Syndromic Conundrums in Diabetes: Seek and Ye Shall Find: The Dorfman-Chanarin Syndrome

Stephen Charles Bronson, Alagianambi Shanmugam, and Chelliah Mythili

Case Presentation

A 15-year-old girl from the southern part of India presented to us with a history of recent detection of increased blood glucose levels. About 3 weeks earlier, she had had an episode of abdominal pain and vomiting that lasted for about 3 days, and she was treated elsewhere symptomatically. During that episode, she was found to have increased blood glucose levels, was given dietary advice, and was referred to us. In presenting to us, she did not have any abdominal pain, fever, or vomiting. There was no history of weight loss, polyuria, or polydipsia. She was conscious, well-oriented, and afebrile. There were no other specific complaints.

Even from her childhood, the girl had been hard of hearing and was prescribed hearing aids elsewhere. She was born to consanguineous parents; the girl's parents were first cousins. The paternal grandmother had had diabetes and hypertension. She had 12 siblings, of whom only eight survived into adulthood. Of the grandmother's surviving eight siblings, five had diabetes. The girl's father had three sisters and one brother. Hearing was affected in the girl's father and in his eldest sister, who also had diabetes. The girl's mother (deceased) did not have a hearing defect or diabetes. The girl had an older sister who did not have hearing loss or diabetes (Figure 1). The girl's developmental history showed a mild delay in language-related milestones. She attained menarche at 12 years and continued to have regular menstrual cycles, with excessive bleeding now and then, for which she took an oral combined pill (OCP) containing ethinyl estradiol and levonorgestrel, which was prescribed elsewhere.

On examination, the girl was thinly built with a BMI of 15 kg/m^2. Her blood pressure was 110/70 mmHg; pulse rate was 90 bpm and regular in rhythm. She had hyperhidrosis of the palms and soles. Her skin was dry in other areas. Her father, too, had sweaty palms and feet. The girl had no goiter. There were hyperpigmented, scaly, ichthyotic lesions on the dorsal aspect of feet (Figure 2) and also on the forearms. She had more severe dark, scaly lesions in her axillae. The skin over the cubital fossae was thickened and had dark linear corrugations. However, there was no typical feature of a thick, velvety texture of skin, suggestive of acanthosis nigricans. There also were no skin tags. History revealed that she used to have similar scaly lesions in other areas of the body such as the neck, upper chest, and behind the ears that had become better in course of time because she used to apply emollients. Her sexual development was normal.

Laboratory investigations were performed. The fasting plasma glucose (PG) was 105 mg/dL (5.8 mmol/L), and postprandial PG measured 2 hours after a mixed meal was 215 mg/dL (11.9 mmol/L); A1C was 8.7% (71.6 mmol/mol). The patient was not yet on any antidiabetic medications when the PG values were measured. Urine ketones and albumin were absent. Kidney and liver function tests were within normal limits. The blood cell counts and peripheral smear were normal except for a mild microcytic, hypochromic anemia. Her C-peptide response, which was checked after achieving glycemic control, was adequate. Anti-GAD autoantibody testing was negative. Antinuclear antibody and other autoantibodies screened for connective tissue diseases were negative. Her thyroid profile was normal. What was remarkable was the severe sustained elevation of serum triglyceride levels of >2,000 mg/dL (22.6 mmol/L) observed in her lipid profile (Figure 3). This hypertriglyceridemia was disproportionate to the PG levels and remained elevated even after glycemic control was achieved and after withholding the OCP. Other routinely measured lipids, including LDL cholesterol, were within normal limits. At this point, a possible syndromic association was considered, and she was evaluated further.

Institute of Diabetology, Stanley Medical College & Hospital, Chennai, Tamil Nadu, India

