Scoliosis, blindness and arachnodactyly in a large Turkish family: Is it a new syndrome?

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Abstract

In this report we have described an affected sib in a large Turkish family who appears to have a new distinct dominantly-inherited blindness, scoliosis and arachnodactyly syndrome. The combination of clinical abnormalities in these patients did not initially suggest Marfan syndrome or other connective tissue disorders associated with ectopia lentis. The proband was a 16-year-old boy who was referred to our clinics for scoliosis. He had arachnodactyly of both fingers and toes. He had been suffering from progressive visual loss and strabismus since he was eight-years-old. His 20-year-old brother had severe kyphoscoliosis, and arachnodactyly of fingers and toes. He was 130 cm tall and was bilaterally blind. His 23-year-old sister had only eye findings but no arachnodactyly or scoliosis. His 60-year-old father had mild scoliosis, blindness and arachnodactyly and mother was normal. We performed routine mutation analyses in the genes FBN1, TGFBR1 and TGFBR2, but no mutation has been detected. Our Turkish patients are most likely affected by a hitherto unrecorded condition which is caused by an autosomal dominant gene defect with variable expression but we can not exclude multigenic inheritance. Further studies are needed to assess the contribution of sex influence to the syndrome because the female relative is less affected.

SCOLIOSIS, BLINDNESS AND ARACHNODACTYLY IN A LARGE TURKISH FAMILY: IS IT A NEW SYNDROME?

Running Title: Scoliosis, Blindness and Arachnodactyly Syndrome

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Summary

In this report we have described an affected sib in a large Turkish family who appears to have a new distinct dominantly-inherited blindness, scoliosis and arachnodactyly syndrome. The combination of clinical abnormalities in these patients did not initially suggest Marfan syndrome or other connective tissue disorders associated with ectopia lentis. The proband was a 16-year-old boy who was referred to our clinics with scoliosis. He had arachnodactyly of both fingers and toes. He had been suffering from progressive visual loss and strabismus since he was eight years old. His 20-year-old brother had severe kyphoscoliosis, and arachnodactyly of fingers and toes. He was 130 cm tall and was bilaterally blind. His 23 year old sister had only eye findings but no arachnodactyly or scoliosis. His 60-year-old father had mild scoliosis, blindness and arachnodactyly and mother was normal. We performed routine mutation analyses in the genes *FBN1, TGFBR1* and *TGFBR2,* but no mutation has been detected. Our Turkish patients are most likely affected by a hitherto unrecorded condition which is caused by an autosomal dominant gene defect with variable expression but we can not exclude multigenic inheritance. Further studies are needed to assess the contribution of sex influence to the syndrome because female relatives are less affected.

Key-words: Blindness; Dislocated lens; Genetics; Scoliosis; Syndrome

INTRODUCTION

In this report we have described an affected sib in a large Turkish family who appears to have a new distinct dominantly-inherited blindness, scoliosis and arachnodactyly syndrome. This family has been followed since 1996. Biochemical analyses, urine analyses for aminoaciduria, echocardiography, and chromosomal analyses revealed normal results for this family. Their psychomotor development and the intellectual levels were normal. All affected individuals had blindness and scoliosis of variable degrees as well as arachnodactyly (Fig. 1, Table I). All affected family members had sufficient vision for their childhood activities and they started to lose vision due to lens luxation due to unknown causes between 8-12 years of age. Ocular progress included total retinal detachment, phthisis, opaque small cornea and finally blindness due to retinal detachment.

In our literature review, we didn't find any known syndrome equally or approximately matching the combination of blindness, scoliosis, and arachnodactyly as proposed by this report. We performed mutation analyses in the genes *FBN1, TGFBR1* and *TGFBR2* for excluding Marfan or Marfanoid syndromes. The aim of the present paper is to describe new genetic entity, probably autosomal dominant.

CLINICAL REPORT

Case 1

In the first presentation, the proband (I.B) was a 16-year-old boy, referred to our clinic with a severe scoliosis (Figs 2a-2e). He had been operated on for this reason.

During the second admission, he had more significant scoliosis compared to previous operation (Figs 2f and 3). Age of his mother was 55 and his father was 60 years old at time of first presentation. The parents are first cousins and their family history was unremarkable. The proband has two sibs with similar clinical features and five sibs were unaffected. On admission, the proband was 153 cm tall (<25p) with upper segment 76 cm, upper/lower segment ratio is 0.987 (+1 SD), and armspan 156 cm. There was arachnodactyly (>95p) (Fig. 4) in both fingers and toes. The fourth and fifth toes were bilaterally situated in back position but he has neither joint laxity nor wrist and thumb signs. Furthermore, he has not any skin, facial, teeth, and palate malformation. We revealed no skeletal findings related to Marfan syndrome by whole body radiography (e.g. protrusion acetabulae, medial rotation of the medial malleolus).

