A RARE CASE OF GROW RETARDATION ASSOCIATED TO DISGENETIC SYNDROME

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Abstract

Stickler syndrome is a connective tissue disorder that can include ocular findings of myopia, cataract and retinal detachment. It can also cause hearing loss that is both conductive and sensorineural. Under-development of the middle part of face, ogival palate, spondylo-epiphyseal dysplasia and/or precocious arthritis can also occur. The authors present the case of a 7 months old infant with failure to thrive associated to a particular phenotype; facial dysmorphism and congenital cataract, who was referred for admission presenting an upper respiratory tract infection. Corroborating the clinical examination with the paraclinical evaluation and genetic assessment, including the karyotype, the authors established in this case the diagnosis of Stickler syndrome.

Key words: Stickler syndrome, congenital cataract, myopia, conductive and sensorineural hearing loss.

Introduction

Stickler syndrome is a connective tissue disorder that can include ocular findings of myopia, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural; midfacial underdevelopment and cleft palate (either alone or as part of the Robin sequence); and mild spondyloepiphyseal dysplasia and/or precocious arthritis. Variable phenotypic expression of Stickler syndrome occurs both within and among families; interfamilial variability is in part explained by locus and allelic heterogeneity. Stickler syndrome is the commonest inherited cause of retinal detachment in childhood and although the systemic features are widespread, the sight threatening complications are the most serious manifestations. (1)

Case report:

T.V., a 7 months old boy, was admitted in hospital in June 2015 for an upper respiratory tract infection.

The personal history showed that T.V. was a young couple's first child from rural area. T.V. was born at term, in cranial presentation, with weight at birth 3250 grams and height at birth of 49 cm. Apgar score was 10, and the infant presented good neonatal adaptation. His diet consisted of breast milk for one month and after that he was fed with cow's milk. The complementary feeding was incorrectly initiated at the age of three months. He has been vaccinated only with BCG and Engerix in maternity and the other vaccinations were not performed by the age of 7 months when he presented in our clinic. In infancy he presented several episodes of upper respiratory tract infections treated at home.

The interesting aspect of this case was the fact that the family history showed an involvement of ocular disorders in two maternal uncles with acquired amblyopia of unknown etiology, one of whom died in a car accident and the other being alive and presenting blindness. (Figure 1)

Clinical examination upon admission revealed an infant with mild failure to thrive, presenting the following anthropometric indices: weight of 6300 g, high 63 cm, 43 cm cranial perimeter, thoracic perimeter of 47 cm and 45 cm abdominal perimeter. Particular facial phenotype was characterized by underdevelopment of the middle part of face, micrognathia, ogival palate.

The infant presented a pronounced horizontal nystagmus and the skin was pale. The pharynx was congested, the baby presented nasal obstruction and a rare irritating cough but presented normal lung auscultation. On auscultation a second degree systolic murmur was heard. The infant showed generalized hypotonia with pronounced tendon reflexes in the legs. The baby maintained its own head, was not sitting upright, not able to stand alone or with support or say polysyllabic words. He presented chaotic eye movements, was not able to follow the examiner face, nor respond to his mimic, nor follow moving objects with his eyes. No other changes were detected in the rest of examination.

Laboratory examinations revealed severe iron deficiency anemia, hypochromic microcytic, hypocalcemia, hypomagnesemia, hipogammaglobulin and moderate elevation of liver tranaminases. (Table 1).

TORCH serology was negative, we excluded citomegalvirus infection, toxoplasma gondii, treponema palidum and HIV infection, chronic B and C hepatitis.

Skull radiography revealed normal thickness cap, suture according to age, Turkish saddle according to age.

