Two Consecutive Pregnancies with Simpson-Golabi-Behmel Syndrome Type 1: Case Report and Review of Published Prenatal Cases

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Keywords

Fetal overgrowth · *GPC3* · Prenatal symptoms · Simpson-Golabi-Behmel syndrome · Ultrasound

Abstract

Fetal overgrowth and numerous congenital malformations can be detected in every trimester of pregnancy. New technologies in molecular testing, such as chromosomal microarray analysis and next-generation sequencing, continually demonstrate advantages for definitive diagnosis in fetal life. Simpson-Golabi-Behmel (SGB) syndrome is a rare but well-known overgrowth condition that is rarely diagnosed in the prenatal setting. We report 3 cases of SGB syndrome in 2 consecutive pregnancies. In our series, distinctive prenatal sonographic findings led to molecular diagnosis. Exome sequencing from fetal DNA revealed a hemizygous splice site variant in the *GPC3* gene: NM_004484.3:c.1166+1G>T. The mother is a heterozygous carrier. We also provide an overview of the previously published 57 prenatal cases

of SGB syndrome with prevalence estimation of the symptoms to aid prenatal differential diagnosis of fetal overgrowth syndromes.

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Simpson-Golabi-Behmel (SGB) syndrome type 1 (OMIM 312870) is a rare X-linked disorder with characteristic pre- and postnatal overgrowth and numerous visceral and skeletal anomalies. The prevalence of SGB syndrome is unknown. Approximately 250 cases were published in 2014 [Tenorio et al., 2014]. Multiple congenital anomalies have been described, mostly in postnatal series. Typical findings in SGB syndrome are macroglossia, facial “coarseness,” hepatosplenomegaly, cardiac malformations, skeletal anomalies, omphalocele, facial clefts, and high birth weight [Neri et al., 2013; Tenorio et al., 2014]. Due to the specificity of the presentation, SGB syndrome is usually diagnosed after birth, although affected fetuses may present with distinctive features on ultra-

Fig. 1. Dysmorphic features of twin fetuses on the 20-week scan. **a** Hypertelorism (proband 1). **b** Prefrontal edema and flat facial profile (proband 2). **c** Hyperechogenic kidneys (proband 1). **d** Micropenis (proband 1).

sound [Li and McDonald, 2009] or affect the maternal serum biochemical markers [Hughes-Benzie et al., 1994]. Careful ultrasound examination followed by chromosomal microarray analysis and whole-exome sequencing (WES) are effective tools for prenatal diagnosis of SGB syndrome [Kehrer et al., 2016; Magini et al., 2016].

We report 3 cases of SGB syndrome type 1 in 2 consecutive pregnancies. The first was a dichorionic twin pregnancy, where diagnosis was made using fetal DNA WES after very preterm delivery. The same variant was confirmed during the next pregnancy via amniocentesis.

We also provide an overview of the prenatal symptoms of SGB syndrome based on our series and previously published cases. For the purpose of literature review, a PubMed search was performed using the medical subject heading terms “Simpson-Golabi-Behmel” and “prenatal.” Of 17 available publications matching the search terms, we selected 11 articles. We only chose the articles clearly describing SGB type 1 prenatal features. We also included a review on SGB syndrome, in which the inci-

dence of prenatal symptoms was estimated [Cottureau et al., 2013]. As a result, 57 cases of prenatally detected SGB syndrome were found and calculations of the incidence of prenatal symptoms were made, together with our own 3 cases.

Clinical Report and Results

A 28-year-old primiparous Caucasian woman was referred for first-trimester screening at 13+3 weeks of pregnancy. She had a history of a spontaneous miscarriage in the first trimester, but was otherwise healthy. Ultrasound examination revealed a dichorionic/diamniotic twin pregnancy with markedly increased (5.25 and 4.18 mm) nuchal translucency (NT) in both twins. There was no evidence of anatomical defects at that point of time.

