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Stickler's syndrome: review and differential diagnosis

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Stickler's syndrome is an autosomal dominant connective tissue disorder also known as hereditary progressive arthro-ophthalmopathy. It is estimated to affect 1 in 10,000 Americans. The clinical findings include myopia, retinal detachment, vitreal degeneration, premature degenerative changes, hypermobility of joints, sensorineural hearing loss, cleft palate and midfacial hypoplasia. The syndrome is usually diagnosed in childhood. However, varying degrees of presentation may delay the diagnosis. This case illustrates the clinical history of a woman who presented to a chiropractic office with low back pain, seven years after a diagnosis of Stickler's syndrome, after suffering many of the symptoms of this condition throughout her life.
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KEY WORDS: Stickler's syndrome, arthro-ophthalmopathy.

Le syndrome de Stickler est caractérisé par des troubles des tissus cellulaires autosomals dominants, également connu sous le nom d'arthro-ophtalmopathie héréditaire progressive. On estime qu'un Américain sur 10 000 en est atteint. Les résultats cliniques font état de myopie, de décollement de la rétine, de nécrose de coagulation, de modifications de dégénérescence prématurée, d'hypermobilité des articulations, de perte d'audition sensitivo-neurale, de bec de lièvre et d'hypophasie médiofaciale. Le syndrome est également diagnostiqué dans l'enfance. Cependant, des degrés variables de la manifestation peuvent retarder le diagnostic. Ce cas décrit l'histoire clinique d'une femme, se présentant à un cabinet de chiropraxie, avec des douleurs dorsales inférieures, sept ans après un diagnostic de syndrome de Stickler, et après avoir souffert de nombreux symptômes liés à cet état tout au long de sa vie.
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MOTS CLÉS : syndrome de Stickler, arthro-ophtalmopathie.

Introduction

Stickler's syndrome, also known as hereditary progressive arthro-ophthalmopathy, was first described by G.B. Stickler et al. in 1965.[1] This syndrome was the first human condition recognized as a result of a heritable defect involving the principal collagenous component of cartilage.[2] It is thought to be due to an autosomal dominant inherited connective tissue disorder characterized by; vitreoretinal degeneration, myopia, retinal detachment, cataract formation, hearing loss, skeletal disorders including premature osteoarthritis, maxillofacial hypoplasia, and spondyloepiphyseal dysplasia.[3] Therefore clinical manifestations of this syndrome are those affecting the eyes, joints, or facial structure. The syndrome may be under diagnosed due to failure of the clinician to obtain a complete patient and family history and due to the fact that the patient may not demonstrate the full syndrome.[2,4] Recognition of the syndrome is important so that genetic implications can be considered.[5] Prophylactic retinal cryotherapy may prevent retinal detachment and blindness.[5]

Stickler's syndrome is the most common autosomal dominant connective tissue dysplasia in North America.[3] The incidence of Stickler's syndrome is estimated at 1 per 10,000 in the United States while Marfan is estimated at 4-6 in 100,000.[3,6]

Case history

A 68 year old retired cook presented to our chiropractic clinic with a chief complaint of low back pain. The family history revealed that both the patient and her son were diagnosed with Stickler's syndrome (progressive arthro-ophthalmopathy) by an ophthalmologist seven years earlier. She suffered from bi-

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lateral knee pain beginning when she was a teenager and complained of bilateral knee pain and locking knees at presentation. She suffered from occasional generalized joint pain over the years, that was considered due to arthritis. The patient suffered a retinal detachment in 1948. Her son, described as tall and "double jointed" was 14-years-old at the time of diagnosis. He suffers from multiple joint pain as well as deterioration of his vision.

Discussion

Stickler's syndrome is an inherited condition. It is an autosomal dominant condition that is not sex linked.[1] The penetrance is high, perhaps complete with variable expressivity.[1] Stickler's syndrome is due to a connective tissue abnormality of type II collagen. The possible genetic linkage of the disease locus is thought to be on the structural gene for type II procollagen (COL2A1).[3] Type II collagen is present in secondary vitreous, cartilage, and the nucleus pulposus.[3] The exact pathophysiological mechanism is not known. Questions still remain as to the role of type II collagen in the development of retinal detachment, craniofacial defects and arthropathy.[3]

Clinical Features

Ophthalmologic manifestations

Stickler described three ophthalmologic clinical findings[1]. The first is a high degree of myopia associated with chorioretinal degenerative changes. The myopia that occurs in this syndrome is 8–18 diopters.[3,4,7] The myopia is congenital and progressive, usually beginning in the first decade of life.[4,7,8]

The second clinical finding is sudden total retinal detachment without trauma within the first decade of life. Retinal detachment has variable phenotypical expression with near complete penetrance.[3] The classical findings of this retinal detachment include vitreous membrane structures visible with slit lamp biomicroscopy and indirect ophthalmoscopy in an optically empty vitreous.[3] Retinal detachment occurs in nearly 50% of patients and is bilateral in 40% of these patients.[3] When extensive, the retinal detachment can lead to blindness.[4]

The third clinical finding is the late appearance of myopic eyes that have previously been affected by retinal detachment.[1]

