	38	3290	1.8	1.24	1594	Yes
Alabbas et al. [17]	22,683	Yes	6.6	39,000	4600	3200	19	9	670	229	-	3	1.6	-	Yes
Present case	5370	Yes	7.6	656,000	820	10	7.2	5.8	2930	603	2690	2.9	-	1110	-

Hb hemoglobin concentration, WBC white blood cell count, Bili T bilirubin total, Bili D bilirubin direct, AST aspartate transaminase level, ALT alanine transaminase level, TG triglyceride level, BM bone marrow

triglycerides. With a diagnosis of familial erythrophagocytic lymphohistiocytosis, they were treated by chemotherapy and bone marrow transplant, respectively. Autopsy of the second infant revealed accumulation of cholesterol crystals and lipids in many organs, and a hypertrophied and calcified adrenal, leading to the diagnosis of WD following the finding of low acid lipase activity in liver biopsy. The third patient was a 25-day-old boy with hepatosplenomegaly, elevated liver transaminases and adrenal calcification. The patients died at a median age of 67 days [11].

In 2018, Santos *et al.* presented two cases of Wolman disease. The first patient was a 2-month-old boy admitted with hepatosplenomegaly, fever, anemia, elevated liver transaminases, hypertriglyceridemia, and elevated ferritin level. Based on the criteria, the patient was treated according to HLH protocol [12]. Signs and symptoms subsided but recurred after a month. Peripheral blood smear showed lymphocyte cytoplasmic vacuolation and adrenal appeared calcified on X-ray. LAL activity in blood and fibroblasts was low. Later on, molecular PCR analysis revealed [*LIPA*] c.966+2T>G-intron 9 (in homozygosity), compatible with lysosomal acid deficiency. Sebelipase alfa was administered, which caused slight improvement, yet the patient died eventually with multiorgan failure. The second patient was a 4-month-old girl with hepatosplenomegaly, icterus, elevated liver transaminases, severe coagulopathy, hyperferritinemia, hypertriglyceridemia, and hypercholesterolemia. Hemophagocytosis in bone marrow and elevated CD25 were found. HLH therapy made no improvement. Further investigations showed a calcified adrenal and low LAL activity. Although sebelipase alfa was administered as a bridge therapy for HSCT, the patient died of cardiopulmonary compromise due to hepatic insufficiency. Molecular analysis of the *LIPA* gene identified two pathogenic mutations in compound heterozygous state: c.509C>A (p. S103R)/c.796G>T (p. G266X) [4].

Taurisano *et al.* in 2014 discussed a 4-month-old female case with hepatosplenomegaly, icterus, anemia, thrombocytopenia, elevated liver transaminases, and hypertriglyceridemia. Liver biopsy portrayed Kupffer cells with lysosomes containing crystals of cholesteryl esters. Bone marrow aspiration revealed giant histiocytic cells and signs of hemophagocytosis. Reduced LAL confirmed the diagnosis of WD. The patient went through supportive therapies, and died due to respiratory failure when she was 5 months old [3].

Yavas *et al.* reported a 2-month-old girl in 2015 with fever, diarrhea, failure to thrive (FTT), and hepatosplenomegaly. Anemia, thrombocytopenia, elevated liver transaminases and hypertriglyceridemia were also found. Hemophagocytic lymphohistiocytosis was

observed in bone marrow aspiration. She was primarily diagnosed with HLH, then a diagnosis of WD was made because of low LAL activity. The patient died 1 month later, and molecular analysis revealed exon 4 heterozygous variation at the *LIPA* gene, location c:260G>T (GGC>GTC), p. Gly87Val [13].

Elsayed *et al.* in 2015 reported three patients with diagnosis of WD. The first patient was a 2.5-month-old boy with fever, hepatomegaly, anemia, and erythropoiesis in bone marrow aspiration. Hyperferritinemia, hypertriglyceridemia, and high LDH level were also observed. Sequencing of the *LIPA* gene demonstrated homozygous G969A (W130X) mutation which made the diagnosis of WD. The second patient was a 3-month-old girl presented with the same presentations as the first one. Vacuolated macrophages were found in bone marrow aspiration as well as histiocytosis. Sequencing of all coding sequences of the *LIPA* gene revealed homozygous mutation c.438delC (p.S112X) and led to the diagnosis of WD. The third patient, a 3-month-old boy, also with the same presentation and laboratory findings, went through sequencing of *LIPA* gene, which revealed homozygous mutation c. G969A (p. W289X), leading to the diagnosis of WD [14].

