Journal of Pediatric Sciences

A patient with Shprintzen-Goldberg syndrome. Clinical follow-up for twelve years

V. Pavone, R. Leonardi, G. Sorge, P. Pavone, A. Pratico, G. Sessa

Journal of Pediatric Sciences 2012;4(4):e164

How to cite this article:

Pavone V, Leonardi R, Sorge G, Pavone P, Pratico A, Sessa G. A patient with Shprintzen Goldberg syndrome. Clinical follow-up for twelve years. Journal of Pediatric Sciences. 2012;4(4):e164

CASE REPORTS

A patient with Shprintzen-Goldberg syndrome.

Clinical follow-up for twelve years

V. Pavone [*], R. Leonardi [**], G. Sorge [**], P. Pavone[***], A. Pratico' [**], G. Sessa [*]

[*]Orthopedic Division, Department of Medical-Surgical Sciences, University of Catania, Catania, [**] Department of Medicine and Surgery, Division of Dentistry, University of Catania, Catania, [***] Unit of Pediatrics and Pediatric Emergency "Costanza Gravina", University Hospital "Vittorio Emanuele-Policlinico, Catania, Italy;

Abstract:

Shprintzen-Goldberg syndrome (SGS) is an uncommon disorder characterized by distinct patterns of malformation. We here report a 16-year-old boy who showed the typical SGS phenotype with Marfan-like habitus, craniosynostosis, cranio-facial anomalies, pectus excavatum, joint hyperlaxity and skeletal anomalies. From birth the boy displayed many dysmorphic features as hypertelorism, broad nasal bridge, low set years, retromicrognathia, down-slanting palpebral fissures, inguinal and umbilical hernia, hypotonia. The hands and feet were long and slender with camptodactyly of the 2nd and 4th fingers of the right hand, hammer toes and hallux valgus. The orthopanoramic X-ray taken at the age of 10 years showed a complex of dental anomalies including hypodontia, abnormalities of root anatomy and pulp canal shape and impacted teeth. Spinal X-ray examination showed convex scoliosis in the dorsal tract. Malformative signs in SGS have been widely described in literature, but those regarding the type and number of teeth anomalies have been not well pointed out. We maintain that teeth anomalies are one of the several signs which clinically define the syndrome. At the age of 16 years, scoliosis was mildly progressive. Teeth malformations, as the others typical features, remained unmodified. Puberty delay, mild-moderate mental delay, fragile skin and facial dysmorphism are the present concerns.

Keywords: *Shprintzen-Goldberg syndrome, multiple anomalies, scoliosis, Marfan-likehabitus, teeth*

Accepted: *08/16/2012* ***Published:*** *12/01/2012*

Corresponding author: *Piero Pavone MD, UO of Pediatrics, AUO OVE-Policlinico, Via Plebiscito 767, 95124, Catania, Italy, Tel++39-0957435254, Fax++390957436632, ppavone@unict.it*

Introduction

Shprintzen-Goldberg Syndrome (SGS) is a disorder of the connective tissue involving several body regions [1-3]. It is characterized by a Marfan-like habitus, craniosynostosis, craniofacial findings, including dolichocephaly, high prominent forehead, hypertelorism, telecanthus, downslanting palpebral fissures, maxillary hypoplasia, high narrow palate, severe rethromicrognathia, little posteriorly rotated ears. Additional findings, skeletal, cardiovascular and brain anomalies with cognitive delay are also present.

We report on a boy, now 16 years old aged, affected by SGS who we followed up for 12 years to evaluate the clinical course and to underline the presence of the teeth malformations among the clinical signs of the syndrome previously not well remarked.

Case Report

The patient, a 16-year-old boy, was born to healthy, non-consanguineous parents. The father was 36 years-old and the mother was 32 years-old at the time of birth. He has a healthy 10-year-old sister and the family history is negative for skeletal diseases or malformations. The mother denied taking drugs or having any infections during the pregnancy. The boy was born full term weighing 3300 g, measuring 50 cm in length and with a head circumference of 34.5 cm, all within normal limits. From birth, he displayed many dysmorphic features: craniosynostosis, pectus excavatum, hypertelorism, broad

nasal bridge, low set ears, retromicrognathia, down-slanting palpebral fissures, inguinal and umbilical hernia, hypotonia, and joint hyperlaxity. His hands and feet were long and slender with camptodactyly of the 2nd and 4th fingers of the right hand, bilateral feet camptodactyly, hammer toes and hallux valgus At the age of one year, an inguinal hernia was surgically corrected.

