Syndrome of the month

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Stickler's syndrome

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In 1965, Stickler *et al*¹ documented the association of severe myopia and degenerative joint changes in a five generation family. They termed this autosomal dominant condition hereditary progressive arthro-ophthalmopathy, but it is now more commonly called Stickler's syndrome. Two years later Stickler and Pugh² noted deafness in the original proband and his mother and also remarked on a characteristic flat facial appearance.

In 1972, Opitz *et al*³ pointed out the association with the Pierre-Robin sequence and Herrmann *et al*⁴ made an important contribution when they described 64 cases of Stickler's syndrome, stressing the variable manifestations of the condition.

Controversy remains as to whether the syndrome described by Stickler is a distinct entity or should be incorporated into part of a larger connective tissue disorder which includes Marshall's,⁵ Wagner's,⁶ and Weissenbacher-Zweymuller syndromes.^{7,8}

Clinical features

The variable manifestations of Stickler's syndrome can lead to diagnostic difficulties. The clinical findings can be divided into three groups—signs relating to the eyes, joints, and facial appearance. In any subject, signs from one group can predominate and lead to presentation to a number of specialities. In families, the pattern of findings cannot be accurately predicted nor the severity assumed from previously affected relatives.

OCULAR MANIFESTATIONS

Myopia is generally severe (>-8 diopters), probably congenital, and progression is minimal.⁹ Myopic degeneration of the retina can occur with lattice degeneration and myopic crescents visible on funduscopy.

Chorioretinal degeneration is characterised by areas of abnormal retinal pigmentation, choroidal

atrophy, retinoschisis, and retinal holes.¹⁰ These can occur independently of myopia. Degeneration may progress to retinal detachment and when extensive this leads to blindness. Detachment occurs spontaneously and can be bilateral. It is more likely in patients with a family history of detachment and in those under 30 years of age.

When vitreal degeneration occurs, the vitreous appears optically empty on slit lamp examination with a few floating strands.¹¹

There can be nuclear sclerotic cataracts, which tend to occur in a younger than expected age group, cortical cataracts,⁴ or cataracts secondary to retinal surgery.

JOINT CHANGES

Although arthropathy was stressed by Stickler *et al*,¹ symptoms are very variable, age dependent, and often so mild that only x ray changes are present.

Birth to infancy

Clinical findings include prominent joints and hyperextensibility. Talipes equinovarus can occur. X ray findings include enlargement of epiphyses and metaphyses (fig 1). If severe the long bones appear 'dumb bell' shaped (fig 2). These findings characteristically improve with age and there is usually a period of several years when the long bones appear normal.

Childhood

Clinical findings include pain and stiffness in any joint on overuse and symptoms may mimic juvenile arthritis when severe. There is hypermobility of joints. X ray findings include mild spondylo-epiphyseal dysplasia with widening of the ends of long bones. The femoral epiphysis is commonly flat and irregular and associated with a broad femoral neck (fig 3). In the spine the changes can be severe with irregularity of the vertebral end plates (fig 4).

Adulthood

Osteoarthritis of large joints developing in the third

FIG 1 Radiograph of the right upper limb of a neonate showing the flared humeral metaphysis.

FIG 2 Radiograph of the right femur of a neonate showing a dumb bell configuration with broad metaphyses.

FIG 3 Pelvic x ray of an older child showing short, wide femoral necks, prominent lesser trochanters, and small flattened capital femoral epiphyses with irregular ossification.

and fourth decades is frequently the first manifestation of joint disease and it tends to progress. X ray findings show secondary degeneration of the articular surfaces with irregularity and widening of the joint spaces and flattening and irregularity of the vertebral bodies. Skull x ray can show small facial bones and a small anterior fossa.

Occasional features include thoracic kyphoscoliosis and intra-articular loose bodies, genu valgum, pronated feet, pectus carinatum, and arachnodactyly with a Marfanoid habitus.

Height is generally normal but from our series of four multigeneration families with Stickler's syndrome, 23% (3/13) were under the third centile for height. These subjects were the more severely affected and tended to be the probands in the families. Two of these patients had associated chronic illnesses contributing to the short stature.

Orofacial features

Cleft palate

One of the most serious presentations of the syndrome is with the Pierre-Robin sequence (fig 5) which can occasionally be fatal in the neonatal period. Cleft palate or lesser degrees of clefting such as a bifid uvula can occur without micrognathia and sometimes a high arched palate may be the only manifestation.

FIG 4 AP and lateral radiographs of the spine in an older child showing a pronounced thoracolumbar kyphosis with an increase in AP diameter of the vertebral bodies and irregular vertebral end plates, especially in the upper lumbar region.

Midfacial hypoplasia

This gives the face a characteristic appearance (fig 6) and is often associated with a flat nasal bridge, prominent eyes, epicanthic folds, a short nose, and anteverted nares (figs 7 and 8). The flat facial

FIG 6 Typical facial features of a neonate with Stickler's syndrome. Note the flat nasal bridge, small nose, anteverted nares, and prominent eyes.

