International Journal of Contemporary Pediatrics
Nandy A et al. Int J Contemp Pediatr. 2020 Jan;7(1):212-216
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20195756

Case Report

Deviation of paradigmatic mutations found in Shprintzen-Goldberg syndrome

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Received: 03 October 2019
Revised: 04 November 2019
Accepted: 11 November 2019

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ABSTRACT

Shprintzen-Goldberg (S-G) Syndrome known as rare congenital connective tissue disorder where craniosynostosis and marfanoid habitus found to be the usual presentation. Craniofacial dysmorphism with multi-organ involvement documented to be amongst prominent features of this syndrome. Case characteristics is five-month-old male infant with craniosynostosis, and motor developmental delay was evaluated for congenital connective tissue disorder. Dysmorphic craniofacial features like dolichocephaly, triangular forehead, ocular hypertelorism, micrognathia and retrognathia were noticed besides congenital umbilical hernia, empty scrotal sac, clinodactyly with long slender fingers, hyper-mobile joints, hypotonia. Subsequent investigations revealed normal male karyotype (46, XY) while genetic analysis depicted missense mutations in six different genes. Conventionally, mutation in SKI gene reported for its' associated with S-G syndrome where dysregulation of TGF-β signaling was discussed as the primary reason. In the present case discussed here, it was found to have polygenic mutational association where few novel genetic mutations were seen.

Keywords: Craniofacial abnormality, Craniosynostosis, Germline mutation, Marfanoid habitus, Shprintzen-Goldberg Craniosynostosis syndrome, Undescended testis

INTRODUCTION

Shprintzen-Goldberg (S-G) Syndrome recognized as a rare congenital connective tissue disorder characterized by craniofacial dysmorphism, craniosynostosis, and multisystem abnormalities.[1] Although craniosynostosis and marfanoid habitus known as common expression here yet a wide variety of phenotypic presentations could be noticed.[2,3] Often S-G syndrome mimic Marfan syndrome and Loeys-Dietz syndrome owing to their phenotypic overlapping.[4] Considering the rarity, S-G syndrome being primarily diagnosed with its' clinical features as genetic basis of the condition observed to be deciphered gradually over time.[5] So far, autosomal dominant pattern of inheritance and sporadic incidences being reported for S-G syndrome where germline mutations which considered to be responsible for dysregulation of TGF-β cytokine during embryogenesis leading to such phenotypic presentation.[6] A patient with similar condition was evaluated where conventionally reported mutations were found to be absent.

CASE REPORT

A five-months old male infant was evaluated for congenital connective tissue disorder, initially presented with dysmorphic craniofacial features and developmental delay although ante-natal and perinatal history were insignificant. The infant was born full-term AGA with normal birth weight and recorded to have natal teeth and empty scrotal sac at birth. His elder male sibling was doing well. On examination, fused sagittal suture,

prominent forehead with dolichocephaly, ocular hypertelorism, proptotic and down slanting eyes, narrow high arched palate, broad and depressed nasal bridge, malar hypoplasia, micrognathia and retrognathia, low set of ears with low hairline were observed. Occipito-frontal circumference and Canthal index was documented to be 43.7 cm and 46.6 cm respectively. Scrotal sac found to be empty and soft tissue swelling in the mid-inguinal region on both sides were observed. No ambiguity of external genitalia was noticed. Examination of the hands revealed presence of clinodactyly, and long slender fingers shown in Figure 1 alongside prominent craniofacial dysmorphic features of the present case under discussion. Congenital umbilical hernia and hyper-mobility of different major joints of the limbs were noticed. No abnormality detected on meticulous systematic examination including eyes, ears and the back. Figure 2 depicted the empty scrotal sac (A) and congenital umbilical hernia (B) observed in the present case. Neck holding and rolling over was absent. Upon pull to sit test, head was noticed to be lagging behind with poor head control.

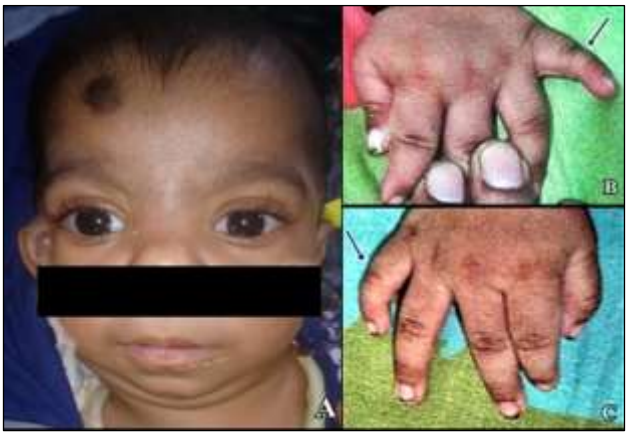

Figure 1: Dysmorphic craniofacial features (A) alongside long slender fingers and clinodactyly of left (B) and right(C) hand in the present case.

