Berardinelli Seip syndrome with insulin-resistant diabetes mellitus and stroke in an infant

C. K. Indumathi, S. Lewin, Vageesh Ayyar
Departments of Pediatrics and Endocrinology, St. John’s Medical College Hospital, Bangalore, India

ABSTRACT
Berardinelli Seip congenital lipodystrophy (BSCL) is a rare metabolic disorder characterized by severe generalized lipodystrophy, insulin resistance, and dyslipidemia since infancy, and onset of overt diabetes mellitus in adolescence. Here we report a 5-month-old infant with clinical and metabolic manifestations of Berardinelli Seip syndrome including overt diabetes mellitus and stroke, which are very rare at this age.

Key words: Berardinelli Seip syndrome, diabetes mellitus, dyslipedemia, infancy, stroke

INTRODUCTION
Berardinelli Seip congenital lipodystrophy is a rare autosomal recessive disease characterized by generalized absence of fat since birth and severe metabolic derangements such as severe insulin resistance, hyperglycemia, diabetes mellitus, and dyslipidemia (especially hypertriglyceridemia and low HDL). Diabetes mellitus generally develops during second and third decade. We describe a 5-month-old infant with BSCL presenting with diabetes mellitus.

CASE REPORT
A 5-month-old male infant was admitted with the history of progressive abdominal distension since one and a half months. He was a second baby born out of second-degree consanguinity. Birth weight was 2.5 kg. Antenatal and neonatal periods were uneventful. There was no history of polyuria, increased thirst or fast breathing. Elder sibling was 4-year-old male and doing well. On examination, weight was 5.2 kg (3rd centile) and height was 63 cm (25th centile). Blood pressure was 90/60 mm of mercury. Baby had generalized absence of fat including buccal pad of fat (empty cheeks sign). There were dysmorphic features such as triangular face, low anterior hair line, depressed nose, large protruding tongue, long fingers and toes, large hands and feet, prominent veins over hands and feet and, excessive hair over thighs and legs with muscular hypertrophy [Figures 1 and 2]. There was no acanthosis nigricans. Per abdominal examination revealed massive hepatomegaly of 9 cm. [Figure 1], which was firm in consistency, and splenomegaly of 2 cm. Development was appropriate for age. Hearing was normal.

Investigations: lipid profile-cholesterol-119 mg/dl (114-203 mg/dl), HDL-<10 mg/dl (40-60 mg/dl), LDL-34 mg/dl (<130 mg/dl), triglycerides-1391 mg/dl (29-99 mg/dl), RBS 400 mg/dl. Frequent monitoring of blood glucose revealed persistent hyperglycemia (300-415 mg/dl). Serum insulin was elevated to 44 µIU/MI (normal upto-23 µIU/MI) suggesting insulin resistance and simultaneous glucose was 300 mg/dl. Liver function test was normal except mild elevation of AST and ALT. Urine ketone bodies were negative. X-ray of wrist revealed normal bone age. Echocardiogram was normal. Liver biopsy revealed extensive steatosis involving 95% of parenchyma with marked fibrosis with a fibrotic score of 3/4. Leptin...
estimation and genetic analysis could not be done because of lack of resources.

Baby was started on NPH insulin (H insulotard) 1 unit twice daily and omega 3 fatty acids (decosa hexanoic acid and eicosapentaenoic acid) to control hyper triglyceridenemia. After a month, blood glucose was under control. Three months later, baby was readmitted with left-sided hemiplegia. CT brain revealed infarction in right middle cerebral artery territory. Child was started on aspirin. Presently child is 3-year old and weighing 12 kg. He is requiring two units of insulotard twice daily. Blood glucose is maintained between 100 and 150 mg/dl. His motor power in left upper and lower limb is 4/5. Mile stones are near normal except speech delay. Triglyceride has come down from 1391 mg/dl to 800 mg/dl.

