Pediatr Pol 2023; 98 (3): 77-83
DOI: https://doi.org/10.5114/polp.2023.131546
Submitted: 22.06.2023, **Accepted:** 16.08.2023, **Published:** 25.09.2023

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

CASE REPORT

A rare case of family suffering from Simpson-Golabi-Behmel syndrome with an uncommon manifestation in a mother and 2 sons

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ABSTRACT

Simpson-Golabi-Behmel syndrome (SGBS) is a rare X-linked disorder resulting from mutations in the genes *GPC3* or *GPC4*. Symptoms of SGBS vary but commonly include overgrowth, craniofacial dysmorphias, and multiple birth defects. This syndrome has 2 subtypes, known as type I and type II. This report presents a case of SGBS occurring in several members of the same family, showing varying symptoms, including an 8-year-old boy, his older brother, mother, and mother's maternal half-brother. Exome sequencing identified the c.1159C > T variant of the *GPC3* gene in all members of the family mentioned above. Family history suggests that the maternal grandmother of the reported boys also presented symptoms of SGBS, although she was never tested. The purpose of this study is to present various clinical manifestations of SGBS, which may assist clinicians. We also note the manifestation of SGBS in a female because it is uncommon for carriers of the gene to present symptoms.

KEY WORDS:

Simpson-Golabi-Behmel syndrome, SGBS, congenital malformation syndrome, GPC3 gene mutation, excessive growth.

INTRODUCTION

Simpson-Golabi-Behmel syndrome (SGBS) is a rare genetic disorder that causes pre- and postnatal hypertrophy and a combination of multiple birth defects [1, 2]. This syndrome is the result of a semi-dominant gene mutation on either Glypican 3 (GPC3) or Glypican 4 (GPC4), both of which are X-chromosome-coupled genes that influence cell division and growth processes [2–4]. The most common clinical symptoms of SGBS, starting with the head, include macrocephaly (in about 70% of cases) and craniosynostosis. Characteristic features include frontal bossing, square head, coarse facial features, hypertelorism, oversized nose, macrostomia, and macroglossia [5, 6]. A cleft lip or palate is observed in 13% of cases. However, swallowing difficulty and laryngeal web are rare [6]. Computed tomography scans can reveal some respiratory abnormalities that occur infrequently. These abnormalities may include tubular bronchiectasis, subsegmental atelectasis, ectatic bronchi, and variations in the number of lobular bronchi [7]. Airway obstruction can also be caused by glossoptosis or micrognathia [1]. Cardiovascular malformations, conduction abnormalities, and cardiomyopathies are the most common cardiovascular lesions found in SGBS. Carotid artery dissections and hepatic vascular malformations are also frequently

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FIGURE 1. Elder brother on the left side and younger brother on the right side

Head enlargement, facial dysmorphia, thick facial features, extremities deformities, shortening of the index fingers, and macroglossia are visible in the younger brother. The elder brother presents head dysmorphias including enlarged head circumference, and hand dysmorphias including hand enlargement and syndactyly of index and middle fingers of left hand

FIGURE 2. Extremities deformities and shortening of the index fingers present in the younger brother

observed [3]. Supernumerary nipples are a very common feature of SGBS. A diaphragmatic hernia occurs in fewer than 10% of cases [3]. Abdominal anomalies including hepatomegaly, splenomegaly, and nephromegaly are present in a significant proportion of cases. It is possible that genital system defects occur, and hypospadias and cryptorchidism are relatively common [3]. Particular attention should be paid to the degree of intellectual impairment, characterized by high clinical variability. Some patients may maintain a normal level of intellectual performance. Speech disorders occur regardless of the degree of mental impairment. Skeletal abnormalities are frequent and encompass toe anomalies, rib malformations, scoliosis, and an altered number of vertebrae, as well as postaxial polydactyly or syndactyly [1, 5, 8]. Simpson-Golabi-Behmel syndrome can result in central nervous system abnormalities such as epilepsy, hypotonia, and obstructive sleep apnoea. Affected individuals may experience hyperactivity and significant difficulty in focusing attention [3].

This study presents a description of a family from Europe, specifically Poland, with a mutation causing SGBS. Family members diagnosed with the mutation comprised a woman in her twenties, her two sons, and her maternal half-brother. All of them exhibited symptoms of the disorder. The mother's mother is also suspected of suffering from SGBS; however, data on her was only collected from her medical history without genetic tests.

