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CASE REPORT

Berardinelli Seip congenital lipodystrophy presenting with neonatal diabetes mellitus due to a mutation in the AGPAT2 gene

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Introduction

Neonatal diabetes mellitus (NDM) with hypoinsulinism is an uncommon condition with an estimated incidence from 1 in 3,00,000 to 4,00,000 live births [1]. Diabetes mellitus with hyperinsulinism due to Berardinelli Seip Congenital Lipodystrophy(BSCL) presenting in the neonatal period is even rarer [2]. We report a child with neonatal onset BSCL having mutation of the AGPAT 2 gene diagnosed at the age of 42 days.

Case history

A 42 day old, 3rd born male infant of a non-consanguineous marriage was admitted with lethargy, breathlessness and poor weight gain. A full term baby (2 kg birth weight) was treated for suspected sepsis at the age of 28-day of life. Hyperglycemia was identified at the time of hospital discharge when he was referred to us.

Clinical examination of the baby revealed hirsutism, triangular acromegaloid facies, thick tongue, absent buccal and gluteal pad of fat. Baby weighed 2.5 Kg, with a length of 51.5 cm and head circumference of 34.5 cm. He was tachypneic and had hepato splenomegaly.

Investigations revealed persistent hyperglycemia, without acidosis and ketonuria. Electrolytes and renal parameters were normal. Other investigations are summarized below (Table 1). With a diagnosis of neonatal diabetes mellitus he was started on injection insulin stabilized at 3.5u/kg/day. Hyperglycemia persisted despite this high dose of insulin. The infant was 42 days of age at the time of HbA1c sampling, with a hemoglobin of 9.9 g/dl. Initial HbA1c values were in the normal range and this could be due to the recent onset of hyperglycemia hence the insufficient duration to cause an elevated HbA1c levels at diagnosis. Follow up value was found to be 10.75 %.

The differential diagnosis for insulin resistance considered were lepreuchaunism, congenital lipodystrophy and Rabson Mendenhall syndrome. Genetic studies for common mutants were performed : KCNJ11 (kir 6.2), AGPAT2 (Type 1) and BSCL 2 by PCR and direct sequencing. Novel mutations in the AGPAT2 gene were identified. One novel mutation homozygous Val67Met (c.119 G>A) in Exon 2 of AGPAT2 gene (non-synonymous) and one synonymous variant Gly137Gly (c.411C>A) in Exon 3 of the AGPAT2 gene were identified (Fig 1). KCNJ11 (kir 6.2), SUR, INS and BSCL 2 gene did not show mutations. The parental samples could not be obtained for genetic analysis. Cardiac evaluation was normal. The diagnosis was Berardinelli Seip congenital lipodystrophy. During follow up he developed loss of subcutaneous fat all over the body, enlarged genitalia, prominent veins over the abdomen, acanthosis nigricans and muscular hypertrophy. He was on twice-a-day combination of short acting and intermediate acting insulin at 3.5 units/kg/day, but his blood glucose values remained high. He was hospitalized at 9 months of age with gross hepato-splenomegaly and was treated for anemia caused by falciparum malaria infection. Echocardiogram done twice during the follow up did not show evidence of cardiomyopathy. He did not have any lytic bone lesions. HbA1c values were 10.75 % and later declined to 8.16 %. He showed both motor and mental developmental delay with poor weight gain at the age of 12 months and died due to anemia with cardiac failure.

Discussion

Generalized lipodystrophy is characterized by alterations in body fat distribution and insulin resistance manifested by acanthosis nigricans, hyperandrogenism, muscular hypertrophy, hepatomegaly, glucose intolerance or diabetes and

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Table 1 showing the laboratory parameters of the infant

Parameters	Values
Blood glucose	250-600mg/dl
Serum insulin levels	2049 μIU/ml (N = 3-28 μIU/ml
C Peptide levels	86.6ng/ml (1.1 -5ng/ml)
HbA1c levels	6.4%(N<6)
TGL	361 mg/dl(25-200mg/dl)
VLDL	72 mg/dl(5-40mg/dl)
Thyroid profile	Normal
Liver enzymes	SGOT 143 U/L
GAD levels	7.0IU/ml(N≤10 IU/ml)
Bone age	Less than one year
MRI abdomen	Normal pancreas

hypertriglyceridemia. This can be localized or generalized. In the generalized form, both subcutaneous and visceral adipose tissues are near absent. The congenital form is Berardinelli-Seip congenital lipodystrophy and the delayed form called Lawrence syndrome. Berardinelli–Seip Syndrome (BSCL) is a rare autosomal recessive disease. Two loci for BSCL have been identified recently on chromosome 9 (AGPAT2) and chromosome 11 (Seipin).

The diagnostic of BSCL is made on the basis of either three major criteria or two major criteria plus two or more minor criteria. Major criteria include lipoatrophy affecting the trunk, limbs, and face, acromegaloid features, hepatomegaly, elevated serum concentration of triglycerides and insulin resistance. Minor criteria include hypertrophic cardiomyopathy, psychomotor retardation or mild (IQ 50–70) to moderate (IQ 35–50) cognitive impairment, hirsutism, precocious puberty in females, bone cysts and phlebomegaly. The infant described here had all the major features of BSCL. Incidence of BSCL varies between regions from 1 in 10,000,000 to 1 in 500 000. BSCL is usually diagnosed at birth or soon after. Acromegaloid features are the result of insulin cross-reacting with insulin-like growth factor-1 (IGF-1) receptors [3]. Because of the absence of functional adipocytes, lipid is stored in other tissues, such as muscle and liver [3]. Individuals are insulin resistant and 25 %–35 % develop diabetes mellitus between ages 15 and 20 years. There are a few case reports of earlier onset diabetes mellitus, including one at the age of 12 days [2]. Hepatomegaly secondary to hepatic steatosis and skeletal muscle hypertrophy are common. Hypertrophic cardiomyopathy is reported in 20–25 % of individuals and is a significant cause of morbidity from cardiac failure and early mortality as encountered in this infant.

