ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
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Andes pediatr. 2025;96(4):531-536
DOI: 10.32641/andespediatr.v96i4.5544

CLINICAL CASE

A novel homozygous variant in THSD1 causes non-immune hydrops fetalis in a premature infant

Una nueva variante homocigota en THSD1 causa hidropesía fetal no inmune en un lactante prematuro

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Received: December 2, 2024; Approved: April 3, 2025

What do we know about the subject matter of this study?

The spectrum of monogenic causes of hydrops fetalis has been increasing. In 2015, variants in the THSD1 gene were described for the first time as causing non-immune hydrops fetalis.

What does this study contribute to what is already known?

We describe a new homozygous variant in the THSD1 gene, not previously described in the literature, as a cause of non-immune hydrops fetalis in a premature infant, expanding the genotypic spectrum of this entity.

Abstract

Hydrops fetalis is the final stage of several conditions that lead to fluid accumulation in the fetal tissues and body cavities, which can be life-threatening. With the advances and greater access to genome sequencing technologies, the spectrum of monogenic causes of hydrops fetalis has been increasing. **Objective:** To describe the case of an infant diagnosed with non-immune hydrops fetalis who presents a previously undescribed homozygous pathogenic variant in the *THSD1* gene, expanding the genotypic spectrum of this entity. **Clinical Case:** A 31-week premature newborn with hydrops fetalis diagnosed at 19 weeks of gestation, who presented ascites, pleural effusion, bilateral hydrocele, and edema, without chromosomal abnormalities and negative TORCH study. After an emergency cesarean delivery, signs of hypotonia, bradycardia, and cyanosis were observed, with multiple complications such as chylothorax, intestinal perforation, patent ductus arteriosus, and capillary hemangiomas. On physical examination, there were downward and outward slanted palpebral fissures, a depressed nasal bridge, low-set auricles, a globular abdomen, bilateral hydrocele, and midline hemangiomas at the occipital, cervical, and lumbar levels. Whole-exome sequencing revealed a homozygous truncating variant in the *THSD1* gene (c.1009delC:p.Gln337Argfs*73), not previously

Keywords:
Hydrops Fetalis;
Fetal Diseases;
Prenatal Diagnosis;
Ascites;
Exome Sequencing;
THSD1 Protein;
Human

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Edited by:
Luisa Schonhaut Berman

How to cite this article:Andes pediatr. 2025;96(4):531-536. DOI: 10.32641/andespediatr.v96i4.5544

described in the literature. **Conclusions:** Reporting new cases of recently described conditions helps to delimit the phenotype and prognosis of the entity. Although, given the scarcity of reported cases, it is not possible to perform a genotype-phenotype evaluation; these cases indicate that the patient is likely to have a favorable prognosis.

Introduction

The hydrops fetalis (HF) is the last stage of several entities that lead to fluid accumulation in fetal tissues and body cavities. This condition is not a diagnosis in itself but is a symptom of a wide variety of disorders[1]. HF, defined as an abnormal accumulation of fluid in two or more fetal compartments, can be life-threatening to the fetus[2], can be diagnosed by prenatal ultrasound, and is characterized by ascites, pleural effusion, pericardial effusion, or generalized skin edema. In addition, HF may be associated with polyhydramnios and placental edema[3]. Within the etiologies of HF, these can be classified into immune and non-immune, the latter being the most frequent, accounting for 90% of HF cases[1,4]. Among the non-immune causes, cardiovascular, hematological, and chromosomal disorders stand out. With advances and greater access to genome sequencing technologies, the spectrum of monogenic causes of non-immune HF has been expanding[4,5].

In 2015, bi-allelic pathogenic variants in the gene encoding thrombospondin type 1 domain-containing protein 1 (*THSD1*) were described for the first time as causing non-immune HF (OMIM #620244)[6]. To date, 15 cases have been reported of non-immune HF associated with variants in the *THSD1* gene[1,6,7].

The objective of this article is to describe the case of an infant diagnosed with non-immune HF who presents a pathogenic homozygous variant in the *THSD1* gene, not previously described in the literature, broadening the genotypic spectrum of this entity.