CASE REPORTS

PATIENT 1

The case subject is an 8-year-old boy diagnosed with SGBS type I at the age of 4 years. The patient was delivered by caesarean section at 36 weeks and 6 days of gestation due to polyhydramnios. The neonate showed prematurity features alongside macrosomia, with a birth weight of 3930 g (> 97%), length of 56 cm (> 97%), head circumference of 36 cm (75–90%), and chest circumference of 35 cm. His Apgar score was 6/7/9/9 at 1/3/5/10 minutes after birth. The patient presented multiple dysmorphic features and developmental defects from birth such as macrocephaly, hypertelorism, cleft palate, macrostomia, macroglossia, and coarse facies due to the rounded chin, frontal bossing, and broad nose (Figure 1). He also presented deformations of extremities including shortening of index fingers (Figure 2). The patient was diagnosed with congenital heart defects, namely ventricular septal defect, atrial septal defect, and patent ductus arteriosus, which were subsequently surgically corrected. Furthermore, the patient was diagnosed with cryptorchidism, micropenis, hepatomegaly, bilateral inguinal hernia, and anal atresia. Surgical intervention was performed to address, at first, anal atresia (with transient colostomy) and then both cryptorchidism and bilateral inguinal hernia.

The patient also presented symptoms from the central nervous system such as global development delay associated with partial intellectual disability and epilepsy. There were no variants of uncertain significance found on the exome that could be responsible for epilepsy. Additionally, the patient suffered from frequent respiratory infections. Based on the symptoms presented by the child, SGBS type I was suspected, and genetic tests were conducted at the mother's request to confirm the diagnosis. Whole exome sequencing using the Twist Human Core Exome + Twist mtDNA Panel + Twist RefSeq Panel + ClinVar Custom Panel kit was performed using the DNA isolated from the patient's peripheral blood. The laboratory test revealed the presence of a hemizygous genetic mutation in GPC3 (chrX: 133699902-G > A, NM_004484.3: c.1159C > T, p. Arg387Ter). Subsequently, the specific GPC3 gene mutation was analysed in the patient and his relatives by amplicon deep sequencing using the NEXTERA XT Illumina kit with the next-generation sequencing method on the Illumina HiSeq 1500 platform. The GPC3 gene mutation (c.1159C > T variant) was detected in the patient, his brother, and his mother, as well as the mother's half-brother. The mother was a heterozygous carrier, and all tested male representatives were hemizygotes. Additionally, the exam revealed that the patient's sister – the youngest sibling – and his father did not have the mutation. The segregation of the c.1159C > T variant of the *GPC3* gene in the family indicates a recessive X-linked pattern of inheritance. According to the literature, variant c.1159C > T of the GPC3 gene is associated with SGBS type I [9, 10].

As described above, the patient presented variable phenotypes that are frequently associated with SGBS type I. Upon follow-up, other development abnormalities, including accelerated growth, could be observed. During his physical examination at 6 years and 9 months old, his assessed growth age was 10 years and 6 months. Mid-parental height was 186.5 cm (> 97 centile), and his body weight was proportionate to his height. The patient was diagnosed with Meckel's diverticulum at the age of 2 weeks and underwent an operation *via* laparotomy.

The patient had also other disorders that are not associated with SGBS type I, including urinary incontinence, asthma, short-sightedness, and adrenal insufficiency.

PATIENT 2

Patient 2 is an 11-year-old maternal half-brother of Patient 1, who was also diagnosed with SGBS type I at the age of 7 years but manifested less severe symptoms. He was delivered at the 39th week by caesarean section due to foetal distress. He had macrosomia with the birth weight of 4000 g (90%) and a length of 60 cm (> 97%). His Apgar score was 4/5/6/9 at 1/3/5/10 minutes after birth. He presented dysmorphias characteristics for SGBS type I including an enlarged head circumference of 37 cm (> 97%) (Figure 1), cleft palate, hand enlargement, and syndactyly of the index and middle fingers of the left hand. He had various symptoms that are typical of this syndrome, such as patent foramen ovale, bilateral inguinal hernia, polycystic kidney disease, bilateral hearing loss, and excessive height. The bilateral inguinal hernia was treated *via* surgery. Like his younger brother, he was also diagnosed with epilepsy, which is a rare manifestation.

PATIENT 3

Patient 3 is the 25-year-old mother of the 2 presented boys, who was diagnosed as a heterozygous carrier at the age of 21 years. She had excessive height (182 cm), thick facial and hand features, first-degree atrioventricular block, precocious puberty, hyperopia (+6), and astigmatism. Furthermore, she was diagnosed with microprolactinoma.

Although the mother of Patient 3 was never diagnosed, her daughter listed her symptoms, such as dysmorphic features, excessive height (approximately 180 cm), defect of vision, and 3 myocardial infarctions. Figure 3 presents the chart of inheritance of SGBS in the family.