Corresponding author: Stephen Charles Bronson, dr.s.charlesb@gmail.com

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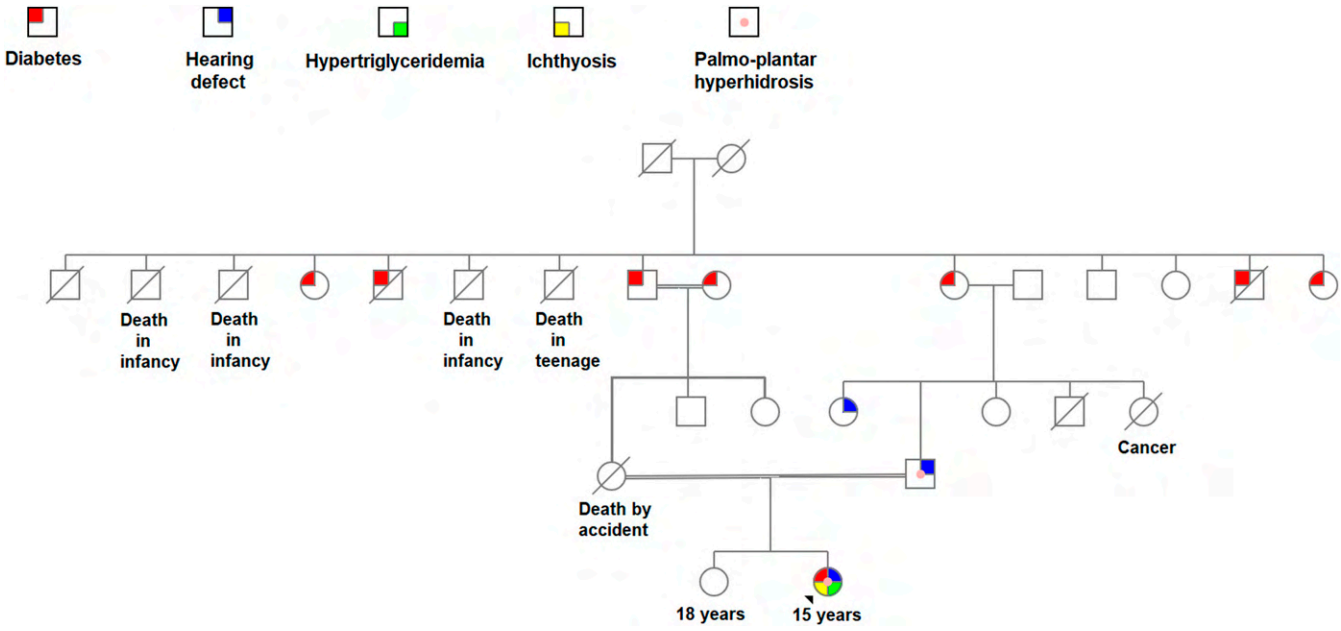

FIGURE 1 Pedigree showing the distribution of the traits—diabetes, hearing loss, hypertriglyceridemia, ichthyosis, and hyperhidrosis—in the family.

The girl did not have any vision disturbance. There was no nyctalopia or photophobia. Her fundus was normal. Audiometry showed bilateral, moderately severe sensory neural hearing loss (SNHL). She was able to hear loud voices and read lip movements. She was also able to speak, albeit with mild stuttering. There were no other neurological deficits, nor was there any muscular weakness. Serum creatine kinase and lactate dehydrogenase levels were within normal limits. Chest X-ray, electrocardiogram, and echocardiogram were normal. Her abdomen was soft and nontender. Upper gastrointestinal endoscopy showed no abnormality. Transabdominal ultrasonography showed hepatomegaly. The spleen was normal in size.

In light of her severe hypertriglyceridemia, we sought to look for pancreatic involvement. A contrast enhanced computed tomography scan of the abdomen revealed features of an acute interstitial edematous pancreatitis with pseudocyst. Serum amylase and lipase levels were normal. The peripheral smear was once again examined to look for Jordans' anomaly, which denotes lipid-laden vacuoles in granulocytes. Jordans' anomaly was not seen. The girl's father and paternal grandmother, who had accompanied the girl, could not be evaluated along similar lines because they were not willing.

The maternally inherited diabetes and deafness (MIDD) syndrome, also known as the Ballinger-Wallace syndrome, was considered as a differential diagnosis (1). Although the girl had deafness and diabetes, she did not have features such as myopathy or macular pattern dystrophy. The patient's mother did not have features of the disease, and her father had traits such as hearing defect and palmo-plantar hyperhidrosis. Also, the patient's sibling was not affected. All of these factors suggested that there was no mitochondrial disease such as MIDD.

