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Case report

Stickler syndrome: case report

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Abstract

Introduction: Stickler syndrome is a connective tissue disorder that can include midfacial underdevelopment and cleft palate, ocular findings (myopia, cataract, and retinal detachment), hearing loss that is both conductive and sensorineural and mild spondyloepiphyseal dysplasia and/or precocious arthritis. The phenotypical expression of Stickler syndrome is variable and typically associated with allelic heterogeneity.

Description of case: Full-term newborn, cesarean delivery at 40 weeks. Fetal ultrasounds with orofacial malformation and mild hydronephrosis. The prenatal genetic screening test was negative. Fetal karyotype and array were normal with a male genomic profile. Fetal cerebral MRI showed brachycephalic skull configuration. At 10 minutes of life, the newborn had hypoxemia and was admitted to the Neonatal Intensive Care Unit. He had macrocephaly, but height and weight were adequate for the gestational age. At observation, he had axial hypotonia, craniofacial dysmorphia and posterior cleft palate. Mandibular hypoplasia and findings were compatible with connective tissue disease in 3D-CT. He had marked retinal choroiditis and pathological myopia and did not pass the neonatal hearing screening. Echocardiogram and capnography were normal. The hypothesis of Stickler syndrome was confirmed genetically with the *COL11A1* gene mutation, variant c.2952+1G>T. Nowadays, at 13 months old, he maintains a multidisciplinary approach, with normal growth and psychomotor development.

Conclusion: This case aims to illustrate a patient with a typical phenotype of a rare syndrome with posterior genetic confirmation. Multidisciplinary monitoring is essential to allow the timely diagnosis of complications associated with this syndrome (mitral valve prolapse or retinal detachment) and to assess the evolution of growth and psychomotor development.

Keywords

Stickler syndrome, case report, retinal choroiditis, bilateral exophthalmos, craniofacial dysmorphia.

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Introduction

Stickler et al. described in 1965 a family with joint manifestations and progressive myopia, associated with retinal detachment in the first decade of life, which resulted in blindness [1]. Mild sensorineural hearing impairment was later added by the same authors to the typical features of this syndrome [2]. Stickler syndrome is a connective tissue disorder affecting about 1 in 7,500 to 9,000 newborns [3]. It is characterized by ocular findings (myopia, cataract, and retinal detachment), hearing loss (conductive and sensorineural), distinctive facial appearance (midfacial underdevelopment and cleft palate) and joint problems (mild spondyloepiphyseal dysplasia and/or precocious arthritis). Phenotypic expression of Stickler syndrome varies widely within and among families; interfamilial variability is in part explained by locus and allelic heterogeneity [4, 5]. In **Tab. 1** are presented the typical characteristics of Stickler syndrome.

Based on its underlying genetic collagen defect, Stickler syndrome is subdivided into several subtypes. Currently, defects in three different collagen genes have been found in patients with Stickler syndrome. Type I Stickler syndrome (STL1) is associated with mutations in *COL2A1* (type II collagen encoding gene) [6], while mutations in *COL11A1* and *COL11A2* (type XI collagen encoding gene) are associated with type II (STL2) [7] and type III Stickler syndrome (STL3) [8], respectively. In some families, mutations have been described in *COL9A1* (STL4) [9] and *COL9A2* (STL5) [10] encoding type IX collagen. Stickler syndrome can be transmitted as an autosomal dominant or autosomal recessive trait. The autosomal dominant form is caused by mutations in *COL2A1*, *COL11A1*, or *COL11A2* [11], while the autosomal recessive form is caused by mutations in *COL9A1* [12], *COL9A2* [10], *COL9A3* [13] or *LOXL3* [14]. STL1, the most common subtype of Stickler syndrome (80-90% of the cases), is caused by mutations in *COL2A1*. STL2 is caused by mutations in *COL11A1* and is responsible for 10-20% of the cases [15].

Table 1. Summary of the typical characteristics of Stickler syndrome.