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	17.06.2014	23.06.2014	01.07.2014
Hemoglobin **RBC**	6.8 g/dl $1.87x10^6/\mu L$	10.2 g/dl $3.80x10^6/\mu L$	11.5 g/dl $4.0x10^6/\mu L$
WBC and leukocytes formula	$6.6x10^3/\mu L$ Sg=27%, E=1%, Ly=63%, M=9%	$8.8x10^3/\mu L$	
Platelets	175.000 / µL	220.000 / µL	
Inflammation	ESR=6mm/h CRP: negative		
Electrolytes	Na=134, K=3.99, Ca=2.2, Cl=98, Mg=0.76 mmol/l	Na=138, K=4.33, Cl=104 mmol/l	
Astrup	pH = 7.34, pCO2 = 17.6mmHg BE = -9.6mmol/l HCO3 = 9.8mmol/l		
Proteinemia and electrophoresys	60 g/l; A = 66.7%, α1=3.2%, α2 = 10.4%, β = 10.8%, γ = 8.9%	64.6g/l	
LDH	820 U/L		
Liver tests	GPT = 65U/l GOT = 76U/l GGT = 22 U/L	GPT = 71U/l GOT = 73U/l	GPT = 16 U/L GOT = 12 U/L
Renal tests	BUN = 6.87mmol/l Serum creatinine = 45µmol/l		
Serum Glucose	3.5 mmol/l		
Microscopic examination of urinary sediment	Absent albuminuria, 1-3 WBC per high power field, rare hyaline cylinders, rare epithelial cells		
Stool parasitology test **Stool culture**	NEGATIVE NEGATIVE		

Table 1. Laboratory results

A pediatric cardiologic examination was performed. Echocardiography showed aorta = 12.7 mm, opening aorta = 7.14 mm, left atrium = 14.4mm, left ventricle = 16.6 / 23.6 mm, ejection fraction = 0.59, shortening fraction = 29.79 mm, interatrial septum = 5.18 mm, apparently without defects, right atrium = 17.1 mm, right ventricle = 13.5 mm. The anterior mitral valve presented protosistolic prolapse with regurgitation. The examiner detected aortic insufficiency. There was no fluid in pericardium.

Ophthalmologic examination showed microphthalmia in both eyes. Cornea transparency was reduced in size in both the horizontal and vertical axis. Normal iris. Pupil round, central. Anterior subcapsular crystalline opacities, white color. Ocular pressure was normal (Figure 2).

- Papillary and photomotor reflexes were present.
- Oftalmometry = 8 mm
- Ophthalmoscopy (Dilated Fundus Exam - DFE): no shine.
- Neurologic exam showed muscular hypotonia, horizontal nystagmus; opsoclonus; psychomotor retardation with stereotypy.
- Electroencephalogram (EEG Test) showed theta-delta rhythm, with many artifacts.
- Ear, nose and throat (ENT) examination was normal.

- Audiogram revealed mixed hearing loss, conductive and sensorineural.

A genetic consultation was performed. The karyotype was 46 XY 1qh+, 21s+, yq +; with chromosomal heteromorphysm with elongation of secondary constriction of chromosome 1, increase satellites on chromosome 21 and heteromorphysm of the Y chromosome.

Taking into consideration clinical and laboratory criteria: ophthalmic, otic, cardiac and cranio-facial changes and the karyotype, we sustained the diagnosis of Stickler syndrome.

During hospitalization in our clinic, the infant presented several episodes of watery diarrhea, possibly of viral etiology, which resolved under medical and dietary treatment (lactose-free milk, Racecadotril, Smecta, probiotics), without dehydration syndrome and electrolyte disorders. Pale skin was associated with pronounced low values of hemoglobin and the number of red blood cells, which required red blood cells transfusion. The treatment for upper respiratory tract infection was performed with acetaminophen syrup orally and 1% ephedrinated serum intra-nasal. For muscle hypotonia Cerebrolizyn treatment was initialized which was well tolerated. For transient hepatocytolitic syndrome accompanying the viral enterocolitis, the infant received intravenous infusion of Arginine and Aspatofort and transaminases return to normal in 14 days. Roborant treatment given to infant was consisted from group B vitamins (B1, B6, C) and gluconic calcium 10% in slow iv injection.

