Marfan syndrome: ocular findings and novel mutations—in pursuit of genotype–phenotype associations

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ABSTRACT • RÉSUMÉ

Objective: To analyze ocular involvement in patients diagnosed with Marfan syndrome (MFS), study their clinical findings and prognosis based on the type of *FBN1* mutation, and evaluate possible genotype–phenotype correlations.
Design: Observational single-centre case series.
Participants: Eleven patients diagnosed with MFS were included. All subjects met the Ghent criteria of MFS, the diagnosis was confirmed by genetic testing.
Methods: All subjects underwent a complete ophthalmologic examination. We evaluated clinical data, the incidence of ectopia lentis (EL), and other eye disorders. The association of ocular signs with the type of mutation was analyzed.
Results: Four of the 11 patients had EL, of which 3 developed secondary glaucoma, and 62.5% of the phakic patients had myopia. Other ocular abnormalities included strabismus, retinal tears, retinal detachment, and amblyopia. The encountered types of mutations were premature termination codon (PTC) in 7 patients, missense in 2 cases, 1 aberration of splicing, and 1 indel mutation. Two novel mutations were found. Of the patients with EL, 2 had a missense, 1 an indel, and 1 a nonsense mutation.
Conclusions: Myopia was the most frequent ocular involvement. Patients with a PTC mutation revealed to have a smaller risk of EL; however, more studies are required to indicate the mechanism of the correlation.

Objectif : Analyser l'atteinte oculaire chez les patients ayant reçu un diagnostic du syndrome de Marfan (MFS), étudier leurs résultats cliniques et le pronostic en fonction du type de mutation dans le gène FNBN1 et évaluer les corrélations génotype-phénotype possibles.
Nature : Observation d'une série de cas dans un seul centre.
Participants : 11 patients ayant reçu un diagnostic du syndrome de Marfan. Tous les sujets répondaient aux critères de Gand du syndrome de Marfan, et le diagnostic a été confirmé par des tests génétiques.
Méthodes : Tous les sujets ont subi un examen ophtalmologique complet. Nous avons évalué les données cliniques et l'incidence de l'ectopie du cristallin (EC) et d'autres troubles oculaires. Nous avons aussi analysé les liens entre les signes oculaires et le type de mutation.
Résultats : 4 des 11 patients avaient une EC, dont 3 ont développé un glaucome secondaire. 62,5 % des patients phaques étaient myopes. Entre autres anomalies oculaires constatées, mentionnons le strabisme, des déchirures rétiniennes, un décollement de la rétine et l'amblyopie. Nous avons constaté les types de mutation. suivants: 7 cas de terminaison prématurée du codon, 2 cas de faux-sens, 1 cas d'aberration de l'épissage et 1 de mutation indel. Deux nouveaux types de mutations ont été trouvées. Chez les patients atteints d'EC, nous avons relevé 2 cas de faux-sens, 1 cas d'indel et 1 cas de non-sens.
Conclusions : La myopie est l'atteinte oculaire la plus fréquente. Les patients chez qui nous avons constaté une terminaison prématurée du codon couraient un risque plus faible d'EC, mais d'autres études sont nécessaires pour déterminer le mécanisme de la corrélation.

The Marfan syndrome (MFS) is a genetic autosomal dominant disorder of the connective tissue that affects multiple systems, primarily the skeletal, cardiovascular, and ocular.

The disease is caused by a mutation in the gene for fibrillin-1 (*FBN1*) located on chromosome 15q21.1. Fibrillin is a widely expressed glycoprotein of the elastic fibres of the aorta and nonelastic tissues such as ciliary zonules of the eye, the periosteum of bones, and tendons. There are over 1500 mutations identified, which are distributed along the *FBN1* gene; thus, the affected patients may exhibit a broad phenotypic spectrum. The diagnosis is usually clinical by fulfilling criteria according to the Ghent nosology, which includes many characteristics, including a wide spectrum of systemic features (mainly cardiovascular, skeletal, and ocular), family history, and *FBN1* mutation.[1] In the revised Ghent nosology from 2010, ectopia lentis (EL) is one of the major criteria; another ocular feature included in the classification is myopia greater than 3 diopters, which comprises one of the minor criteria.

The main ocular manifestations in MFS are myopia and EL (Fig. 1). The subluxation or luxation of the lens is reported in approximately two-thirds of patients (45–87%).[2–4] Glaucoma secondary to aphakia may be observed.[3,4] The lens dislocation is a result of insufficiency