Clinical Case

Preterm newborn of 31 weeks of gestation, first child of a non-consanguineous couple. Pregnancy check-ups started at 14 weeks, showing hydrops fetalis from 19-20 weeks. Amniocyte karyotype was normal (46,XY), and TORCH study was negative. At 29 weeks, prenatal and cutaneous edema, ascites, bilateral hydrocele, hypoplastic thorax, and moderate polyhydramnios were observed, leading to an amnioreduction at 30 weeks of gestation.

An emergency cesarean section was performed at 31 weeks due to premature rupture of membranes and breech presentation with hand prolapse. The newborn was delivered after a difficult extraction, with scant amniotic fluid. Physical examination revealed hypotonia, cyanosis, bradycardia, cervical and eyelid edema, bell-shaped chest, significant ascites, bilateral hydrocele, and Apgar scores of 2 and 7 at 1 and 5 minutes, respectively.

Physical examination showed downslanting palpebral fissures, depressed nasal bridge, low-set ears, distended abdomen with diastasis of the rectus abdominis muscles, bilateral hydrocele, and midline hemangiomas at the occipital, cervical, and lumbar levels.

The patient required orotracheal intubation, which improved heart rate. Bilateral thoracentesis and paracentesis were performed, draining 100 ml of citrine fluid. The newborn developed pleural effusion, ascites, and edema that were difficult to manage despite pharmacological treatment and multiple paracenteses. In addition, the patient experienced multiple complications. On the first day of life, chylothorax was diagnosed, requiring pleurodesis with good response. At 24 days of life, the newborn presented with intestinal perforation of unknown cause, not associated with necrotizing enterocolitis, requiring surgical intervention. As part of the systemic workup, an echocardiogram showed a patent ductus arteriosus with hemodynamic significance, which was surgically corrected at 35 days of life.

Due to an episode of poorly characterized paroxysmal events, an electroencephalogram was performed, revealing occasional multifocal interictal epileptiform activity predominantly in the right hemisphere; therefore, phenobarbital treatment was indicated, with good response.

Among the tests performed, the expanded newborn screening was normal (including aminoacidopathies, organic acidurias, β-oxidation defects, congenital adrenal hyperplasia, cystic fibrosis, congenital hypothyroidism, biotinidase deficiency, and classic galactosemia). Brain ultrasound showed bilateral grade II intraventricular hemorrhage and mild lenticulostriate vasculopathy. Brain MRI showed signs of decreased periventricular white matter volume and calcifications, as well as supratentorial ventriculomegaly, without findings suggestive of cavernous hemangiomas.

A postnatal karyotype was performed with normal result (46,XY), followed by molecular analysis with whole-exome sequencing (including copy number

variants, CNVs), which revealed a homozygous variant in the *THSD1* gene (NM_018676.4:c.1009delC:p.Gln337Argfs*73). This variant was classified as pathogenic according to ACMG 2015 criteria [criteria PVS1 (null variant in a gene where loss of function is a known disease mechanism), PM2 (low frequency in population databases), PM3 (variants in trans for a recessive disease)], confirming the diagnosis of non-immune HF associated with the *THSD1* gene.

At two months of age, extubation was achieved, with decreasing oxygen requirements. The patient was transferred from the neonatology service to pediatrics at 4 months of age, with diagnoses of chylothorax, chylous ascites, hydrocele, sucking-swallowing disorder, bronchopulmonary dysplasia, and corrected patent ductus arteriosus.

The patient was reevaluated by the genetics team at 5 months of age, in good general condition, with baseline oxygen requirements via nasal cannula, and feeding through a nasogastric tube due to a swallowing disorder. Physical examination showed persistent ascites and bilateral hydrocele, as well as capillary hemangiomas in the occipital, cervical, and lumbar regions (figure 1).

The patient progressed favorably, feeding orally with good tolerance, allowing removal of the nasogastric tube and gradual reduction of additional oxygen requirements to 0.1 L/min via nasal cannula, and was discharged at 6 months of age.

Discussion

The *THSD1* gene, located on chromosome 13q14.3, encodes the THSD1 protein involved in the complement pathway and extracellular matrix-protein adhesion, and probably plays a role in angiogenesis and maintenance of vascular integrity. It is predominantly expressed in endothelial cells as a cell surface protein that presents an extracellular domain, in the N-terminal region, which contains the thrombospondin 1 domain (340Thr-393Ala), a transmembrane helical domain, and a long intracellular domain in the C-terminal region[1,6] (figure 2).