Typical findings	
Ocular	Myopia
	Cataract
	Retinal detachment
Craniofacial	Midfacial underdevelopment (retrognathism)
	Cleft palate
	Low-set ears
	Large anterior fontanelle
Bone and joint	Spondyloepiphyseal dysplasia
	Precocious arthritis
Auditory	Sensorineural hearing impairment

The phenotypic distinction between patients with mutations in different causative genes is difficult, but some differences may be present. For example, STL3 does not exhibit ocular abnormalities, as *COL11A2* is not expressed in the vitreous [16]. Another example is the vitreous anomaly, which is mostly "membranous" in STL1 and "beaded" in STL2 [6].

However, as stated before, there are variable phenotypic differences not explained solely by the affected gene. Even within the same family or within unrelated families carrying the same mutation, the clinical expression shows high variability [17].

Hearing loss in STL1 seems to be present in about 60% of affected patients and is likely to be sensorineural. STL2 and STL3 are more frequently associated with hearing loss that is more severe [18]. However, the pathogenesis of this sensorineural hearing loss is not well understood. Associated findings are a hypermobile tympanic membrane and cleft palate resulting in middle ear effusion and conductive hearing loss [19].

The most common ocular manifestations are myopia, vitreous degeneration and retinal detachments. Myopia is usually found in STL1 and STL2 and is present in 40% before age 10, 75% by age 20. However, 20% are not myopic. They have one of four phenotypes of the vitreous: membranous congenital vitreous anomaly, beaded congenital vitreous anomaly, hypoplastic congenital vitreous anomaly, or normal. STL1 has the highest risk of retinal detachment; it can occur in up to 70% of the cases. STL2 also has ocular

abnormalities, with retinal detachment reported in up to 40-50% of the cases [20]. STL3 is often called the non-ocular Stickler syndrome.

Case report

We report the case of a male newborn with healthy non-consanguineous parents. After the diagnosis of Stickler syndrome, the newborn's father was enrolled in a genetic study due to some facial features (exophthalmos and prominent forehead). Fetal ultrasounds (2nd and 3rd trimester) revealed orofacial malformations and left mild hydronephrosis (6 mm). The prenatal genetic screening test was negative. Fetal karyotype and array were normal with a male genomic profile. Fetal brain MRI showed brachycephalic skull configuration.

He was cesarean delivered at the 40th week of gestation. Apgar scores were 9/10/9. The body weight was 3,705 grams (P50/75), length 47 cm (P3/10), head circumference 38.5 cm (> P97). The patient started hypoxemia at 10 minutes of life and was admitted to the Neonatal Intensive Care Unit (NICU). At observation, he had axial hypotonia, craniofacial dysmorphia with flat face and prominent forehead, bilateral exophthalmos, retrognathism, wide rhomboid fontanelles, low-set ears and posterior cleft palate (**Fig. 1** and **Fig. 2**). The remaining physical examination was unremarkable. 3D cranio-encephalic CT was performed and revealed mandibular hypoplasia and findings compatible with connective tissue disease (**Figures 3-5**). He was observed by a Geneticist and was diagnosed with probable Stickler syndrome. The Ophthalmology examination showed marked choroiditis of the retina and near-sightedness. During the Otorhinolaryngology examination, he did not pass the universal neonatal hearing screening. The main differential diagnosis considered were Marshall syndrome and Wagner syndrome. Marshal syndrome [21] is a rare autosomal dominant genetic disorder caused by mutations in the *COL11A1* gene (as in STL2) and phenotypically has overlapping features with Stickler syndrome. Some researchers believe that the two disorders are the same or different expressions of the same disorder,