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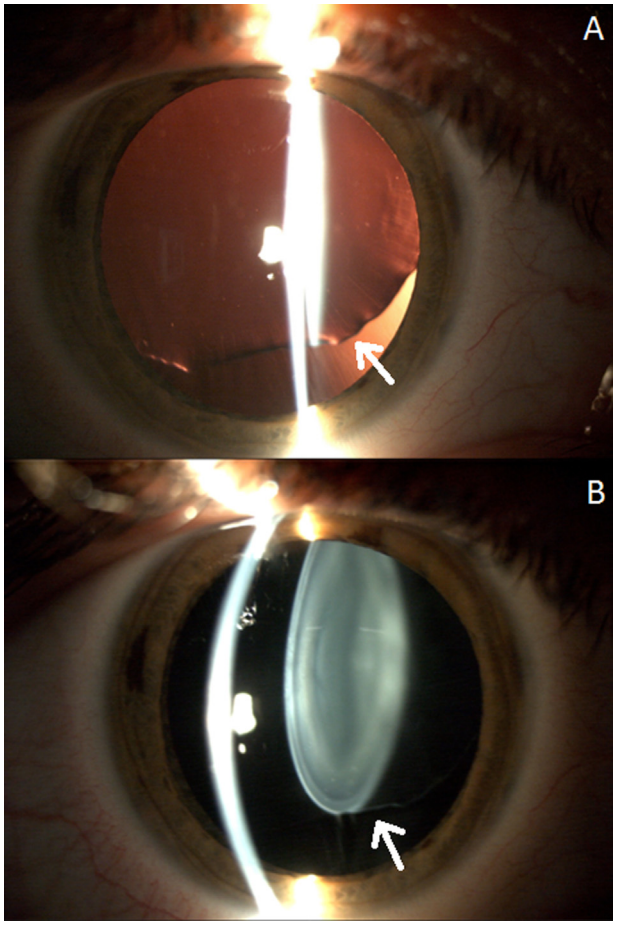

Fig. 1—Ectopia lentis of the right eye in patient number 8 observed in maximum pupil dilation in different illumination (A, B), arrows pointing to subluxated lens, visible inferior zonular fibres.

of the ciliary zonules and in MFS is typically in the superotemporal direction. The defective zonular fibre production and fewer or abnormal ciliary processes observed in MFS contribute to lens dislocation. Additionally, the zonular microfibrils are exposed to proteolytic damage that may affect the zonular function.[5]

Although EL is not pathognomonic, it is quite characteristic, and encountering it on examination of an undiagnosed patient should be followed by a thorough systemic workup. The lens dislocation is typically superior in MFS; however, it may occur in any direction. Other genetic disorders with EL include the ectopia lentis syndrome, in which EL is an isolated ocular feature; the Weill–Marchesani syndrome, where it is associated with microspherophakia and characteristic skeletal features; and homocystinuria presenting with usually inferior dislocation of the lens and is an important distinction as the metabolic consequences of the disease can be treated.[6]

Myopia is a very common feature of MFS, and it usually appears in early childhood and progresses rapidly. Although myopia is very unspecific because of the high prevalence in the healthy population, it is one of the minor criteria, and should be evaluated especially in the absence of EL. Myopia is included in the criteria because it is very common and routinely measured on ophthalmological examination. Astigmatism observed in MFS is often attributed to lens dislocation. Other ocular findings include abnormally flat cornea, increased axial length of the globe and hypoplastic iris or ciliary muscle responsible for decreased miosis, and an increased risk of retinal detachment.[1,7]

It is still poorly understood how the nature of the *FBN1* mutation affects the ocular involvement. Indicating a direct phenotype–genotype correlation could serve in the direction of an appropriate medical treatment and monitoring.

Materials and Methods

The study was approved by the institutional review board of the Hospital Clinic of Barcelona, Spain, and the research work was carried out in accordance with the Declaration of Helsinki. All patients received written and oral information about the study and written consent was obtained from all subjects. In case of children, a parent provided the written consent.

The subjects selected for the study were patients diagnosed with MFS with an identified mutation of the *FBN1* gene who were under the care of the ophthalmology and genetics departments, and agreed to participate in the study. The studied group included 11 patients, 7 male and 4 female, with a mean age of 35.5 years (range 6 to 65 years). We also included the living relatives with MFS; therefore, subjects 2 and 3 are directly related, and so are patients 5, 6, and 7. All the subjects fulfilled the 2010 Revised Ghent Criteria.

A complete medical and family history with emphasis on ophthalmological background was taken, and a full eye examination was performed. Previous medical records were analyzed when available. All measurements in the eye examination were performed during 1 visit by the same ophthalmologist.

The examination included refraction with spherical equivalent and best-corrected distance visual acuity measured in the logMAR scale. Slit-lamp biomicroscopy of the anterior segment was performed with evaluation of the cornea, iris, and lens; exploration of the posterior segment was realized after pupil dilation with topical tropicamide and phenylephrine. The lens was evaluated for EL and any abnormalities such as "notch" in the edge in phakic eyes in maximal mydriasis in different gaze positions during slit-lamp examination—EL was classified as any dislocation or displacement of the crystalline lens. The studied subjects were assessed for possible glaucoma: intraocular pressure (IOP) was taken by Goldmann applanation tonometry; visual perimetry (24-2 SITA-Standard, Humphrey, Carl Zeiss Medic 2007) and optic coherence tomography (Carl Zeiss Cirrus HD-OCT) of the retinal nerve fibre