Discussions

Stickler syndrome is a genetic disorder with autosomal dominant transmission. Mutations affecting one of three genes: COL2A1, COL11A1, COL11A2 have been associated with a disease. Because a small number of families with Stickler syndrome features showed no mutations in these three mentioned genes, it appeared the hypothesis of mutations occurred at the level of other genes.

Given the autosomal dominant mode of transmission of the disease, affected patients shows a 50% risk of transmitting the mutant gene to each of succesors. Because of the wide clinical variability of the disease that can occur within the same family, it must be assessed the relative risk of developing the disease and providing genetic counseling, like in the case of infant T.V. (Figure 3)

The Stickler syndrome diagnosis is mainly established on clinical data. There is currently no consensus on the minimum number of clinical criteria that must be met for a diagnosis.

Prevalence

There have been no studies done to determine the exact prevalence of Stickler syndrome. However, an approximate incidence among newborns can be estimated given the data regarding the incidence of Pierre-Robin syndrome (1:10 000) and taking into account the percentage of those infants who develop signs or symptoms of secondary Stickler syndrome (35%). Summing these datas, it was obtain an approximate incidence of 1:7500 of Stickler syndrome in newborns. (1)

Diagnosis

There is not a specific clinical diagnosis criteria for Stickler syndrome however its diagnosis takes into account subjects who have two or more of the following conditions: (2, 3, 4, 5, 6)

1. Ophthalmologic disorders: congenital cataract or early onset in infancy, myopia greater than - 3 diopters, abnormal vitreous, retinal detachment. Usually, babies are farsighted (1 diopter or more), so the discovery of a degree of myopia in newborns at risk (with Pierre-Robin phenotype or with a parent affected) is suggestive for the diagnosis of Stickler syndrome. Among patients with this disease, there were observed two types of vitreous abnormalities. Type I, which is most commonly seen, consists of a persistent vestgial vitreous gel in the retrolental space, bounded by a membrane. Type II which is rarer, is characterized by the presence of bands thickened, irregular, and dispersed into the vitreous cavity. In our case, infant T.V. showed the phenotype Pierre-Robin described above and ocular changes: mycrophthalmia, corneal decreased in size in horizontal and vertical axis, and crystalline opacities, subcapsular above, white color.
2. Ear disorders: hearing loss, conductive or sensorineural. The degree of hearing damage is variable and can grow progressively. Approximately in 40% of the studied cases it has been described sensorineural deafness typically with loss of hearing for high tones. The exact mechanism is unclear and has been linked to the expression of collagen type II and IX in the inner ear. In type I Stickler syndrome, sensorineural hearing impairment is mild and with no progressive evolution, and is less severe compared with the audiological degradation in types II and III Stickler syndrome. Conductive deafness in some cases may be secondary to recurrent ear infections favored by ogival vault or due to a defect of the middle ear ossicles. Infant audiometry performed for T.V. infant showed mixed hearing loss, conductive and sensorineural.
3. Craniofacial changes: hypoplasia of the middle part of the face, deepened nose base, sharp nose, with nostrils anteversion, long filter, uvula bifida, ogival palate, micrognathya, Pierre Robin phenotype (micrognathya, ogival arch, glosoptosis). Flat facial profile, caused by underdeveloped jaw and nose base, can cause telecanthus and epicanthus folds. Hypoplasia of the middle face is more pronounced in infants and young children, some subjects may have a normal facial profile.

T.V. baby facies was characteristic for Pierre-Robin phenotype, involving extra microcephaly.