Systemic evaluation revealed grade 2 diastolic murmur in the tricuspid region and gross hypotonia of the skeletal muscles. Ultrasound of inguinal region depicted two well defined hypoechoic structure of 14.8 mm*9.8 mm in right side and 19.7 mm*10.1mm in left side suggesting bilateral undescended testes located in bilateral mid-inguinal region. No abnormality of intra-abdominal organs was found. Echocardiography revealed patent foramen ovale of 3 mm in size with left to right shunt, mild tricuspid regurgitation (pressure gradient 25 mm of Hg) with confluent pulmonary artery branches. Cytogenetic analysis with GTG banding showed normal male karyotype (46, XY) with no structural or numerical chromosomal aberrations. Afterwards, next generation advanced clinical exome sequencing (NGS) revealed missense mutations in six different genes elaborated in Table 1.

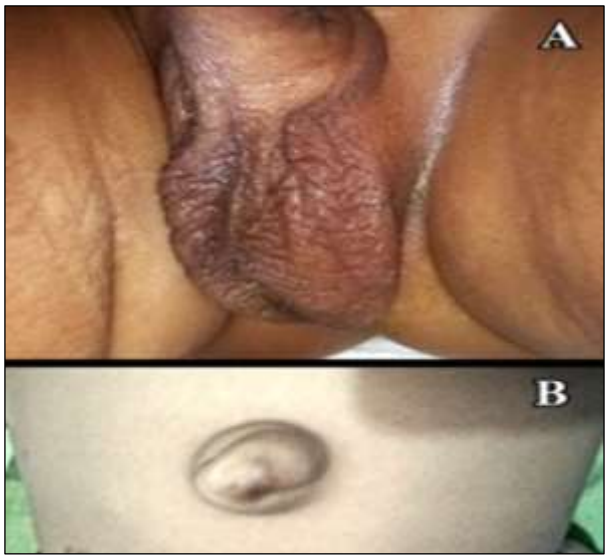

Figure 2: Empty scrotal sac (A) and Congenital umbilical hernia (B) observed in the case under discussion.

Table 1: Mutated genes found on NGS (Including those found as variants of unknown significance).

Mutated gene	Chromosome: Position	Exon no.	Zygosity	Pattern of inheritance	Type of mutation
ARHGAP31	Chr3: 119121122	10	Heterozygous	Autosomal Dominant	Missense
PRRX1	Chr1: 170705189	4	Heterozygous	Autosomal Dominant	Missense
ZFPM2	Chr8: 106814703	8	Heterozygous	Autosomal Dominant	Missense
SEMA3E	Chr7: 83014651	16	Heterozygous	Autosomal Dominant	Missense
TRPM4	Chr19: 49686441	12	Heterozygous	Autosomal Dominant	Missense
IGF1R	Chr15: 99467854	13	Heterozygous	Autosomal Dominant	Missense

DISCUSSION

S-G Syndrome known for its' classical phenotypic presentation of craniosynostosis, craniofacial dysmorphism and marfanoid features. The index case was discussed by Shprintzen RJ and Goldberg RB after the initial introduction by Sugarman and Vogel.[7] Due to the rarity of this disease, a unanimous consensus being yet to be developed for its' diagnostic approach. According to different similar cases discussed so far in the literature, it

was observed that different combinations of variety of phenotypic manifestations of the S-G syndrome noticed to be the usual presentation for this rare congenital connective tissue disorder.[2,5,8]

The important clinical features observed to be associated with S-G syndrome described as follows - a) Craniosynostosis, b) Craniofacial features like dolichocephaly with or without scaphocephaly, prominent forehead, ocular proptosis, widely spaced eyes, anti-mongoloid slanting of palpebral fissure, malar hypoplasia, high narrow palate, micrognathia and/or retrognathia, broad/bifid uvula, cleft palate, apparently low-set and posteriorly rotated ears, c) Musculoskeletal findings like dolichostenomelia, arachnodactyly, camptodactyly, cervical and vertebral anomalies, pes planus, pectus excavatum or carinatum, scoliosis, joint hyper-mobility, congenital umbilical hernia, inguinal hernia, d) Cardiovascular findings like mitral valve prolapse, mitral regurgitation, aortic regurgitation, aortic root dilatation, e) Neurological anomalies in the form of delayed achievement of developmental milestones, intellectual disability, mental retardation, hydrocephalus and Chiari 1 malformation, f) and others like cryptorchidism, arterial tortuosity and aneurysms, dural ectasia etc. It could be noticed that certain clinical features like skeletal and other findings might be subtle during early childhood period due to non-weight bearing of the spine and limbs.[2,8]

In the present case, presence of craniosynostosis involving sagittal suture, dysmorphic cranio-facial features in the form of prominent triangular forehead, ocular hypertelorism, down-slanting eyes, narrow high arched palate, malar hypoplasia, micrognathia and retrognathia were observed. There was motor developmental delay, hypotonia, long slender fingers and clinodactyly, hypermobility of joints, congenital umbilical hernia, bilateral undescended testis and patent foramen ovale.

