Stickler Syndrome – A Review

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Abstract-

The hereditary diseases arediseases that are inherited genetically. These disease or disorders are due to defective genes. Stickler syndrome is a congenital and genetic disease. Stickler syndrome is a genetically heterogeneous arthro-ophthalmopathy caused by defects in collagen, exhibiting a wide specter of manifestations in connective tissue. There are five subdivision of this disease which affects the different parts of the body. Stickler syndrome is present at birth but, depending on the severity of your child's symptoms, may not be diagnosed immediately.There is no direct method for diagnosis and treatment of this disease. Diagnosis and treatment of signs and symptoms of this disease can be done to prevent the pain. In this article we will see the overall signs and symptoms, causes, diagnosis and treatment of stickler syndrome.

Keywords: Stickler Syndrome, Genetic Disease, Mutations, Autosomal Recessive, Autosomal Dominant.

Introduction

Stickler syndrome was originally described by pediatrician Gunnar B. Stickler in 1965, as hereditary progressive arthro-ophthalmopathy.[1]Stickler syndrome is a systemic connective tissue disorder characterized by defective collagen production.[2] The condition is commonly associated with ophthalmologic manifestations including vitreous abnormalities, congentialmegalophthalmos, radial perivascular retinal lattice degeneration and retinal detachment, in addition to systemic findings which may include orofacial, auditory and musculoskeletal abnormalities.Stickler syndrome affects an estimated 1 in 7,500 to 9,000 new born. [2,3]

Subdivisions of Stickler Syndrome:

Stickler syndrome is classified into five types, namely, Type-1, Type-2, Type-3, Type-4, and Type-5. [3]

Type-1:

About 70% of reported cases of stickler syndrome are affected by type-1. It affects eye, ear, facial appearance, palate and musculoskeletal system. It occurs due to mutation of entire COL2A1 gene on chromosome 12q13.11. These mutations are majorly associated with normal stature and early onset of osteoarthritis. The inheritance pattern for Stickler syndrome type-1 is autosomal dominant. [3]

Type-2:

This type occurs due to mutation of COL11A1 gene on chromosome 1p21. The patients with type-2 show up less prominent facial dysmorphism less pronounced midfacial flattering (Figure 2), myopia and retinal degeneration is not always present, Cataracts and more severe early onset of hearing loss are seen. The inheritance pattern is autosomal dominant. [3]

Type-3:

The type-3 is non-ocular form of stickler syndrome. This occurs due to mutation of COL11A2 gene on chromosome 6p21.3. This type affects the joints and hearing without involving eyes. The inheritance type is Autosomal dominant. [3]

Type-4:

The type-4 occurs due to mutation COL9A1 on chromosome 6q13. The inheritance pattern is autosomal recessive. [3]

Type-5:

The type-5 occurs due to mutation of COL9A2 gene on the chromosome 1p33. The

Inheritance pattern is Autosomal recessive. [3]

Clinical Features of Stickler syndrome:

1. Ophthalmologic Features:

a. Vitreoretinal degeneration occurs, which causes tiny floaters that obstructing a person's field of vision [3].

b. Retinal detachment occurs, which causes blurred vision, increased number of tiny floaters, sudden flashes of light and sudden decrease in vision and leads to blindness if untreated.[3]

c. Other abnormalities are Opacity of lenses of eye, crossed eyes, abnormal curvatures to cornea or lens of eye. [3]

d. A very small population may develop Glaucoma (a condition in which increased pressure within eyes causes characteristic damage to optic nerves.[3]

2. Otolarngologic Feature:

a. Hearing loss may occur in the stickler syndrome. It can occur due to conductive hearing loss, sensorineural hearing loss or mixed hearing loss. [3]

b. Chronic infection of middle ear may occur. Accumulation of thick, sticky fluid behind eardrum (Glue ear). Hypermobility of middle ear bones can be seen. [3]

c. Individuals with stickler syndrome often have distinctive facial features including mid-facial hypoplasia with abnormally flat cheek bones and nasal bridge, small nose, longer philtrum, prominent eyes and small chin.[3]

d. Affected individuals may also have PIERRE-ROBIN sequence (an assortment of abnormalities that may occur as the distinct syndrome or as a part another underlying disorder). [3]

e. Dental anomalies such as failure of the upper and lower teeth to meet when biting down may also occur. They also have abnormal small jaws so there often isn't enough room for the full complement of adult teeth. [3]

f. Cleft palate may occur, which causes feeding or breathing difficulties in some children and Subclinical midline cleft may also occur[3]

3. Skeletal Features:

a. Affected individuals may have abnormally flexible or hypermobile joints that may prone to joint

dislocation. Joint pain and stiffness are common findings. Inflammation of joints in third or fourth decade of life. [3]

b. Spinal abnormalities such as abnormal sideways curvature of spine, front-to-back curvature of spine and forward displacement of one vertebra over another can occur. [3]

c. Chest deformities such as depression of chest bone or prominent chest bone can occur. [3]

d. Diminished muscle tone, abnormally long and slender fingers, flat feet, and osteochondritis deformans of hips can occur. [3]