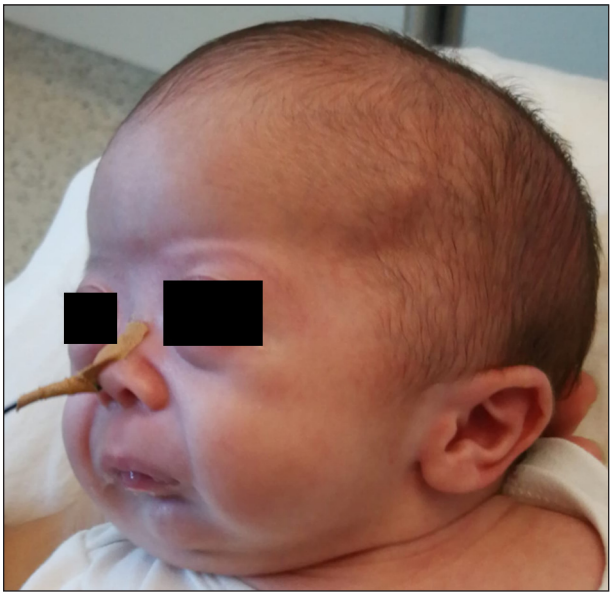

Figure 2. Lateral view of the face, being particularly visible the low-set ears and retrognathism.

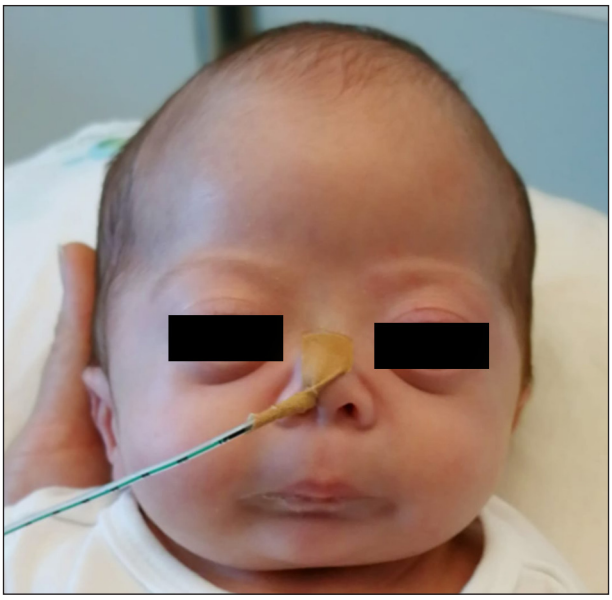

Figure 1. Frontal view of the face demonstrating the typical phenotype: prominent forehead, bilateral exophthalmos, low-set ears and retrognathism.

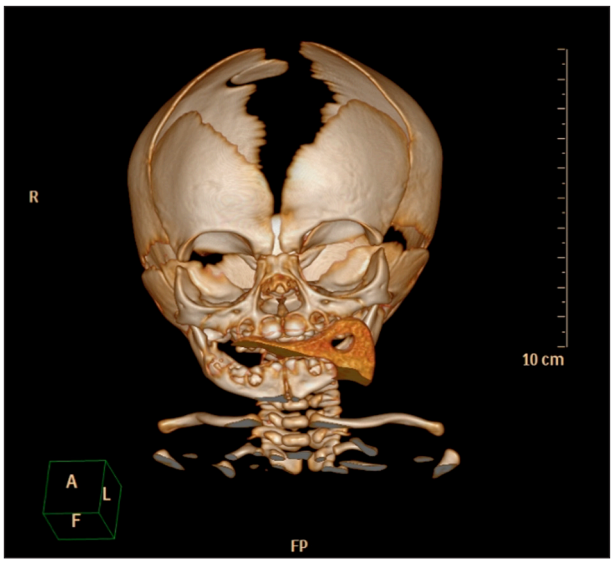

Figure 3. Frontal view of 3D cranio-encephalic CT scan highlighting large anterior fontanelle.

