CLINICAL QUIZ (p129) ANSWER

What is the diagnosis?

Pierre Robin sequence: Our proband has both cleft palate and micrognathia (small jaw) and thus Pierre Robin sequence (PRS) should be considered. PRS is a malformation sequence comprising respiratory obstruction, glossoptosis (backward and downward falling of the tongue) and mandibular hypoplasia, often associated with palatal clefting. The incidence is about 1:8500-14000 worldwide.

What are the differential diagnoses?

PRS is associated with various genetic syndromes and chromosomal anomalies and clinically it is helpful to classify patients into isolated or syndromic forms of PRS, which can be further classified into PRS with skeletal dysplasia, PRS with neuromuscular involvement or PRS with multiple congenital anomalies. Clinical geneticists should be involved in the early assessment of a newborn with PRS. Since 22q11.2 deletion and Stickler syndrome are the 2 commonest underlying genetic diagnoses in a child initially diagnosed with PRS, early minimal investigations for newborn with PRS should include high-resolution chromosomal microarray and detailed ophthalmological assessment at birth and at 6 months with detailed and targeted prenatal history (fetal constraint, oligohydramnios, teratogen exposures) and family history (short stature, myopia, premature joint degeneration). A neurologist should be involved in in the care of patients with suspected neuromuscular conditions. Detailed discussion of the diagnostic approach and differential diagnoses is beyond the scope of this quiz, but is reviewed in Tan et al.[1]

How is the diagnosis established in this patient?

Stickler syndrome is a common cause of PRS: Besides PRS, our proband has high degree myopia, progressively flattened mid-face (Figure 1), and a family history of retinal detachment (his father). These features are consistent with Stickler syndrome, which was molecularly confirmed by Sanger sequencing of the *COL2A1* gene (in Connective Tissue Gene Tests, USA). The result showed a single nucleotide substitution in exon 9 of the *COL2A1* gene (c.625C>T, CGA>TGA), resulting in a substitution of arginine (CGA) to a termination codon (TGA). This mutation of the *COL2A1* gene confirms the clinical diagnosis of Stickler syndrome Type I. This mutation has been reported before by Ahmad et al. in 1993.[2] Parental testing confirmed that the *COL2A1* gene mutation was paternally inherited which is consistent with the family history of the father having myopia and retinal detachment at 8 years of age. Skeletal survey of our proband showed mild scoliosis with no obvious epiphyseal abnormality.

Stickler syndrome was first described by Stickler et al in 1965. It is a genetically heterogeneous syndrome predominantly characterized by problems in the articular, auditory, ophthalmic and orofacial systems.[3] Stickler syndrome is one of the most common autosomal dominant connective tissue disorders[4] and has a prevalence of 1 in 7500 to 9000 births.[5] Full clinical findings can be found in Table 1. Stickler syndrome can be inherited by both autosomal dominant (Types I, II and III) and recessive (Types IV and V) mode. Mutations in genes *COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, and *COL9A2* lead to Stickler syndrome types I to V respectively. Type I is the most common, accounting for about 75% of all patients.[6] *COL2A1* gene located on chromosome 12q13 encodes for the α1 chain of collagen II[7] which is found in cartilage, vitreous and nucleus pulposus.[8] Collagen II is made up of 3 alpha-1 chains and is secreted by chondrocytes into the extracellular space as propetides which are cleaved to form collagen II molecules and bind onto other cartilage.[9] The single nucleotide substitution found (c.625C>T, CGA>TGA) caused a substitution of arginine leading to a premature termination codon. When present in a coding sequence of a fibrillar procollagen α-chain domain, the premature termination signal may prevent synthesis of any polypeptide chains that can participate in the formation of procollagen molecules[2] which reduces the amount of collagen II found in cartilage. This explains the various phenotypes found in Stickler syndrome Type I, such as ophthalmic problems, degenerative changes in joints, hearing deficit, etc.

The diagnosis of Stickler syndrome is usually established in a clinical setting and there are no consensus minimal clinical diagnostic criteria. It has been proposed that diagnostic criteria should be based on the vitreous phenotype and involvement of other organ anomaly. But this would require a slit-lamp examination which is not always possible for young children or patients with prior retinal surgery.[10] In 2005, Rose et al proposed a set of diagnostic criteria for Stickler syndrome Type I based on examining the ocular, orofacial, auditory and musculoskeletal systems which is shown in Table 2.[10] The criteria proposed by Rose et al are based on the detection of anomalies found in different

Table 1 Clinical findings found in different Stickler syndrome subtypes of autosomal dominant mode of inheritance and features found in our proband

