Ocular findings in 87 adults with Ghent-1 verified Marfan syndrome

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ABSTRACT.

Purpose: To study ocular characteristics in 87 patients with verified Marfan syndrome (MFS) based on the Ghent criteria from 1996 (Ghent-1).

Methods: The position of the lens was noted by observing the eye in different gaze directions in maximal mydriasis during slit lamp examination. Ectopia lentis (EL) was classified as subluxated (dislocation slightly backwards) or luxated (vertical or horizontal displacement). Corneal curvature, axial length (AL), corneal diameter, central corneal thickness, anterior chamber depth, lens thickness, condition of the iris, intraocular pressure, spherical equivalent and visual acuity were also investigated.

Results: EL was found in 108 eyes (62.1%). Of the 68 phakic eyes with EL, 43 (63.2%) had subluxation. Mean AL was 24.80 ± 2.57 mm, and the AL was above 23.5 mm in 65.3%. Mean keratometry (K) in phakic eyes was 41.79 ± 1.70 diopters (D), and the K value was <41.5D in 46.8%. Iris hypoplasia was found in 3.4%. Myopia above 3D occurred in 38.4% of the phakic eyes. Mean binocular logMAR was 0.10 ± 0.32. Only five patients (5.7%) had a logMAR more than 0.5. These 5 patients had EL, and 4 of them were amblyopic.

Conclusion: In this strictly defined MFS group fulfilling the Ghent-1 criteria, the prevalence of EL was 62.1%. In many cases, the dislocation of the lens was subtle. On average, the corneas were flattened and the globe length was increased. Only a few patients were visually impaired. Children with MFS should have a thorough follow up to avoid amblyopia.

Key words: amblyopia – corneal curvature – ectopia lentis – eye axial length – Marfan syndrome

Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder affecting a number of organ systems. It is usually caused by mutations in *FBN1*, the gene encoding the connective tissue protein fibrillin-1 (De Paepe et al. 1996). Dissection of the ascending aorta following enlargement of the vessels results in a reduced life span. However, timed aortic graft surgery and use of β-blockers have improved the prognosis. The patients often have long, tubular bones, resulting in a tall, slender stature, and a long, narrow head with deep-set eyes, giving them what is called a 'Marfanoid habitus.' The prevalence is usually reported as 2–3 per 10 000 inhabitants (Pyeritz 2000). However, two prevalence studies based on defined geographical areas report 6.81 per 100 000 (Gray et al. 1994) and 4.6 per 100 000 (Fuchs 1997).

Ectopia lentis (EL) was found to be part of MFS by Börger in 1914 (Börger 1914), and MFS is reported to be the most prevalent cause of EL (Fuchs & Rosenberg 1998). Since the report of Börger, additional ophthalmological abnormalities have been associated with the syndrome (Maumenee 1981; Beighton et al. 1988).

MFS is not characterized by any pathognomonic features, so diagnostic criteria must be applied. The fourth set of criteria, the Ghent nosology (De Paepe et al. 1996), hereafter called the Ghent-1 criteria, describes seven systems and defines four levels of pathology: 'Major criteria' are described for five systems (skeletal, ocular, cardiovascular, dura and family/genetics). There are eight 'manifestations' included for the skeletal system; for a person to fulfil the major skeletal criterion, four of these eight manifestations must be present. 'Organ system involved' and 'minor criteria' are described for five organ systems (skeletal, ocular, cardiovascular, lungs, skin and integument). For a person to fulfil

the Ghent-1 criteria, two major criteria in two different organ systems must be fulfilled, and a third organ system must be involved. The requirements for having an organ system involved vary for each organ system. Concerning the ocular manifestations, EL is a major criterion. The minor criteria are 'abnormally flat cornea', 'increased axial length (AL) of the globe' and 'hypoplastic iris or hypoplastic ciliary muscle causing decreased mioses.'

In 2010, new diagnostic criteria were presented (the Ghent-2 criteria) (Loeys et al. 2010) in which aortic root - aneurysm/dissection and EL are the cardinal features. Aside from EL, 'myopia > 3 diopters (D)' is the only ocular feature in the revised nosology.