He first came to the Pediatric Clinic of the University of Catania at the age of four years for a diagnostic work-up. At the physical examination the boy presented with the above-mentioned anomalies and his height was 100 cm. He had mild- moderate psychomotor delay (IQ = 70), pectus excavatum, and moderate scoliosis. There was a normal cardiac murmur and his blood pressure was 90/60. Routine laboratory testing was normal, as well as an EEG, and EKG with echocardiogram. The ophthalmologic examination was normal. An X-ray of the skull and the hands at the age of six years showed scaphocephaly with craniosynostosis and a delay in the nuclei of ossification of the trapezius, scaphoid, and bilateral proximal epiphyses of the ulna (Fig. 1).

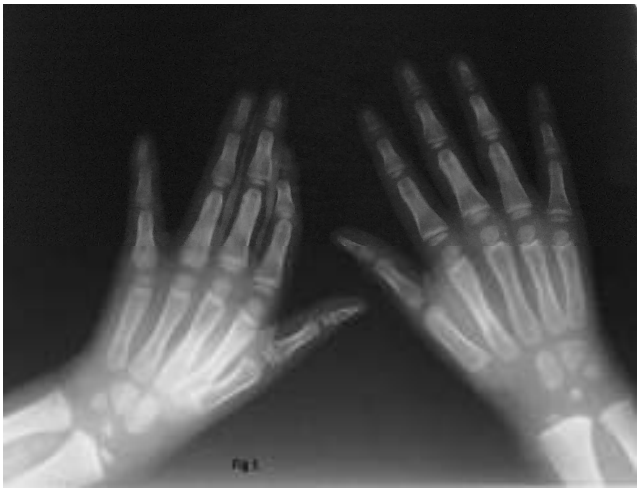


Fig 1: age of 6 years: X-ray shows long and slender hands with delay of the nuclei of ossification of the trapezius, scaphoid, and proximal epiphyses of the ulna.

Brain MRI displayed no anomalies. DNA analysis of the FBN1 gene revealed no mutations. At clinical oral examination at age of 10 years, the patient showed an increased overjet (9 mm) and a decreased overbite (- 2 mm), a severe dental crowding and mandible retrognathia, were present too. The orthopanoramic X-ray taken at the same time showed dental anomalies, including hypodontia ,abnormalities of root anatomy and pulp canal shape and impacted teeth. Dental anomalies were mostly symmetric, in that they were frequently observed on the right and left sides of maxillary and mandibular arches. All the 4 second premolars (15,25,35,45) were missing with persistence of primary molars. Tooth germs of 3 second molars (17,27,37) could not be appreciated in the X-ray, the second molar on the mandibular right side was hypoplastic. Furthermore, hypodontia of the first left mandibular molar was also observed. Maxillary and mandibular canine were impacted (13 and 33), may be due to the lack of space and dental crowding. Abnormalities of root anatomy and pulp canal shape were detected in the upper first molars (16 and 26).. In the mandible a deep antegonial notch with a shorter corpus, smaller ramus height, and a greater gonial angle was appreciated (Fig 2). This is representative of a diminished mandibular growth potential and a vertically directed mandibular growth pattern .

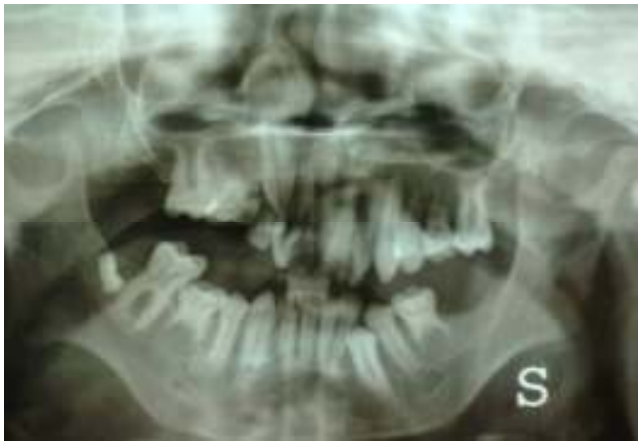


Fig 2: age of 10 years: showing teeth anomalies: dental crowding, persistence of primary molars, maxillary and mandibular canine impacted.

At 12 years, a skeletal X-ray was interpreted as delayed, with a skeletal age of six years.

