

Chanarin–Dorfman syndrome: a novel mutation in a Turkish girl

Aysel Ünlüsoy-Aksu, Sinan Sarı, Ödül Eğritaş-Gürkan, Buket Dalgıç

Department of Pediatric Gastroenterology, Hepatology and Nutrition, Gazi University Medical Faculty, Ankara, Turkey.
E-mail: ayselun@gmail.com

Received: 22 July 2014, Accepted: 26 September 2014

SUMMARY: Ünlüsoy-Aksu A, Sarı S, Eğritaş-Gürkan Ö, Dalgıç B. Chanarin–Dorfman syndrome: a novel mutation in a Turkish girl. *Turk J Pediatr* 2015; 57: 300-303.

Chanarin–Dorfman syndrome (CDS) is an autosomal recessive disorder, characterized by intracellular accumulation of lipid droplets in most tissues. It is very difficult to find a correlation between the phenotypic and genotypic features due to the occurrence of novel *ABHD5* [α/β hydrolase domain-containing protein-5; originally called CGI-58 (comparative gene identification-58)] mutations and the fact that there are only a few cases in the literature. The protein encoded by this gene is a cofactor for adipose triglyceride lipase (ATGL), which promotes the catabolism of stored fat. The clinical phenotype involves multiple organs and systems. Ichthyosis, nonbullous congenital ichthyosiform erythroderma and cytoplasmic accumulation of lipid droplets in granulocytes (Jordans' bodies) are always present. Peripheral blood smear is an easy method for diagnosing CDS; its use can also avoid unnecessary further testing. Herein, we report a patient with a homozygous mutation in *ABHD5* that has never previously been described. Moreover, the case was diagnosed as Chanarin–Dorfman syndrome with only a peripheral blood smear.

Key words: Chanarin–Dorfman syndrome, *ABHD5* mutation, Jordan's body.

Chanarin–Dorfman syndrome (CDS) (Online Mendelian Inheritance in Man No. 275630) is one of the non-lysosomal neutral-lipid storage diseases, which are characterized by intracellular accumulation of lipid droplets in most tissues, including the liver, muscles, intestinal mucosa, leukocytes and skin fibroblasts. It is an autosomal recessive disorder. Mutations in the *ABHD5* [α/β -hydrolase domain-containing protein-5; originally called CGI-58 (comparative gene identification-58, UniGene Hs. 19385)] gene, located on chromosome 3p21, are associated with CDS. Herein, we report a patient with a homozygous mutation in CGI-58, c.G413A (p.W138X), which has not previously been described.

Case Report

A 7½-year-old girl was referred to our department for elevated aminotransferase levels and hepatomegaly. She was the fourth child of consanguineous healthy parents; her siblings were also in good health. There was no history

of maternal infection or exposure to drugs, radiation, smoking or alcohol during pregnancy. Her aunt and uncle had been diagnosed with cirrhosis. The patient had been treated in the neonatal unit for 13 days due to colloidan membrane. Scaly skin had been present in the patient since birth. No other family members had presented with a similar eruption. There was no history of any feeding difficulties, vomiting, fever, jaundice, dark-colored urine or clay-colored stools.

Growth and development were normal. Her weight was 21.3 kg (percentile 25-50), and her length, 115.3 cm (percentile 3-10). She had scaly skin. The eyelids showed ectropion, and she had strabismus (Fig. 1). The liver was palpable 8 cm below the costal margin in the midclavicular line and 12 cm below the xiphoid. The spleen was palpable 10 cm below the costal margin in the midclavicular line. She had no ascites, edema, gait abnormality or neurological deficit. Audiological examination revealed mild conductive deafness.