4. Articular changes: Skeletal manifestations consist of early-onset osteoarthritis, hypermobility (joint laxity), short stature and radiographic changes of medium spondylo epiphyseal dysplasia. Some individuals may have "marfanoid" features, but with no tall stature. Joint laxity can be found in children and become less important with age. Stickler syndrome common spinal abnormalities

(scoliosis, kyphosis) can lead to chronic back pain. In T.V.'s case no skeletal changes were detected on admission.
5. Cardiac disorders: In the literature there were reported associations with mitral valve prolapse in 50% of the cases studied in a clinical trial and in a much smaller proportion of cases in another series (3, 5). This malformation – prolaps of mitral valve, was associated in our case.

According to recent studies, not all criteria are needed to comply with Stickler syndrome.

Fig. 1. The two maternal uncles of T.V. infant with

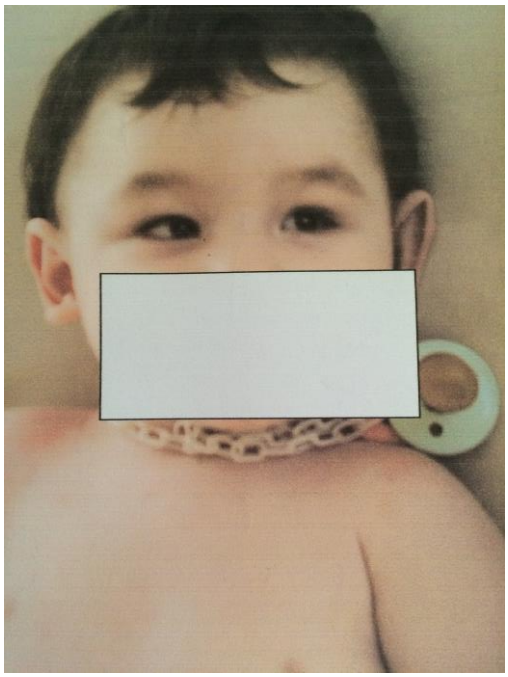

Fig. 2. T.V. clinical aspect

Genetics

Stickler syndrome is a genetic disorder with autosomal dominant transmission. Mutations produced in the following three genes were associated with the appearance of type I, II and III Stickler syndrome: COL2A1 (chromosome 12, 12q13.11-q13.2 locus), COL11A1 (chromosome 1, 1p21 locus), COL11A2 (chromosome 6 , 6p21.3 locus). (Table 2)

In some families with characteristic clinical changes of Stickler syndrome were not uncovered any one of these three mutations mentioned. It has been hypothesized the existence of mutations in other genes, still unidentified, present also in this disease.

Most patients diagnosed with Stickler syndrome presents the type I of the disease, with mutations in COL2A1 gene, while mutations in the gene COL11AI (type II) were only recently described. Lately, in a few cases have been describing mutations in COL11A2 gene that causes Stickler syndrome type II, where all eye changes are missing.

Normal results of the COL2A1 gene activity is represented by chains of type II collagen, a major structural component of cartilage tissue. Mutations in this gene cause the premature termination of translation and consequently reduces type II collagen synthesis.

COL11A1 gene encode anα chain synthesis of collagen type XI, which is supposed to play an important role in collagen fibrils genesis, controlling the lateral growth of collagen II fibrils. COL11A1 gene mutations alter the synthesis and function of collagen type XI.

COL11A2 gene encode α 2 chain synthesis of collagen type XI, expressed in cartilage, but not at the level of liver, skin and tendons. COL11A2 gene mutations also cause abnormal synthesis of collagen XI.

Genotype-phenotype correlations

In the COL2A1 gene appears a premature stop mutation that causes failure of the normal gene product synthesis, type II collagen. Most patients shows the type I vitreous anomaly and are at increased risk of retinal detachment, do not present hearing impaired or have a mild form of sensorineural deafness and shows early arthritis and craniofacial changes are variable.

COL11A1 gene mutation was observed in patients with typical phenotype of Stickler syndrome. Usually these patients have a more severe hearing impairment and type II congenital vitreous anomaly.