Severe forms of BSCL may have prenatal onset with intrauterine growth retardation. Presentation in the first months of life includes failure to thrive, hepatomegaly, lipoatrophy, facial dysmorphia, enlarged tongue, or developmental delay. All children with the neonatal or infantile presentation demonstrate lipoatrophy in the first year of life.

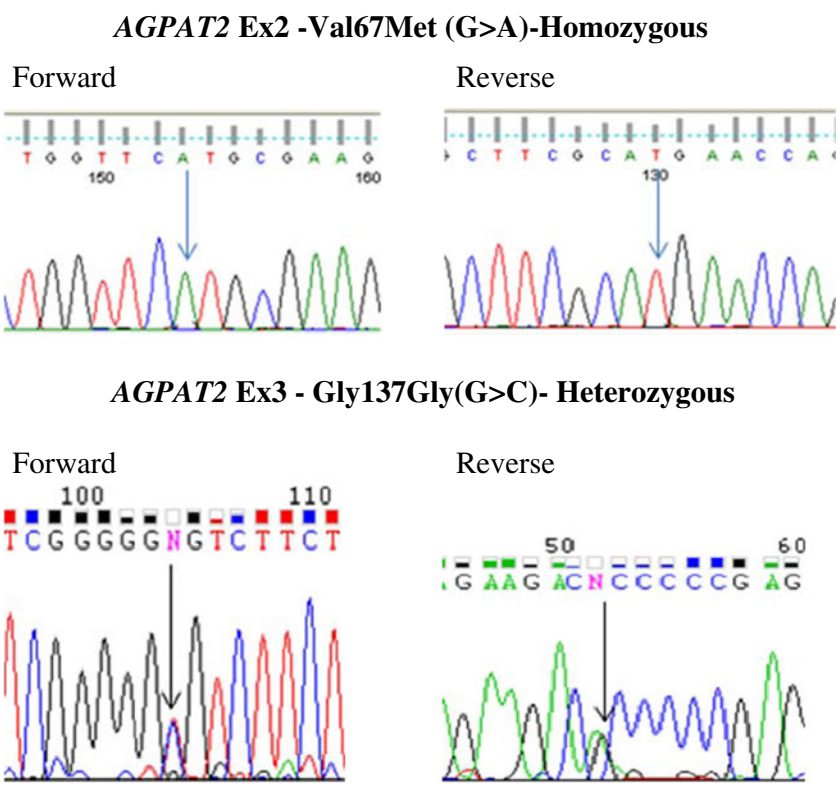

Fig. 1 Electropherogram showing Val67Met mutation in AGPAT 2 Gene

The neonate described in this report has severe BSCL. As a direct consequence of the absence of subcutaneous adipocytes, circulating levels of leptin are nearly undetectable in children with BSCL [4]. Based upon the existing literature, the clinical features , progression and severity in this infant, it is more likely to be a case of CGL Type 2. However the genetic diagnosis confirmed it to be AGPAT 2, which favours CGL Type 1. This is one of the rare case reports which has documented a severe involvement and early death with CGL Type 1 AGPAT2 mutation. This only confirms the need for a definite genetic diagnosis in all children with congenital generalized lipodystrophy (CGL) whatever be the phenotype.

Insulin resistance makes metabolic control of diabetes very difficult, often requiring high doses of insulin up to 6 units/kg/day [5]. Literature shows use of insulin up to 1000 units/day in those with CGL [6]. Restriction of total fat intake between 20 and 30 % of total dietary energy is often sufficient to maintain normal triglyceride serum concentration. Fibric acid derivatives and n-3 polyunsaturated fatty acids derived from fish oils can be tried for the treatment of extreme hypertriglyceridemia. Leptin treatment has proven successful in controlling both hypertriglyceridemia and diabetes mellitus but its availability outside clinical trials is limited [7]. Management of diabetes mellitus does not differ from that of childhood-onset diabetes mellitus, but glycemic control may be difficult in view of the high insulin resistance. Special education is required for individuals with psychomotor retardation or intellectual disability.

Pre-implantation genetic diagnosis is available for families with known genetic mutations and prenatal diagnosis by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks gestation or chorionic villus sampling (CVS) at approximately 10 to 12 weeks gestation.

To summarize, the proband in this case report harbours a novel mutation and a novel synonymous variant. The former mutation is homozygous. However, functional genetic studies and screening the AGPAT2 gene for mutation in the parents are mandatory to establish the pathogenicity of this mutation. Unfortunately, we have not been able to do any functional genomic studies which is a limitation in our report.

Neonatal diabetes with dysmorphic features and organomegaly raises the rare possibility of congenital lipodystrophy. This must lead one to consider genetic investigations and appropriate genetic counseling.

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