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Case Report

Simpson-Golabi-Behmel Syndrome and Pituitary Insufficiency: Genetic Predisposition or Coincidence

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Abstract

Simpson-Golabi-Behmel syndrome (SGBS) is a rare genetic disorder that is characterized by the overgrowth of various parts of the body. We present a unique case of a young man with SGBS associated with pituitary insufficiency. This association has not been described yet in the literature. The patient was diagnosed with SGBS at 12 years, which was further confirmed through genetic testing (de novo nonsense mutation of the GPC3 gene). At the age of 18, the patient consulted for alteration of the general condition with asthenia. Laboratory evaluation revealed pituitary insufficiency consisting of central hypothyroidism associated with partial secondary adrenal insufficiency. The pituitary MRI was unremarkable. So far, Pituitary insufficiency has never been described in SGBS cases. To our knowledge, this is the first case reported in the literature.

Keywords: Simpson-Golabi-Behmel syndrome, pituitary insufficiency, overgrowth syndrome, mutation of the GPC3 gene, central hypothyroidism, secondary adrenal insufficiency.

INTRODUCTION

Simpson–Golabi–Behmel syndrome (SGBS) is a rare X-linked disorder caused mainly by a loss-of-function of the glypican-3 gene (GPC3) and characterized by multiple congenital anomalies with overgrowth syndrome. It was first reported by Simpson et al. in 1975 and subsequently described by Golabi and Rosen and Behmel *et al*., in 1984 (Vuillaume ML *et al*., 2018). The clinical phenotype ranges from very mild forms in carrier females to lethal forms in affected males (Fernandes C *et al*., 2021). The diagnosis of SGBS is usually suspected based on suggestive clinical manifestations, and in some cases, where family history is consistent with X-linked inheritance, it is confirmed through genetic testing of the glypican-3 gene (Vuillaume ML *et al*., 2019).

We report the case of an 18-year-old Arab male with SGBS associated with pituitary insufficiency.

CASE PRESENTATION

We present an 18-year-old male of consanguineous parents with a history of bilateral cryptorchidism surgery in childhood. The patient was initially consulted at the age of 12 for mental retardation and difficulties at school associated with tall stature and special facies. Based on the strong clinical suspicion, a genetic analysis of the GPC3 gene was performed, which revealed that the patient carries a de novo nonsense mutation (his mother is not a carrier of this mutation) thereby confirming the diagnosis of SGBS. At the age of 18, the patient consulted for alteration of the general condition with asthenia. The patient's physical examination revealed a blood pressure of 120/60 mmHg, a heart rate of 64 beats/min, tall stature (height: +3 standard deviations), macroskelia, craniofacial dysmorphism (prominent forehead, hypertelorism, a broad nasal bridge, anteverted nostrils, and macrostomia), pectus excavatum, supernumerary nipples, polydactyly, and hyperpigmented plaques over the chest and upper portion of the abdomen (Figure 1). Pubic hair and genitalia were both on a 4-point ordinal Tanner scale. Informed consent was obtained from the patient for the publication of this case report and its accompanying images.

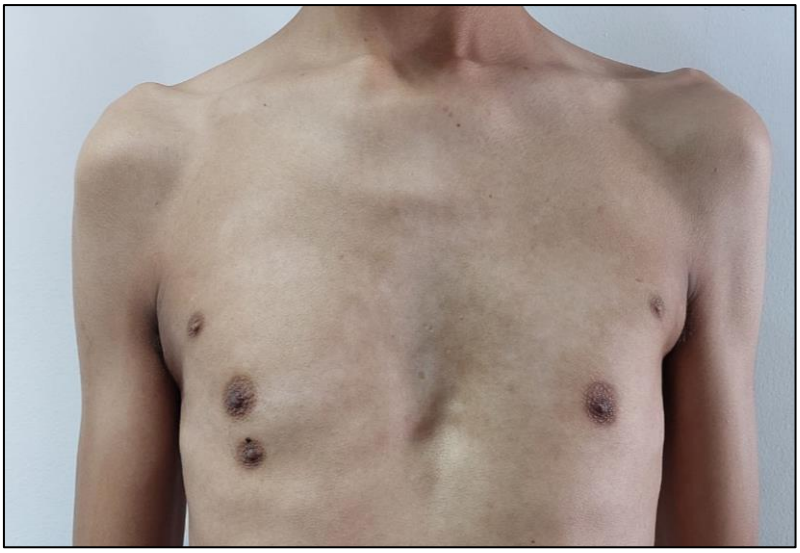

Figure 1: Supernumerary nipples in our patient

Laboratory tests revealed central hypothyroidism (free T4 levels were low with normal TSH levels) associated with partial secondary adrenal insufficiency: 8 am serum cortisol levels were 60 ng/ml, and 117 ng/ml after the Insulin-induced hypoglycemia test (Table 1). Kidney function and liver function tests were normal. Tumor marker tests came back negative (Table 2). Other laboratory results are summarized in Table 3.

