



Shprintzen-Goldberg syndrome presenting as umbilical hernia in an Indian child

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CASE REPORT

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Abstract

Shprintzen-Goldberg syndrome (S-G) is a rare connective tissue disorder characterised by craniosynostosis, craniofacial dysmorphism, skeletal, cardiovascular, neurological, and other abnormalities. We herein present a case of a five-year-old Indian child who presented to our clinic with reducible umbilical hernia since birth, mental retardation, and delayed developmental milestones. After meticulous clinical examination with subsequent integration of clinical findings and investigations, we diagnosed her to possibly have Shprintzen-Goldberg syndrome. An attempt to compare the findings of our index case with the classical features as described by Greally et al. has been made. Given the rarity of this syndrome and the paucity of medical literature measuring the magnitude of this condition in the Indian population, this case serves to promote awareness of this rare entity.

Key Words

Shprintzen-Goldberg syndrome; umbilical hernia; craniosynostosis; marfanoid habitus; Indian

Implications for Practice:

1. What is known about this subject?

Shprintzen-Goldberg syndrome is a rare connective tissue disorder characterised by craniosynostosis and marfanoid features with approximately 60 cases reported in literature since its first description in 1981 by Sugarman and Vogel.

2. What is the key finding in this case report?

An Indian child presenting with an umbilical hernia since birth, mental retardation, and delayed developmental milestones.

3. What are the implications for future practice?

A high degree of clinical suspicion is essential to diagnose a case of Shprintzen-Goldberg syndrome should a patient present with a congenital umbilical hernia, along with features of craniosynostosis and marfanoid habitus. In addition, other life-threatening conditions associated with this syndrome, especially cardiac and musculoskeletal should not be missed while evaluating such patients.

Background

Shprintzen-Goldberg syndrome (S-G) is a rare congenital connective tissue disorder, characterised by craniosynostosis and marfanoid habitus.¹ Patients with this syndrome have characteristic facial dysmorphism along with other abnormalities, including cardiovascular, musculoskeletal, neurologic, genitourinary, and others.²⁻⁴ We herein report a case of a five-year-old female child who presented to our clinic with umbilical hernia and delayed developmental milestones. She was later diagnosed to possibly have S-G syndrome based on the collaboration of peculiar clinical findings and subsequent investigations. The findings of our index case have been compared with the classical features of Shprintzen-Goldberg syndrome as described by Greally et al.^{1,4} (Table 1). We reported this case because of the syndrome's rarity and the paucity of medical literature measuring the magnitude of the condition in the Indian population.

Case details

A five-year-old female child, born to non-consanguineous parents presented to our clinic with reducible umbilical swelling since birth, mental retardation, and delayed developmental milestones: initiated walking without support at 27 months; delayed speech and language onset at age three with an expressive and receptive language disorder; and a persistent nasal twang until age four. Her birth history includes a normal vaginal delivery at term with no known exposure to teratogens during perinatal life. Clinical examination revealed dolichocephaly, anteroposterior elongation of the skull, flattening of sides of head, mild proptosis, hypertelorism (Figure 1a), low set ears and micrognathia (Figure 1b), hyper extensible thumb (Figure 1c, 1d), reducible umbilical hernia (Figure 1e), hypotonia, pes planus with relatively long toes and talipes equinovarus associated with osteopenia (Figure 1f).

A strong suspicion of an underlying genetic condition was made. Routine blood investigations, including haemogram, coagulation profile, and liver and kidney function tests were within normal limits. Cerebrospinal fluid analysis was unremarkable. A radiograph of the skull revealed flattening of the cranial base and signs of craniosynostosis compatible with early synostosis of the sagittal suture. Ultrasound of the abdomen and pelvis was unremarkable except for an underlying defect of a non-strangulated, uncomplicated umbilical hernia. Chest roentgenogram was remarkable for 13 pairs of ribs (Figure 2a). An X-ray of the foot showed osteopenia with the loss of medial arches of the foot (Figures 2b, 2c).

A two-dimensional echo showed marked aortic root dilatation (Figure 2d). Karyotyping and genetic analysis could not be performed owing to the poor affordability of the parents. Considering various craniofacial, skeletal, cardiovascular, neurological, and other abnormalities^{1,4} (Table 1), well supported by clinical examination, radiographic findings and an extensive literature search, this case was provisionally diagnosed as Shprintzen-Goldberg syndrome. Differentials included Loeys-Dietz syndrome^{5,6}, Marfan syndrome⁷, congenital contractural arachnodactyly (CCA)^{8,9} Idaho syndrome-II, Antley-Bixler syndrome, and other craniosynostotic syndromes (Table 2).

