The Egyptian Journal of Medical Human Genetics (2014) 15, 87–90

Ain Shams University

The Egyptian Journal of Medical Human Genetics

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CASE REPORT

Intrafamilial variability in Simpson–Golabi–Behmel syndrome with bilateral posterior ear lobule creases

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Received 1 August 2013; accepted 12 August 2013
Available online 8 September 2013

KEYWORDS

Simpson–Golabi–Behmel syndrome;
Over growth syndromes;
Glypican (GPC) 3;
Polydactyly;
Macroglossia;
Accessory nipples

Abstract We report a family having two male sibs with Simpson–Golabi–Behmel syndrome (SGBS). Both have many typical features of the syndrome. These features included macrocephaly, macroglossia, post axial polydactyl of the left hand, bilateral low insertion of the thumb, multiple accessory nipples, hepatomegaly, and congenital heart. The patients have bilateral anterior helical ear pits, and characteristic posterior ear lobule creases. The older one has severe mental retardation and died at the age of 13 months with bronchopneumonia, and the younger one is 7 months old with normal mentality. The mother looks broad, stocky, and tall.

1. Introduction

Simpson–Golabi–Behmel syndrome (SGBS) is a rare inherited X-linked recessive multiple congenital abnormality/intellectual disability syndrome characterized by pre- and post-natal overgrowth, distinctive craniofacial features, macrocephaly, variable congenital malformations including supernumerary nipples, organomegaly, increased risk of tumor and mild/moderate intellectual deficiency [1].

There is great variability in severity of this syndrome, and mutations in the gene encoding glypican (GPC) 3 appear to be responsible for most type 1 cases of Simpson–Golabi–Behmel syndrome . Duplication of the GPC4 gene has also been associated with this syndrome; however, no duplications involving GPC3 have been related. The absence of a functional GPC3 may alter the normal differentiation of embryonal mesodermal tissues predisposing to the development of embryonal tumors [2].

Here we present a family having 2 sibs with many of the typical features of the SGBS with some unusual features.

2. Case report

Our case was a 7 month old male infant, forth in order of birth of one and half consanguineous Egyptian parents. The patient was delivered at 38 weeks of gestation and he was 3.4 kg weight at birth (at 75th percentile) after cesarean section delivery. No problems were noted during pregnancy.

The patient was referred to the Genetics Clinics, Pediatric Hospital, Ain Shams University for abnormal features. He has a broad stocky appearance, he can sit with support, and can recognize his mother (normal mentality). His weight is 10.4 kg (>97th percentile), length 73 cm (75th percentile), skull circumference 46.2 cm (95th percentile), with open anterior fontanel measuring 4 × 4 cm.

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Peer review under responsibility of Ain Shams University.

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http://dx.doi.org/10.1016/j.ejmhg.2013.08.001

The patient has macrocephaly with prominent hairy forehead, thick eyebrows, hypertelorism, broad nasal root with short nose, upterned nares, low set ears with bilateral helical ear pits on the front and characteristic ear lobule creases on the back. The mouth is large with thin upper and thick everted lower lip, unerupted teeth, and macroglosia (Figs. 1–3). The neck is short.

Both hands are large with low insertion of the thumb. The left hand shows postaxial polydactyly with clinodactly and partial cutaneous syndactyly of the 5th, and 6th fingers. In both hands the nail of the index finger is dysplastic, and partially embedded in terminal phalynx (Figs. 4 and 5).

There are bilateral supernumerary nipples on the anterior chest wall (Fig. 6). The abdominal wall shows diastasis recti. Cardiac examination detected harsh left parasternal pansystolic murmur propagated all over the heart. The liver is enlarged 4 cm below costal margin at the mid clavicular line. Chest, neurological, and genital examinations are normal. Vision and hearing are also normal.

ECHO cardiography detected perimembranous ventricular septal defect (VSD) measuring 0.42 cm. Abdominal ultrasonography detected hepatomegaly. Karyotype revealed 46, XY normal male karyotype. X-ray spine and ribs were normal.

The older brother of the patient suffered delayed motor and mental development. He was macrosomic, with same facial features together with pectus excavatum, ventricular septal defect and dysplastic embedded nails of both index fingers. He suffered from recurrent chest infection and died at the age of 13 months with bronchopneumonia.

The mother looks broad, stocky, and tall (2SD above the mean for age and sex) with no dysmorphic features.

3. Discussion

Patients with Simpson–Golabi–Behmel syndrome (SGBS, MIM: 312870) were first described by Simpson et al. in 1975 [3]. It is an X-linked syndrome characterized by pre- and postnatal overgrowth (gigantism), which clinically resembles the autosomal Beckwith–Wiedemann syndrome (BWS) [4].

SGBS is characterized by developmental delay, macrocephaly, abnormal facial appearance with prominent eyes, macroglossia, macrosomia, renal and skeletal abnormalities, supernumerary nipples, congenital heart defects, diaphragmatic hernia, polydactyly, rib malformations, hypoplasia of index finger and of the same fingernail, 2nd–3rd finger syndactyly, increased risk of neonatal death and of embryonal cancers during early childhood [5–7].