Gene mutation in COL11A2 cause Stickler syndrome without eye changes. (7, 8, 9, 10, 11, 12)

Clinical examination, biological investigations, laboratory and karyotype, performed in conjunction with interdisciplinary exams excluded a number of related genetic disorders. The karyotype of the case presented described mutations in the gene COL11A1 - locus 1p21 (46 XY, 1qh +, 21s +, yq +; chromosomal heteromorphysm with elongation of secondary constriction of chromosome 1, increase satellites on chromosome 21, and heteromorphysm of the Y chromosome), framing the presented case as Stickler syndrome type II.

Type of disease	Mutant gene	Mutant locus	Synthesis product of the gene
Stickler syndrome type I	COL2A1	12q13.11-q13.2	**α1 chain of type II collagen**
Stickler syndrome type II	COL11A1	1p21	**α1 chain of type XI collagen**
Stickler syndrome type III	COL11A2	6p21.3	**α2 chain of type XI collagen**

Table 2. Stickler syndrome's types

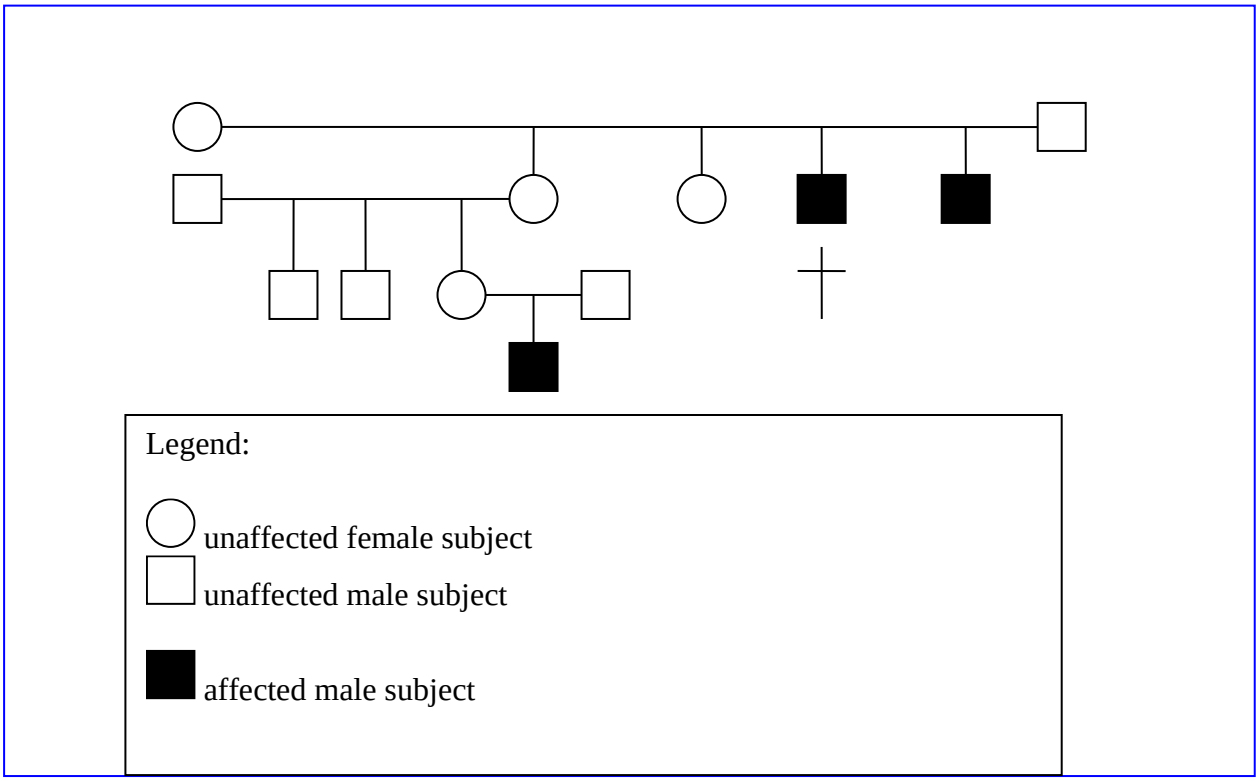

Fig. 3. Genetic family tree of T.V. infant

Conditions that show phenotypes associated with COL2A1 and COL11A2 gene mutations were excluded; in our case it is not type I or III of Stickler syndrome according to the karyotype.