Tinsa *et al.* reported a 3-month-old girl in 2018 with fever and hepatosplenomegaly. Laboratory values were consistent with HLH disease. Bone marrow biopsy illustrated abnormal macrophages, but no evidence of hemophagocytosis. Three weeks later, adrenal calcification was found and bone marrow aspiration was repeated, revealing bubble-like cytoplasm in macrophages, compatible with Wolman disease. There was a novel homozygous mutation in *LIPA* gene exon 3: NM_000235.3: c.153 C>A (p. Tyr51*), which interrupted the reading frame by a premature STOP codon and confirmed the diagnosis of Wolman disease. The parents were heterozygous for this mutation [15].

Rabah *et al.* reported a 2-month-old boy in 2014, primarily diagnosed with HLH due to fever, hepatosplenomegaly, icterus, anemia, thrombocytopenia, elevated liver enzymes, hyperferritinemia and hypofibrinogenemia. Soap bubble-like macrophage cytoplasm in addition to hemophagocytosis were observed in bone marrow biopsy. Diagnosis of WD was made by leukocytic cholesteryl esterase assay, and molecular analysis showed no mutation [16].

Alabbas *et al.* reported a male infant in 2021, previously diagnosed with WD, but not treated due to unavailability of medication. He presented with secondary HLH at 4 months. They reported a novel mutation in *LIPA* gene; a deletion/duplication genetic analysis by real-time quantitative PCR (qPCR) confirmed the presence of homozygous deletion c. (428+1_967-1) _ (*1_?)

del in the *LIPA* gene (NM_000235.3; chr.10): (OMIM 613,497) [17].

The discussed patients, including ours, consist of 14 cases. They aged from 25 to 135 days (median 90 days). Consanguinity was reported in nearly all of the cases. Hepatosplenomegaly was observed in all cases and fever was seen in most of them. Laboratory findings included anemia in all patients and thrombocytopenia, elevated liver enzymes, hypoalbuminemia, hypofibrinogenemia, and elevated LDH and triglycerides in most cases. Bone marrow hemophagocytosis was observed in 9 patients and adrenal calcification was reported in 8. Except for one report, which did not point to the patient's survival, all the other patients were dead in less than 2 months from admission. A molecular analysis concordant with Wolman disease was found in 9 patients.

Witeck *et al.* conducted a systematic review in June 2020 in which they included all published articles on WD, finally incorporating 108 articles [18]. According to Witeck's review, the median reported ages of the patients at onset and at diagnosis were 1.5 and 3 years, respectively. The most common clinical presentations were reported as hepatomegaly (93%), splenomegaly (77%), abdominal distension (52%), failure to thrive (66%), diarrhea (51%), vomiting (36%), and jaundice (8.2%). Laboratory values revealed anemia (55%), elevated transaminases (33%), low high-density cholesterol (37%), hypertriglyceridemia (22%), and hypercholesterolemia (8%). By meticulously studying features of patients presenting with HLH and keeping the important differential diagnosis of WD in mind, we can reach the correct diagnosis, which, by leading to initiation of the proper treatment, can save the patient's life.

WD and CESD are two phenotypes of the same disorder in which there is low or absent LAL activity. CESD is presented by hyperlipidemia, atherosclerosis, and hepatic fibrosis, and has lower mortality than WD. CESD patients typically present missense mutations, correlating with some residual enzyme activity (5–10%). The mutation of c.894G.A in exon 8 is the most common mutation found in CESD patients, which comprises more than 50% of all reported variants [19]. Very low or absent LAL activity can be found in WD due to several dozens of mutations in the *LIPA* gene; that is deletions, insertions, and nonsense mutations [20].

The family that we are reporting presents a novel variant, caused by a glycine to aspartic acid substitution within exon 4 of the *LIPA* gene, which is predicted as likely pathogenic. This prediction was made using variant disease and population databases in silico tools (Fig. 3) and segregation analysis (Fig. 2) in the nuclear family and was thus presumed to be the cause of LAL-deficiency in this infant [21]. The literature was sought in regular time intervals and still, no description of this mutation was found.