The prevalence of the different features seen in MFS is reported with diverging figures (Rand-Hendriksen et al. 2009). Most studies present results from one or a few organ systems, whereas others report groups of patients recruited from undefined populations. We have not found any papers presenting the full range of ocular features for larger groups of patients fulfilling the Ghent-1 criteria. A number of papers have presented the prevalence of EL (Maumenee 1981; Setala et al. 1988; Sultan et al. 2002; Arbustini et al. 2005; Rybczynski et al. 2008; Kara et al. 2012; Konradsen et al. 2012; Konradsen & Zetterstrom 2013; Chandra et al. 2014). Maumenee (Maumenee 1981) reported full ocular status for 160 persons with MFS, according to the criteria from 1979 (Pyeritz & McKusick 1979). This is still the main reference article for ocular features in MFS.

This paper presents several relevant ocular characteristics in MFS, based on a well-described adult population with verified MFS diagnosis based on the Ghent-1 criteria, recruited from Norway (4.9 million inhabitants); the Norwegian Marfan study (Tjeldhorn et al. 2006; Rand-Hendriksen et al. 2007, 2009, 2010; Lundby et al. 2009, 2011, 2012).

Materials and Methods

Study population

The participants were recruited as described in previous publications from this cohort (Rand-Hendriksen et al. 2009). The participants, all of whom were Caucasian, were each investigated for every part of the Ghent-1 criteria by the same group of physicians. Genetic sequencing and genetic copy number variant (CNV) analyses were carried out as previously described (Tjeldhorn et al. 2006; Rand-Hendriksen et al. 2007). Eighty-seven patients were found to fulfill the criteria, and these patients constitute the study population of the present work. Mean age of the 87 patients was 39.6 ± 12.9 years (range, 20–69 years). There were 31 men (35.6%) and 56 women (64.4%). The study was approved by the regional ethics committee, and written informed consent was obtained from all subjects. The research work was carried out in accordance with the Declaration of Helsinki.

Eye examination

All measurements were conducted in the same examination session by the same ophthalmologist. One patient had a prosthetic right eye, which was excluded from the analyses except for prevalence of EL. Due to poor patient co-operation or technical problems, we were not able to obtain measurements of all ocular characteristics in all cases. Most missing values (15%) occurred in lens thickness due to difficulties in obtaining measurements in some of the eyes with advanced lens dislocation. Concerning the minor criteria of 'abnormally flat cornea' and 'increased AL of the globe,' K values $<41.5D$ and $AL > 23.5$ mm were applied, respectively.

EL was evaluated by slit lamp examination under complete pupillary dilation (cyclopentolate 10 mg/ml and phenylephrine 100 mg/ml). EL was classified as subluxated when only a subtle posterior dislocation was seen (most commonly located inferonasally and seen as a minimal posterior tilt of the most peripheral part of lens), and often not seen until the patient looked in different directions. Subtle iridodonesis was also looked for – as a sign of subluxation. The EL was classified as luxated when the lens had any displacement (most commonly superotemporally).

Keratometry (K) measurements (mean value of K_{max} and K_{min}) were performed using an auto refractor (Automatic Refractor Model 597, Humphrey-Zeiss, Carl Zeiss Meditec AG, Jena, Germany). Mean simulated K (K_{sim}) was also measured in a subset of patients with Orbscan corneal topography system II (Bausch & Lomb Inc., Salt Lake City, UT). The patients who wore hard or soft contact lenses were asked to remove them 2 weeks and 1 week before examination, respectively.

Refraction and measurement of corrected distance visual acuity (CDVA) were performed applying the Early Treatment of Diabetes Retinopathy Study (ETDRS) visual acuity chart. CDVA was converted to logarithms of the minimum angle of resolution (logMAR) for statistical analysis. Visual impairment was defined according to the tenth edition of the International Classification of Diseases (ICD-10) of the World Health Organization (WHO) from 2007, and identified in patients having binocular visual impairment of category 1 or more (decimal <0.3, logMAR > 0.5).