PATIENT 4

Patient 4 is the maternal half-brother of Patient 3. He manifested several symptoms including the following: excessive height (202 cm), gait abnormalities, dysmorphias including coarse facies, hypertelorism, and macrostomia, and he experienced cardiac, renal, and psychiatric problems. Initially, he was diagnosed with mucopolysaccharidosis type 3, probably due to the presence of elevated urine mucopolysaccharides (complete medical data are not available). The genetic test later revealed the GPC3 gene mutation. He died at the age of 40 years due to multiple organ failure.

Table 1 compares the prevalence of SGBS-related symptoms among all relatives of this family.

DISCUSSION

Simpson-Golabi-Behmel syndrome is a very rare disease, and so far there are not many cases described in the world literature. Two subtypes of this syndrome can be distinguished. Type I, also called classical SGBS, is much more common, while type II is rare with a high risk of death in the first 8 weeks of life and the presence of hydrocephalus [3]. Simpson-Golabi-Behmel syndrome is an X-linked disorder because the responsible genes –

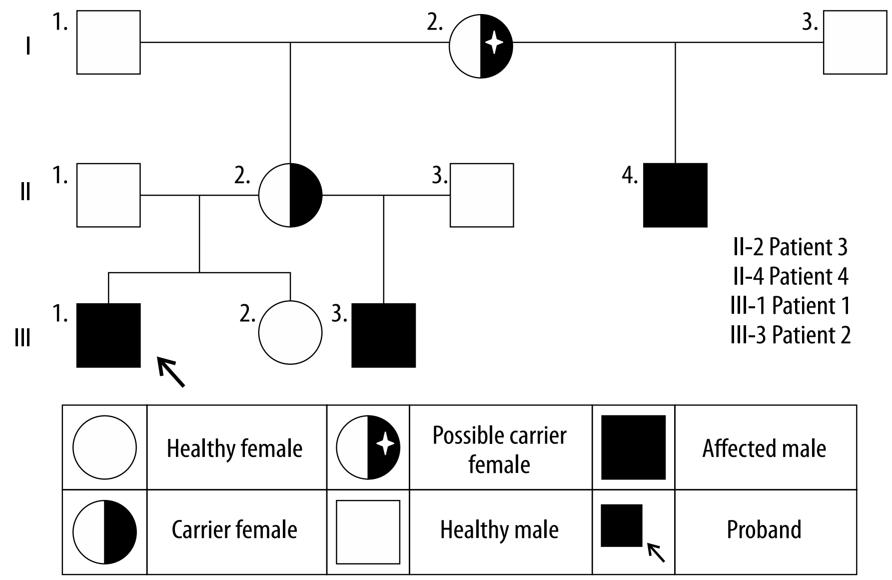

FIGURE 3. Genetic tree showing the occurrence of Simpson-Golabi-Behmel syndrome in the affected family

"Possible" refers to a case when a patient was not genetically tested but had symptoms. Other affected patients and carriers were tested genetically

GPC3/4 – are located on Xq26.2. To a limited extent, the GPC3 gene mutation can arise de novo, while a link between type I SGBS and the GPC4 gene mutation has not been established. Some researchers consider SGBS type II to be a separate disease entity with clinical manifestations overlapping with SGBS type I [3]. Statistically, SGBS increases the incidence of cancer, particularly kidney and liver cancer [1].