Table 1: Serum cortisol levels after insulin-induced hypoglycemia test

Time (min) after insulin injection (0.15 U/kg)	t = 0	t = 15	t = 30	t = 45	t = 60	t = 90	t = 120
Serum cortisol level (ng/ml)	87	84	86	104	109	117	105
Blood glucose (g/L)	0.84	0.54	0.36	0.43	0.66	0.98	1.20

Table 2: Serum tumor markers of the patient

Marker	**Serum level**	**Normal range**
HCGβ: free β-subunit of human chorionic gonadotropin (mUI/ml)	< 1.2	
AFP : α-fetoprotein (ng/ml)	1.44	< 7
LDH : lactic dehydrogenase (U/L)	176	125-220
CEA : carcinoembryonic antigen (ng/ml)	1	< 5
CA 19-9 : carbohydrate antigen 19-9 (UI/ml)	< 2	< 33
CA 125 (UI/ml)	6.4	< 36
CA 15-3 (UI/ml)	15.5	< 28

Table 3: Other laboratory results of the patient

	Serum level	**Normal range**
Free T4 (ng/dl)	0.68	0.7-1.48
TSH (uUI/ml)	4	0.35-4.9
8 am cortisol (ng/ml)	60	37-194
Luteinizing hormone (LH) (mUI/ml)	3.57	1.2-10
Testosterone (ng/ml)	4.3	
Prolactin (ng/ml)	10.4	2.6-18

The pituitary MRI was unremarkable. Echocardiography showed a structurally normal heart. Abdominal ultrasonography revealed dilatation of the left renal vein (Nutcracker syndrome), and Grade II varicocele was noted based on the Sarteschi scoring system and left seminal vesicle cyst.

Treatment consisted of thyroid hormone replacement therapy with levothyroxine (LT4) and hydrocortisone substitution therapy during stress and intercurrent illness. The patient is clinically normal and the FT4 levels returned to the upper third of the reference range. Otherwise, the patient was referred to the urological department for further evaluation and treatment of his urologic problems.

DISCUSSION

SGBS is a very rare genetic syndrome. The prevalence of this condition remains unknown (Vuillaume ML *et al*., 2019). Most cases were observed to follow an X-linked inheritance though some cases (25%) are due to de novo mutations (De Paepe ME *et al*., 2018). Classical SGBS (also known as SGBS type I) is caused as a result of defective glypican-3 (GPC3) and glypican-4 (GPC4) genes on chromosome Xq26 (De Paepe ME *et al*., 2018). The majority of SGBS1 patients have point mutations or deletions in GPC3 (Schirwani S *et al*., 2019). GPC3 encodes a membrane-associated heparan sulfate proteoglycan that plays an important role in growth control (Fernandes C et al, 2021). To date, 86 distinct GPC3 variants have been reported in 120 unrelated patients, ranging from single nucleotide variations to complex genomic rearrangements (Vuillaume ML et al, 2018).

Clinically, SGBS in males is characterized by fetal macrosomia, postnatal overgrowth, macroglossia, and visceromegaly, particularly facial features, extremities abnormalities, supernumerary nipples, cardiac, skeletal, gastrointestinal, and genitourinary malformations, learning difficulties in some cases, and an increased tumor risk (especially Wilms and liver tumors) (Vuillaume ML *et al*., 2019). In our current case, there was no evidence of a tumor on the imaging, and tumor markers were negative.

In most cases with SGBS type, I survive into childhood or adulthood. However, neonatal mortality rates of up to 50% have been reported in affected males, generally attributed to cardiac malformations and/or arrhythmias (De Paepe ME *et al*., 2018). Thankfully, in our case, the echocardiography did not show any cardiac malformations.

The association between Simpson-Golabi-Behmel syndrome and pituitary insufficiency has not been reported in the literature. The observation of this association in our patient raises the following questions: is it a fortuitous association or is there a variant in GPC3 that predisposes to the development of pituitary hormone deficiencies?

Youn Hee Jee *et al*., have discovered a variant in GPC3 in a young male patient with growth hormone deficiency and ectopic posterior pituitary gland, however, other pituitary hormone deficiencies were not observed (Jee YH *et al*., 2021).

We believe that the presented case may contribute to expanding the clinical spectrum of SGBS and open up prospects for screening the risk of pituitary insufficiency in SGBS patients.

CONCLUSION

Simpson-Golabi-Behmel syndrome is a rare x-linked disorder. Its diagnosis is usually made based on typical clinical manifestations and is confirmed through genetic testing of the glypican-3 gene. Our case is unique in its presentation, where SGBS is associated with pituitary insufficiency highlighting the interest in evaluating pituitary functions in patients with GBS and may contribute to broadening the clinical spectrum of SGBS.

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