Figure 1: Gross images showing characteristic features of the Shprintzen-Goldberg syndrome in our index case

(a) Hypertelorism, mild proptosis, flattening of sides of head; (b) low set of ears and mandibular micrognathia; (c) and (d) showing hyper extensible thumb and joint laxity; (e) umbilical hernia since birth; (f) pes planus with relatively large toes and talipes equinovarus



The patient underwent surgical repair for her umbilical hernia with an uneventful post-operative period. She received regular physiotherapy and advice for pes planus and hypotonia. A cardiology consultation for aortic root dilatation was obtained and the patient received prophylaxis for subacute bacterial endocarditis. Speech and language pathologists' referrals were done for speech therapy. Genetic counselling was recommended for the parents; they were advised to visit a genetic clinic that provides information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members. The parents were advised to bring the patient for regular follow-ups.



Table 1: Comparison of clinical findings of Shprintzen–Goldberg syndrome in our index case versus the classical features described by Greally et al.^{1,4}

Classic features of Shprintzen-Goldberg syndrome ^{1,4}	Features present in our index case
Craniosynostosis Usually involves the coronal, sagittal, or lambdoid sutures	Present: Skull radiograph showed flattened cranial base; signs of craniosynostosis compatible with early synostosis of the sagittal suture
Craniofacial findings <u>Head</u> : Dolichocephaly with or without scaphocephaly; tall or prominent forehead <u>Jaw/mouth and palate</u> : Micrognathia and/or retrognathia; malar flattening/hypoplasia; high narrow palate with prominent palatine ridges <u>Ears</u> : Apparently low-set and posteriorly rotated ears <u>Ocular</u> : Myopia; telecanthus; hypertelorism; proptosis; strabismus; down-slanting palpebral fissures	Present: Dolichocephaly Present: High palate Present: Low set ears Present: Hypertelorism; proptosis; downslanting palpebral fissures
Neurologic anomalies Delayed motor and cognitive milestones Mild-to-moderate intellectual disability	Present: mental retardation with delayed developmental milestones
Brain anomalies Hydrocephalus Dilatation of the lateral ventricles Chiari 1 malformation	None present or detected until now
Cardiovascular findings Mitral valve prolapse Mitral regurgitation/incompetence Aortic regurgitation Dilatation of the aortic root	Present: Aortic root dilation
Skeletal findings <u>Joints</u> : Joint hypermobility or contractures; osteopenia <u>Skull</u> : Craniosynostosis; wide anterior fontanel <u>Spine and vertebrae</u> : C1-C2 vertebral abnormality (fusion or subluxation); scoliosis; square-shaped vertebral bodies <u>Extremities</u> : Dolichostenomelia; arachnodactyly; camptodactyly; metatarsus adductus; talipes equinovarus; pes planus; <u>Chest</u> : Pectus excavatum or carinatum; thin ribs; 13 pairs of ribs	Present: Hyper extensible thumb; osteopenia Present: Craniosynostosis None present or detected until now Present: Arachnodactyly; talipes equinovarus; pes planus Present: 13 pairs of ribs
Genitourinary External genitalia, male: Inguinal hernia; Internal genitalia, male: Cryptorchidism External genitalia, female: Inguinal hernia	Not applicable Not applicable Not present
Other Hernias and abdominal wall defects Loss of subcutaneous fat Arterial tortuosity and aneurysms Broad/bifid uvula Cleft palate Dural ectasia	Present: Umbilical hernia
Molecular genetic testing SKI is the only gene in which mutations are known to cause this syndrome	Could not be performed due to poor affordability of parents