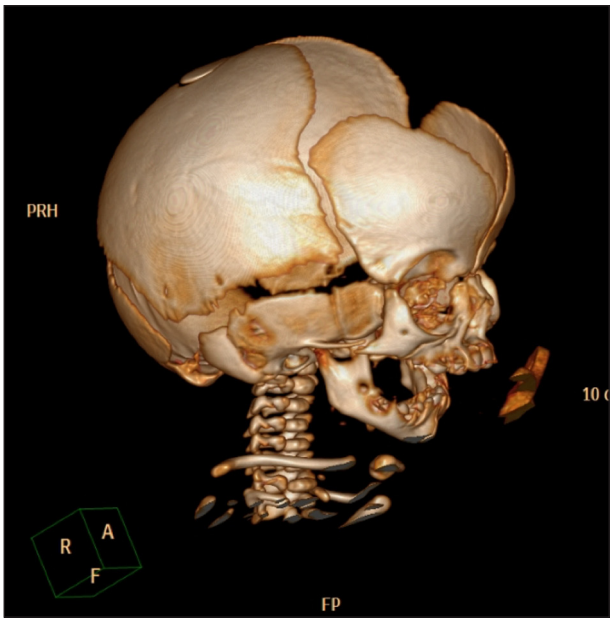

Figure 4. Lateral view of 3D cranio-encephalic CT scan highlighting large anterior fontanelle and mandibular hypoplasia.

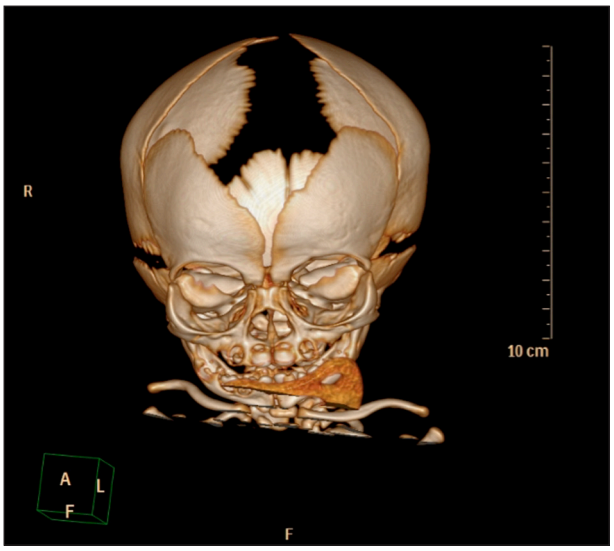

Figure 5. Upper view of 3D cranio-encephalic CT scan demonstrating a large sagittal suture and anterior fontanelle.

but it remains controversial. Wagner syndrome [22] is an autosomal dominant eye disorder resembling Stickler syndrome but without retinal detachment.

Since admission to the NICU, there was no need for supplemental oxygen, no episodes of hypoxemia, only periods of transient tachypnea. Echocardiogram was normal.

Due to feeding difficulties, he started fluids on the 1st day of life, which he maintained until the 5th, with a slow progression of enteral feeding through a special needs' teat. He was observed by a Physiatrist and started speech therapy to improve his feeding abilities.

He was discharged to the Pediatrics Ward on the 8th day of life, for continued care. A subsequent evaluation in a Neonatology consultation, with poor weight evolution at 21 days of life, with no birth weight recovery, led to his readmission to the NICU. During hospitalization, he presented periodic noisy breathing, tachypnoea and subcostal retractions. To highlight some episodes of desaturation with spontaneous recovery, during feeding and associated with head positioning, observation by a Pediatric Pulmonologist was requested; he underwent capnography that came back normal. Due to his poor weight gain and feeding difficulties, he started feeding by orogastric tube nutritional supplementation with MCT oil. He was discharged at 1 month and 6 days of age, with pulse oximetry at home and supplemental oxygen as needed. He maintained multidisciplinary follow-up in Pediatric Pulmonology, Otorhinolaryngology, Ophthalmology, Cardiology, Neonatology and Orthopedics.

Auditory evoked potentials from the brain stem were normal, but he is still in auditory follow-up.