Cataracts are common in Stickler's syndrome and may develop as part of the degenerative progressive myopia.[7,9] In a study of 113 Stickler's patients, Seery et al found cataracts in 49%. Cataracts occur in early adulthood in 50%-60% of patients.[3,4,9] Open angle glaucoma may be associated with Stickler's syndrome and can occur secondary to uveitis.[3]

Articular manifestations

Joint symptoms are variable and usually begin in childhood. Radiographic changes may precede the joint symptoms.[4] Symptoms include pain and stiffness in any joint with overuse.[1,3] When severe, the joint symptoms can mimic juvenile arthritis. The joint symptoms in adult life include those associated with premature osteoarthritis, beginning in the third and fourth decade, involving the large joints. Weight bearing joints may wear out in middle age.[4,7] The knees and ankles are most commonly affected. Other joints affected by premature wear and tear include wrists, elbows, and less commonly shoulders, spine and fingers.[1]

Hypermobility of joints can occur due to the abnormal connective tissue.[1] This hypermobility may be demonstrated in fingers, wrists and elbows.[3] Some patients notice swelling, heat, crepitation, and temporary locking. Some patients may experience joint hypomobility.[2]

A slender Marfanoid body habitus is typical, but may be subtle.[3] Other less common joint features include thoracic kyphoscoliosis, intra-articular loose bodies, genu valgum, pronated feet, talipes equinovarus, pectus carinatum and arachnodactyly associated with the Marfanoid habitus.[4]

The radiographic changes present in childhood may be detected during the first year of life.[8] These include spondyloepiphyseal dysplasia with widened ends of long bones in a dumbbell shape. The femoral epiphysis is commonly flat and irregular. The femoral neck may be broadened. These abnormal radiographic findings characteristically evolve with age and over a period of several years the long bones appear normal before the onset of premature degenerative changes.[4]

Radiological examination in adult patients demonstrates premature degeneration of articular surfaces with irregularity and widening of joint spaces despite minimal evidence of primary degeneration of cartilage.[1,4] The abnormally wide appearance of the joint spaces is due to unusually thick cartilage. Enlargement of epiphyses and metaphyses occur.[3] Coxa-valga is a common radiographic finding associated with widening of the femoral neck.[3,8] The knee and ankle joints demonstrate abnormal articular surfaces, with impaired joint alignment.[1]

Spinal changes include flattening and irregularity of the vertebral bodies in the thoracic and upper lumbar spine.[3,8,10] A review of six cases reported epiphyseal irregularity with anterior wedging and flattening leading to thoracic kyphosis.[10] The reported narrowing of the intervertebral discs, were a result of softened endplates.[10]

Hearing manifestations

Hearing loss is reported in Stickler's syndrome[3]. Both sensorineural and conductive defects occur. Sensorineural deficits are more common and can be severe and progressive.[4] Patients with sensorineural hearing loss who are less than thirty years old are usually asymptomatic while those over fifty years old are aware of the loss.[3] The hearing loss may be due to the skeletal abnormalities of the skull and facies or to infections.[8]

Facial manifestations

Skull and facial abnormalities include palate malformation, midfacial hypoplasia, shortening of cranial base length, midfacial depth/height, maxillary depth, and mandibular depth.[3]

Palate malformations range from cleft palate to submucous

Table 1
Differential diagnosis of Stickler's Syndrome

Syndrome	Joint findings	Ocular findings	Facial findings	X-ray findings	Other findings
Stickler's	hypermobility, premature degenerative changes and symptoms	myopia, retinal detachment, vitreal degeneration	cleft palate, midfacial hypoplasia	irregularity articular surface, secondary osteoarthritis, vertebral body irregularity anterior wedging/flat, decrease IVD space	sensorineural hearing loss
Marfan's	connective tissue disorder, joint laxity, hyper-extensibility, arachnodactylia	high myopia, ectopic lentis, retinal detachment		excessively long bones	cardiovascular anomalies
Ehlers-Danlos	connective tissue disorder, hyper-extensibility	fragile ocular lobe			skin hyper-extensibility, tissue fragility, rupture arteries and bowel
Reiter's	seronegative arthritis, asymmetrical, oligo/poly knees, ankles, low back pain, swelling fingers, toes, achilles tendon	noninfectious conjunctivitis, iritis, uveitis, episcleritis, corneal ulceration		enthesopathies	skin lesions, non gonococcal urethritis
Ankylosing spondylitis	seronegative spondylarthritis sacroiliac, spine, some peripheral joints	self limiting uveitis		sacroiliitis	fatigue, weight loss, low grade fever lung field fibrotic changes, aortic incompetence, cardiomegaly, conduction defects

cleft, or high arched palate. Cleft palate occurs in 20% of patients with Stickler's syndrome.[3] One of the most serious presentations of cleft palate in Stickler's is associated with Pierre Robin malformation complex, which includes micrognathia, glossoptosis, and cleft-palate. This complex is sometimes fatal in the neonatal period.[4] Lesser degrees of cleft palate can occur in Stickler's patients. Midfacial hypoplasia is associated with flat nasal bridge, prominent eyes, epicanthic folds, short nose, and anteverted nares. Although the midfacial features may appear severe many will improve with age to near normal.[4] However some of the more severe midfacial abnormalities require corrective surgery.[4]

Other manifestations

Congenital heart defects are associated with Stickler's syndrome especially in those patients with the Pierre Robin anomaly.[8] Early hypoxia associated with the Pierre Robin malformation can lead to impaired intelligence.[4]

Differential Diagnosis

Other rheumatological conditions must be considered as differential diagnoses when presented with a patient with ocular and joint symptoms. These include Marfan's syndrome, Ehlers-Danlos syndrome, Reiter's syndrome, and ankylosing spondylitis (Table 1, Table 2).