He had been suffering from progressive visual loss and strabismus since he was eight years old. Ophthalmic examination revealed esotropia in the right eye, bilateral lens luxation through the vitreous and atrophy of retinal elements, and hypertrophy of retinal pigment epithelium (Fig. 5a). Visual acuity was 0.2 with +6.0 glasses in both eyes. These findings were consistent with severe myopia in childhood and after lens luxation occurred he became hyperopic. Corneal diameters were 10 mm horizontally which was borderline microcornea. Two years later, we observed total retinal detachment in his right eye.

Case 2

Physical examination of the proband's 20-year-old brother (S.B.) revealed severe kyphoscoliosis and arachnodactyly bilaterally in both fingers and toes (Figs 7a, 7b, 7c). He was 130 cm tall. His ophthalmic examination revealed bilateral phthisic**,** totally opaque and

small lenses and complete blindness. He has neither skin and facial malformation nor joint laxity.

Case 3

The proband's 23-year-old sister (U.B.) also had only eye findings but no arachnodactyly or scoliosis (Fig. 6). She was 150 cm tall. Ophthalmic examination revealed bilateral phthisic, totally opaque and small lenses and absolute blind eyes (Fig. 5b). She has neither skin and facial malformation nor joint laxity.

Case 4

The proband's 60-year-old father (M.B) had mild scoliosis, blindness, and arachnodactyly. He was 160 cm tall. He has neither skin and facial malformation nor joint laxity.

Methods and Results

DNA Extraction

Genomic DNA was extracted starting from 2 ml of peripheral blood of the affected patients, using commercial kit (Flexigene, Qiagen).

Molecular Analyses of FBN1, TGFBR1 and TGFBR2

For polymerase chain reaction (PCR) amplification of all the 65 exons of the *FBN1* gene, a set of 65 pairs of primers (Sigma-Genosys, Pampisford, Cambridgeshire, UK) was used, including flanking splice sites. The oligonucleotide sequences were those described in previous studies (7,14,19). Genomic DNA (100-200 ng) was amplified with 5-10 pmol from each pair of primers, 200 µM each dNTPs, 1.0-1.5 mM $MgCl_2$, 1x PCR buffer, and 1-2 U *Taq* DNA polymerase, in a final volume of 25-50 µl. All PCR reagents except primers were supplied by Invitrogen. The amplifications were performed under the following variable conditions: one cycle of denaturation for 5' at 95°C, followed by 30-35 cycles of denaturation (30" at 95°C), annealing (30" at 52°-58°C, depending on the fragment) and extension (30" at 72°C), followed by a 5' final extension step at 72°C. A small aliquot of each PCR sample, together with a molecular weight marker, was run on agarose gel and stained with ethidium bromide to confirm PCR amplification and size of the fragment. Mutation screening was carried out employing a dHPLC method, using a WAVE Nucleic Acid Fragment Analysis system (Transgenomic). The PCR samples were injected into a DNASep Column and run using protocols and conditions determined using Wavemaker software (V. 4.2), following manufacturer's directions.

For the *TGFBR1* and *TGFBR2* genes, all exons and flanking intronic regions were amplified and directly sequenced under routine conditions as described elsewhere (15).

In order to detect large genomic rearrangements, multiplex ligation-dependent probe amplification (MLPA) was carried out using the SALSA kits P065 (probes for *FBN1* and *TGFBR2*), P066 (probes for *FBN1*), and P148 (probes for both *TGFBR1* and *TGFBR2*), commercially available from MRC-Holland (Amsterdam, The Netherlands) as previously described (16).

As a result we didn't find any mutation in *FBN1, TGFBR1* and *TGFBR2* genes.

DISCUSSION

Nontraumatic subluxation or dislocation of the crystalline lens is most commonly observed in Marfan syndrome. It is also a major manifestation of homocystinuria, the Weill - Marchesani syndrome and a few less common autosomal recessive disorders (31).

Radiographically defined scoliosis has many causes (20). The hereditary musculoskeletal disorders, such as osteogenesis imperfecta (28), Marfan syndrome (12), Stickler syndrome (9), Ehlers-Danlos syndrome (23) and the muscular dystrophies (30) can all include scoliosis as a manifestation. Neuromuscular diseases, such as spina bifida, cerebral palsy, and myelomeningocele are associated with the development of scoliosis, secondary to muscle imbalance (3,26). Paralytic disorders resulting from polio or spinal trauma lead to a progressive scoliosis. Radiation therapy, tumors, and syrinx formation have also been implicated among the causes of scoliosis. However, at least 80% of all scoliosis is classified as idiopathic (IS) because no cause can be identified. Evidence for a genetic component to IS is strong, but support for any specific mode of inheritance is limited.