In the analysis of spherical equivalent (SE), only phakic eyes were included. In addition, we excluded the phakic eyes in which the lens was totally dislocated out of the optical zone causing aphakic refraction.

Central corneal thickness (CCT), AL, anterior chamber depth (ACD) and lens thickness were measured with A-scan ultrasound (Tomey AL-1000, Tomey Corporation, Nagoya, Japan). In the analyses of CCT and ACD, only phakic eyes were included. CCT was also measured with Orbscan. In addition, Orbscan was used to measure the corneal diameter; horizontal white-to-white (WTW). Goldman applanation tonometry was performed before dilating the pupils.

Concerning WTW, CCT, AL, ACD, IOP and lens thickness, there was a highly significant correlation between right and left eyes, and only the right eye is presented.

In a previous report on the same cohort, EL, abnormally flat cornea and increased AL were found in 62%, 53% and 71% of the patients, respectively (Rand-Hendriksen et al. 2009). In the present study, we have performed a more extended presentation of these parameters. Furthermore, for the K and AL analyses, the percentages will somewhat differ from the previous report, as we now have excluded relevant ocular surgery to obtain the most reliable results possible. For the K analyses, we excluded eyes with previous intraocular and refractive surgery,

and for the analysis of AL we excluded eyes with previous surgery for retinal detachment.

Reduced crypts or iris hypoplasia were looked for in the slit lamp before dilatation of the pupil. Previous eye diseases and intraocular surgeries were noted after reviewing the medical records.

Statistical methods

All the quantitative data passed the normal distribution test and are presented as the means ± SD. The Student's t-test was used to calculate significance for biometric means between eyes with and without EL. Paired analysis was done when appropriate. A chi-square or Fisher exact test was used for categorical data. The Spearman rank test was used for correlation between right and left eyes. A backward stepwise multiple logistic regression analysis was performed to compare eyes with and without EL (dependent variable) to different ocular characteristics, age and gender. $P < 0.05$ was considered statistically significant. All statistical tests were performed using SPSS software (SPSS Statistics 20, IBM Corp., Armonk, NY, USA).

Results

Ectopia lentis (EL) – Major criterion

Sixty-eight (50.7%) of the phakic eyes ($n = 134$ eyes; 66 right eyes, 68 left eyes) had EL. Of these 68 eyes, 43 had subluxated lens and 25 had lens luxation. One right eye had been enucleated because of complications following EL surgery. Thirty-five aphakic eyes had had pars plana lensectomia or intracapsular cataract extraction. These cases were evaluated as having had luxation of the lens after reviewing the medical records. Five eyes were pseudophakic (4 of these originally had luxation of the lens). Thus, the total number of EL was 108 (62.1%) of the 174 eyes. Of all EL cases, subluxation represented 39.8% (Fig. 1). The ectopia was bilateral and symmetrical in all but one patient, in whom EL (subluxation) was present only in the left eye. There were no significant differences in age and sex distribution between eyes with and without EL. Cataract was observed in five of the phakic eyes; none of these had EL.

Flattened cornea, increased AL of the globe and hypoplasia of the iris - Minor criteria

The distributions of the different minor criteria are presented in Fig. 1. In eyes with and without EL, K < 41.5D was found in 17 (54.8%) and 14 eyes (42.4%), respectively. This difference was not statistically significant. Moreover, for eyes with and without EL, the distributions of AL > 23.5 mm were 23 (56.1%) and 26 (76.5%), and for AL > 24.5 mm, the distributions were 19 (46.3%) and 16 (47.1%), respectively. These differences were not statistically significant.

Three patients had bilateral iris hypoplasia with reduced crypts. All of these had EL.