For the differential diagnosis, we ruled out the following conditions:

1. Phenotypes associated with mutations in COL2A1 gene:

- Achondrogenesis type II: characterized by virtual absence of ossification of the spine, sacrum and bin, with the consequent appearance of shortening of the trunk and limbs, with prominent abdomen and dropsical issue. Death occurs in utero or in early neonatal period.
- Hypochondrogenesis - term used for describing a medium form of achondrogenesis
- Congenital spondylo epiphyseal dysplasia: although skeletal changes are similar to those described in Stickler syndrome, these are more severe and cause significant short stature. In addition, affected subjects may present flat profile, myopia or vitreous and retineal degeneration.
- Kneist dysplasia: affected subjects may present disproportionate short stature, flat facial profile, myopia, vitreous and retineal degeneration, ogival palate, kyphosis scoliosis, and multiple radiological spinal changes.
- Early-onset arthropathy: the disease is transmitted autosomal dominant, in 1990 being identified the COL2A1 gene mutation incriminated in the disease - the substitution of arginine to cysteine in position 519 of the α1 chain of type II collagen.

2. Phenotypes associated with mutations in COL11A2 gene:

- Autosomal recessive spondylo-metaepiphyseal dysplasia: the disease is characterized by flat facial profile, sharp hard palate and severe deafness. Recently it has been hypothesized that type III Stickler syndrome - a form

without eye changes could be considered a type of this disease.

- Weissenbach-Zweymuller syndrome (WZS) was described as "neonatal Stickler syndrome", but now is a distinct entity, characterized by hypoplasia of the middle part of face, clogged nose and top with the sharp nose, micrognathya, sensorineural hearing loss and limb shortening. Radiological changes include the femur and humerus in the form of "weightlifting". Skeletal changes are less obvious in their lives and resume growth after 2-3 years of life is common.
- Non-syndromic sensorineural deafness: in 1999 were described mutations in the COL11A2 gene in two unrelated families suffering from non-syndromic nonprogressive deafness.

3. Stickler syndrome type II seen in infant T.V. and must be differentiated from other similar genetic diseases that present similar phenotype and also associate mutations in the gene COL11A1:

- Marshall syndrome: Affected individuals present hypertelorism, maxillary hypoplasia and hypoplasia of the nasal bones as well as a clogged nose and a pointed nasal tip. Unlike Stickler syndrome, flat facial profile is more evident in adults. Eyes' imapirement includes: myopia, vitreous humor fluid and early onset cataracts. Sensorineural hearing loss is common and may progress. Nanism and early arthritis may occur. Skin manifestations are also described - hipotricosis and hipohidrosis.

T.V. baby did not have early cataracts, skin manifestations or early onset arthritis, but the differential diagnosis remains questionable, taking into consideration the opinions of some authors which categorizes Marshall syndrome as a variant of Stickler syndrome II. (13, 14, 15, 16, 17, 18, 19, 20)

Conclusions

Stickler syndrome is often under-diagnosed in neonates with particular facial dysmorphism.

There are not any established precise clinical diagnosis criteria for Stickler syndrome. The diagnosis should be considered in children who presents two or more of the following conditions: ophthalmologic disorders, ear affections, particular craniofacial phenotyp, articular injuries or cardiac disorders.

Medical family history, clinical examination and karyotype assessment are necessary for diagnosis of Stickler syndrome.

The particularity of the presented case was the delay in diagnosis untill the age of 7 months in a child with particular phenotype with facial dysmorphism, failue to thrive, microcephaly, congenital cataracts and mild psycho-motor retardation.

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