The patient was referred for chorionic villous sampling (CVS). Her CVS result was normal, i.e., 46,XY

Fig. 2. 20-week ultrasound showing dysmorphic features in twin fetuses. **a** Dysgenetic corpus callosum and flat fetal profile (proband 1). **b** Hypoplastic cerebellum (proband 1). **c** Enlarged liver (proband 2).

karyotype in both twins. We also preformed FISH analysis on metaphase chromosomes for CATCH syndrome (22q11.2) and Phelan-McDermid syndrome (22q13.3) to rule out these syndromes as the reason for large NT measurement; the results were normal. In addition, arrayed primer extension assay excluded certain variants for monogenic disorders associated with NT increase (CYP21A2, PTPN11, SOS1, KRAS, RAF1, MEK1, DHCR7, and SMN1 gene variants) [Kurg et al., 2000].

At 20+2 weeks, numerous anomalies were found during the fetal ultrasound scan. Both fetuses were highly dysmorphic, which strongly suggested monozygosity despite the dichorionic pregnancy.

The dysmorphic features in both twins included a flattened facial profile, hypertelorism, prefrontal edema, dysgenesis of the corpus callosum, hypoplastic cerebellum in 1 twin, hepatomegaly, mildly enlarged hyperechogenic kidneys, and a micropenis (Fig. 1, 2). Both fetuses were near the 90th centile in terms of weight, and both had polyhydramnios. In 1 fetus, we found an aberrant right

subclavian artery with suspicion for double aortic arch. Also in 3D-rendered images of the fetal face, unusual “edematous” appearance was noted as well as marked hepatomegaly (Fig. 3).

Chromosomal microarray analysis was performed in 1 twin. A small 1-Mbp microduplication in the 22q11.2q11.3 region was found, which was not consistent with the profound fetal findings. The patient was counseled by a clinical geneticist and a maternal-fetal medicine specialist in accordance with the fetal findings. The conclusion was that there was a high clinical suspicion of genetic syndrome. The option of pregnancy termination with postmortem examination and WES was offered. However, the patient opted for expectant management and decided to continue the pregnancy.

The patient developed severe polyhydramnios at 24+6 weeks and despite tocolysis went into preterm labor at 25+2 weeks. She delivered 2 premature boys: 1,044 g, Apgar 2/4/6 and 1,090 g, Apgar 5/4/7, both on the 75th weight centile.

Fig. 3. 22-week scan showing dysmorphic features in twin fetuses. **a** Round edematous face (proband 2). **b** Measurements of fetal liver (proband 1): antero-posterior length = 48.2 mm; cranio-caudal length = 40.2 mm. **c** Abdominal circumference of the fetus (proband 1) with transverse width of the liver (56.4 mm).

The postnatal phenotypic findings included marked macroglossia, hypertelorism, low-set ears, contractures of the fingers, and dysmorphic genitalia. General body edema in both neonates was noted as well. Intubation was very difficult in both twins due to macroglossia. Both babies were transferred to the neonatal intensive care unit. The first twin died on the sixth day of life due to acute necrotizing enterocolitis, while the second twin died on the fourth day of life due to infant respiratory distress syndrome. To investigate the molecular etiology, parent-offspring trio WES was performed on fetal DNA and identified a hemizygous splice site variant in the *GPC3* gene: NM_004484.3:c.1166+1G>T. The mother is a heterozygous carrier. This variant was absent from the BIOBASE Human Gene Mutation Database (HGMD Professional) [Stenson et al., 2009], Exome Aggregation Consortium (ExAC), and Genome Aggregation (gnomAD) databases [Lek et al., 2016]. Splice site variants usually cause the loss

of protein function; therefore, the detected variant was classified as pathogenic according to American College of Medical Genetics and Genomics (ACMG) guidelines [Richards et al., 2015]. Pathogenic hemizygous variants in the *GPC3* gene cause SGB syndrome [Pilia et al., 1996].

Pathoanatomical autopsy was performed for both twins. The main findings included hypertelorism, cardiomegaly, and hepatosplenomegaly (Fig. 4). Both twins had enlarged kidneys and adrenal glands, and both had cryptorchidism. No cardiac malformations were found.