On laboratory investigation, complete blood counts were normal but the peripheral smear showed prominent leukocytic vacuolations (Fig. 2). Liver function tests revealed mildly elevated aspartate aminotransferase (75 IU/L) and alanine aminotransferase (107 IU/L) (normal for both: 0–40 IU/L). Blood lipid profile, coagulation parameters, fasting serum glucose, alkaline phosphatase, gamma-glutamyl transpeptidase, bilirubin, serum albumin, thyroid function tests, renal function parameters, alpha 1 antitrypsin and seruloplasmin levels were within normal ranges. She had elevated creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) levels (CPK: 453 IU/L, normal: 25–175; LDH: 396 IU/L, normal: 110–295). Electromyography (EMG) findings were normal. Viral hepatitis markers (anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV) were all negative. Hematological parameters including serum iron, total iron-binding capacity and ferritin were normal. Cardiomyopathy was not detected. Chest and skeletal X-rays were also



Fig. 1. Appearance of the patient, with ichthyotic skin, strabismus and eyelids showing ectropion.

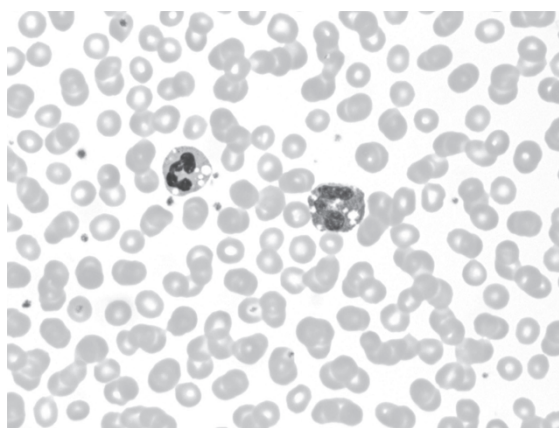


Fig. 2. Peripheral blood smear showing vacuoles in the neutrophils and eosinophils (Jordan's anomaly), original magnification $\times 1000$.

normal. Ultrasound of the abdomen revealed hepatomegaly with increased echotexture suggesting hepatosteatosi, along with mild splenomegaly. Doppler ultrasonography imaging of splenic and major hepatic vessels was normal. Our patient had average mentality, and her IQ and motor development were found normal in psychometric analysis. Upper gastrointestinal endoscopy (UGE) was performed. Liver biopsy revealed diffuse steatosis and fibrosis (Fig. 3). Histopathologic evaluation of duodenal biopsy showed lipid vacuoles in the villi epithelium (Fig. 4). After obtaining informed consent from the parents, we searched for CGI-58 mutation in the patient. To identify the molecular basis of the disease in the proband, we established the entire coding sequence of *ABHD5*. We identified a homozygous G>A transition at position 413 of the cDNA sequence (c.G413A), predicted to result in premature termination of translation due to the substitution of a stop codon for a tryptophan residue at amino acid position 138 (p.W138X).

The patient was put on a low-fat diet containing medium-chain triglycerides, along with ursodeoxycholic acid (20 mg/kg/day) and vitamin E (100 IU/day).

Discussion

In 1966, Rozenszajn described two sisters who had severe ichthyosis and leukocytic vacuoles¹. In the 1970s, Dorfman and Chananin reported clinical manifestations of a syndrome^{2,3}. The higher frequency of this syndrome observed in Middle Eastern and Mediterranean

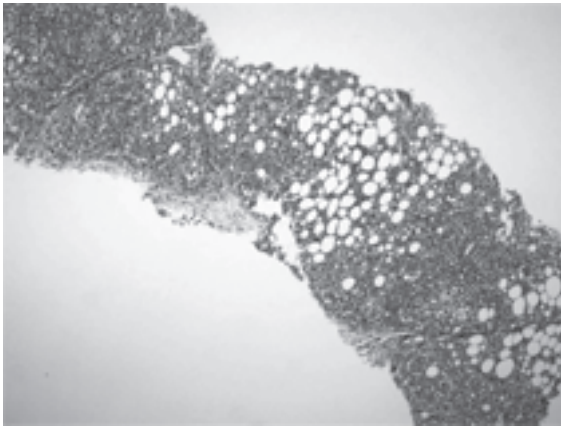


Fig. 3. Photomicrograph of liver biopsy: micronodular cirrhosis with macrovesicular steatosis.