Other ocular characteristics

Different ocular characteristics and a comparison between eyes with and without EL are presented in Table 1. A statistically significant difference was found for SE, AL, logMAR and IOP in eyes with and without EL. In a subset of patients, Orbscan was performed (right phakic eyes, $n = 38$) to obtain K values. In this group, the mean Ksim was 41.31 ± 1.48D (range, 38.30–43.85D). In this same subset of eyes, the auto refractor mean K values were 41.60 ± 1.44D (range, 37.63–44.38D). The difference in K values using these two devices was statistically significant ($p < 0.001$). The measurement of CCT differed significantly when applying Orbscan (502 ± 43.9 μm) as compared to A-scan ultrasound (530 ± 37.6 μm); $p < 0.001$.

Forty-eight eyes were myopic >3D (38.4%). Of these 48 eyes, there was a statistically significant difference between the 32 eyes (51.6%) with EL and the 16 eyes (25.8%) without EL ($p = 0.003$).

The presence of EL was associated with lower K and SE values, and increased AL in multivariate analysis (Table 2).

Visual acuity

The mean binocular CDVA for all patients was 0.10 ± 0.32 logMAR (range, −0.24 to +2.00 logMAR), equivalent to decimal 0.8 ± 3.2 lines. The difference in logMAR between right phakic eyes with and without EL was statistically significant (Table 1). Five patients (5.7%) had binocular visual impairment of category 1 or more (logMAR > 0.5). All these patients had EL (Table 3).

Retinal detachment

Eighteen eyes (10.3%) in 13 patients had had surgery for retinal detachment. Of these eyes, all but one eye had been diagnosed with EL. In nine of the eyes, the retinal detachment occurred
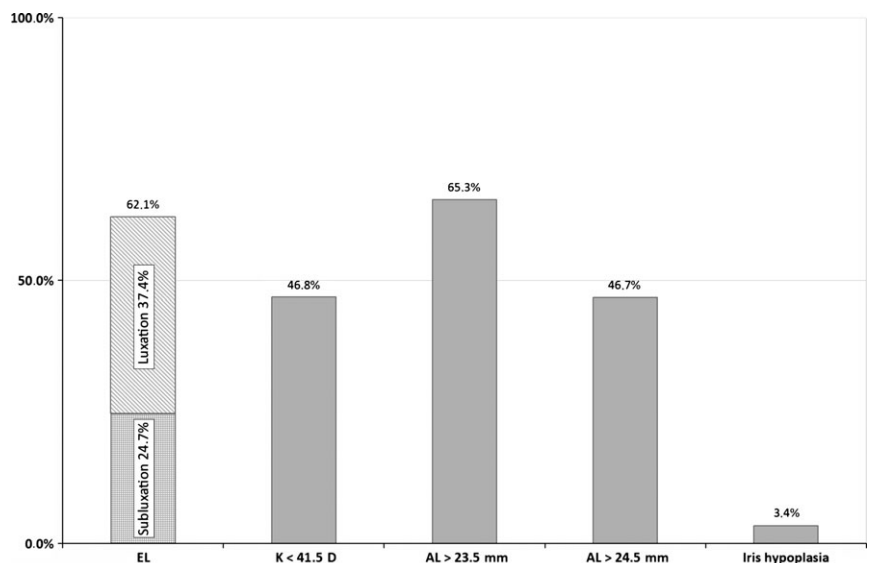

Fig. 1. The frequencies of the major criterion (ectopia lentis), and minor criteria (increased axial length (AL), flattened cornea and iris hypoplasia) according to the Ghent-1 nosology in Marfan syndrome.

Table 1. The mean (range) of ocular features in Marfan syndrome.