The patient became pregnant again 4 months after the first delivery. She was referred for a first-trimester scan at 12+6 weeks. A right-sided facial cleft and NT enlargement were diagnosed. We did not perform CVS as the WES results from the previous pregnancy were pending. A follow-up scan at 17+0 weeks confirmed the diagnosis of a right-sided cleft palate and lip, dysmorphic male genitalia, and flattened facial profile with prefrontal edema.

Fig. 4. Autopsy findings. **a** Right-sided facial cleft, macrostomia, macroglossia (proband 3). **b** Flat facial profile (proband 2). **c** Marked hepatomegaly (proband 1).

Amniocentesis with targeted sequencing for the *GPC3* variant was performed from fetal DNA at 17+0 weeks. The same hemizygous c.1166+1G>T variant in the *GPC3* gene was identified and thereby molecularly confirmed SGB syndrome. The patient opted for pregnancy termination after multidisciplinary counseling.

The pathoanatomical findings of the fetus were consistent with SGB syndrome: macrosomia (590 g), hypertelorism, macrostomia, and hepatosplenomegaly, with 3 additional spleens (Fig. 4). The fetus had a right-sided cleft lip and hard palate. No cardiac malformations were found.

Discussion

Due to its distinctive features, such as high birth weight, organomegaly, and numerous anomalies of the viscera, genitalia and central nervous system, SGB syndrome is usually diagnosed postnatally. It has been proposed that polyhydramnios with prenatal overgrowth and elevated maternal plasma alpha-fetoprotein may be

prenatal markers of SGB syndrome [Hughes-Benzie et al., 1994].

Several authors have reported certain features on prenatal ultrasound that can facilitate SGB syndrome diagnosis before birth [Chen et al., 1993; Yamashita et al., 1995; Enns et al., 1998; Weichert et al., 2011; Garavelli et al., 2012; Cottureau et al., 2013; Kehrer et al., 2016; Magini et al., 2016; Mujezinović et al., 2016; Støve et al., 2017; Zimmermann and Stanek, 2017]. Table 1 summarizes the described prenatal findings from previously published cases and our cases.

As expected in overgrowth syndromes, the main prenatal feature of SGB syndrome is fetal macrosomia. In the prenatal series, fetal biometry data were available in 36 of 60 cases. Fetal macrosomia was detected in 86% of the cases. In our series, all 3 cases were macrosomic by week 20 of pregnancy.

Another typical finding in the SGB syndrome prenatal series was excess amniotic fluid. Polyhydramnios was reported in 70% of cases. In our patient's first pregnancy, extreme polyhydramnios was a reason for the very early preterm birth. However, how often preterm birth occurs