Cottereau *et al.* described a significant cohort of 42 patients with SGBS type I resulting from a mutation of the GPC3 gene, which is a remarkable number of cases considering the rarity of the syndrome. This study contains a table that elucidates the frequency (numerical and percentage) of various SGBS symptoms experienced by patients [11]. Given the qualification of SGBS into a set of diseases characterized by hypertrophy, SGBS should first be differentiated from Beckwith-Wiedemann syndrome (BWS), which has a similar clinical presentation to SGBS, although it is inherited in a different way. Because overgrowth, facial dysmorphism, and macroglossia are some of the most common symptoms of BWS, they may also be present in SGBS patients, as shown in our case [12]. It is crucial to differentiate between these 2 conditions. Therefore, we present certain features that, as well as the genetic test, which is the most reliable, may aid in distinguishing between the 2 disorders. Firstly, BWS is characterized by an absence of relative macrocephaly and skeletal abnormalities. Hemihypertrophy and omphalocele are frequently observed in BWS but not in SGBS. Additionally, individuals with BWS generally have smaller stature and are less dysmorphic than those with SGBS. Simpson-Golabi-Behmel syndrome is associated with a higher prevalence of developmental delay. Facial features also differ between the 2 conditions. Midface flattening and retrusion, infraorbital creases, ear creases, or posterior helical ear pits and thin vermilion of the upper lip are characteristic for BWS. In SGBS, a broader forehead, coarse features, down-slanted palpebral fissures, hypertelorism, macrostomia, and midline groove in the vermilion of the lower lip are more prevalent. Some of the key features of SGBS may not be present during infancy. There are few reported cases of structural and conduction cardiac abnormalities in BWS [1, 13]. Other conditions with a similar clinical presentation to SGBS are fragile X syndrome, Perlman syndrome, Weaver syndrome, neurofibromatosis type I, Marfan syndrome, Bannayan-Zonana syndrome, phosphatase and tensin homologue gene hamartoma tumour syndrome, Elejalde syndrome, Nevo syndrome, Gorlin syndrome, Fryns syndrome, mosaic trisomy 8, trisomy 15q26-qter, Pallister-Killian syndrome, and mucopolysaccharidoses should be considered in the differential diagnosis, depending on the symptoms and genetic testing. Because some symptoms of these disorders overlap with those of SGBS, misdiagnosis is possible, e.g. in our case, Patient 4 was first diagnosed with mucopolysaccharidosis. For the diagnosis of SGBS, it is necessary to establish the presence of typical clinical symptoms (visible hypertrophy, head and facial lesions, and defects in the extra-articular systems) and perform pedigree analysis and genetic testing, with special attention to the X chromosome and the *GPC3*, *GPC4* genes [3, 14].

The nonsense variant in the GPC3 gene: c.1159C > T, p.(Arg387*), which was identified in all 4 of our patients, is one of the most frequent mutations that cause SGBS type 1. In their research, Vuillaume *et al*. mentioned 6 unrelated families in which this variant was identified. It made it the second most frequent mutation causing SGBS type I after c.256C > T, p.(Arg86*), which was detected in 7 families [2]. Other types of mutations responsible for SGBS type I include large deletions, large duplications, frameshift indels, other types of nonsense mutations,

TABLE 1. Symptoms of Simpson-Golabi-Behmel syndrome present in the described patients

	Patient 1	Patient 2	Patient 3	Patient 4	Mother of Patient 3 and 4
Sex	Male	Male	Female	Male	Female
Symptoms *					
Macrosomia	+	+	+	nd	nd
Excessive height	+	+	+	+	+
Macrocephaly	+	+	–	nd	nd
Facial features					
Coarse/square face	+	+	+	+	+
Hypertelorism	+	–	–	nd	nd
Broad nasal bridge	+	–	–	nd	nd
Macrostomia	+	+	+	nd	nd
Macroglossia	+	–	+	nd	nd
Cleft palate	+	+	–	nd	nd
Cleft lip	–	–	–	nd	nd
Extremities					
Hand enlargement	+	+	+	nd	nd
Syndactyly of index finger	–	+	–	nd	nd
Shortening of index finger	+	–	–	nd	nd
Genito-urinary					
Hypospadias	–	–	/	nd	/
Cryptorchidism	+	–	/	nd	/
Micropenis	+	–	/	nd	/
Polycystic kidney disease	–	+	–	nd	nd
Nephromegaly/renal dysplasia	–	–	–	nd	nd
Gastro-intestinal					
Hepatomegaly	+	–	–	nd	nd
Splenomegaly	–	–	–	nd	nd
Inguinal hernia	+	+	–	nd	nd
Diastasis rectii/umbilical hernia	–	–	–	nd	nd
Diaphragmatic hernia	–	–	–	nd	nd
Cardiovascular					
Congenital heart disease(ASD or VSD or PFO)	+	+	–	nd	nd
Carotid artery dissections	–	–	–	nd	nd
Hepatic vascular malformations	–	–	–	nd	nd
Conduction heart defects	–	–	+	nd	nd
Respiratory					
Recurrent respiratory infections	+	–	–	nd	nd
Anatomical respiratory defects	–	–	–	nd	nd
Central nervous system					
Epilepsy	+	+	–	nd	nd
Hearing loss	–	+	–	nd	nd
Intellectual impairment	+	–	–	nd	nd
Other					
Supernumerary nipples	–	–	–	nd	nd
Microprolactinoma	–	–	+	nd	nd
Precocious puberty	–	–	+	nd	nd