The original wild-type residue (glycine) and newly introduced mutant residue (aspartic acid) each have their own specific size, charge, and hydrophobicity value. The wild-type residue charge is neutral compared with the negative charge of the mutant residue and is more hydrophobic than the mutant. The mutation imposes a charge which can repulse ligands or other residues with the same charge. The mutant residue is bigger than the wild-type and might lead to the formation of bumps. The torsion angles for this residue are unusual. Only glycine is flexible enough to make these torsion angles and mutation into another residue will

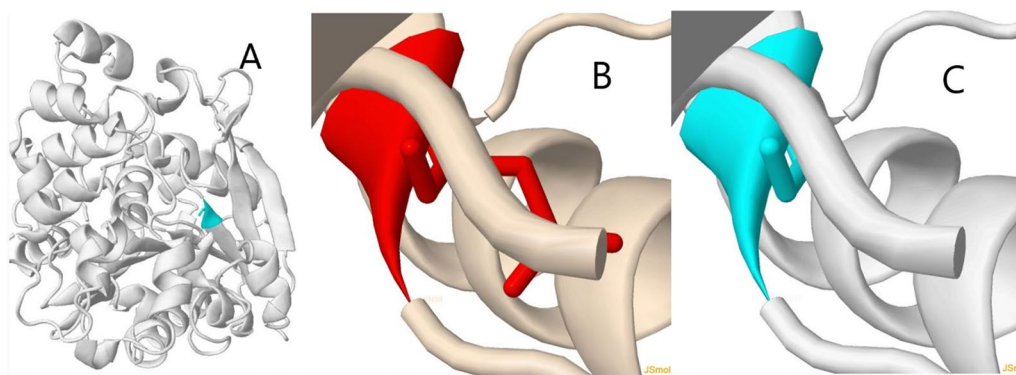


Fig. 3 Three-dimensional illustration of the original *LIPA1* molecule with wild-type glycine residue (A) and a more detailed look inside the *LIPA1* molecule with wild-type (B) and the mutated residue (C). Considering the similarities in presentations of WD and HLH, the patient's life can be saved if special attention is paid to presenting features of a patient with suspected HLH, that is symptoms, findings on physical exams, laboratory values, and radiologic findings, and if the proper treatment is urgently initiated. Reporting the novel mutations of WD can help geneticists interpret the results of their patients' genetic studies appropriately, leading to correct diagnosis and treatment

force the local backbone to change into an incorrect conformation, which will disturb the local structure and impair the protein's function. The original residue is conserved to a large extent, but a few other residue types have also been found at this position. Considering the conservation scores, this mutation can disrupt the protein's function. The mutated residue is placed in a domain that plays a crucial role in the main activity of the protein and mutation of the residue can disrupt this function [21, 22].

In this case report, the causative point mutations result in the substitution of a glycine (the smallest amino acid) residue by a bulkier amino acid (aspartic acid) (Fig. 3). However, a loose correlation between the location of the point mutation along the molecule and disease severity exists for *LIPA1*. Previous research has revealed severely pathogenic and even lethal outcomes for glycine to aspartic acid substitutions within fibrillar collagen genes [23]. In our case, however, we are dealing with an enzyme molecule and not a structural protein; thus, these findings cannot be extrapolated to our case. Finally, we have to bear in mind that the context of the sequence surrounding the substitution, or mutations within special helical domains, significantly influence the effect of particular mutations.

Abbreviations

WD	Wolman disease
HLH	Hemophagocytic lymphohistiocytosis
LAL	Lysosomal acid lipase
HSCT	Hematopoietic stem cell transplantation
NK	Natural killer
CESD	Cholesteryl ester storage disease
PT	Prothrombin time
PTT	Partial thromboplastin time
AST	Aspartate transaminase
ALT	Alanine transaminase
ALP	Alkaline phosphatase
WBC	White blood cells
FTT	Failure to thrive
Hb	Hemoglobin
TG	Triglyceride
BM	Bone marrow
PE	Paired-end

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Author contributions

VZ and KA gathered the patient's data. MS did the genetic analysis. KA did the literature review. KA and AA wrote the discussion. All authors read the draft, edited, and confirmed the data.

Funding

None.

Availability of data and materials

The datasets generated and/or analyzed during the current study include patient's data; that is why they are not published online, but they are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

We obtained the consent of our patient's parents to participate in our case report. It should be noted that the results of the genetic study were available after the patient's demise, and we did not intend to report the case before that. This being said, our research did not have any influence on the course of the treatment. The study adhered to the tenets of Helsinki Declaration, and the ethical committee of our institution, Tehran University of Medical Sciences (TUMS). We used no experimental protocol, and the article was written after the patient's demise.

Consent for publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

There are no competing interests to declare.

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