The results of serial spinal X-ray examinations were as follows: at 6 years (Fig 3a), dorsal convex right scoliosis; at 10 years (Fig. 3b), the previous findings were confirmed and there was an anteversion trend of the physiologic lumbar lordosis; at 16 years (Fig. 3c), a left convex scoliosis in the dorsal tract with vertebral body longitudinal axis rotation, and increased dorsal kyphosis with straightening of the physiological lumbar lordosis were seen. At the age of 16 the orthopanoramic X-ray examination is unchanged; facial dysmorphism, craniosynostosis and pectus excavatum, feet deformity (Fig. 4) and scoliosis (Fig. 5) are still present. Neither cardiological problems, nor brain anomalies were seen at ECG and echography and at brain MRI. The patient shows mild- moderate mental delay, puberty delay and skin fragility. The height was at upper limits

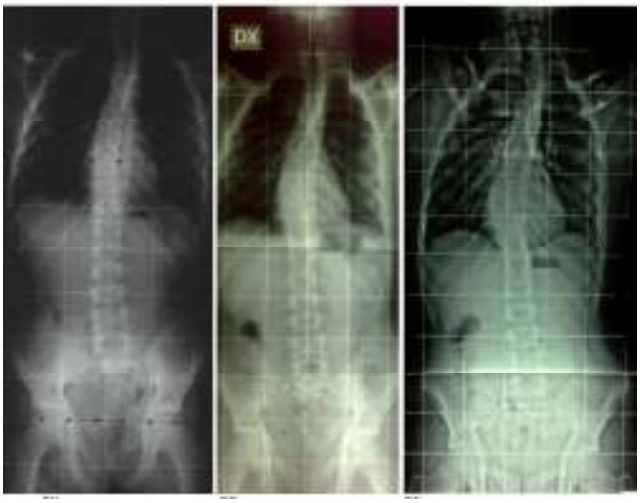
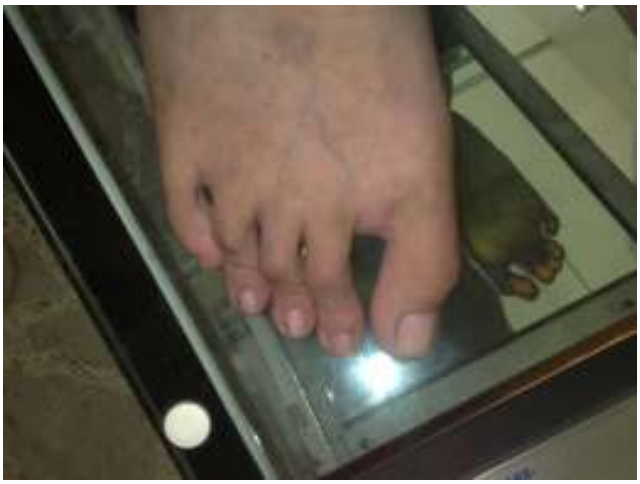


Fig 3a-c: Spinal X-ray at the age of 6 (a), 10 (b) and 16 (c) years respectively: showing the mildly progressive dorsal convex right scoliosis.



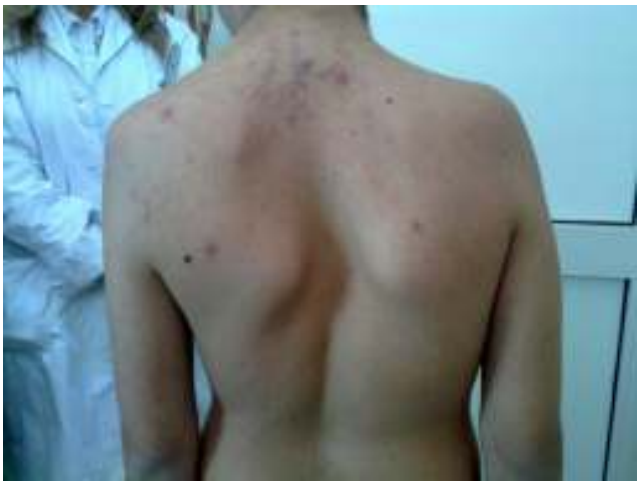


Fig. 4 – Feet anomalies at the age of 16 years

Fig. 5 – Left convex scoliosis at the age of 16 years.