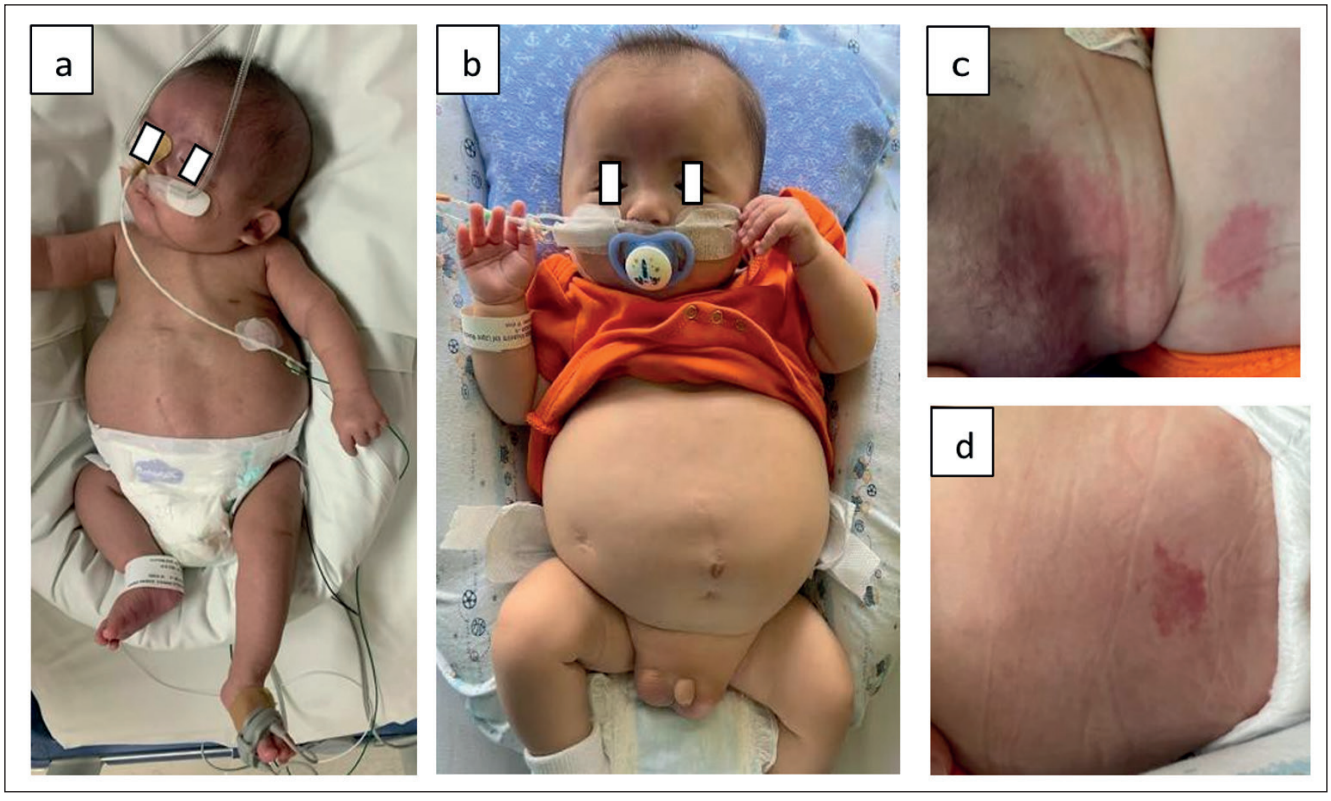

Figure 1. Patient at one month of age **(a)** and at five months of age **(b-d)**. In **(a)** significant ascites and diastasis recti abdominis muscles are observed. In **(b)** facial dysmorphisms such as downslanted palpebral fissures and a depressed nasal bridge are observed. Other alterations include significant ascites and bilateral hydrocele. Three lesions compatible with capillary hemangiomas are observed in the occipital, cervical **(c)**, and lumbar **(d)** regions.