Table 1. Prenatal findings in Simpson-Golabi-Behmel syndrome type 1

	Hughes-Benzie et al., 1994	Yamashita et al., 1995	Weichert et al., 2011	Mujezinović et al., 2016	Chen et al., 1993	Garavelli et al., 2012	Kehrer et al., 2016	Magini et al., 2016	Stove et al., 2017	Enns et al., 1998	Cotterau et al., 2013	Zimmermann and Stanek, 2017	Li and McDonald, 2009	Our cas- es	Patients, N	%
Patients, #	1	1	1	1	3	1	4	4	1	2	36	1	1	3	60	
Prenatal findings																
Macrosomia/ overgrowth ^a	1/1	1/1	1/1	1/1	NA	NA	3/4	1/4	-	NA	19/20	NA	1/1	3/3	31/36	86
Polyhydramnios ^b	1/1	1/1	1/1	1/1	1/3	1/1	3/4	1/4	-	NA	24/33	1/1	1/1	2/3	38/54	70
Organomegaly ^c	NA	1/1	NA	NA	NA	NA	NA	1/4	-	-	18/29	NA	NA	2/3	22/37	60
Renal anomalies ^d	-	1/1	-	-	1/3	1/1	-	4/4	-	-	9/31	-	1/1	2/3	19/60	32
CDH	-	-	-	-	3/3	-	4/4	-	-	2/2	8/33	1/1	-	-	18/60	30
Enlarged NT/NF	NA	NA	1/1	NA	NA	NA	NA	2/4	-	NA	5/36	1/1	1/1	3/3	13/47	28
Craniofacial anomalies ^e	-	-	1/1	-	1/3	-	2/4	2/4	-	-	-	1/1	1/1	-	8/60	13
Cardiac anomalies	-	-	-	-	-	-	-	3/4	-	-	3/30	1/1	1/1	1/3	8/60	13
Elevated MSAFP ^f	1/1	NA	NA	NA	2/3	NA	NA	NA	NA	NA	3/5	NA	1/1	NA	7/60	12
Flat fetal profile	-	-	1/1	-	-	-	2/4	2/4	-	-	-	-	-	3/3	6/60	10
Genital anomalies	-	-	-	-	-	-	-	2/4	-	-	-	-	-	3/3	5/60	8
Ventriculomegaly	-	-	-	1/1	-	1/1	-	1/4	-	-	1/36	-	-	-	4/60	7
Cystic hygroma	-	-	-	-	2/3	-	-	1/4	-	-	-	NA	-	-	3/60	5
Facial cleft	-	-	-	-	-	-	-	1/4	-	-	-	-	1/1	1/3	3/60	5
CNS anomalies	-	-	-	1/1	1/3	-	-	-	1/1	-	-	-	-	2/3	3/60	5
Polydactyly	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/60	5
Omphalocele	-	-	-	-	-	-	2/4	1/4	-	-	1/1	-	-	-	2/60	3
Skeletal anomalies ^g	-	-	-	-	1/3	-	-	-	1/1	-	-	-	-	-	1/60	1.6
SUA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

CDH, congenital diaphragmatic hernia; CNS, central nervous system; NA, not available; NF, nuchal fold; NT, nuchal translucency; MSAFP, maternal serum alpha-fetoprotein; SUA, single umbilical artery. ^a Only prenatally detected macrosomia. ^b Not reported in every patient. ^c Data not available in every case. ^d Prenatally detected renal anomalies, including pyelocystitis and hydronephrosis. ^e Including absent nasal bone and hypertelorism, excluding facial clefts. ^f Reported in only 7 cases. ^g Only detected prenatally.

in pregnancies with SGB syndrome is not clearly reported. The largest review with prenatal series of SGB syndrome to date reported a high proportion of preterm births (13/42, 31%); most of the cases were moderately premature [Cotterau et al., 2013]. Four pregnancies in that series were terminated in the late second trimester; therefore, the true incidence of preterm birth could be even higher. It is very likely that the reason for most preterm deliveries was a marked excess of amniotic fluid.

In terms of visceral anomalies, the most frequent were organomegaly (60% of the prenatal cases), renal malformations (32%), and congenital diaphragmatic hernia (30%). Omphalocele was rare (5% of the prenatal cases). Cardiac malformations in SGB syndrome are very common. In a series of 101, mostly postnatal cases, Lin et al. [1999] found structural cardiac anomalies in 26% of the cases. In our analysis of published prenatal cases, cardiac anomalies were present in only 13% of cases. This can be explained by the fact that some minor cardiac anomalies are relatively difficult to diagnose prenatally and therefore are identified only after birth. Furthermore, our review includes only cases with clearly described prenatal findings. The distinctive facial features of individuals with SGB syndrome, usually described as facial “coarseness,” may already be present in fetal life. A “flat” fetal profile has been described in 10% of the cases. Our 3 cases all had prefrontal edema.