FIG 5 Photograph of a child with Stickler's syndrome in early infancy. Note in particular the marked micrognathia. He also had a cleft palate and initial feeding difficulties.

FIG 7 Facial features of an infant aged four months. The flat nasal bridge and small nose are marked. Note the presence of epicanthic folds.

FIG 8 Flattening of the midface with micrognathia is obvious from this side view of the same neonate as shown in fig 6.

features can be severe and very worrying to the parents of affected children. However, many of these features, especially the micrognathia, improve with age, so that the face can look normal in adulthood (figs 5, 9, 10, and 11).

Hypodontia

Dental maleruption and enamel hypoplasia have been described.⁴

Deafness

Sensorineural deafness originally described by Stickler and Pugh² can be severe and progressive. Glue ear associated with cleft palate can exacerbate the problem but is remedial to surgery. In some patients a mild conductive element remains owing to ossicular defects.

OTHER FEATURES

Mitral valve prolapse has been reported in 45% of 57 patients reviewed by Liberfarb and Goldblatt.¹² Intelligence is usually normal unless affected by early hypoxia secondary to the Pierre Robin sequence or deafness.

Management

(1) All patients presenting with the Pierre Robin sequence or at a 50% risk should have their eyes

FIG 9 The same child as shown in fig 5.

examined for myopia and retinal degeneration in early infancy and at regular intervals thereafter. (2) Deteriorating visual acuity is usually the result of a complication rather than progressive myopia and warrants careful examination for cataract or retinal changes.

FIG 10 The same child as seen in figs 5 and 9 aged three years. There has been good mandibular growth and these pictures emphasise the change in facial appearance that occurs with time.

- (3) Blindness through retinal detachment can be largely prevented by yearly follow up by an ophthalmologist until the age of 30 years. Treatment after detachment is difficult.
- (4) In families presenting with dominant myopia the diagnosis of Stickler's syndrome should always be considered and the 'exclusion list' followed (table 1).
- (5) All children diagnosed must have an audiological examination to exclude deafness.
- (6) Severe midfacial hypoplasia may require plastic surgery with nasal reconstruction.
- (7) Mitral valve prolapse should be looked for and, if present, appropriate prophylactic antibiotics given before surgery.
- (8) Genetic counselling is important for other family members at risk and the 'exclusion list' should be followed before reassuring relatives that they are unaffected (table 1).

TABLE 1 An exclusion check list to follow in patients with a positive family history of Stickler's syndrome. The variable manifestations of the condition make complete reassurance of subjects at risk difficult.

(1) Ophthalmology	Visual acuity—severe myopia and blindness Slit lamp examination—cataracts and vitreous Fundoscopy—retinopathy
(2) Audiology	Deafness
(3) Radiology	AP and lateral spine AP pelvis Lateral skull AP hand AP knee
(4) Palate examination—clefting	
(5) Early photographs	

FIG 11 Mother and child with Stickler's syndrome showing the relatively normal facial appearance in adulthood. The mother is myopic and had a cleft palate. She had four affected children. The flat nasal bridge and midfacial hypoplasia are more marked in her four year old child.

Inheritance

Inheritance is autosomal dominant with variable expression.

Incidence

The incidence of Stickler's syndrome is unknown but the condition is not rare and had tended to be underdiagnosed in the past. The diagnosis should be considered in all families with dominant cleft palate or myopia.

Aetiology

A candidate gene for Stickler's syndrome has been proposed and linkage established with the type II collagen gene, COL2A1, on chromosome 12. Lod scores of 3.96 at $\theta=0$ have recently been reported by Francomano *et al.*¹³ Type II collagen is made up of three $\alpha 1(\text{II})$ collagen chains and is the major collagen of vitreous, nucleus pulposus, and cartilage. A structural defect in this protein could therefore explain the connective tissue defects found in Stickler's syndrome in at least some families.

It remains a possibility that clinical heterogeneity is the result of several gene loci and linkage in further families is awaited. Gene tracking will also help to show whether there is a distinction between Stickler's syndrome and other connective tissue dysplasia syndromes.

Differential diagnosis

The following dominant syndromes should be excluded.

MARSHALL'S SYNDROME

In 1958, Marshall¹⁴ described the association of cataract, myopia and fluid vitreous, deafness, and marked midfacial hypoplasia. Since then Zellweger *et al.*,¹⁵ Keith *et al.*,⁶ and O'Donnell *et al.*¹⁶ have reported further families and included short stature, cleft palate, and spondyloepiphyseal dysplasia indistinguishable from that in Stickler's syndrome. Every sign described in Marshall's syndrome has been seen in families with Stickler's syndrome, with one exception, namely that thickening of the calvarium and dural calcification have been seen in Marshall's syndrome and not Stickler's syndrome.

However, when Ayme and Preus¹⁷ sought to resolve this question they performed computerised cluster analysis on 17 fully documented patients with either Marshall's or Stickler's syndrome and found that two phenotypically separate groups corresponding to the two syndromes emerged. This might support the presence of separate mutations or could simply reflect the fact that gene expression depends on other inherited factors which alter the features that predominate in different families.