	Eyes with no EL	EL eyes	Total eyes (n)	p
K (D)	42.01 ± 1.68 (39.88–46.50)	41.55 ± 1.73D (37.63–45.00)	41.79 ± 1.70 (64)	ns
SE (D)	−2.20 ± 3.52 (−13.63 to +2.50)	−5.85 ± 8.69 (−40.00 to +0.25)	−4.08 ± 6.9 (124)	0.003
CCT (μm)	524 ± 33.4 (469–608)	536 ± 41.1 (430–608)	530 ± 37.6 (61)	ns
WTW (mm)	11.63 ± 0.50 (10.4–13.1)	11.60 ± 0.48 (10.2–12.7)	11.61 ± 0.48 (83)	ns
AL (mm)	24.58 ± 1.33 (22.78–27.37)	24.99 ± 3.27 (20.28 ± 37.80)	24.80 ± 2.57 (75)	0.003
ACD (mm)	2.87 ± 0.28 (2.20–3.44)	2.78 ± 0.39 (2.06–3.79)	2.83 ± 0.34 (62)	ns
LT (mm)	4.09 ± 0.38 (3.32–4.76)	4.31 ± 0.50 (3.28–5.37)	4.20 ± 0.45 (56)	ns
logMAR	0.01 ± 0.20 (−0.24–0.58)	0.18 ± 0.27 (−0.16–0.92)	0.09 ± 0.25 (66)	0.004
IOP (mmHg)	11.09 ± 1.80 (8–15)	12.69 ± 3.49 (6–28)	12.00 ± 3.0 (86)	0.016

A comparison is made between eyes with and without ectopia lentis (EL). The phakic right eyes were included for keratometry (K), central corneal thickness (CCT) and anterior chamber depth (ACD). For axial length (AL), eyes with previous surgery for retinal detachment were excluded. For spherical equivalent (SE), both eyes are included. However, aphakic eyes and eyes in which the lens was totally dislocated into the vitreous were excluded.
WTW = white-to-white (corneal diameter). D = diopters. IOP = intraocular pressure. LT = lens thickness.

Table 2. In a logistic regression model, a possible association between the presence of ectopia lentis (dependent variable) in Marfan syndrome and different characteristics (keratometry, axial length, spherical equivalent, central corneal thickness, logMAR, intraocular pressure, lens thickness, age and gender) were analysed.

Variables	Odds ratio	95% CI	p
Keratometry	0.400	0.200–0.801	0.010
Spherical equivalent	0.401	0.213–0.755	0.005
Axial length	0.208	0.064–0.679	0.009

The right phakic eyes are included. Only the statistically significant variables are presented (p < 0.05).
CI = confidence interval.

after surgery for EL, five eyes had had intracapsular cataract extraction, and four eyes had had lensectomy via pars plana. In two of these four eyes, a secondary implantation of an anterior chamber intraocular lens (IOL) had been performed.

Glaucoma

One patient developed secondary glaucoma in one eye after luxation of the lens into the anterior chamber. Another patient was diagnosed with phacolytic glaucoma in one eye.

Discussion

Maumenees's study from 1981 is a reference article for ocular features in MFS (Maumenee 1981). Since that time, six more articles have been published, reporting on the frequency of EL and at least one of the following relevant ocular features: AL, corneal curvature or SE, and, in addition, defining the way to measure ocular characteristics. Table 4 presents these studies, along with the present, according to criteria used for the MFS diagnosis, size of the material, age distribution, design, whether or not previous eye surgery had been excluded, whether one or both eyes had been included in the analyses, and the devices used for measurements. As seen, the different studies vary significantly in all these features. In other studies, frequencies of both major and minor ocular criteria according to Ghent-1 are reported; however, they are presented without describing the devices used or definitions of cut-off values (Faivre et al. 2008; Rybczynski et al. 2008).

Our cross-sectional study based on the Ghent-1 criteria (De Paepe et al. 1996), showed that 62.1% of the patients studied had EL, compared to previous figures varying from 37% to 87% (Maumenee 1981; Setala et al. 1988; Sultan et al. 2002; Arbustini et al. 2005; Faivre et al. 2008; Heur et al. 2008; Rybczynski et al. 2008; Kara et al. 2012; Konradsen et al.

Table 3. Patients with Marfan syndrome presenting binocular visual impairment of logMAR 0.5 or more.