Marfan's syndrome

Marfan's syndrome is an autosomal dominant disorder of connective tissue.[6] It is associated with joint laxity, hyperextensibility and arachnodactylia.[11] Patients with Marfan's syndrome demonstrate high myopia, ectopia lentis and retinal detachment. However, retinal detachment rarely exceeds the two quadrants found in Stickler's.[6] The eyes do not show the characteristic optically empty vitreous cavity that is demonstrated in Stickler's syndrome.[5] The extremities are inappropriately long related to the trunk.[6] There is no hearing loss associated with Marfan's syndrome. Marfan's syndrome is frequently complicated by cardiovascular anomalies such as aortic insufficiency which is absent in Stickler's.[5,6]

Ehlers-Danlos syndromes

The Ehlers-Danlos syndromes are a group of nine heritable disorders of connective tissue. The features of these syndromes relate to the joints and skin. The joints demonstrate hyperextensibility. Skin abnormalities include hyperextensibility and tissue fragility. Some patients have a propensity of spontaneous rupture of arteries and bowel.[11] One of the syndromes (EDS IV) demonstrates fragility of the ocular globe.[2] However in contrast to Stickler's syndrome, there is no associated retinal detachment.

Reiter's syndrome

Reiter's syndrome is a seronegative arthritis associated with urethritis, cervicitis or dysentery. Other features include inflammatory eye lesions, balanitis, oral ulcers and keratoderma.[11] The oligo or polyarthritis is asymmetrical, affecting mainly the knees and ankles. Three typical features of Reiter's are diffuse swelling of the fingers or toes (sausage digits), swelling at the region of the achilles tendon insertion, and low back pain.[11] Other features of Reiter's include unilateral or bilateral non-infectious conjunctivitis in about 40% of patients.[11] Other ocular involvements include iritis, uveitis, episcleritis, and corneal ulceration. Reiter's is also associated with non-gonococcal urethritis. Cutaneous lesions occur but not in Stickler's. These include balanitis circinata a small shallow painless ulcer on the glans penis and urethral meatus.[11]

Table 2
Summary of differential diagnosis of Stickler's Syndrome

Syndrome	Joint findings	Ocular findings	Facial findings	Hearing findings	Cardiovascular findings
Stickler's	+	+	+	+	+/–
Marfan's	+	+	–	–	+
Ehlers-Danlos	+	+	–	–	+/–
Reiter's	+	+			
Ankylosing spondylitis	+	+	–	–	+/–

Keratoderma blennorrhagica, a hyperkeratotic skin lesion also occurs in Reiter's.[11] Radiological features of Reiter's include enthesopathies at ischial tuberosities, greater trochanter or insertion of achilles tendon or plantar fascia.[11] A symptomatic sacroiliitis is seen in 25% of Reiter's patients and tends to be asymmetric.[11]

Ankylosing spondylitis

Ankylosing spondylitis is a seronegative spondyloarthropathy. The clinical features include arthritis of the sacroiliac joints and spine and to a lesser extent peripheral joints.[11] The history reveals an insidious onset of discomfort, at an age of less than 40 years, that persists for more than three months, is associated with morning stiffness, and improves with exercise.[11] There is often radiographic evidence of sacroiliitis. Extra-articular involvement includes fatigue, weight loss, and low grade fever. Uveitis develops in 25% of patients and is usually self limiting. Other findings can include chronic infiltrative and fibrotic changes in upper lung fields, aortic incompetence, cardiomegaly and cardiac conduction defects.

Summary

Stickler's syndrome is an inherited connective tissue disorder that includes myopia, retinal detachment, vitreal degeneration, premature joint degenerative changes, hypermobility of joints, sensorineural hearing loss, cleft palate and midfacial hypoplasia. It is believed that Stickler's syndrome is a common condition that may be under diagnosed due to varied clinical presentations. The diagnosis is usually made in childhood. However, in this case the syndrome was not recognized until the mother was in her sixties and the son a teenager.

A diagnosis of Stickler's may be considered in a child who presents with swollen, painful joints, myopia and retinal detachment or in an adult with premature degenerative arthritis and similar ocular complaints. A thorough history including family history is helpful in determining the diagnosis. An early diagnosis is also important for proper management of these patients. The progressive arthropathy may be lessened by avoiding heavy use of weight bearing joints.[7] Blindness as a result of retinal detachment may be avoided with early management.[4] Genetic counselling is important for the families involved for the recognition of siblings and offspring who are at risk of developing the syndrome.[4]

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