WEISSENBACHER-ZWEYMULLER SYNDROME

In 1964 the authors^{17a} described a newborn male

TABLE 2 *Differential diagnosis in Stickler's syndrome.*

	Stick	Marsh	WZ	Kniest	Med	Sed	Wag	Cerv	NS
Eye									
Myopia	+	+	+	+	-	+	+	+	-
Retinal degeneration	+	+	+	+	-	+	+	+	-
Cataract	+	+	-	-	-	-	+	-	-
Joints									
Epiphyseal dysplasia	+	+	+	+	+	+	-	-	+
Flared metaphyses	+	+	+	+	-	-	-	-	+
Platyspondyly	+	+	+	+	+	+	-	-	+
Orofacial									
Flat midface	+	+	+	+	-	+	-	+	+
Cleft palate	+	+	+	+	-	+	-	+	+
Deafness	+	+	+	+	-	+	-	-	+
Other differentiating features		Thick calvarium, dural calcification	-	Rhizomelic dwarfism	-	Truncal dwarfism	-	-	Aut rec

Stick=Stickler's syndrome, Marsh=Marshall's syndrome, WZ=Weissenbacher-Zweymuller syndrome, Kniest=Kniest's syndrome, MED=multiple epiphyseal dysplasia, SED=spondyloepiphyseal dysplasia, WAG=Wagner's syndrome, Cerv=Cervenka's syndrome, NS=Nance-Sweeny syndrome. + = symptom reported in syndrome. - = symptom not reported.

Stickler's syndrome

with the Pierre Robin sequence and chondrodysplasia. He had rhizomelic shortening of the limbs and x rays showed a dumb bell appearance of the femora and humeri. Follow up of this and other patients¹⁸ showed normal growth of limbs and mandible with regression of the x ray findings and normal intelligence. Later, Kelly *et al*⁸ described a neonate with these characteristic changes who had first degree relatives with Stickler's syndrome. It is now widely believed that the Weissenbacher-Zweymuller syndrome is the same condition as Stickler's syndrome, the neonatal x ray findings representing a more severe form of the metaphyseal flaring which caused the 'prominent joints' in Stickler's original article.

Three other neonates described by Winter *et al*⁷ with Weissenbacher-Zweymuller syndrome had midfacial hypoplasia and deafness characteristic of Marshall's syndrome, providing further evidence that all three syndromes result from the same mutant gene.

KNIEST'S SYNDROME

Described in 1952 by Kniest,¹⁹ this syndrome is characterised by short trunked dwarfism with kyphoscoliosis, deafness, myopia, and depressed nasal bridge. Cleft palate and detached retina can also occur. X rays show broad metaphyses and irregular epiphyses of long bones and platyspondyly with thoracolumbar kyphoscoliosis.

It is only likely to be confused with Stickler's syndrome in the neonatal period. Unlike the normal growth in Weissenbacher-Zweymuller syndrome, deformity increases with age and stature is markedly reduced, making follow up a most important factor in differentiating the two conditions.

The dumb bell appearance of the long bones seen in metatropic dwarfism is much more pronounced than in Stickler's syndrome.

MULTIPLE EPIPHYSEAL DYSPLASIA

Similar joint changes are seen in both conditions but multiple epiphyseal dysplasia is not associated with the non-skeletal manifestations of Stickler's syndrome. Spinal changes are very mild.

SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA

This is differentiated by extreme short stature, usually prenatal in origin. Myopia, retinal detachment, and flat facies are features of the syndrome and occasionally the epiphyseal changes can be confused but tend to be more severe, particularly in the spine and hip where there is invariably severe coxa vara.

CERVENKA'S SYNDROME

The combination of myopia, retinal detachment,

cleft palate, and flat facies was described by Cervenka and reviewed by Cohen *et al*.²⁰ Other families have since been reported and thought to have Stickler's syndrome.²¹

WAGNER'S SYNDROME

This refers to a dominantly inherited ocular syndrome of myopia, cataract, and vitreoretinal degeneration progressing to retinal detachment. The findings cannot be distinguished from those seen in Stickler's syndrome. In 1979, Liberfarb *et al*⁶ looked at 15 index cases and their families and discovered on close inspection the presence of non-ocular manifestations which had been previously overlooked. They suggested that Wagner's and Stickler's syndromes were the same condition. However, over 250 subjects have been described with only eye signs and it cannot be excluded that Wagner's syndrome is a separate entity.

The following recessive syndromes should be considered.

NANCE-SWEENEY SYNDROME

Insley and Astley²² described sibs with deafness, marked flattening of the midface, cleft palate, and generalised skeletal anomalies with short long bones, flaring of metaphyses, and large epiphyses. Vertebral changes were also present resulting in progressive spinal curvature.

Recently Miny and Lenz²³ described two similar sibs again with spinal deformity as an important clinical feature. Winter *et al*⁷ referred to this syndrome as the Nance-Sweeney syndrome after an original description of a 52 year old man,²⁴ but comparison with childhood reports is difficult.

In all these reports myopia is not a feature.

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