Patient no/years of age	Binocular LogMAR (decimal)	EL/lens surgery	Causes of visual impairment
1/48	0.52 (0.30)	Phakic with EL from childhood	Bilateral visual field defect (lower right quadrants) after stroke. Equator of the lenses interferes with optical zone. Amblyopia.
2/40	0.70 (0.20)	EL from childhood. Lensectomia both eyes at 35 years of age	Spectacles from 13 years of age. Amblyopia.
3/37	0.88 (0.13)	Phakic with EL from childhood	Excessive myopia (-20D both eyes) diagnosed at 18 months of age, at that time began wearing contact lenses/spectacles. Myopic optic nerve and macular degenerations. Present myopia of -40D both eyes.
4/58	0.98 (0.10)	EL from childhood. Lensectomia both eyes	Spectacles from 8 years of age. Right eye blind after lensectomia (retrobulbar haemorrhage). Left eye amblyopia
5/55	2.00 (0.01)	EL from childhood. Lensectomia both eyes	Excessive myopia from childhood. Spectacles from 7 years of age (?). Amblyopia. Retinal detachment following EL surgery both eyes.

EL = ectopia lentis. D = diopters.

Table 4. Listing of publications from 1981 until now reporting ocular features in Marfan syndrome.

Publications	N (Patients)	Criteria	Study design	Control group	Excluded previous surgery	Age in years (mean, range)	EL (%)	Myopia > 3D (%)	SE in D (mean)	K < 41.5D (%)	K in D (mean)	AL > 23.5 mm (%)	AL in mm (mean)
Maumenee 1981;	160	(1) No genetic data	Cross-sectional, number of eyes differ in measurements	No	?	3–60	60	29 (16% > 7D)		? 19% ≤ 40D (ophthalmometer)	41.38		24.65 (A-scan)
Setala et al. 1988;	41	No genetic data	Cross-sectional, both eyes	No	No	29 (9–60)	37						25.0 in EL/ 24.3 in no EL (A -scan)
Sultan et al. 2002;	31	(2)	Cross-sectional, both eyes	Yes	?	24 (5–50)	87		−1.1	53 (autokeratometer)	41.4		
Heur et al. 2008;	62	Ghent-1	Retrospective, both eyes,	Yes	?	22	79			? (75% < 42D) (topography)	40.8		
Kara et al. 2012	38	Ghent-1	Cross-sectional, right eye	Yes	Yes	19 (8–31)	45		−2				24.0 (PCI)
Konradsen et al. 2012;	39	Ghent -1 criteria, Lack details about genetic data	Cross-sectional, the more myopic eye chosen for analysis	Yes	Yes	36 (above 12 years of age)	46		−1.75	38 (topography)	42.2		
Konradsen & Zetterstrom 2013;	51	As Konradsen et al. 2012	Cross-sectional, both eyes	No	Yes	39 (13–72)	54	31	−3.46		42.2 (topography)	? 51% > 24.5 mm	24.73 (PCI)
Present study	87	Ghent -1	Cross-sectional, right eye	No	Yes	40 (20–69)	62	39	−4.1	47 (autorefractor)	41.8	65	24.80 (A- scan)

EL = ectopia lentis. SE = spherical equivalent. D = diopters. AL = axial length. K = keratometry. PCI = partial coherence interferometry (1) Criteria according to Pyeritz & McKusick 1979. (2) Berlin criteria (Beighton et al. 1988).

2012; Konradsen & Zetterstrom 2013; Chandra et al. 2014). We made a great effort to verify the diagnosis of MFS, including a multidisciplinary approach (Rand-Hendriksen et al. 2007, 2009, 2010; Lundby et al. 2009, 2011, 2012). Of the total phakic EL cases, we found minimal dislocation (subluxation) in as many as 63%. Thus, to determine the true prevalence of EL, it is necessary to look for any discrete dislocation of the lens, including those ELs not detected in the slit lamp without maximally dilated pupil and the patient looking in different directions. A subtle iridodonesis in the subluxated area may also alert the physician to the presence of EL. We found bilateral symmetrical EL in all but one patient. According to some previous reports, EL in MFS may be both unilateral and bilateral (De Paepe et al. 1996; Nemet et al. 2006). However, only two studies specified bilateral versus unilateral EL in MFS (Cross & Jensen 1973; Chandra et al. 2014). Chandra et al. reported bilateral EL in 75% of the patients; however, this study was based on a questionnaire given to patients with MFS. Cross et al. found EL in 79% of 115 patients with MFS, and the EL was bilateral in all except three patients.