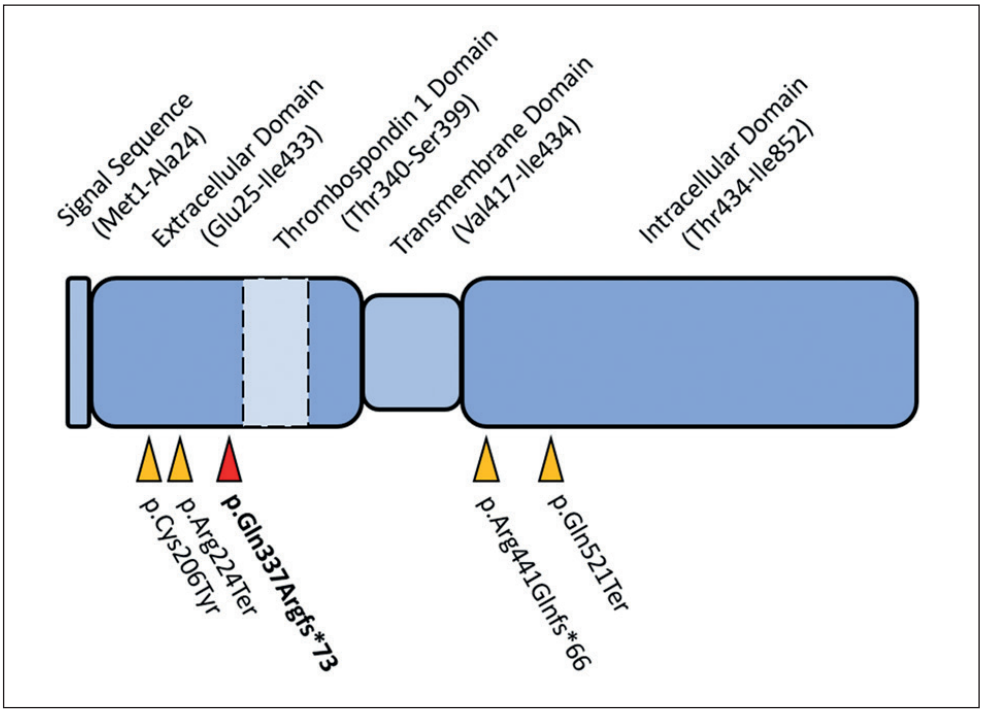

Figure 2. Schematic representation of the THSD1 protein, with the relative location of the pathogenic variants associated with non-immune hydrops fetalis previously described (orange arrows) and the pathogenic variant found in the current case (red arrow).

Loss-of-function variants in the *THSD1* gene give rise to a variety of clinical presentations, ranging from lethal forms with HF to non-immune HF, which manifests prenatally and in early childhood, and usually resolves in late childhood[7]. A series of four families presenting with non-immune HF associated with variants in the *THSD1* gene was reported in 2015[6]. In 2018, a new homozygous variant was reported in four individuals from a consanguineous family, who presented, in addition to non-immune HF, prematurity, congenital heart defects such as atrial septal defect, patent ductus arteriosus, mitral insufficiency, and/or patent foramen ovale, capillary hemangiomas, and mild facial dysmorphisms including prominent forehead, depressed nasal bridge, and hypertelorism[1]. A new truncating variant was reported in 2021 in a patient from a consanguineous family who also presented with prematurity, non-immune HF that resolved at two months of life, congenital heart disease (patent ductus arteriosus, mitral insufficiency), and multiple cavernous hemangiomas[7].

Our patient, as in the previously described cases, presented pre- and postnatal HF, prematurity, congenital heart disease (patent ductus arteriosus), and capillary hemangiomas. Cavernous hemangiomas were ruled out through MRI. Unlike previous cases, the patient presented with feeding difficulties, intestinal perforation, and acute renal failure in the context of volume depletion. Table 1 shows a comparison between our case and those previously described in the literature.

Conclusion

We describe a new homozygous truncating variant in the *THSD1* gene as a cause of non-immune HF. Reporting new cases of recently described pictures helps to delimit their phenotype, as well as to evaluate the prognosis of the entity. Early identification of monogenic causes allows for guiding clinical management and prognosis, as well as providing accurate genetic counseling to families. Although given the scarcity of reported cases, it is not possible to perform a genotype-phenotype correlation, these, together with the patient's progression, indicate that he is likely to have a favorable prognosis.

