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SIMPSON-GOLABI-BEHMEL SYNDROME: A RETROSPECTIVE CASE REPORT WITH LITERATURE REVIEW

ENT

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ABSTRACT

Simpson-Golabi-Behmel Syndrome is a rare overgrowth syndrome which is X-linked. The disease was reported for the first time by Joe Leigh Simpson et al. in 1975. Its prevalence is not known and so far 250 cases have been reported in literature. It is characterized by prenatal and postnatal overgrowth, variable congenital anomalies, distinctive craniofacial features, organomegaly and increased risk of tumor. There can be involvement of central nervous system, skeletal system, heart, gastrointestinal tract, kidneys. There can be intellectual impairment with speech delay though normal intelligence has been seen in number of cases. It has 2 different clinical subtypes: SGBS type I is due to mutation in genes GPC3 and GPC4, located on the X chromosome. In SGBS type II, there is mutation in the genes OFD1 and PIGA on the X chromosome. Here we represent a retrospective case of the classical form of Simpson-Golabi-Behmel Syndrome (Type I), a 12 year old male and discuss relevant management and considerations.

KEYWORDS

Simpson-Golabi-Behmel Syndrome, rare overgrowth syndrome, X-linked, GPC3 mutation.

INTRODUCTION:

Simpson-Golabi-Behmel Syndrome is a rare overgrowth syndrome which is X-linked. This disease was first reported by Joe Leigh Simpson et al. in 1975 [1] and subsequently by Golabi and Rosen [2] as well as Behmel [3] in 1984. In 1988, Neri summarized previous case reports and named the disease as SGBS [4]. Earlier terms like "Gigantism-dysplasia syndrome", "Golabi-Rosen syndrome", "Simpson dysmorphia syndrome", "Bulldog syndrome", "Encephalotropho-schisis syndrome" are not used any more.

Its prevalence is not known and about 250 cases have been reported in literature.

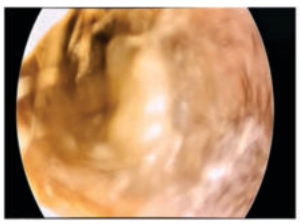
Being X-linked disorder females are carrier but lyonisation phenomenon may cause mild physical findings in females. In lyonisation one of the two X chromosomes is randomly and permanently inactivated and if the inactivated X chromosome carries the normal as opposed to the mutant gene, it may result in clinical expression of disease.

Two different clinical subtypes of the disease have been known. The classical form (SGBS or SGBS type I) associated to mutations in GPC3 and a lethal form (SGBS type II) associated to a different region of chromosome X (Xp22.2) [5].

As very small number of cases have been reported here we present a retrospective case report of Simpson-Golabi-Behmel Syndrome type I.

Case Report:

A 12 year old male patient came to the ENT OPD with complaint of pain in Left ear. Pain was moderate in intensity, increased by pressure on tragus. On examination: debris was present in ear; meatal lining was inflamed and swollen. Ear toilet was done, debris was removed gently. Tympanic membrane was congested and oedematous. Patient was advised conservative treatment for Left Otitis Externa.



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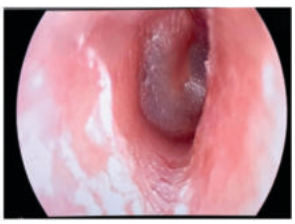
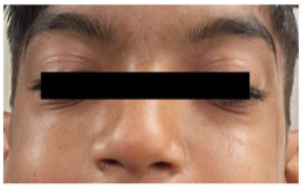
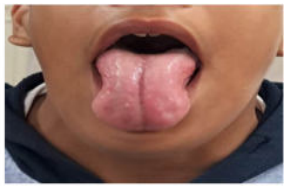


After suction cleaning

On inspection child had coarse facial features : hypertelorism, B/L epicanthal folds, depressed nasal bridge with bulbous tip, thick everted lower lip, macrognathia, macrostomia, macroglossia, fissured tongue, frontal bossing.





He looked bigger than his age. His height was 169 cm which is greater than 97 percentile and weight was 70 kg which is again greater than 97 percentile. So, there were clear signs of overgrowth.

Mother gave history of normal vaginal delivery in some civil hospital. He was 1st born baby of non- consanguineous couple. He was a post mature baby with birth weight of 4.4 kg with no birth asphyxia born to 21 year old mother; antenatal NAD. Following birth mother noticed that the baby was not feeding properly. They took baby to nearby hospital where child was found to have cleft palate and delayed milestones. Developmental delay with social smile at 6 months .At eight and half months infant was not able to sit and walk. The child was referred to higher centre. On basis of clinical features genetic testing was recommended. Genetic testing confirmed mutation in GPC3 gene and the child was diagnosed with SGBS Syndrome type I.