Discussion

The Shprintzen- Goldberg syndrome phenotype is variable as it combines craniofacial, skeletal, cardiovascular, neurological, and other connective tissue abnormalities [4-5]. The gene in which SGS-causing mutations occur is unknown [4]. A mutation in the gene for fibrillin-1 (FBN1), located on the long arm of chromosome 15 (15q21.1) is involved in Marfan syndrome (MFS) and related fibrillinopathies [6-9]. Mutations in FBN1 have been reported in 3 patients with clinical diagnosis of SGS [10-11]. On the contrary no FBN1 mutations were reported by Ades et al [5] in their patients. At the same time no mutations regarding TGFBR1 and TGFBR2 were focused by Ades et al [5] and Loeys et al [12].

Recently Shanske et al [13] report a child born from a maternal half-sibs with classical SGS who displayed germline mosaicism and Levy et al [14] described a phenotype like SGS in a patient with tetrasomy 15q26. It remains unclear whether variants in FBN1 contribute to the phenotype of SGS directly, indirectly, or at all.

The early manifestation of SGS may be subtle, and the syndrome may be misdiagnosed. According to Robinson et al [15] who collected 37 patients, 23 of which were previously reported and 14 belonging to their series, the clinical aspect of SGS is quite variable but well characterized: A typical facial appearance is observed in two thirds of the patients with hypertelorism, down slanting palpebral fissures, high-arched palate, micrognathia, apparently low set and posteriorly rotated ears. Other manifestations but less frequently reported are hypotonia in neonatal period, developmental delay from middle to severe and inguinal or umbilical hernia.

Because of the large degree of overlap between SGS and those of several other hereditary disorders, clinicians need to recognize a characteristic combination of signs in order to diagnose SGS. Skeletal changes, i.e. arachnodactily, pectus excavatum, scoliosis and long fragile ribs are frequent [16]. However, none of the skeletal signs alone is specific for SGS. According to Robinson et al. [15] the diagnosis of SGS should be strongly considered in individuals with a combination of the common craniofacial, skeletal, developmental, and radiographic signs and symptoms.

SGS shares many of the clinical features of MFS, but ocular features (myopia, displacement of the lens, early cataract formation) and typical cardio-vascular manifestations are not seen in SGS. More difficult is the differential diagnosis with the Loeys-Dietz Syndrome, but

bifid uvula, generalized arterial tortuosity, aortic root aneurysm, septal defects, blue sclera are not features of SGS [4]

There are numerous other genetic conditions that also share some degree of phenotypic overlap with SGS, such as Stickler syndrome, Melnick-Needles syndrome, and otopalatodigital syndrome, but the characteristic facial appearance of SGS allows differentiation from these disorders. An important differential diagnosis is congenital contractural arachnodactyly (CCA or Beals- Hecht syndrome), in which there is no craniosynostosis.

In our patient, the marfanoid habitus associated with craniosynostosis, camptodactyly, mental retardation, pectus excavatum, and craniofacial anomalies are suggestive of classical SGS. Moreover, our patient at the clinical and X-ray investigations showed an oral involvement characterized by hypodontia and tooth abnormalities. In this respect, literature is scanty in fact just a few studies have reported a tooth involvement in the syndrome. In the review of Robinson et al., [15] teeth anomalies were recognized in 3 patients but the type of the anomalies has not been reported, in 9 patients no information were available and others two patients the anomaly was not observed. The same Authors report a photo a 25 years old patient with a severe narrow palate in whom several teeth were extracted because of dental malocclusion. Topouzelis et al., [17] report on a 8 years old girl with class ii/1, division 1 malocclusion. A panoramic radiograph showed multiple congenital absences of permanent teeth with lower lateral incisors and second maxillary premolars. The maxillary dental arch was narrow with very high and narrow palate. Maxillary hypoplasia is mentioned by Greally (4) among the clinical signs of SGS.

Scoliosis in this syndrome is also quite common. According to Robinson et al., [15], the most common skeletal manifestations of SGS are arachnodactyly and a pectus deformity followed by camptodactyly, joint hypermobility, and scoliosis Stoll [18] reported the presence of scoliosis in one patient at the age of eight years, which worsened between the age of 14 and 15 years, and remained unchanged after 15 years. Watanabe et al. [19] report on four SGS patients (2 boys and 2 girls) with a mean age at the time of surgery of 7.3 years) who underwent surgical treatment for progressive scoliosis. They mentioned this procedure was associated with a high incidence of perioperative and postoperative complications. In our patient, the scoliosis was recognised at the age of 4 years: its clinical and radiological course was mildly progressive. At the age of 16 years, scoliosis has been slightly progressive and did not necessitate at the present any surgical treatment.

