A Case of Shwachman-Diamond Syndrome Presenting With Diabetes From Early Infancy

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Shwachman-Diamond syndrome (SDS; OMIM 260400) is a rare autosomal recessive disorder characterized by pancreatic insufficiency, bone marrow failure, skeletal dysplasia, and short stature (1). Diabetes is a rare complication of SDS, and only a few SDS patients have been reported to develop diabetes (2–6). We report the first case of SDS with diabetes in which mutations of the *SBDS* gene have been identified.

RESEARCH DESIGN AND METHODS

— A 15-month-old Japanese girl was born uneventfully to a healthy mother after 36 weeks gestation. Pregnancy was complicated by intrauterine growth retardation. Her parents are nonconsanguineous. There was no family history of inherited disorders. The birth weight was 1,530 g (−2.4 SD) and length was 41.0 cm (−2.5 SD). After birth, she developed respiratory distress syndrome and pulmonary hemorrhage. Neutropenia was noted from the neonatal period, and a bone marrow examination revealed a maturation arrest of myelopoiesis. After 3 weeks of age, she developed postprandial hyperglycemia with >200 mg/dl in blood glucose. The treatment with insulin was not begun because of normal insulin response in the oral glucose tolerance test performed at the age of 3 months. At 5 months of age, her weight was 2,950 g (−5.2 SD) and length was 51.0 cm (−4.1 SD). At 15 months of age, the patient was admitted to our hospital for evaluation of growth retardation. On admission, her weight was 4.13 kg (−6.6 SD) and length was 59.6 cm (−5.2 SD). Neurological examination showed generalized hypotonia.

RESULTS

— Laboratory findings were as follows: hemoglobin, 11.3 g/dl; leukocytes, 5,900/cmm with 11.5% of neutrophils; fasting blood glucose, 111 mg/dl; insulin, 2 μU/ml; C-peptide, 0.5 ng/ml (normal range 0.8–3.0); HbA_{1c}, 6.7%; serum glucagon, 127 pg/ml (normal range 23–197); IGF-I, 7 ng/ml (normal range 37–229); serum amylase, 4 units/l (normal range 45–150); serum lipase, 2 units/l (normal range 8–50); and serum trypsin, <10 mmol/l (normal range 100–500). Antibodies to GAD were negative. Chromosomal karyotype was 46, XX. The stools were greasy and contained excessive fatty droplets in microscopic examination. Metaphyseal dyschondroplasia was not found on the bone radiograph. Brain magnetic resonance imaging showed no structural malformation but delayed myelination. Abdominal computed tomography demonstrated an enlarged pancreas replaced by fat. Normal sweat chloride concentrations ruled out cystic fibrosis (CF). Clinically, she was diagnosed as having SDS. An oral glucose tolerance test revealed a diabetic pattern of blood glucose levels (282 mg/dl at 120 min) with a poor insulin response (5 μU/ml). Neither metabolic acidosis nor ketosis was found during the hospitalization. Treatment with insulin and the replacement of pancreatic enzymes were started, resulting in no effect on her growth retardation. At 17 months of age, the child died of septic shock. An autopsy was not performed. Sequence analysis of the *SBDS* gene using genomic DNA was performed as previously described after her parents' informed consent (7). We identified compound heterozygous mutations: 183-184TA to CT and 258 + 2T to C. The former mutation introduces an in-frame stop codon (K62X) and the latter disrupts the donor splice site of intron 2, with the resulting 8-bp deletion causing premature truncation of the encoded protein by frameshift (84Cfs3) (7).

CONCLUSIONS

— Although our patient presented with most of the cardinal features of SDS, metaphyseal dyschondroplasia was not found. The SDS disease gene, *SBDS*, was recently mapped to chromosome 7q11 (7). While the function of the gene remains unknown, it is proposed that SDS results from deficient RNA processing in a pathway essential to development of the exocrine pancreas (7). The mutations found in our patient have been commonly identified in both Japanese and European affected families (7,8). Analysis of the *SBDS* gene is therefore thought to be effective in establishing a diagnosis in the absence of typical clinical features.