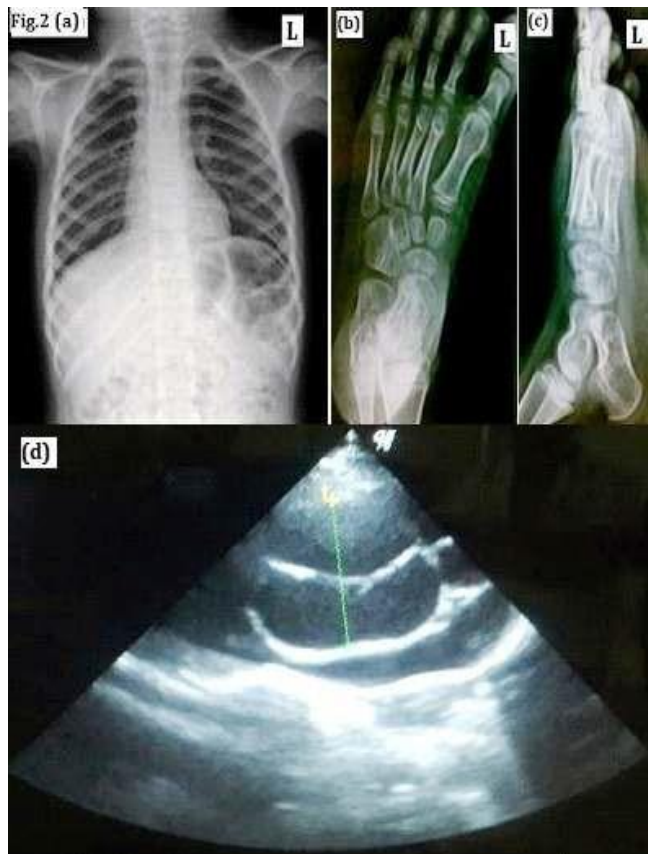
Mode of Inheritance Isolated cases	Present
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Table 2: Characteristic features of other craniosynostotic syndromes in comparison to our index case

Loeys-Dietz syndrome (LDS)^{5,6}	LDS is a recently described autosomal dominant entity characterised by a triad of arterial tortuosity and aneurysms (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections), hypertelorism, and bifid uvula or cleft palate along with skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus). Occasionally, it could be difficult to clinically differentiate LDS from S-G syndrome; it was possibly excluded as a diagnosis in our index case due to the absence of peculiar aneurysms/vascular abnormality that predominantly exists in LDS.
Marfan Syndrome⁷	Marfan syndrome is an autosomal dominant, systemic connective tissue disorder characterised by mutation in the <i>FBN1</i> gene. Patients affected with this disorder have classical ocular features (myopia; lens dislocation), skeletal (dolichostenomelia; joint laxity; scoliosis), and cardiovascular abnormalities (aortic root dilatation; mitral valve prolapse with or without incompetence; tricuspid valve prolapse; and enlargement of the proximal pulmonary artery). ⁷ Even though our index case had few overlapping features like aortic root dilatation and joint laxity, characteristic ocular and skeletal features of Marfan syndrome were absent.
Congenital contractural arachnodactyly (CCA)^{8,9}	Inherited in an autosomal dominant fashion, individuals affected with CCA have a constellation of clinical findings: abnormal pinna ("crumpled" ears); flexion contractures of multiple joints at birth; muscular hypoplasia; kyphoscoliosis; severe form of the disease in infants with multiple cardiovascular and gastrointestinal anomalies. ^{8,9} CCA has been implicated to mutations in the <i>FBN2</i> gene and resembles closely to Marfan syndrome (tall, slender habitus in which arm span exceeds height and arachnodactyly). The clinical findings of our case were inconsistent with those described for CCA.
Frontometaphyseal dysplasia (FMD)¹⁰⁻¹²	FMD, one of the otopalatodigital spectrum disorder, it manifests itself as severe supraorbital hyperostosis, a skeletal dysplasia that includes campomelia, cortical irregularity and undertubulation of the long bones and deafness. ¹⁰⁻¹² Even though FMD shares skeletal findings with S-G syndrome including tall, square-shaped vertebrae, bowed tibiae, and occasionally, fusion of upper cervical vertebrae, the presence of intellectual disability and craniosynostosis usually distinguishes S-G syndrome from FMD.
Melnick-Needles syndrome (MNS)^{13,14}	Another otopalatodigital spectrum disorder, MNS is female predominant and like FMD, intelligence is unimpaired in MNS as well. The affected females exhibit distinctive dysmorphism (supraorbital hyperostosis, exorbitism, full cheeks, micrognathia), thoracic hypoplasia due to short, irregular ribs, pronounced irregularity of the long bones, and long digits ¹³ , urteric obstruction either at the pelvicaylceal or vesicoureteric junction. ¹⁴ While MND shares some radiographic similarity with the S-G syndrome, it can be clinically differentiated by the presence of craniosynostosis and mental retardation in the latter condition. ⁴
Idaho syndrome-II¹⁵	Has less severe craniofacial problems than S-G syndrome and is accompanied by abnormal leg bones and absent patellae ¹⁵ . The latter was absent in the presented case.
Antley-Bixler syndrome¹⁶	Inherited syndrome with craniofacial abnormalities, abnormal arm and leg bones, and fractures in the femur. ¹⁶ These skeletal findings were absent in our index case