Figure 1 Facial features including hairy forehead, transverse slanting of palpebral fissures, broad nasal root, and low set ears.

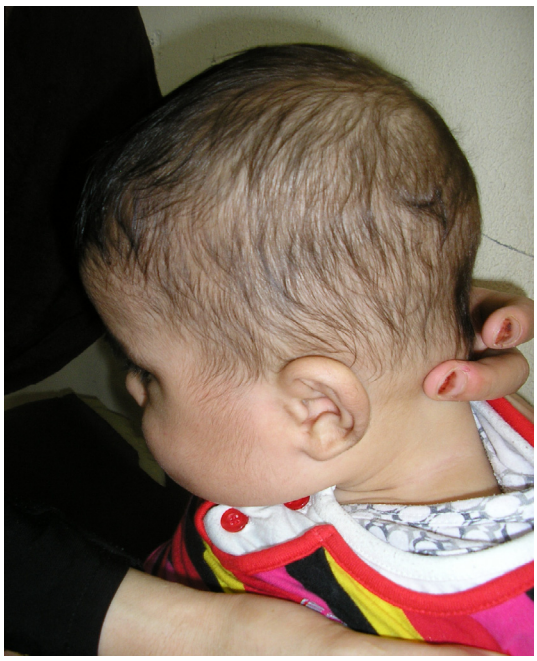

Figure 2 Short neck, and low set ears.

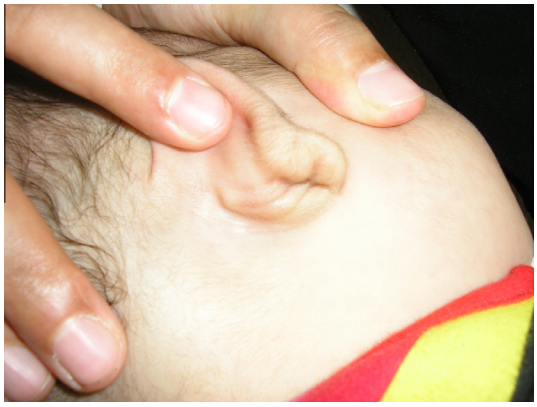

Figure 3 Longitudinal and transverse creases over the back surface of the ear lobule.

We present a family having two male sibs with SGBS. The young one, 7 months old has pre, and postnatal overgrowth, short nose with broad bridge, large mouth with enlarged tongue, and thick lower lip, mild hypertelorism, large ears with pits on the front and characteristic creases on back of the ear lobules (not reported before), short neck, supernumerary nipples, VSD, hepatomegaly, diastasis recti, dysplastic embedded nails of both index fingers with unilateral postaxial polysyndactyly in the left hand. The mentality is normal and there are no hypoglycemic attacks, sleeping or feeding difficulties.

The older sib of our patient had the same facial features with macrosomia, VSD, dysplastic embedded nails of both index fingers with polydactyly. However the mentality was

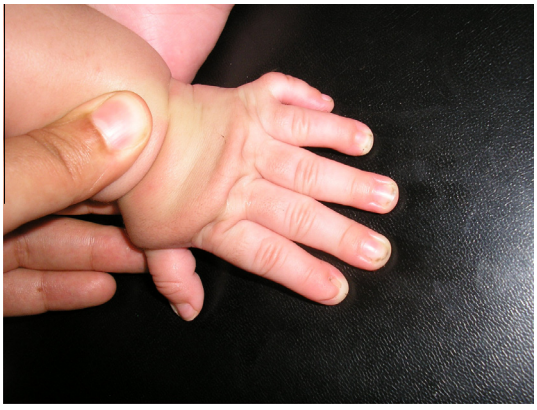

Figure 4 The left hand showed postaxial polydactyly, partial syndactyly between 5th and 6th fingers, low insertion of the thumb, clinodactyly of the 5th, and 6th fingers with dysplastic embedded nail of the index finger.

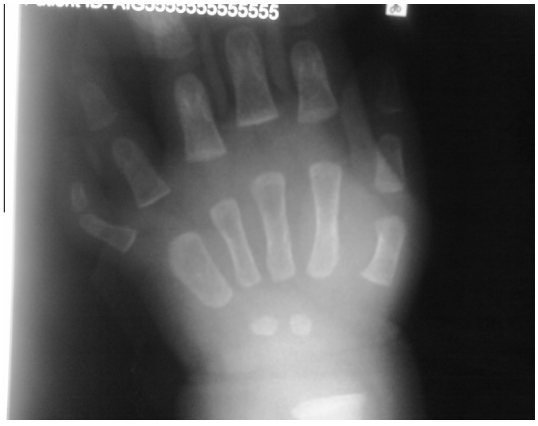

Figure 5 X-ray of left hand shows extra finger.