Shmerling et al. (2) have reported a family with both SDS and diabetes. Aggett et al. (3) have reported an adult SDS patient with a diabetic glucose tolerance test. Mack et al. (4) have reported one SDS patient presenting with insulin-dependent diabetes during adolescence. Ginzberg et al. (5) have described 1 child with noninsulin-dependent diabetes out

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Abbreviations: CF, cystic fibrosis; SDS, Shwachman-Diamond syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

of 88 pediatric SDS patients. Recently, Fillipi et al. (6) have described a newborn infant with SDS and transient diabetes probably caused by anti-GAD antibody transmitted from the mother with type 1 diabetes. In our case, insulin secretion had been kept to some extent at the onset of diabetes, but the impairment of β-cell function had progressed with age. Although coexistence of SDS and diabetes is unlikely to be incidental, the onset and severity of diabetes varies with each patient, and the pathophysiology of developing diabetes remains unclear. CF is considered to be a condition quite similar to SDS, because both disorders have congenital exocrine pancreatic insufficiency. It is well known that diabetes is an important complication of CF and is increasingly prevalent with age in CF patients (9). The lower prevalence of diabetes in SDS than in CF may be associated with the improvement of exocrine pancreatic function with increasing age in SDS patients (4,5). A pathological study of the pancreas in adult CF patients has shown ductule dilatation, acinar fibrosis, and acinar atrophy with fatty cell infiltration (9). Abdul-Karim et al. (10) have observed islet tissue in ribbon-like strands and the islets themselves quantitatively reduced with greater size variability in CF-related diabetes. While no pathological study has been reported in SDS patients with diabetes, Aggett et al. (3) have reported that the majority of acinar cells are replaced by fat, interstitial connective tissue is increased, a few ductules are dilated, and the islets of Langerhans appear normal in SDS patients without diabetes. Therefore, a younger SDS infant such as our patient is unlikely to develop diabetes through the same pathophysiological changes in the pancreas as those seen in CF-related diabetes. In our case, intrauterine growth retardation and respiratory failure in the neonatal period may contribute to the β-cell dysfunction. Further studies are needed to clarify the association between the SBDS gene and the β-cell embryonic development or β-cell function.

References

1. Shwachman H, Diamond LK, Oski FA, Khaw K: The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr* 65:645–663, 1964
2. Shmerling DH, Prader A, Hitzig WH, Giedion A, Hadorn B, Kuhni M: The syndrome of exocrine pancreatic insufficiency, neutropenia, metaphyseal dysostosis and dwarfism. *Helv Paediatr Acta* 24:547–575, 1969
3. Aggett PJ, Cavanagh NP, Matthew DJ, Pincott JR, Sutcliffe J, Harries JT: Shwachman's syndrome: a review of 21 cases. *Arch Dis Child* 55:331–347, 1980
4. Mack DR, Forstner GG, Wilschanski M, Freedman MH, Durie PR: Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. *Gastroenterology* 111:1593–1602, 1996
5. Ginzberg H, Shin J, Ellis L, Morrison J, Ip W, Dror Y, Freedman M, Heitlinger LA, Belt MA, Corey M, Rommens JM, Durie PR: Shwachman syndrome: phenotypic manifestations of sibling sets and isolated cases in a large patient cohort are similar. *J Pediatr* 135:81–88, 1999
6. Filippi L, Tronchin M, Pezzati M, Chiti G, Dani C, Vichi GF, Rubaltelli FF: Shwachman syndrome in a preterm newborn associated with transient diabetes mellitus. *J Pediatr Gastroenterol Nutr* 34:219–223, 2002
7. Boocock GR, Morrison JA, Popovic M, Richards N, Ellis L, Durie PR, Rommens JM: Mutations in SBDS are associated with Shwachman-Diamond syndrome. *Nat Genet* 33:97–101, 2003
8. Nakashima E, Mabuchi A, Makita Y, Masuno M, Ohashi H, Nishimura G, Ikegawa S: Novel SBDS mutations caused by gene conversion in Japanese patients with Shwachman-Diamond syndrome. *Hum Genet* 114:345–348, 2004
9. Mackie ADR, Thornton SJ, Edenborough FP: Cystic fibrosis-related diabetes. *Diabet Med* 20:425–436, 2003
10. Abdul-Karim FW, Dahms BB, Velasco ME, Rodman HM: Islets of Langerhans in adolescents and adults with cystic fibrosis: a quantitative study. *Arch Pathol Lab Med* 110:602–606, 1986