countries may be related to consanguinity. Ichthyosis, nonbullous congenital ichthyosiform erythroderma and cytoplasmic accumulation of lipid droplets in granulocytes (Jordans' bodies) are always present⁴. Lipid droplets may also be seen in keratinocytes and fibroblasts. The clinical phenotype involves multiple organs and systems. Myopathy (skeletal and heart muscle), liver damage, ataxia, neurosensory hearing loss, cataract, nystagmus, strabismus and mental retardation are clinical manifestations⁴. Rarely, eccrine gland vacuolations⁵, renal involvement⁶, rickets⁷, patchy alopecia, elevated triglyceride level, intestinal anomalies⁸, growth retardation, retinal dysfunction, areflexia, hypotonia, proximal muscle weakness, ptosis, cranial nerve involvement, psychiatric disorders, neural tumors of the mediastinum, microcephaly and small ears⁹ have also been reported. The rapid progression of steatohepatitis to cirrhosis has been found to occur in CDS¹⁰. End-stage liver disease and portal hypertension has been described in only 15% of cases¹¹. Neurological involvement is thought to be a delayed finding⁴.

Possible differential diagnoses that may present with vacuolated leukocytes include ichthyotic (multiple sulfatase deficiency, ichthyosis-sclerosing cholangitis syndrome) and degenerative disorders (systemic carnitine deficiency, Refsum disease, Wolman disease). But the presence of congenital ichthyosis with systemic neutral lipid deposition is characteristic of CDS⁶. Peripheral blood smear is an easy method to make a diagnosis of CDS; its use can avoid unnecessary further testing.

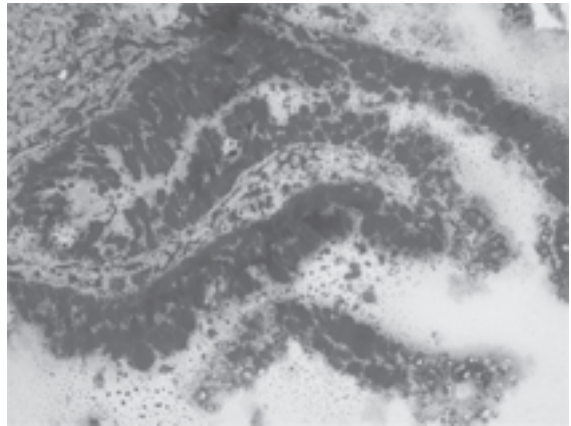


Fig. 4. Duodenal lipid vacuoles; hematoxylin-eosin, oil-red.

Lefèvre first reported CGI-58 mutations in 2001¹². The protein encoded by this gene is a cofactor for adipose triglyceride lipase (ATGL), which promotes the catabolism of stored fat. Consequently, fatty acid mobilization is impaired⁴. CGI-58 is distributed predominantly on the surface of lipid droplets (LD)¹³. Yamaguchi demonstrated that mutated CGI-58 is not able to interact with perilipin¹⁴. The perilipin on the surface of lipid droplets plays a critical role in the translocation of hormone-sensitive lipase, involved in lipolysis. This gene's protein also acts as an acyl-CoA-dependent lysophosphatidic acid acyltransferase that prefers arachidonoyl-CoA and oleoyl-CoA substrates to catalyze the initial step of de novo triacylglycerol synthesis¹⁵.

It is very difficult to find a correlation between the phenotypic and genotypic features due to the occurrence of novel *ABHD5* mutations⁴ and the fact that there are only a few cases in the literature. In Turkey, 11 mutant alleles have been revealed in 6 CDS patients. The most frequent mutation is N209X (58, 3%)¹⁶.

Emollients and retinoids could be useful for skin and muscle manifestations in the management of patients with this syndrome. However, retinoids (acitretin) cannot be given to the patient discussed here in view of her deranged liver function. Dietary changes, i.e., decreasing the intake of long-chain fatty acids and increasing the intake of medium-chain fatty acids, have been reported to be beneficial in such cases⁵. Further understanding of the mechanism of CGI-58 should help to develop proper approaches to treatment.