Wolfram syndrome, also called DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) syndrome was another differential. It was ruled out because there was no optic atrophy or diabetes insipidus (2). Alström and Bardet-Biedl syndromes were ruled out because there was no retinal dystrophy (3). Inherited ichthyosis vulgaris, the most common form of ichthyosis, follows an autosomal dominant pattern, is associated with atopy in almost half of the patients, and usually spares

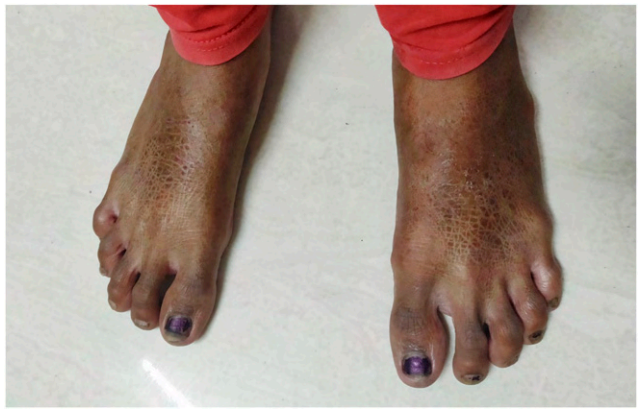

FIGURE 2 Ichthyosis on the dorsum of the feet.

FIGURE 3 Turbid serum resulting from elevated triglycerides.

areas such as axillae, cubital fossae, and the neck region (4). In this case, only the patient had ichthyosis, there were no atopic conditions in the family, and the skin in all the above-mentioned regions was involved. Furthermore, the severe hypertriglyceridemia seen in this case is not a feature of any of the above syndromes.

Our patient had hypertriglyceridemia, ichthyosis, SNHL, diabetes, hepatomegaly, and pancreatitis probably secondary to hypertriglyceridemia. The diagnosis was narrowed down to two closer syndromes: neutral lipid storage disease (NLSD) with ichthyosis and NLSD with myopathy. The girl had no myopathy. Thus, by way of excluding the other differential diagnoses as discussed above, the diagnosis of NLSD with ichthyosis was determined. This condition is also called the Dorfman-Chanarin syndrome (DCS) (Online Mendelian Inheritance in Man database #275630) (5), which is among the rarest of diseases described so far in medical literature.

The girl was started on insulin, and glycemic control was achieved. Later on, the insulin dose was reduced, and metformin was added. She was treated with a statin and fenofibrate, and her triglyceride levels came down considerably. She was advised appropriately regarding diet and lifestyle modifications, especially with reference to managing her hypertriglyceridemia and diabetes. The pancreatitis was managed conservatively. Relevant expert consultations were done. The girl is now on regular follow-up.

Questions

1. Why is the early recognition of syndromic associations of diabetes important?
2. What are NLSDs?

Commentary

NLSDs are inherited disorders of lipids characterized by variable clinical manifestations that include elevated triglycerides, myopathy, ataxia, SNHL, ichthyosis, liver damage, nystagmus, and cataracts (6). When ichthyosiform dermatosis predominantly manifests in association with NLSD, the condition is called DCS (6,7).

DCS is named after Maurice Dorfman and Israel Chanarin, who described the condition, along with their respective colleagues, in the early 1970s (7,8). Since its first description, only about 128 cases of DCS have been reported worldwide (9). DCS is an autosomal recessive disease the incidence of which is not yet known. It is caused by mutations in the *CGI58/ABHD5* gene mapped to chromosome 3p21. This gene encodes a coactivator for a novel lipase called the adipose triglyceride lipase, which catalyses the initial hydrolysis of triglyceride (6,9). Diabetes, although not a constant feature of DCS, has been reported earlier (10). We may speculate that diabetes in DCS could be secondary to pancreatic involvement or the result of insulin resistance arising because of lipotoxicity caused by dyslipidemia. Furthermore, the *CGI58/ABHD5* gene is postulated to be involved in the generation of signaling lipids and in insulin action (11).

One of the peculiarities observed in our patient was the almost asymptomatic and clinically inapparent pancreatitis with a consequent pseudocyst formation. The pancreatitis was likely longstanding and secondary to hypertriglyceridemia. She did not have Jordans' anomaly. Although this feature was not seen at the time of evaluation, there is a possibility that it may develop in the course of time. The girl also had palmo-plantar hyperhidrosis, which, to the best of our knowledge, is the first report so far in association with DCS.

Clinical Pearls

- Given the recent epidemic nature of diabetes, any young patient with diabetes should be approached with a wider anticipation for other systemic involvement, especially when a clue such as hearing loss or visual disturbance is present.
- Syndromic associations, although rare, are very much present in the population of patients who comes to a practitioner with an incidental finding of diabetes.
- Early detection and comprehensive management are crucial in such patients.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

S.C.B. diagnosed the condition, treated the patient, and wrote the manuscript. A.S. supervised the writing of the manuscript. C.M. did the laboratory investigations and assisted in writing the manuscript. S.C.B. is the guarantor of this work and, as such, had full access to all the data and takes responsibility for the integrity of the case presentation.

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