Clinical findings	Stickler syndrome		Present case
	Type I & II *(COL2A1 & COL11A1)*	Type III *(COL11A2)*	
High myopia	+	-	√
Vitreoretinal degeneration	+	-	
Retinal detachment	+	-	
Cataracts	+	-	
Hearing loss	+	+	
Mid-face hypoplasia	+	+	√
Cleft palate/Pierre Robin sequence	+	+	√
Anteverted nares	+	+	√
Small chin	+	+	√
Short stature	+/-	+/-	
Spondyloepiphyseal dysplasia	+	+	
Early-onset osteoarthritis	+	+	(mild scoliosis)
Other features	-	-	

Apart from the autosomal dominant mode of inheritance as show above, Stickler syndrome may also be caused by mutations in *COL9A1*, *COL9A2* and *COL9A3* genes which are reported to be inherited in an autosomal recessive manner. However cases caused by autosomal recessive mode of inheritance are rare comparing to cases caused by autosomal dominant mode of inheritance. + Present; - Absent.
(Modified from Faletra F, D'Adamo AP, Bruno I, Athanasakis E, Biskup S, Esposito L, et al. Autosomal recessive Stickler syndrome due to a loss of function mutation in the *COL9A3* gene. Am J Med Genet A 2014;164A:42-7.[11])

Table 2 Diagnostic criteria for Stickler syndrome Type 1

Orofacial abnormalities (2 points maximum)	
2 points	**Cleft palate**
1 point	**Characteristic face**
Ocular abnormalities (2 points maximum)	
2 points	Characteristic vitreous changes or retinal abnormalities
Auditory abnormalities (2 points maximum)	
2 points	High frequency sensorineural hearing loss Age<20: threshold 20 dB at 4-8 kHz Age 20-40: threshold 30 dB at 4-8 kHz Age >40: threshold 40 dB at 4-8 kHz
1 point	Hypermobile tympanic membranes
Skeletal abnormalities (2 points maximum)	
1 point	Femoral head failure
1 point	Radiographically demonstrated osteoarthritis before age 40
1 point	**Scoliosis**, spondylolisthesis, or Scheuermann-like kyphotic deformity
Family history/molecular data	
1 point	**Independently affected 1st degree relative in a pattern consistent with autosomal dominant inheritance** or presence of *COL2A1*, *COL11A1*, or *COL11A2* mutation associated with Stickler syndrome
Positive diagnosis requires	
	5 or more points **At least one major 2-point manifestation** **Absence of features suggestive of a more severe skeletal dysplasia or other syndrome**

Clinical features present in the patient are bolded.
(Modified from Levy HP, Liberfarb RM, Davis J, Szymko-Bennett Y, Rubin BI, Tsilou E, et al. Stickler syndrome: clinical characteristics and diagnostic criteria. Am J Med Genet A 2005;138A:199-207.[10])

organ systems such as auditory, ocular, orofacial and musculoskeletal systems. However borderline cases such as the propositus who would score only 4 points according to Rose et al's criteria (cleft palate-2 points; family history-1 point, mild scoliosis-1 point), may still require further evidence for a more confident clinical diagnosis. Molecular analysis would be helpful to confirm the underlining genetic cause of the phenotype. Specific genes should be tested according to the clinical presentation of the patient, i.e. *COL2A1* gene should be tested if the patient presents with the Type I phenotype where vitreous gel in the retrolental space appears to be bound by a folded membrane and hearing deficit is mild. If the patient has a type II phenotype where thickened bundles are found in the vitreous cavity and hearing deficit is more significant, then the *COL11A1* gene should be targeted first.

What are the management issues for the patient and other family members?

Once a diagnosis of Stickler syndrome has been confirmed, immediate multidisciplinary approach to management is desirable.[6] This should include 1) surgical intervention to close the cleft palate, tracheostomy for airway management and orthopaedic procedures may be required. 2) Ophthalmological assessment with refraction and correction of myopic/astigmatic error. Long term follow up should assess for retinal detachment. Urgent ophthalmologist assessment should be sought if new floaters and shadows are detected in vision. 3) Regular hearing surveillance should be made to monitor for hearing problems. 4) Although Stickler syndrome does not affect intellect and development, school age patients may encounter difficulties due to myopia and hearing problems. Therefore schools or education authorities may need to provide support for these patients. 5) Proper genetic counseling and testing of family members can also be initiated with the confirmed molecular diagnosis. Since the father is found to carry the *COL2A1* mutation, he is also recommended to have surveillance by ophthalmologist and orthopaedic surgeons for retinal detachment and premature osteoarthritis.

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