Genetic confirmation of STL2 (*COL11A1* gene, variant c.2952+1G>T) was made at 2 months of age.

Nowadays, at 13 months of age, he maintains multidisciplinary follow-up (Neonatology, Ophthalmology and Otorhinolaryngology). The facial features (**Fig. 6** and **Fig. 7**) are still present; the height is 72.5 cm (P3), weight is 10.03 kg (P50), head circum-

Figure 6. The patient at 13 months of age, highlighting the typical features visible since birth, like prominent forehead, bilateral exophthalmos, low-set ears and retrognathism.

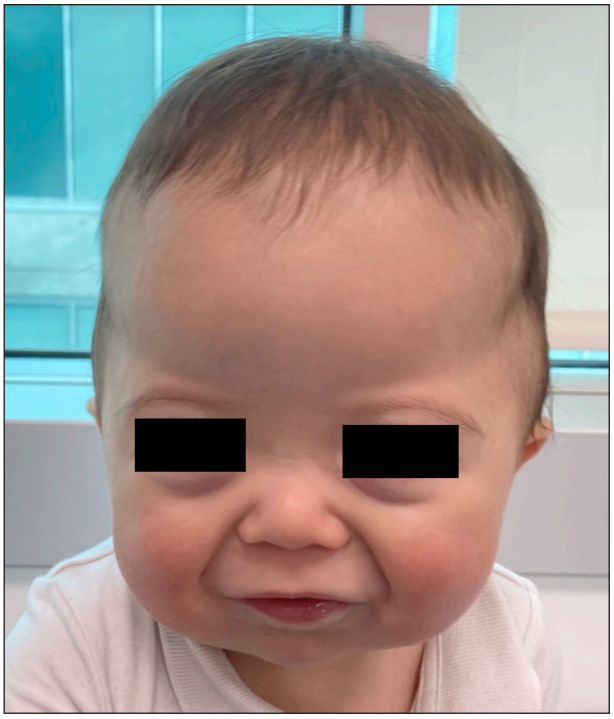

Figure 7. Detail of the face, being visible the typical facial characteristics.

ference is 50 cm (> P97); he has a normal psychomotor development.

Discussion

The diagnosis of Stickler syndrome is based on clinical features. The flattened facial appearance is characteristic of Stickler syndrome. The Pierre Robin sequence is also common in patients with Stickler syndrome. Although Robin et al. proposed clinical diagnostic criteria for STL1, at present, there are no validated consensus nor diagnostic criteria, which makes it hard to diagnose promptly unless there is a high level of knowledge and suspicion of this syndrome. Several disorders resembling Stickler syndrome have been described, and their status as distinct entities remains somewhat controversial. Molecular genetic data are beginning to inform this debate, but uncertainty remains. This patient has a mutation in the *COL11A1* gene, being an STL2 case. It is estimated to be present in about 15% of the patients with Stickler syndrome. Hearing loss is found in 82.5% of these patients, and most of them have a sensorineural loss [7]. Hearing loss in STL2 seems to be more pronounced than in STL1, and is already apparent at a young age. Although this patient did not pass the universal neonatal hearing screening, the auditory evoked potentials were normal to date.

What first appeared as abnormal in this patient were the evident facial features that he presented since day one and are still present nowadays.

The aim of this report is to describe a case of a patient with STL2 with a genetically confirmed *COL11A1* gene mutation, variant c.2952+1G>T. Genetic counseling is important as this syndrome has marked medical and personal consequences, both for the patients and their families. Multidisciplinary team approach including Ophthalmology, Pediatrics, Genetics, Otorhinolaryngology, Orthopedic Surgery, Oral and Maxillo-facial Surgery is crucial in the management of a patient with Stickler syndrome to help them to get the best possible outcome and quality of life.

Informed consent

The written informed consent was obtained from the patient's legal guardian for the publication of this case.

Declaration of interest

The Authors declare that there is no conflict of interest.

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