Rarity of the condition and lack of resources noticed to pose hindrance for detecting genetic mutations.[9,10] Mutated genes found in this case and their role in normal development described in the table 2. The ARHGAP31 gene code forGAP31 protein, involved in cellular signaling and contributing for normal development of limbs, skulls, heart and brain.[11,12] The PRRX1 gene code for homeobox proteins involved in growth and differentiation of mesoderm during embryogenesis. Mutation in this gene known to cause mandibular hypoplasia, ear anomalies, oroglossal hypoplasia, skeletal, neurological, genitourinary and cardiovascular anomalies. The ZFPM2 gene code for zing finger protein which belongs to FOG family of transcription factors involved in morphogenesis of heart and gonadal differentiation. The SEMA3E gene code for semaphorin proteins involved in inter-cellular signaling through cell surface receptor PLXND1 and contribute to neuronal synapse formation. The TRPM4 gene code for TRPM4 channel protein required for normal development and functioning of nervous system. The IGF1R gene code for tyrosine kinase receptor of IGF-1 involved in cell growth and survival during embryogenesis.

Table 2: Mutated genes in the present case and their contribution in development of organs during embryogenesis.

Genes	Protein encoded	Normal function
ARHGAP31	Rho GTPase activating protein 31 (GAP31)	Normal development of limbs, skulls, hear and brain
PRRX1	Homeobox protein	Growth and differentiation of structures of mesodermal origin
ZFPM2	Zing finger protei (FOG family of transcription facto	Morphogenesis of heart and gonadal differentiation
SEMA3E	Semaphorins (Class 3-7)	Neuronal synapse formation
TRPM4	Transient receptor potential cation channel subfamily M member 4 (TRPM4)	Normal development and functioning of nervous system
IGF1R	Tyrosine kinase receptor of insulin like growth factor	Normal intrauterine and postnatal growth

Conventionally, mutation in fibrillin 1 gene or SKI gene causing overexpression of the cytokine TGF-β found to be responsible for phenotypic manifestation S-G syndrome.[3,6,13-14] TGF-β involved in cellular proliferation and differentiation during embryogenesis. Recently a novel missense mutation in TGF-β Receptor 2 (TGFBR2) gene was documented to be associated with S-G syndrome.[15] But it was noticed that aberration in cytokine TGF-β signaling pathway also involved in other congenital connective tissue disorders with similar phenotypic presentation like Marfan syndrome, Loeys-Dietz Syndrome (LDS), Furlong Syndrome, etc.[4,16] Evidently it could be perceived that as the other mutations associated with this condition get deciphered over the time, it would help in its' diagnosis and better understanding of the disease pathology further.

In the present case, Author found a polygenic association over a monogenic mutational association. Moreover, these were novel genetic mutations that led to the phenotypic presentation of S-G syndrome observed here. Thus, it could be inferred that multiple genes might be involved in this condition which were responsible for its' phenotypic presentation of S-G syndrome. Predominantly

sporadic cases of S-G syndrome had been reported till now in literature and author did find the present case to be sporadic too, where mutations were observed to follow autosomal dominant pattern of inheritance with heterozygosity suggestive of germline mutation. Genetic analysis of more such similar cases and parental genetic screening could help in establishing these associations further.[17]

While evaluating a case of S-G syndrome, the differential clinical entities with congenital connective tissue disorders like Loeys-Dietz Syndrome (LDS), Marfan syndrome must be kept in view during assessment of such cases, due to overlapping of clinical features in between them.[4,18] LDS defined as an entity to follow autosomal dominant pattern of inheritance and characterized by a triad of vascular anomalies in the form of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate along with skeletal manifestations like pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus. Marfan syndrome known as an autosomal dominant condition with systemic connective tissue disorder characterized by mutation in the fibrillin 1 gene. Affected individuals are observed to have ocular features like myopia, lens dislocation, and skeletal features like dolichostenomelia, joint laxity, scoliosis, and cardiovascular abnormalities like aortic root dilatation, mitral valve prolapse with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. Cardiovascular anomalies noticed are usually less severe in cases of S-G syndrome. However, pathognomonic features distinguishing them outrightly could be difficult to elicit. Thus, as per present day scenario certain clinical suspicion might be helpful in diagnosing such rare cases like S-G syndrome.[19,20]

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee (IEC/NBMC/2019-20/07)

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Cite this article as: Nandy A, Das SK, Roy S, Das S. Deviation of paradigmatic mutations found in Shprintzen-Goldberg syndrome. Int J Contemp Pediatr 2020;7:212-6.