There are suggestions that expression of stretched abnormal fibrillin in MFS may lead to enlargement of the eye globe and thinning of the cornea, and may take part in the pathogenesis of the EL, and one may further speculate that EL represents a more advanced stage of ocular disease in MFS (Wheatley et al. 1995; Traboulsi et al. 2000). In the present study, we found that the AL was longer in eyes with EL. This has also been shown in other studies (Maumenee 1981; Kara et al. 2012). We found no difference in CCT between eyes with and without EL, which is consistent with some reports (Setala et al. 1988; Heur et al. 2008; Konradsen et al. 2012). Others have reported a thinner cornea in EL eyes (Sultan et al. 2002; Kara et al. 2012). However, one should bear in mind that we left out eyes with previous retinal detachment surgery for AL analyses and included only phakic eyes in the K and CCT analyses to avoid the influence of ocular surgery. Being able to include these excluded eyes with their preoperative biometric values might have changed the results, as almost all of them were EL eyes. These

eyes may have represented a more serious stage of ocular disease in MFS. Even though Maumenee implied that lens dislocation was progressive in 7.5–13.2% of the patients (Maumenee 1981), longitudinal studies are needed to get more knowledge about the natural course of ocular features in MFS.

In our study, the limit for flat cornea was set to K < 41.5D, and we found that 46.8% of the eyes fulfilled this criterion. These findings clearly show that even though the values varied widely, the corneal curvature was on average significantly flattened (mean K 41.8D compared to reference values around 43.5D) (Fledelius & Stubgaard 1986; Olsen et al. 2007), and our results correspond with other reports (see Table 4). There are several devices available for measuring corneal curvature, and the results may vary (Shirayama et al. 2009). The present study shows significant differences between the K values measured by corneal topography as compared to those measured by auto refractor.

Population studies suggest a normal AL around 23.5 mm based on A-scan ultrasound measurements (Olsen et al. 2007). In the present study, mean AL was 24.8 mm, which confirms previous reports showing longer AL in eyes with MFS (see Table 4). Our cut-off was AL values > 23.5 mm and 65.3% of the patients fulfilled this criterion. Perhaps a cut-off at 24.5 mm would have been more appropriate, as almost half of the cases (46.7%) met this criterion. However, none of the patients were dependent on ocular minor criteria to fulfill the MFS diagnosis, which means that in terms of making this diagnosis in the present study, assessing an 'involved ocular system' did not make any difference. Similar to corneal curvature, the AL values differ depending on the devices used (Olsen & Thorwest 2005), and in the end determining the exact cut-off values may be inadequate. Instead, as a guideline, one should be suspicious of MFS the longer the AL and the flatter the cornea are.

As flat cornea will move the focus of light in the hyperopic direction, while a long AL will bring the focus towards myopia, the SE will depend on the mutual effect of these two parameters. In addition, tilt or decentration of the lens will change the refraction, in most cases in the myopic direction. In the present study, 38.4% of the patients were myopic above 3D (the only ocular feature besides EL in the Ghent-2 nosology). Two other studies on MFS patients have reported myopia > 3D – and – both of them found the frequency to be around 30% (Maumenee 1981; Konradsen & Zetterstrom 2013). When compared to the refraction in the normal population with the same age group and ethnicity as in the present study, about 11% were myopic > 3D (Fledelius & Stubgaard 1986), suggesting that myopia may be a rather nonspecific criterion in diagnosing MFS.