Figure 2: Radiographic images

(a) Postero-anterior view of the chest showing 13 pair of ribs; (b) Antero-posterior and lateral view (c) of the left foot showing osteopenia, loss of medial arch of the foot/pes planus (d) two-dimensional echo showing marked aortic root dilatation

**Discussion**

Our case describes the diagnostic dilemma faced in evaluating an Indian child presenting with a congenital umbilical swelling and delayed milestones, and demonstrates the importance of considering abdominal wall defects or umbilical hernia as a presenting feature in patients with Shprintzen-Goldberg syndrome. In addition to a meticulous clinical examination, a high degree of suspicion is critical in corroborating the clinical and imaging findings to that of a classical case described by Greally et al.^{1,4} to diagnose such cases. A careful review of systems and general physical examination along with imaging findings led to the suspicion of and workup for an underlying genetic disorder responsible for the presenting symptoms and the craniofacial dysmorphism. Most of the dysmorphic features present in our index case were consistent with those described by Greally et al.^{1,4} (Table 1)

Sugarman and Vogel¹⁷ reported the first case of what is now known as Shprintzen-Goldberg syndrome in a 17-year-old male with plagiocephaly, multiple craniofacial, vertebral and skeletal anomalies, umbilical and inguinal herniae,

hypotonia, and mental retardation; however, Shprintzen and Goldberg established this as a separate clinical entity in the year 1982.⁴ Since then, approximately 60 such cases have been documented in medical literature.^{1,4,5,15,18-24} The phenotypic characteristics may be variable and a comprehensive review of clinical analysis of this syndrome has been reported by Greally et al.^{1,4} (Table 1). Although few cases have been attributed to mutation in the fibrillin-1 gene (FBN1) with locus in the long arm of chromosome 15 (15q21.1)^{3,24-26}, *SKI* is the only gene in which mutations are known to cause Shprintzen-Goldberg syndrome.⁴ In a recent report describing a Japanese boy with clinical findings consistent with Shprintzen-Goldberg syndrome, Kosaki et al. identified a 3662E-A transition (134797.0045) resulting in cys 1221-to-tyr (C 1221 Y) substitution in the FBN 1 gene.²⁷ Pauliks et al.²⁵ reported the first case of complex congenital heart disease in a neonate with Shprintzen-Goldberg syndrome. Likewise, Elmistekawy et al.²⁸ described the first double valve surgery in a patient with Shprintzen-Goldberg syndrome that presented with increasingly severe mitral regurgitation due to bileaflet prolapse, and tricuspid valve regurgitation. Pavone et al.²⁹ reported their findings of a boy aged 16 years, affected by this syndrome that was followed up for 12 years to evaluate the clinical course and underlined the presence of the teeth malformations amongst the various clinical signs of Shprintzen-Goldberg syndrome; fortunately such findings were absent in our patient.

Conclusion

This case demonstrates diagnosis of Shprintzen-Goldberg syndrome requiring a high degree of clinical suspicion as most of these cases are likely to present with subtle clinical features. Patients with such syndromes can often present to a surgeon with a meagre abdominal wall defect, with umbilical or inguinal hernia as the only presenting complaint. Since such patients may have other systemic abnormalities, including but not limited to, cardiovascular, ophthalmological, radiological, muscular-skeletal, etc., a meticulous clinical examination is essential for its diagnosis and a multi-holistic therapeutic approach is vital for management of such patients. Furthermore, molecular and genetic research is warranted for a better understanding of the disease pathogenesis. With the paucity of literature measuring the magnitude of the condition, this case serves best to promote awareness of this rare entity.

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AUTHOR'S CONTRIBUTION

BS and MS participated in the clinical diagnosis, patient care and follow-up. BS and MS were the operating team of surgeons. SS and PK contributed to sequence alignment whereas SS and SY were involved in drafting of the manuscript. SS and VBB made useful contributions to the review of the literature. SS, PK and VBB participated in writing the discussion section. PK and MMAS helped revise the manuscript. All authors read and approved the final manuscript.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

ETHICS COMMITTEE APPROVAL

Not applicable for a case study

PATIENT CONSENT

The authors, *Bhushan Shah and Meena Shaikh*, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient in this report.
2. All possible steps have been taken to safeguard the identity of the patient.
3. This submission is compliant with the requirements of local research ethics committees.