

Chanarin-Dorfman syndrome treatment with acitretin



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INTRODUCTION

Chanarin-Dorfman syndrome (CDS; OMIM 275630), also known as neutral lipid storage disease with ichthyosis, is an inborn error of lipid metabolism. It is a rare autosomal recessive disorder, with most cases reported in consanguineous families from Turkey, India, the Middle East, and the Mediterranean basin. To date, a total of 147 cases of CDS have been identified.¹

The pathogenesis of CDS is related to the cytoplasmic accumulation of triacylglycerol lipid droplets in the cells of various tissues and systems, including skeletal myocytes, hepatocytes, leukocytes, fibroblasts, and keratinocytes as well as the central nervous system and auditory system.² This syndrome is caused by a mutation of the *ABHD5* gene, also known as *CGI-58*, which encodes an activator of adipose triglyceride lipase, an enzyme catalyzing the first step in the triacylglycerol hydrolysis of cytoplasmic lipid droplets to release free fatty acids. In patients with CDS, there is intracellular accumulation of triglyceride droplets because of the loss of function of adipose triglyceride lipase.³⁻⁵

CASE REPORT

A 3-year-old girl presented to our clinic with features of ichthyosis. Her past medical history revealed an uneventful pregnancy for her mother; the girl was born at full term by spontaneous vaginal delivery, with a collodion membrane. The parents were a nonconsanguineous, healthy Emirati couple. The collodion membrane shed within 3 weeks, revealing generalized erythematous skin with mild

Abbreviation used:

CDS: Chanarin-Dorfman syndrome

thickening and scaling. There were no bullous lesions or erosions. The patient continued to meet normal neurodevelopmental milestones. She did not have recurrent infections, vision abnormalities, hearing defects, hair abnormalities, muscle weakness or ataxia, abdominal distention, or a palpable liver.

Therefore, the primary differential diagnosis included nonsyndromic forms of ichthyosis, such as lamellar ichthyosis and congenital ichthyosiform erythroderma. For further investigation, whole exome sequencing was performed, which revealed a homozygous pathogenic *ABHD5* variant [c.838C>T p.(Arg280*)] that creates a premature stop codon. This result was consistent with CDS, which had not been suspected initially because a collodion membrane is rarely reported in CDS. Only 3 other cases of CDS and collodion membrane have been described in the literature to date.⁶⁻⁸

The attempt to control the symptoms with standard intensive moisturization and alkaline baths was unsatisfactory. Because the patient's baseline liver function was normal, oral therapy was implemented, with 0.5 mg/kg/day of acitretin, with regular complete blood cell count, liver function, and lipid testing. During the acitretin treatment, her skin dramatically and constantly improved (Figs 1-4). Her alanine transaminase levels ranged from 38 to 45 IU/L (normal range <33 IU/L), and her aspartate

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Fig 1. Patient at the age of 3 years. Clinical presentation of the neck treated with topical emollients since birth.



Fig 3. Patient at the age of 3 years. Clinical presentation of the hands treated with topical emollients since birth.



Fig 2. Patient at the age of 6 years. Clinical presentation of the neck after 3 years of systemic acitretin therapy and adjuvant topical emollients.



Fig 4. Patient at the age of 6 years. Clinical presentation of the hands after 3 years of systemic acitretin therapy and adjuvant topical emollients.

transaminase levels ranged from 41 to 50 IU/L (normal range <32 IU/L). Her height was not affected; she was in the 50th percentile for growth (normal for her age).

The patient has regular follow-ups with pediatric gastroenterologists for liver assessment, with ophthalmologists for routine checkups, and with

otolaryngologists for the evacuation of accumulated scales from the ear canal. Per the pediatric assessment, she had no neurologic dysfunction.

DISCUSSION

Because of allelic heterogeneity, the clinical presentation of CDS varies on the basis of the type of underlying mutation. To date, a total of 78 mutations related to CDS have been identified. These include splice-site mutations, insertions, deletions, and

nonsense and missense mutations, with the most frequently observed being c.594insC p.N209X.¹ The most common extracutaneous manifestation was hepatomegaly (60% of the patients), followed by myopathy (59%), ocular manifestation (bilateral ectropion in 29% and cataract in 22%), neurosensory deafness (17%), and splenomegaly (13%).¹ However, irrespective of the type of mutation, all patients with CDS had the typical nonbullous congenital ichthyosiform erythroderma–like phenotype and lipid vacuoles in granulocytes known as Jordan anomaly.⁹

Genetic analysis to identify the variant in the *ABHD5* gene is essential to predict the extent of liver involvement. It serves as a significant prognostic factor for patients with CDS.¹ Our patient was found to have the pathogenic variant c.838C>T p.(Arg280*). This same variant has been reported in 1 Chinese patient and was associated with only mild elevation of liver enzymes. In contrast, other variants have been associated with more pronounced liver dysfunction, manifesting as hepatomegaly, cirrhosis, and fatty liver.^{1,10}

Using topical keratolytic agents with or without systemic retinoids (eg, acitretin) is a standard treatment for any type of ichthyosis.⁹ However, because liver impairment affects most patients with CDS, the use of systemic retinoids still needs specific precautions.

Diet modification is suggested as another treatment option. A diet low in fatty acids along with medium-chain triglyceride supplements may decrease hepatomegaly and normalize hepatic enzymes, especially when initiated early and in combination with vitamin E (10 mg/kg/day) and ursodeoxycholic acid (15–20 mg/kg/day).^{1,11} A patient with neutral lipid storage disease with ichthyosis who was on this diet had a 50% decrease in his liver size by the end of the first year of diet modification and a notable improvement of skin lesions after being on this diet for 5 years.⁷

Unfortunately, our patient did not follow the suggested low–fatty acid diet. However, this gives us the option to reduce or withdraw acitretin in the future, especially when the patient reaches child-bearing age.

CONCLUSION

CDS is a rare condition with a variable clinical presentations and genetic features. To our knowledge, this is the fourth case of CDS associated with collodion membrane reported in the literature. The c.838C>T p.(Arg280*) pathogenic variant detected in our patient has only been previously reported once in the literature.^{1,6–8}

This case emphasizes that CDS should be considered in the differential diagnosis in collodion babies before extracutaneous manifestations appear.

The identification of the genotype is a step toward personalized management. Acitretin should be considered safe for individuals with specific gene variants and those experiencing mild-to-moderate effects on the liver. Diet modification is a promising option as either the sole or an adjuvant therapy.

Conflicts of interest

None disclosed.

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