Flat cornea and increased AL are both minor criteria according to the Ghent-1 criteria (De Paepe et al. 1996). These criteria were left out in the Ghent-2 nosology, as it was stated that they had unclear specificity and were not routinely measured by ophthalmologists (Loeys et al. 2010). However, AL is always measured before cataract surgery to calculate the IOL power. Cataract surgery is one of the most commonly performed procedures in the Western world, and so the vast majority of ophthalmologists have the equipment and skill for measuring AL. Furthermore, corneal curvature is measured by ophthalmologists as part of the refraction procedure. Accordingly, at least in patients suspected to have MFS without EL, it seems reasonable to measure the corneal curvature and AL. In eyes with no EL, we found significantly increased AL (above 23.5 mm in 76.5%, mean 24.58 mm) and flattened cornea (below 41.5D in 42.4%, mean 42.01D). In contrast, myopia > 3D was found in only 25.8% (mean -2.2D) in patients without EL.

Retinal detachment is reported to occur in about 4% to 15% of patients with MFS, (Cross & Jensen 1973; Maumenee 1981; Konradsen & Zetterstrom 2013; Chandra et al. 2014) and in most cases is related to EL and lens surgery. In the present study, 10.3% of the eyes had undergone surgery for retinal detachment. Half of them had had previous surgery for EL. The treatment of EL, however, has changed over the last decades with the improvements in cataract surgery, and intervention is now often scheduled at an earlier stage. Experienced surgeons have achieved promising results by performing phaocoemulsification, fixation of the lens capsule with devices such as a Cionni modified capsule tension ring (Morcher GmbH, Stuttgart, Germany) and implantation of the IOL in the capsular bag (Cionni & Osher 1998; Konradsen et al. 2007), or by removing the whole lens through small incision surgery and implanting an IOL fixed either to the iris or the scleral wall (Zetterstrom et al. 1999; Kumar et al. 2012). One may therefore anticipate that modern surgery for both EL and retinal detachment will improve the visual prognosis in these patients. However, further studies with long follow-up are required to draw accurate conclusions on this issue.

Even though retinal detachment is a well-known complication in MFS eyes, the mean binocular CDVA was as good as 0.10 logMAR (equivalent to decimal 0.8), in accordance with two recent studies (Kara et al. 2012; Konradsen & Zetterstrom 2013). Only five of our patients had visual impairment of category 1 or more (WHO definition). Not surprisingly, the phakic patients with EL were found to be more myopic and had lower visual acuity than patients without EL. In advanced EL, that is, the lens equator located in the optical zone, there will be interference with visual function and often induced high myopia and astigmatism. These patients will definitively benefit from modern surgery, providing an uneventful surgery and postoperative course. Amblyopia was a major cause of visual impairment in our study. Postponed surgery in small children with EL due to fear of complications, or surgery using older methods and with increased risk of complications may have caused amblyopia in several of these patients in the past.

The strength of our study is that we present relevant ocular characteristics in the largest cohort of verified disease investigated for all organ affections according to the Ghent-1 criteria. Based on our study, we propose the following clinical implications: (1) EL, flattened cornea and increased AL are present in the majority of the verified MFS patients and each of these criteria should be warning signs for MFS; (2) One should bear in mind that in many cases the EL is subtle and may be overlooked if not searched for thoroughly; (3) The EL is almost always bilateral; (4) Patients with newly diagnosed MFS, especially those without EL, can be informed that their visual prognosis is generally good; (5) Small

children with MFS must receive careful follow-ups and proper treatment in order to avoid visual impairment.

A limitation to the present study is the lack of a control group. Concerning the prevalence of EL, a control group is obviously not necessary. Likewise, the values found for AL, corneal curvature and SE are far from reference values, indicating that a control group is of lesser value. However, as regards CCT, the results in the literature are conflicting, as some report lower CCT in MFS than in the control group (Sultan et al. 2002; Heur et al. 2008; Konradsen et al. 2012), whereas others do not (Maumenee 1981; Kara et al. 2012). Our results are inconclusive in this respect, even though a CCT of 530 (ultrasound) and 502 (Orbscan) may be considered to be somewhat lower than normal values (Williams et al. 2011).

In the future, we recommend more studies to evaluate the natural course of MFS, and to gain more knowledge about whether modern surgery for EL will improve visual function and reduce the risk of known complications in MFS, such as retinal detachment.

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