NT, a well-known marker of chromosomal anomalies, was first described by Nicolaides et al. [1992]. Enlarged NT may be present in cases of chromosomal pathologies [Kagan et al., 2008] as well as cardiac anomalies [Hyett et al., 1996; Sotiriadis et al., 2013] and certain genetic syndromes, especially Noonan syndrome [Pergament et al., 2011]. In 2009, Li and McDonald noted increased NT in the first-trimester scan of the fetus, which later was diagnosed with SGB syndrome. It is difficult to determine the estimated incidence of increased NT as a marker of SGB syndrome because, in most published cases, no data on the first-trimester scan are available. Out of 47 cases, with presumably available first-trimester scan information, increased NT or nuchal fold measurement was found in 13 cases (28%). In the largest review of SGB syndrome in which prenatal symptoms were described, it remains unclear whether NT measurements were available for all cases [Cotterau et al., 2013]. We suggest that increased NT could actually be present in a larger proportion of SGB syndrome cases, but prospective observational data are needed to support this.

Differential diagnosis of SGB syndrome is complex due to the large overlap with other overgrowth syn-

dromes. Vora and Bianchi [2009] proposed a diagnostic pathway for these conditions, suggesting that many factors should be considered, starting with pregnancy dating and the possibility of gestational diabetes. However, in terms of genetic syndromes, the following 5 are the most likely: Pallister-Killian, Sotos, Perlman, Beckwith-Wiedemann, and SGB. Considering the main ultrasound and clinical findings, the main overlap in clinical presentation in the prenatal setting for SGB syndrome would be with Beckwith-Wiedemann syndrome (BWS).

Beckwith-Wiedemann Syndrome

BWS (OMIM 130650) is an imprinting disorder with an estimated population incidence of 1 in 13,700 [Weksberg et al., 2010]. BWS is mainly caused by genomic imbalances or epigenetic alterations in the imprinting cluster at chromosome 11p15.5 [Öunap, 2016]. The majority of known cases of BWS are diagnosed after birth.

The clinical manifestations of BWS are summarized in the International Consensus Statement for Clinical and Molecular Diagnosis, Screening and Management of BWS. The prevalence of the main symptoms is as follows: macroglossia (85%), macrosomia (67%; pre-/postnatal overgrowth defined as >90th or >97th percentile) abdominal wall defects (68%) including omphalocele (44%), umbilical hernia (44%), and diastasis recti (22%). Other major features are organomegaly (53%), neonatal hypoglycaemia (51%), facial naevus flammeus (52%), and ear creases/pits (63%). The incidence of polyhydramnios is 53% [Brioude et al., 2018].

In 2005, Williams et al. proposed prenatal diagnostic criteria for BWS for the first time based on 19 published prenatal cases and 2 new cases described by the authors. Due to the complexity of the underlying molecular basis, prenatal diagnosis of BWS is challenging. In pregnancies without family history of BWS, none of the detectable findings are pathognomonic. The main reason for invasive prenatal testing for BWS is abdominal wall defects [Eggermann et al., 2016].

In comparison to SGB syndrome, abdominal wall defect is expected in numerous BWS cases. The incidence of omphalocele (herniation of the abdominal organs to the umbilical cord) in the prenatal series of SGB syndrome was relatively low (5%) (Table 1). Umbilical hernia or diastasis recti are found in 1/3 of SGB syndrome cases postnatally, but such findings are not diagnosed prenatally [Cottreau et al., 2013]. Renal pathologies are frequent in both syndromes, but cardiac anomalies are expected to be more frequent in SGB syndrome (postnatal series, 26%; prenatal series, 13%) (Table 1) [Lin et al.,

1999]. The major diagnostic features of BWS can also be present in SGB syndrome. This can render differential diagnosis between the 2 syndromes very difficult. BWS is unlikely to present skeletal and cardiac anomalies, except cardiomegaly [Knopp et al., 2015]. Therefore, in suspicious cases of fetal overgrowth with congenital anomalies, *GPC3* gene sequencing would be insufficient; genomic investigations should include BWS testing [Brioude et al., 2018].