Acknowledgement

We would like to thank Dr. Eli Sprecher and Dr. Shirli Israeli, Department of Dermatology, Tel Aviv Medical Center, Israel, for their help with the mutation analysis of this case.

REFERENCES

1. Rozenszajn L, Klajman A, Yaffe D, Efrati P. Jordans' anomaly in white blood cells. Report of case. *Blood* 1966; 28: 258-265.
2. Dorfman ML, Herskho C, Eisenberg S, Sagher F. Ichthyosiform dermatosis with systemic lipidosis. *Arch Dermatol* 1974; 110: 261-266.
3. Chanarin I, Patel A, Slavin G, Wills EJ, Andrews TM, Stewart G. Neutral-lipid storage disease: a new disorder of lipid metabolism. *Br Med J* 1975; 1: 553-555.
4. Redaelli C, Coleman RA, Moro L, et al. Clinical and genetic characterization of Chanarin–Dorfman syndrome patients: first report of large deletions in the ABHD5 gene. *Orphanet J Rare Dis* 2010; 5: 33.
5. Pahwa M, Kar R, Singh A, Goel A, Ramesh V, Jain R. Chanarin–Dorfman syndrome with eccrine gland vacuolation: a case report. *Int J Dermatol* 2008; 47: 1257-1259.
6. Aksu G, Kalkan Ucar S, Bulut Y, et al. Renal involvement as a rare complication of Dorfman–Chanarin syndrome: a case report. *Pediatr Dermatol* 2008; 25: 326-331.
7. Taskin E, Akarsu S, Aygun AD, Ozlu F, Kilic M. Rickets with Dorfman–Chanarin syndrome. *Acta Haematol* 2007; 117: 16-19.
8. Chander R, Varghese B, Garg T, Mittal S, Singh S. Dorfman–Chanarin syndrome in two female siblings: a case report and discussion on approach and management. *Dermatol Online J* 2011; 17: 7.
9. Gandhi V, Aggarwal P, Dhawan J, Singh UR, Bhattacharya SN. Dorfman–Chanarin syndrome. *Indian J Dermatol Venereol Leprol* 2007; 73: 36-39.
10. Srinivasan R, Hadzić N, Fischer J, Knisely AS. Steatohepatitis and unsuspected micronodular cirrhosis in Dorfman–Chanarin syndrome with documented ABHD5 mutation. *J Pediatr* 2004; 144: 662-665.
11. Ronchetti A, Prati D, Pezzotta MG, et al. Severe steatohepatitis in a patient with a rare neutral lipid storage disorder due to ABHD5 mutation. *J Hepatol* 2008; 49: 474-477.
12. Lefèvre C, Jobard F, Caux F, et al. Mutations in CGI-58, the gene encoding a new protein of the esterase/lipase/thioesterase subfamily, in Chanarin–Dorfman syndrome. *Am J Hum Genet* 2001; 69: 1002-1012.
13. Lass A, Zimmermann R, Haemmerle G, et al. Adipose triglyceride lipase-mediated lipolysis of cellular fat stores is activated by CGI-58 and defective in Chanarin–Dorfman Syndrome. *Cell Metab* 2006; 3: 309-319.
14. Yamaguchi T. Crucial role of CGI-58/alpha/beta hydrolase domain-containing protein 5 in lipid metabolism. *Biol Pharm Bull* 2010; 33: 342-345.
15. Ghosh AK, Ramakrishnan G, Chandramohan C, Rajasekharan R. CGI-58, the causative gene for Chanarin–Dorfman syndrome, mediates acylation of lysophosphatidic acid. *J Biol Chem* 2008; 283: 24525-24533.
16. Emre S, Unver N, Evans SE, et al. Molecular analysis of Chanarin–Dorfman syndrome (CDS) patients: Identification of novel mutations in the ABHD5 gene. *Eur J Med Genet* 2010; 53: 141-144.