4. OtherFeatures:

a. Learning disabilities because of hearing and vision abnormalities are seen.

b. Some studies indicate the prevalence of mitral valve prolapsed is 4% in Individuals with stickler syndrome are seen. However other studies seem to show that this is not the case. [3]

Causes of Stickler Syndrome:

Stickler syndrome is caused by mutations in certain genes involved in the formation of collagen — one of the building blocks of many types of connective tissues. The type of collagen most commonly affected is that used to produce joint cartilage and the jellylike material (vitreous) found within the eyes. Most cases of Stickler syndrome are inherited in an autosomal dominant manner, which means that a child needs to have only one abnormal copy of the responsible gene to be affected. Each of us has two copies of each gene (with the exception of those genes on the X chromosome in boys). If a child has Stickler syndrome, the risk for a subsequent sibling to have Stickler syndrome depends upon whether one of the parents is affected. If one of the parents is also affected, there's a 50 percent chance that the next child will also have it. If neither parent has Stickler syndrome, the risk to have another child with Stickler syndrome is thought to be low [2, 4].

Diagnosis:

The diagnosis of Stickler syndrome is established in a proband who meets the proposed clinical diagnostic criteria and/or has a Heterozygous pathogenic variant in COL2A1, COL11A1, orCOL11A2or biallelic pathogenic variants in COL9A1, COL9A2, or COL9A3 [1,4].

Clinical Diagnostic Criteria:

It has been proposed for type 1 Stickler syndrome (in which individuals have the membranous type of vitreous abnormality. The proposed criteria are based on assigning points for clinical features, family history data, and molecular data [5].

Molecular Genetic Testing:

It approaches can include serial single-gene testing, use of a multigene panel, and more comprehensive genomic testing [6].

Serial Single-Gene Testing:

Serial single-gene testing can be considered based on the individual's clinical findings and family history; however, findings should not be used to exclude specific testing:

COL2A1 may be tested first in individuals with ocular findings including type 1 "membranous" congenital vitreous anomaly and milder hearing loss [1].

COL11A1 may be tested first in individuals with typical ocular findings including type 2 "beaded" congenital vitreous anomalies and significant hearing loss [7].

COL11A2 may be tested for in individuals with craniofacial and joint manifestations and hearing loss but without ocular findings [1].

COL9A1, COL9A2, and COL9A3 may be tested for in individuals with possible autosomal recessive inheritance [1].

Sequence analysis of the gene of interest is performed first, followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found [7].

Multigene Panel:

A multigene panel that includes COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3, and other genes of interest may be considered [8].

More comprehensive genomic testing:

More comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered. Example: mutation of a different gene or genes that results in a similar clinical presentation [8].

Treatment:

While there is no cure for Stickler syndrome, treatments can help control symptoms and prevent

complications. In some cases, surgery may be needed to correct some of the physical abnormalities associated with Stickler syndrome [2]. Treatment may require the coordinated efforts of a team of specialists including: geneticist, pediatrician, orthopedic surgeon, rheumatologist, ophthalmologist and retina specialist, otolaryngologist, audiologist, plastic surgeon, orthodontist and other healthcare professionals may need to systematically and comprehensively plan an affected patient's treatment [9]. Patients with ocular forms of Stickler syndrome are restricted from contact sports due to the risk of retinal detachment. Retinal detachment requires prompt surgery to preserve vision. Retinal detachment can recur even after successful surgery. Some physicians recommend prophylactic cryotherapies in certain cases to reduce the risk of developing retinal detachment.Correctivelenses (glasses or contact lenses) are used to treat myopia. Surgery may also be necessary to correct the cataracts [10]. Patients with sensorineural or mixed hearing loss may require hearing aids. Hearing aids may be of benefit for certain individuals [3]. Orthodontic treatment may be necessary to correct dental malalignment[11]. Various anti-inflammatory medications and sometimes prescription pain medications may be used to treat joint disease in individuals with Stickler syndrome. In mild cases, short-term relief may be provided from cortisone injections. Surgical correction of joint abnormalities may be necessary including joint replacement surgery such as a total hip or knee replacement. Surgery may also be necessary for skeletal malformations including abnormal curvature of the spine [12,13].Physical therapy may prove beneficial in some cases.Special education and other services may be helpful for children with learning disabilities due to hearing or vision problems. Genetic counseling may be of benefit for affected individuals and theirfamilies [13].

Conclusion:

Although the symptoms of stickler syndrome are not life threaten, a person suffering from this can develop so much of complication that if are untreated may lead to death. There are many supporting organization for this disease. Stickler syndrome remains under-diagnosed. Heightened awareness of Stickler syndrome could improve visual outcome in affected individuals.

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