He had grade II incomplete cleft palate with tongue tie. Relevant investigations were done for detection and management of other features of the syndrome. He underwent pyeloplasty for left PUJ obstruction at 15 months of age. Palatoplasty for Cleft palate at 16 months of age, right orchidopexy for right undescended testis & tongue tie release at 20 months.

DISCUSSION:

SGBS is a rare overgrowth X-LINKED syndrome which is difficult to diagnose due to different clinical manifestations in different individuals. Since it is an X-linked disorder all males with mutation will have the disease. Females are carriers but some have symptoms which are usually mild. So far about 250 cases have been reported in literature with prevalence not known.

CAUSES:

SGBS type I is due to mutation in genes *GPC3* and *GPC4*, located on the X chromosome. In SGBS type II, there is mutation in the genes

OFD1 and *PIGA* on the X chromosome.

GPC3 gene has important role in control of growth. GPC3 is a growth inhibiting factor which balances growth promoting factors. Therefore, its mutation leads to overgrowth.

Clinical Features:

Clinical features vary from patient to patient. All patients may not have the same symptom, all symptoms may not be present in the same patient. These include wide or protruding jaw, large tongue, palate abnormalities, widened nasal bridge, upturned nasal tip, narrow top lip, grooved tongue, organomegaly, malformations of kidney, congenital diaphragmatic hernia, neoplasm, neonatal hypoglycemia, muscle weakness, bone pain, advanced bone age, malocclusion of teeth, polydactyly, pectus excavatum, supernumerary nipples, defects of the chambers of the lungs, presence of rotated large intestine, structural and conductive cardiac defects, multicystic dysplastic kidneys, seizures, brain malformations, developmental disabilities, intellectual disability- can be inexistent or mild to severe, increased anxiety.

There is increased likelihood of cancers including lung cancers, wilms tumors (kidney and brain), hepatic carcinomas, neuroblastoma and cancer of the adrenal gland. Ninety percent of currently manifested tumors have been found to be localized to the abdominal regions with the majority of those being both wilms and neuroblastoma, then adrenal cancers.

Diagnosis & Management

Diagnosis of SGBS syndrome can be made by prenatal ultrasound. Aids to diagnosing might include the presence of macrosomia, polyhydramnios, elevated maternal serum-α-fetoprotein, cystic hygroma, hydrops fetalis, increased nuchal translucency, craniofacial abnormalities, visceromegaly, renal abnormalities, congenital diaphragmatic hernia, polydactyly, and a single umbilical artery.[6]

Prenatal testing is available. Evaluation by a medical geneticist is recommended for those strong indications or likelihood of SGBS and for immediate relatives of those genetically confirmed to have SGBS. [6]

As high rate of male deaths is seen during neonatal period early detection of tumors is important. In order to detect the presence of tumors, screening in SGBS patients should include abdominal ultrasound, urinalysis, and biochemical markers that screen for embryonic tumors. [7]

On birth hypoglycemia must be assessed along with cardiac, genitalia, liver, and adrenal evaluations. Such tests include chest radiographs, electrocardiogram, echocardiogram, renal sonography, and abdominal sonography and CT to test for possible abnormalities. [8]

An early diagnosis is to be made on basis of clinical features, family history, genetic testing, ultrasound and relevant investigations mentioned above so that necessary interventions can be made on time to save the child.

Genetic testing involves analysis of GPC3 gene. SGBS Type I patients need to be screened regularly for hypoglycemia right after birth, any breathing or feeding problems. Renal function test should be monitored; sideway curvature of spine should be checked. Social and intellectual development should be monitored. The child should be screened for Wilms and hepatic tumors, gonadoblastoma, neuroblastoma.

Genetic counseling of parents and their families should be done.

Differential diagnosis include Beckwith-Wiedemann syndrome with CDKN1C mutations. It has the maximum clinical overlap with SGBS. Other entities that should be considered in the general differential diagnosis of SGBS syndrome are: Weaver syndrome, Perlman syndrome; Fragile X syndrome; Bannayan-Zonana syndrome; PTEN hamartoma tumor syndrome; Marshall Syndrome, Nevo syndrome; Neurofibromatosis type I; Marfan syndrome; nevoid basal cell carcinoma syndrome

(Gorlin syndrome), Fryns syndrome, Elejalde syndrome (acrocephalopolydactylous dysplasia), mosaic trisomy 8, Pallister-Killian syndrome and trisomy 15q26-qter [9].

Prognosis:

Prognosis and survival varies from individual to individual as there is wide range of signs and symptoms. There can be infantile lethal form; milder form and carrier females who live into adulthood.

CONCLUSION:

Simpson-Golabi-Behmel Syndrome is a rare X-linked syndrome with two clinical subtypes. The classical form (SGBS type I) is associated with mutations in GPC3 gene leading to overgrowth. In this case child has features of overgrowth and many other manifestations of syndrome as mentioned. Genetic testing confirms the diagnosis. Counseling of parents should be done.

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