Marfan syndrome [MFS] is an autosomal dominant heritable disorder of connective tissue that involves many systems [skeletal, ocular, cardiovascular, pulmonary, skin and integument, and dura] but its more prominent manifestations are skeletal, ocular, and cardiovascular. MFS is the result of mutations in the *FBN1* gene (11). In previous studies, however, extensive mutational analyses failed to show *FBN1* involvement in almost 10% or more of patients with MFS satisfying the Ghent criteria. That patients were shown to have mutations in the *TGFBR2* gene, which encodes the transmembrane receptor type II of TGFβ (8). A wide variety of skeletal abnormalities occurs with MFS including dolichostenomelia, arachnodactyly, scoliosis, chest wall deformity [pectus carinatum or excavatum], tall stature, ligamentous laxity, abnormal joint mobility, and protrusio acetabulae. Scoliosis is found in

about 60% of adults of both sexes with MFS (21). Pectus excavatum of some degree of severity occurs in about two thirds of all MFS patients, and may have a greater tendency to reoccur after surgical repair than idiopathic pectus excavatum (15). Ectopia lentis occurs in up to 80% of MFS patients and is almost always bilateral (6). The most common cardiovascular manifestations of MFS affect the atrioventricular valves and the aorta. The diagnosis of MFS can be made according to the criteria of Ghent nosology (10). Diagnostic dilemmas may arise because of the considerable inter- and intrafamilial variability of MFS. Also, many features of MFS, such as mitral valve prolapse or scoliosis, are common in the general population or may occur in other connective tissue disorders and many manifestations are age dependent. Arachnodactyly, scoliosis, and lens subluxation may be seen in MFS but low vision in early childhood and progression of visual loss are uncommon in this syndrome. In addition, bilateral anterior microphthalmos, bilateral microcornea, and corneal opacity are not present in MFS and the direction of lens dislocation is typically superotemporal. In our patients the direction of lens dislocation was inferior and our patients' intelligence and echocardiograms were normal and our patients do not fulfill Ghent criteria.

FBN1 mutations have been identified in complete and incomplete forms of MFS, including severe neonatal MFS, dominantly inherited ectopia lentis, isolated skeletal features of MFS such as kyphoscoliosis. The new molecular group of 'type-1 fibrillinopathies' comprises a spectrum of overlapping diseases including the Shprintzen–Goldberg syndrome and, more recently, familial or isolated forms of aortic aneurysms (13). However, neither *FBN1* nor *TGFBR1/2* molecular genetic testing revealed any mutation in our proband.. Hence, either our mutation screening has failed to identify a disease-causing mutation or the clinical conditions reported are not part of the deficiency spectrum of *FBN1*, *TGFBR1* and *TGFBR2*.

In this family, all members suffered from poor vision in early childhood and within a few years they lost their vision. Similar findings may also be found in Stickler syndrome. Stickler syndrome is an autosomal dominant connective tissue disorder that can include ocular findings of myopia, cataract, and retinal detachment; hearing loss that is both conductive and sensorineural, midfacial underdevelopment and cleft palate [either alone or as part of the Robin sequence], mild spondyloepiphyseal dysplasia and/or precocious arthritis (19), but dislocation of the lens is not seen in Stickler syndrome and our patients had no hearing loss, cleft palate, and cataract.

The kyphoscoliotic type of Ehlers–Danlos syndrome [EDS VIA] [MIM 225400] is an inherited connective tissue disorder. It is clinically characterized by severe muscular hypotonia at birth, kyphoscoliosis, which is present at birth or starts in early infancy and is progressive, and severe joint hypermobility and luxation (14). In addition there is often a marfanoid habitus, osteopenia without a tendency to fractures, fragility of the skin with abnormal scarring, microcornea, and rupture of the arteries and the eye globe (7). The diagnosis is often considered very late. Because of the severe muscular hypotonia and delay in gross motor development a neuromuscular disease is often suspected, especially when deformities of the feet and joint dislocations coexist, and therefore an extensive, often invasive, neuromuscular work-up is usually performed with normal results (28). However, clinical features and timing of onset in our cases does not fit with this diagnosis.

We thought that myopia, lens dislocation, retinal detachment and other unknown causes probably lead to blindness and phthisis in this family. Although there are certain similarities between our cases and other known genetic conditions, our literature review and the London Dysmorphology Database (33) did not show any other known syndrome equally or approximately matching the combination of blindness, scoliosis, and arachnodactyly as proposed by this report.

Our Turkish patients are most likely affected by a hitherto unreported condition caused by an autosomal dominant gene defect with variable expression but we can not exclude multigenic additives. Sex- influence has probably contributed to the disease inheritance because the proband's mother and sister are less affected than the his brother and father.

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LEGENDS

FIGURE 1. Family's pedigree

FIGURE 2a, 2b, 2c; the first admission of the proband (I.B).

2d; after the operation of his scoliosis. 2e : a few years later.

2fa,2fb :Progressive scoliosis.

FIGURE 3. X-ray of I.B.

FIGURE 4. Arachnodactyly.

FIGURE 5a and 5b. Eye pictures of the proband I.B and case U.B, respectively.

FIGURE 6. Case U.B.

FIGURE 7a, 7b, 7c; Case S.B when he was 20 years old.