Marfan syndrome: Case series from a single family

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ABSTRACT

Marfan syndrome is an inherited connective-tissue disorder transmitted as an autosomal dominant trait. It is noteworthy for its worldwide distribution, relatively high prevalence, clinical variability, and pleiotropic manifestations. We describe here cases of Marfan syndrome accidentally found from a remote area of western hilly part of Nepal in three children out of eight children of same family. These cases came to attention in an Ophthalmologic diagnosis, screening and treatment camp. With suspicion of having some ocular problem, patients were brought to the hospital and a diagnosis of Marfan syndrome was made. All the children had similar ocular problem, which was diminution of vision, subluxated lens, myopia, increased length of the eye, one of the children had large looking eye ball, of which the patient and family members were unaware of. Family history revealed early demise of the mother at the age of forty two years.

Keywords: Marfan syndrome; megalocornea; subluxation of lens; fibrillin gene

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Introduction:

Marfan syndrome is an inherited connective-tissue disorder transmitted as an autosomal dominant trait.[1] About three quarters of patients has an affected parent; new mutations account for the remainder. Marfan syndrome is fully penetrant with marked interfamilial and intrafamilial variability. Cardinal features of the disorder include tall stature, ectopia lentis, mitral valve prolapse, aortic root dilatation, and aortic dissection.[1] The first report of description of a family with Marfan syndrome was made in 1872 by E. Williams under the title rare cases, with practical purposes.[2] Marfan syndrome is one of the most common single-gene malformation syndromes.[1]

Case Series:

In a diagnosis, screening and treatment camp held by Palpa Lions Lacoul Eye Hospital in a remote hilly area of western Nepal. Three children aging 16, 12 and 10 years of age respectively from a same family presented with complaint of diminution of vision in both the eyes, after a careful ophthalmic examination with available instruments, these children were advised to follow up in the hospital for a detail ocular examination and further management.

The first patient was a female patient while the other two children were males. All the patients underwent detailed ocular examination in the hospital which revealed visual acuity of 6/36 improving to 6/24 in both eyes with pin hole,

there was no improvement in visual acuity after refraction, though all the children had high myopia in refraction. Other ocular examination findings were a prominent looking eye ball in the male patient aging 12 years, who had megalocornea; his corneal diameter on measurement was vertically 13.5 mm and horizontally 14 mm. Other two patients had normal corneal diameters. Other positive findings in ocular examination were subluxated lens in all the patients which was superior/supero temporal in all eyes (Figure 1).

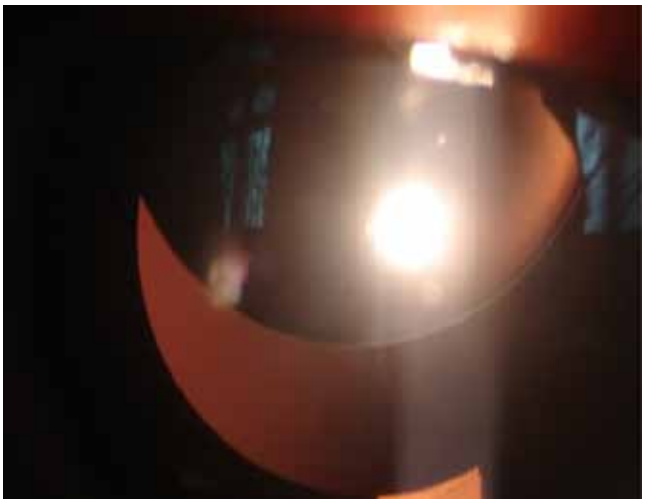

Figure 1: Showing superior subluxation of the crystalline lens, photograph taken in retroillumination

Fundus examination after full mydriasis in all cases revealed features of high myopia. Retinoscopy reading from phakic portion was – 12 to – 13 in all the six eyes, when done from a distance of 66 cms. While axial length varied from 27.5 mm to 29.5 mm mean from three readings in all cases. Retinoscopy reading in these cases from aphakic portion of the pupil ranged from + 10 to + 12.

A physical examination was carried out in all cases, in all patients arm span was more than or equal to their height. Arachnodactyly was present in all the patients. Similarly, there was no hyperelasticity of any joints and no murmurs could be heard in cardiovascular examination. With above mentioned findings in ocular examination, diagnosis of Marfan syndrome was made in all patients who were of familial type; no ophthalmic intervention for the patients was done. Confirmatory genetic test was not done due to various restrains and availability of the tests. Patients were advised for a regular ocular examination every three to six months, because likely hood of improvement in visual status after any ocular intervention was minimal in all cases due to severe myopic fundus degeneration, and patients already had developed ammetropic amblyopia.