Sotos Syndrome

Sotos syndrome (OMIM 117550), or cerebral gigantism, is an autosomal dominant disorder first described in 1964 in 5 children with overgrowth and acromegalic features [Sotos et al., 1964]. The molecular basis of the disease, haploinsufficiency or variants in the *NSD1* gene in the 5q35.3 region, was first described in 2002 [Kurotaki et al., 2002]. The prenatal findings in this overgrowth syndrome include macrocephaly, ventriculomegaly, corpus callosum dysgenesis, and enlarged cisterna magna. Most cases are sporadic and without previous family history [Tatton-Brown et al., 2005]. Brain anomalies in SGB syndrome, such as ventriculomegaly and other central nervous system malformations, are seen in the prenatal setting in 7 and 5% of the cases, respectively (Table 1). Therefore, in cases of overgrowth and macrocephaly with pathological brain findings in the absence of other congenital anomalies, Sotos syndrome should be considered [Vora and Bianchi, 2009]. In our series with 3 cases of SGB syndrome, 2 cases had corpus callosum dysgenesis and 1 had hypoplastic cerebellum. Other brain anomalies were not present.

Perlman Syndrome

This syndrome (OMIM 267000) is a very rare overgrowth syndrome; 29 cases have been described as of 2008 [Alessandri et al., 2008]. The molecular basis for the condition has been recently published: Perlman syndrome is now thought to be caused by mutations in the *DIS3L2* gene in chromosome 2q37.1 [Astuti et al., 2012]. The prenatal findings are very similar to that of SGB syndrome, including polyhydramnios, macrosomia, and renal dysplasia [Alessandri et al., 2008]. Perlman syndrome can be present prenatally with ascites, which has not been described in SGB syndrome. The prognosis of Perlman syndrome is extremely poor.

Pallister-Killian Syndrome

Pallister-Killian syndrome (PKS; OMIM 601803) is a rare genetic syndrome with multiple dysmorphic fea-

tures. PKS is caused by a tissue-limited mosaicism for an isochromosome 12p. Clinical manifestations are wide ranging, including multiple congenital anomalies, distinctive facial features, and mental retardation. A large review reported the incidence of malformations or impaired function in different organ systems in PKS [Wilkens et al., 2012]. The prenatal findings in PKS are well described and can be used in targeted prenatal diagnosis.

In comparison with SGB syndrome, PKS has a very specific and distinctive feature: rhizomelic limb shortening, which could be a reason for specific PKS testing in fetuses with increased NT [Kucińska-Chahwan et al., 2017]. The incidence of CDH is similar between the 2 syndromes as with that for polyhydramnios, which is a frequent finding in both syndromes.

For molecular confirmation of the diagnosis, WES is a promising method, enabling genetic diagnosis in up to 40% of the cases with severely dysmorphic fetuses [Carss et al., 2014; Alamillo et al., 2015; Drury et al., 2015]. WES enabled ultimate molecular diagnosis in our case, but due to the long turnaround time (15–18 weeks in Estonia), the results were available only during the second pregnancy. The turnaround time of the diagnostic test in prenatal setting is critical, especially in countries with a strict pregnancy termination policy. A recently published study from our department demonstrates the high diagnostic yield (26.3%) of large gene panel sequencing in pediatric and adult populations [Pajusalu et al., 2018]. The use of this method in prenatal testing has not been investigated, but the quick turnaround time (~4 weeks) appears very promising in the field of prenatal diagnosis.

Conclusion

We report 3 cases of SGB syndrome, where distinctive ultrasound findings led to molecular diagnosis via prenatal DNA samples. Increased NT thickness, prefrontal edema, organomegaly, facial cleft, and genital malformations were observed as reported in previously published prenatal cases.

The role of detailed ultrasound examination is crucial in cases of suspected genetic syndromes in prenatal life, and the major challenge is to determine the phenotype-genotype correlation at this period of time. Thus, modern sequencing technologies often facilitate the confirmation of diagnosis at molecular level. DNA sequencing, however, is challenged by the timeframe in prenatal diagnostics, and thus there is a need for the implementation of rapid diagnostic sequencing assays.

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Statement of Ethics

Informed consent was signed by the parents of the patients and this study was approved by the Research Ethics Committee of the University of Tartu (approval date 17/10/2016 and number 263/M-19).

Disclosure Statement

The authors declare no conflicts of interest.

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