ASD – atrial septal defect, PFO – patent foramen ovale, VSD – ventricular septal defect
+ present
– not present
nd – no data
** Based on the Genetic and Rare Diseases Information Centre [5]*

missense mutations, in-frame indels, splice sites, and chromosomal translocations [2]. Two cases of duplications are described in the following study by Vuillaume *et al*. This study describes 4 family members with confirmed GPC3 mutations who exhibited diverse symptoms of SGBS syndrome [4]. Sajorda *et al.* [1] and Tenorio *et al.* [3] provided a great amount of information on the topic including possible clinical manifestations. The symptoms observed in our cases closely resemble those presented in the articles on the disease. Sajorda *et al.* mention macrocephaly as one of the key symptoms, observed in 70% of children [1]. Coarse face, cleft palate, and macroglossia, which were present in Patient 1 and Patient 2, can also be observed in numerous cases [11]. This disorder can manifest in various ways, with different levels of severity and progression. Symptoms of SGBS can vary from minor, such as in symptomatic carriers of the gene, to severe, affecting multiple body systems and resulting in intellectual disability and multiple deformities, which is frequently observed in males. In this case, the patient with the most extensive range of SGBS symptoms is Patient 1. He was diagnosed with multiple dysmorphic features, developmental defects, cardiac defects, and genitourinary and pulmonary disorders. One of the symptoms present in both Patient 1 and Patient 2 was cleft palate, which is a prevalent symptom, reported in many cases, e.g. by Thomas *et al.* [15]. Moreover, Liu *et al.* described a case in which the prenatal ultrasound examination at 21 weeks of gestation revealed the presence of an anomaly characterized by a division or gap in the upper lip and palate, which was diagnosed as cleft lip and palate [16]. Also, Chong *et al.* described a similar case in which an ultrasound examination performed at the 30th week of gestation revealed many pathological changes, including a left-sided cleft [17]. It is different from the case we have described because the prenatal examination did not reveal any abnormalities in the patient, and all the defects were diagnosed after birth. Reischer *et al.* described a case of dichorionic-diamniotic twin pregnancies in the first trimester. Using ultrasound and genetic testing, it was observed that one of the foetuses developed polyhydramnios. To protect the unaffected twin, it was decided to selectively remove the affected foetus. This was the first case of SGBS in a multiple pregnancy [18].

Patient 1 exhibits SGBS manifestations in multiple body systems, requiring care from specialists across various fields of medicine. Patient 1 also suffers from central nervous system disorders, including intellectual disability and epilepsy, which is an uncommon and scarcely documented symptom of SGBS. A PubMed search revealed a similar case of another patient with SGBS who exhibited epilepsy and intellectual disability [19]. In addition, Patient 1 faces several urogenital problems, including cryptorchidism, urinary incontinence, and micropenis, previously reported by Verloes *et al*. in 1955 [20]. Anal atresia is another symptom present in Patient 1 that is associated with SGBS [21, 22]. Our patient 1 experiences recurrent respiratory infections, which is a noteworthy symptom. A case in the literature describes a patient with the same symptom due to a particular disease [23].

There are limited reports of female carriers presenting symptoms of SGBS. Several studies have shown that all males with the GPC3 mutation develop clinical symptoms, whereas it is not possible to determine the likelihood of symptoms in a heterozygous female [3]. Similarly to our Patient 3, the female patient described by Fernandes *et al.* exhibited facial dysmorphisms such as up-slanting palpebral fissures, broad and flat nasal bridge, and macrostomia. The case report presented herein is particularly significant because it describes one of the few familial cases of SGBS reported in the literature [24]. In 2019 Schirwani *et al.* reported 4 cases of symptomatic women suffering from SGBS. One female patient in their study presented with an umbilical hernia whereas our Patients 1 and 2 suffered from an inguinal hernia. However, our female Patient 3 did not present any herniae [25]. Schirwani *et al*. also reported dysmorphic features, atrial septal defect, and patent ductus arteriosus. These symptoms were also exhibited by our Patient 1. Two of the described patients presented with developmental delay and mild intellectual disability, without showing any other notable characteristics of SGBS type 1. The third patient experienced speech delay, significant intellectual disability, and received a diagnosis of autism. Two of the described patients also presented developmental delay and mild intellectual disability but did not display any other prominent characteristics of SGBS type 1. The third patient experienced speech delay, significant intellectual disability, and received a diagnosis of autism [25]. Patient 3 did not present any symptoms related to the central nervous system; however, both of her sons (Patient 1 and Patient 2) exhibited intellectual disability and epilepsy.

CONCLUSIONS

Simpson-Golabi-Behmel syndrome is a rare disorder that can display various clinical manifestations. It is our hope that this study will expand the existing knowledge on this disease and be beneficial to clinicians.

DISCLOSURE

The authors declare no conflict of interest.

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