All the patients were advised to go to the physician for a thorough systemic examination and further management if at all needed. All the patients returned with reports of various systemic examinations. Skeletal system was involved; most importantly cardiovascular system was not involved and patients were advised for a regular follow-up. Presently; patients are on constant follow up from ophthalmic side and in last follow up all the three children had similar ocular status.

Discussion:

Marfan (French pediatrician) described in 1896 a child with long thin extremities and Marfan coined a term for the condition "dolichostenomelia". Arachnodactyly and dolichostenomelia were the common term used to describe the disease for a long period of time. It was Weve from Netherlands who used the term Marfan syndrome for the first time with features of Marfan syndrome. Since then various findings and investigations have been done for the disease condition, at present lots regarding this common syndrome is known. [2]

Marfan syndrome affects about 1 in 10,000 individuals and perhaps as many as 1 in 3000-5000. Estimates suggest that at least 200,000 people in the United States have Marfan syndrome or a related connective-tissue disorder. This makes Marfan syndrome one of the most common single-gene malformation syndromes.[1]

Marfan syndrome is a widespread disorder of connective tissue associated with mutation of the fibrillin gene on chromosome 15q.3 Fibrillin is a major building block of microfibrils, which constitute the structural components of the suspensory ligament of the lens and serve as substrates for elastin in the aorta and other connective tissues. Production of abnormal fibrillin-1 (FBN-1) monomers from the mutated gene disrupts the multimerization of FBN-1 and prevents microfibril formation.

This pathogenetic mechanism has been termed dominant-negative because the mutant FBN-1 disrupts microfibril formation though the other fibrillin gene encodes normal fibrillin. This proposed mechanism is evinced by the fact that cultured skin fibroblasts from patients with Marfan syndrome produce greatly diminished and abnormal microfibrils. FBN-1 mutation causes several Marfan like disorders, such as the mitral valve prolapse, aortic dilation,

skin, and skeletal (MASS) phenotype or isolated ectopia lentis.[1]

Classical signs of Marfan syndrome includes Musculoskeletal features like tall thin stature, scoliosis, sternal deformity.[3] Pectus excavatum occurs in approximately two-thirds of patients having Marfan syndrome and, when severe, can be associated with a restrictive ventilatory defects.[4] Disproportionately long limbs compared with the trunk (arm span more than height), long spider like fingers arachnodactyly and mild joint hypermobility, other features include high arched palate.

Cardiovascular features include dilatation of ascending aorta leading to aortic incompetence and heart failure, mitral valve prolapse and heart failure are other common features.[3] Ocular features of Marfan syndrome include bilateral ectopia lentis (40 – 56 %), myopia (28%) and retinal detachment (0.78%). Subluxation of lens usually develops in early childhood, but may first appear in the second decade. Lens dislocation into the anterior chamber may occur. Hypoplasia of dilatator pupillae, angle anomaly is common, but microspherophakia, keratoconus, cornea plana megalocornea are uncommon features. Myopia is associated with an increased length of the globe and an increased risk of retinal detachment. Anisometropia and the possible anterior chamber abnormalities are further important considerations for management.[4]

In this case series of Marfan syndrome in three patients; one had megalocornea, which as already said is quite rare. While all the cases had high myopia and increased length of the globe, and all patients had developed ammetropic amblyopia.

In 1995, a group of the world's leading clinicians and investigators in Marfan syndrome proposed diagnostic criteria popularly known as the Ghent criteria; they identify major and minor diagnostic findings, which are largely based on clinical observation of various organ systems and on the family history. A major criterion is defined as one that carries high diagnostic precision because it is relatively infrequent in other conditions and in the general population. The Ghent criteria were intended to serve as an international standard for clinical and molecular studies and for investigations of genetic heterogeneity and genotype-phenotype correlations. However the diagnosis of Marfan syndrome still remains clinical, seeing at the system involvement and signs present.[1]

The leading cause of premature death in untreated individuals with Marfan syndrome is acute aortic dissection, which follows a period of progressive dilatation of the ascending aorta.[5] Ophthalmological features appear early enough in cases of Marfan syndrome while cardiovascular features appear bit late. But cardiovascular features are the major life threatening problem in cases of Marfan syndrome.[4] Probably in this case series also, premature demise of patients mother was due to cardiovascular involvement.

Conclusion:

Marfan syndrome is a widespread disorder of connective tissue associated with mutation of the fibrillin gene on chromosome 15q. Inheritance is autosomal dominant with variable expressivity. Although neonatal and infant forms of the disease exist, the classic MFS is the most frequent form of presentation in childhood and adolescence.

The cardiovascular involvement appears later but is the major life threatening complication. Ophthalmological assessment is important and regular ocular review is recommended, particularly in childhood. Marfan syndrome requires early integral and update management by a multidisciplinary group, to obtain the best quality of life and survival. Ophthalmologists do play their part in detecting the cases early and for further management.

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