Table 1. Comparison of our case report with previously reported cases of HF associated with THSD1. All cases reported to date have been homozygous

Case / case series	Current case	Al Rawi et al. (2021)[7]	Abdelrahman et al. (2018)[1]	Shamseldin et al. (2015)[6]	Shamseldin et al. (2015)[6]
Variante	c.1009delC: p.Gln337Arg fs*73	c.1561C>T:p .Gln521Ter	c.1322_1329 delGGCTG GCC:p. Arg4 41Glnfs*66 (4/4)	c.670G>A:p. Arg224Ter (4/4)	c.617G>A:p. Cys206Tyr (6/6)
Consanguinity	No	Yes	Yes	Unknown	Unknown
Gender	Male	Female	1 Female, 3 Male	4 Male	2 Female 4 Male
Pregnancy complications	PHA Preterm 31 weeks	Preterm 25+5 weeks	PHA (2/4) Preterm 33-34 weeks	Unknown	Unknown
Decease	Alive	Alive	Alive	2 alive, 2 deceased	3 alive, 3 deceased
Dysmorphias	Downslanted palpebral fissures. Depressed nasal bridge Low-set ears	Prominent forehead. Depressed nasal bridge. Hypertelorism	Prominent forehead. (2/4) Depressed nasal bridge. (2/4) Hypertelorism (2/4) Long, smooth philtrum (2/4)	Unknown	Unknown
HF signs	Pleural effusion Ascites Hydrocele	Pleural effusion Ascites	Pleural effusion (3/4) Ascites (4/4) Hydrocele (3/4)	Unknown	Unknown
Hemangioma	Yes	Yes, cavernous	Yes (4/4)	Unknown	Unknown
Congenital heart disease	PDA	PDA, ASD, MI	PDA (1/4) PFO (2/4) ASD (2/4) MI (2/4)	Unknown	Unknown

HF: Hidrops fetalis; PHA: Polyhydramnios. PDA: Patent ductus arteriosus. ASD: Atrial septal defect. IM: Mitral insufficiency. FOP: Patent foramen ovale.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References

1. Abdelrahman HA, Al-Shamsi A, John A, et al. A recessive truncating variant in thrombospondin-1 domain containing protein 1 gene THSD1 is the underlying cause of nonimmune hydrops fetalis, congenital cardiac defects, and haemangiomas in four patients from a consanguineous family. Am J Med Genet A. 2018;176(9):1996-2003. doi: 10.1002/ajmg.a.40424.
2. Quinn AM, Valcarcel BN, Makhamreh MM, Al-Kouatly HB, Berger SI. A systematic review of monogenic etiologies of nonimmune hydrops fetalis. Genet Med. 2021;23(1):3-12. doi: 10.1038/s41436-020-00967-0.
3. Society for Maternal-Fetal Medicine (SMFM); Norton ME, Chauhan SP, Dashe JS. Society for maternal-fetal medicine (SMFM) clinical guideline #7: nonimmune hydrops fetalis. Am J Obstet Gynecol. 2015;212(2):127-39. doi: 10.1016/j.ajog.2014.12.018.
4. Bellini C, Donarini G, Paladini D, et al. Etiology of non-immune hydrops fetalis: An update. Am J Med Genet A. 2015;167A(5):1082-8. doi: 10.1002/ajmg.a.36988.
5. Yates CL, Monaghan KG, Copenheaver D, et. al. Whole-exome sequencing on deceased fetuses with ultrasound anomalies: expanding our knowledge of genetic disease during fetal development. Genet Med. 2017;19(10):1171-8. doi: 10.1038/gim.2017.31.
6. Shamseldin HE, Tulbah M, Kurdi W, et al. Identification of embryonic lethal genes in humans by autozygosity mapping and exome sequencing in consanguineous families. Genome Biol. 2015;16(1):116. doi: 10.1186/s13059-015-0681-6.
7. Al Rawi WN, Ibrahim FH, El Nakeib OAS, Al Zidgali FM. Manifestations of thrombospondin type-1 domain-containing protein 1 gene mutation in an extremely premature infant with nonimmune hydrops fetalis. Am J Med Genet A. 2021;185(5):1598-601. doi: 10.1002/ajmg.a.62108.