According to this case and the data reported in the literature, we can confirm that scoliosis is one of the most common skeletal signs in SGS. Teeth anomalies must be considered as one of the clinical signs of SGS, a malformative sign not well underlined in the previous literature.

At the clinical follow up of 16 years the teeth anomalies as the skeletal anomalies were almost unmodified, The scoliosis did only show a mild progression without significant increase or worsening. Puberty delay, fragile skin, moderate mental delay and facial dysmorphism were the present concerns.

References

1- Shprintzen, RJ, Goldberg, RB. A recurrent pattern syndrome of craniosynostosis associated with arachnodactyly and abdominal hernias. J Craniofac Genet Dev Biol 1982; 2: 65-74.

2- Furlong J, Kurczynski TW, Hennessey JR. New marfanoid syndrome with craniosynostosis. Am J Med Genet. 1987; 26: 599- 604.

3- Megarbane A, Hokayem N. Craniosynostosis and marfanoid habitus without mental retardation: report of a third case. Am J Med Genet 1998; 77: 170-171.

4- Greally MT. Shprintzen-Goldberg Syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2006.

5- Ades LC, Sullivan K, Biggin A,et al. FBN1, TGFBR1, and the Marfan- craniosynostosis/ mental retardation disorders revisited. Am J Med Genet A 2006; 140: 1047-1058.

6- Loeys B, Nuytinck L, Delvaux I, De Bie S, De Paepe A. Genotype and phenotype analysis of 171 patients referred for molecular study of the fibrillin-1 gene FBN1 because of suspected Marfan syndrome. Arch Intern Med 2001; 161: 2447-2454.

7- Mizuguchi T, Mtsumoto N. Recent progress in genetics of Marfan syndrome and Marfan associated disorders. J Hum Genet 2007; 52: 1-12.

8- Matyas G, Arnold E, Carrel T. Identification and in silico analysis of novel TGFBR1 and TGFBR2 mutation in Marfan syndrome- related disorders. Hum Mutat 2006; 27: 760-769.

9- Katzke S, Booms P, Tiecke F, et al. TGGE screening of the entire FBN1 coding sequence in 126 individuals

with marfan syndrome and related fibrillinopathies. Hum Mutat 2002; 20: 197-208.
10- Sood S, Eldadah ZA, Krause WL, MC Intosh I, Dietz HC. Mutation in fibrillin-1 and the Marfanoid-craniosynostosis (Shprintzen-Goldberg) syndrome. Nat Genet 1996; 12:209-211.
11- Kosaki K, Takahashi D, Udaka T, et al. Molecular pathology of Shprintzen-Goldberg syndrome. Am J Med Genet 2006; 140: 104- 108.
12- Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005; 37: 275–281.
13- Shanske AL, Goodrich JT, Ala-Kokko L, Baker S, Frederick B, Levy B. Germline mosacism in Shprintzen-Goldberg syndrome. Am J Med Genet A. 2012; 158A: 1574-8.
14- Levy B, Tegay D, Papenhausen P, et al. Tetrasomy 15q26: a distinct syndrome or Shprintzen-Goldberg syndrome phenocopy? Genet Med. 2012; 14: 811-8.
15- Robinson PN, Neumann LM, Demuth S, et al.Shprintzen-Goldberg syndrome: fourteen new patients and a clinical analysis. Am J Med Genet A 2005; 135: 251-262.
16- Nishimura G, Nagai T. Radiographic findings in Shprintzen-Goldberg syndrome. Pediatr Radiol 1996; 26: 775- 778.
17- Topouzelis N. Marcovitsi E. Antoniades K. Shprintzen-Goldberg: Syndrome case report. Cleft Palate Craniofac J 2003; 4014: 433-36.
18- Stoll C. Shprintzen-Goldberg marfanoid syndrome: a case followed up for 24 years. Clin Dysmorph 2002;11: 1-7.
19- Watanabe K, Okada E, Kosaki K, Tsuji T, Ishii K, Nakamura M, Chiba K, Toyama Y, Matsumoto M. Surgical treatment for scoliosis in patients with Shprintzen-Goldberg syndrome. J Pediatr Orthop 2011; 31:186-93.