**DISCUSSION**

Berardinelli Seip congenital lipodystrophy is a rare autosomal recessive metabolic syndrome with a prevalence of less than 1 case in 12 million and 200 cases have been reported so far.[1] Berardinelli first described the syndrome in 1954 and later confirmed by Seip in 1959. BSCL is linked to two genetic loci, on chromosomes 9q34 (AGPAT2 gene) and 11q13 (BSCL2 gene).[1-3] BSCL is characterized by generalized loss of subcutaneous fat (including buccal pad of fat), perirenal, mammary and retroperitoneal fat from birth to early infancy in the face of adequate nutrition. Metabolic abnormalities noticed are: severe insulin resistance, hyperglycemia, diabetes mellitus, dyslipidemia (especially hypertriglycerideremia and low HDL), and leptin deficiency. Because of the relative paucity of adipose tissue, triglycerides accumulate excessively in multiple ectopic locations, most notably in the liver, skin, arterial wall, and in the muscles explaining most of the severe clinical complications: hepatic steatosis and cirrhosis, insulin resistance, hyperinsulinemia, diabetes, acanthosis nigricans, and arteriosclerosis.[1-4] As a direct consequence of the absence of subcutaneous adipocytes, circulating levels of leptin are nearly undetectable in children with BSCL.[4] Patients with the early-onset hyperinsulinemia in combination with congenital generalized lipodystrophy develop acromegaloïd features (large hands, feet, and jaw), hypertrichosis, soft tissue hyperplasia, and somatomegaly.[1,2] Index child had all these features. Other associated anomalies include hypertropic cardiomyopathy, hypertropic pyloric stenosis and hydrocephalus, which were not noticed in our child.[2,5] Acanthosis nigricans is generally associated with severe metabolic derangements, which was not evident in our child.[1,2] Though metabolic abnormalities of hyperinsulinemia and insulin resistance are evident early in life, overt diabetes generally develops by second decade or adulthood.[2,5-7] In a report by Shirwalkar *et al*., though insulin resistance was noted at 9 months of life, overt diabetes mellitus was diagnosed only by 13 years.[5] In another report by Mandal *et al*., 3 children (3 year twins and 6 year) have not developed diabetes so far.[6] In a Brazilian study, among eight children with BSCL between 3 months and 19 years, two female patients were diagnosed with diabetes. However, age of onset of diabetes is not mentioned.[6] Similarly a child diagnosed at 4 months of age, developed diabetes at the age of 15 years.[7] Unusual feature in our child being development of diabetes mellitus at very early age of 5 months and there is only one report of overt diabetes mellitus described at 4 months.[8] Generally diabetes is difficult to control because of inherent insulin
Patients with triglyceride levels greater than 1000 mg/dl are also at risk of developing recurrent pancreatitis, predisposition for coronary artery disease, cerebro-vascular accidents, and cutaneous xanthomata. Our child developed stroke at 8 months of age, which could be attributed to hyperlipidemia, which again has not been described at this age. Low fat diet, medium chain triglycerides, polyunsaturated fats, and statins may help to bring down triglyceride levels. Newer promising modalities of treatment include leptin therapy. Several small studies in patients with generalized lipodystrophy and familial partial lipodystrophy have shown that recombinant human leptin replacement improves metabolic abnormalities, reduces hyperglycemia, hyperlipidemia, insulin resistance, fatty infiltration of the liver, and hypermetabolism. One intriguing experimental therapy in animals is transplantation of white fat into mice with severe lipoatrophy, which ameliorated the diabetes. Death occurs mostly in the third decade of life from cirrhosis and its complications, diabetic complications, and hypertrophic cardiomyopathy.

Our child had both clinical and metabolic features consistent with the diagnosis of Berardinelli Seip syndrome. Though Berardinelli Seip syndrome has been described in infancy, additional and unusual features such as overt diabetes mellitus at 5 months and stroke at 8 months of age prompted us to report this case. To the best of our knowledge, this is the second reported case of BSCL with overt diabetes mellitus at 5 months and first reported case of BSCL with stroke at 8 months of age.

References

1. Dong G, Liang L, Zou C. Congenital generalized lipodystrophy in a 4 year old Chinese girl. Indian Pediatr 2005;42:1036-8.
2. Garg A. Acquired and inherited lipodystrophies. N Engl J Med 2004;350:1220-34.
3. Shirwalkar HU, Patel ZM, Magre J, Hilbert P, Van Maldergem L, Mukhopadhyay RR, et al. Congenital generalized lipodystrophy in an Indian patient with a novel mutation in BSCL2 gene. J Inherit Metab Dis 2008. [In press].
4. Beltrand J, Beregszaszi M, Chevenne D, Sebag G, Kerdanet MD, Huet F, et al. Metabolic correction induced by leptin replacement treatment in young children with Berardinelli-Seip congenital lipoatrophy. Pediatrics 2007;120:291-6.
5. Mandal K, Anjea S, Seth A, Khan A. Berardinelli Seip congenital lipodystrophy. Indian Pediatr 2006;43:440-5.
6. Filho PP, Val AC, Diamante R, Cunha CF, Norton RC, Lamounier JA, et al. Congenital generalized lipodystrophy. J Pediatri (Rio J) 2004;80:333-6.
7. Van Maldergem L, Magré J, Khallouf TE, Gedde-Dahl T Jr, Delépine M, Trygstad O, et al. Genotype phenotype relationships in Berardinelli Seip Congenital lipodystrophy. J Med Genet 2002;39:722-33.
8. Friguls B, Coroleu W, del Alcazar R, Hilbert P, Van Maldergem L, Pintos-Morell G. Severe cardiac phenotype of Berardinelli-Seip congenital lipodystrophy in an infant with homozygous E189X BSCL2 mutation. Eur J Med Genet 2009;52:14-6.
9. Lee IH, Chen HL, Jeng YM, Cheng MT, Tsao LY, Chang MH. Congenital generalized lipodystrophy in a 4-month-old infant. J Formos Med Assoc 2001;100:623-7.
10. Nishiyama A, Yagi M, Awano H, Okizuka Y, Maeda T, Yoshida S, et al. Two Japanese infants with Congenital generalized lipodystrophy due to BSCL2 mutations. Pediatr Int 2009;51:775-9.

Cite this article as: Indumathi CK, Lewin S, Ayyar V. Berardinelli Seip syndrome with insulin-resistant diabetes mellitus and stroke in an infant. Indian J Endocr Metab 2011;15:S62-4.

Source of Support: Nil, Conflict of Interest: None declared.