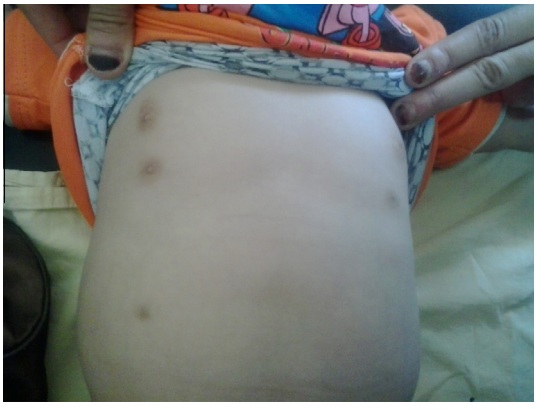

Figure 6 Chest and abdominal wall showed bilateral multiple nipples.

retarded and he suffered from recurrent chest infection and died at the age of 13 months with bronchopneumonia.

The phenotype of the proband mother who is considered as the carrier of the syndrome is also remarkable. She looks stocky and taller by 2SD above the mean for her age and sex, but she has no abnormal features. This probably represents a lyonization effect and should be looked for in all female relatives of SGBS. Extreme lyonization distortion during development can result in heterozygous female with a phenotype as severe as seen in hemizygotes [8]. This was reported previously in two females with typical features of SGBS and X, autosome translocations [9].

Our diagnosis was based on clinical findings together with family history consistent with X linked recessive inheritance.

There is a considerable overlap between SGBS and Beckwith–Weidmann syndrome (BWS), which is the most common overgrowth syndrome in infancy. BWS is characterized by macrosomia, ear creases/pits, macroglossia, omphalocele or umbilical hernia, visceromegaly, hemihypertrophy, embryonal tumors in childhood, renal abnormalities, neonatal hypoglycemia, facial nevas flamus, and diastasis recti [10,11].

However unlike BWS, SGBS has a higher incidence of congenital heart disease and additional features of macrocephaly, supernumerary nipples (a feature not reported in BWS), polydactyly with dysplastic embedded nails of the index fingers as reported in our patient which confirm our diagnosis. In addition BWS has anterior linear ear lobe/posterior helical ear pits which are different from the creases on the posterior side of ear lobules reported in our patient. It is important to differentiate them because genetic counseling varies. SGBS is X-linked recessive syndrome while BWS is autosomal dominant with imprinting [12].

Terespolsky et al. reported a wide clinical spectrum in reported cases of SGBS ranging from a mild form associated with long-term survival to an early lethal form with multiple congenital anomalies and severe mental retardation. It is not known whether severe familial cases are genetically distinct from and map to another locus [13].

Our patient had classic manifestations of SGBS with normal mentality (mild form), while his older brother most probably had a more severe form. He had the same clinical findings in addition to pectus excavatum, severe mental and motor retardation. So here we report not only interfamilial but also intrafamilial variability as reported previously [13].

Individuals with SGBS have been documented to have increased risk for intra-abdominal embryonic tumors such as wilms tumor and neuroblastoma, medulloblastomas, or CNS tumors in general [12,14]. So the family of this patient should be advised to perform regular screening by serum alphafetoprotein and β HCG measurement plus abdominal ultrasound every 4 months between 5 and 8 years and yearly in children older than 8 years [15].

A major gene for SGBS has been identified at Xq26. This gene is a member of the glypican related integral membrane proteoglycans (GPC3), mainly expressed in tissues derived from the mesoderm. Glypican are heparin sulfate proteoglycans. They are also linked to cell surface via glycosyl-phosphatidyl inositol and modulate the interaction between growth factors and receptors, and have a role in the control of cell growth and cell division [16].

Most cases of SGBS appear to arise as a result of either deletions or point mutations within the glypican-3 (GPC3) gene at Xq26, one member of a multigene family encoding for at least six distinct glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycans. As a class of molecules, heparan sulfate proteoglycans have been found to play essential roles in the development by modulating cellular responses

to growth factors and morphogens. Specifically, mutations in both the murine GPC3 gene and the Drosophila glypican, dally, have been found to modify cellular responses to bone morphogenetic proteins, providing important clues to the molecular basis of SGBS in humans. Despite these advances, there remains a paucity of information about the natural history of SGBS and optimal medical management strategies, and whether selective mutations influence the SGBS phenotype and risk of cancer [5].

Although in 1996, Glypican 3 (GPC3) was identified as the major gene causing SGBS, the mutation detection rate was only 28–70%, suggesting either genetic heterogeneity or that some patients could have alternative diagnoses. This was particularly suggested by some reports of atypical cases with more severe prognoses. In the family reported by Golabi and Rosen, a duplication of GPC4 was recently identified, suggesting that GPC4 could be the second gene for SGBS but no point mutations within GPC4 have yet been reported. In the genetics laboratory in Tours Hospital, GPC3 molecular testing over more than a decade has detected pathogenic mutations in only 8.7% of individuals with SGBS. In addition, GPC4 mutations have not been identified thus raising the question of frequent misdiagnosis [1].

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