Photophobia and disability glare in adult patients with Marfan syndrome: a case-control study

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ABSTRACT

Purpose: The aim of the present study was to investigate photophobia and disability glare in adult patients with Marfan syndrome (MFS).

Methods: In this case-control study, 44 patients with MFS (87 eyes) were compared to 44 controls (88 eyes), who were matched for age and sex. The subjects were asked to grade their photophobia and glare using 10-cm visual analogue scales (VAS), which were marked with “never” at zero and “always” at 10-cm. In addition, disability glare was measured with C-Quant straylight meter.

Results: The patients with MFS had significantly higher VAS scores than the controls in four out of seven statements related to photophobia and glare. When including cataract, spherical equivalent, eye colour axial length and corneal curvature, three of the seven statements were still significantly different between the two groups. The mean straylight values were 1.29 ± 0.03 log(s) in the MFS group and 1.01 ± 0.03 log(s) in the control group ($p < 0.001$, mixed model). These differences remained significant after adjusting for cataract, spherical equivalent, iris colour, axial length and corneal curvature.

Conclusion: Patients with MFS reported more photophobia and had a higher straylight value than the control group. Awareness of these findings of more photophobia and glare in the MFS patients is important when counselling and treating these patients.

Key words: Marfan syndrome, photophobia, ocular straylight, disability glare

INTRODUCTION

Marfan syndrome (MFS) is a rare, autosomal dominant, connective-tissue disorder that is caused by mutations in the *FBN1* gene, which encodes for the connective tissue protein fibrillin-1 (Online Mendelian Inheritance in Man ; Sakai et al. 2016). Several organ systems are affected, which typically include the ocular, cardiovascular and skeletal systems and the dura mater (De Paepe et al. 1996; Rand-Hendriksen et al. 2009). However, *FBN1* mutation alone is not conclusive for making an MFS diagnosis (Online Mendelian Inheritance in Man). Therefore, the diagnosis is based on sets of diagnostic criteria which have been revised. The two latest versions are Ghent-1 from 1996 (De Paepe et al. 1996), and Ghent 2 from 2010 (Loeys et al. 2010).

According to the Ghent-2 criteria, the ocular manifestations are dislocation of the crystalline lens and myopia greater than three dioptres (D) (Loeys et al. 2010). The Ghent-1 criteria also include the following ocular characteristics: increased axial length, flattened corneal curvature, and a hypoplastic iris and ciliary body (De Paepe et al. 1996; Konradsen & Zetterstrom 2013; Drolsum et al. 2015).

In addition to these known features, our clinical experience is that patients with MFS often complain of sensitivity of light (photophobia). This symptom has been mentioned previously in these patients (NHS 2021), but we have not identified any scientific publications addressing this observation. Photophobia is a sensory disturbance that has been defined in several different ways. The four most common are: abnormal sensitivity to light that causes pain in the eyes or the head; ocular discomfort (photo-oculodynia); exacerbation of headache by light; and general aversion to light (Lebensohn 1951; Digre & Brennan 2012; Burstein et al. 2019). Photophobia is poorly understood and difficult to measure, thus making it difficult to treat (Digre & Brennan 2012; Albilali & Dilli 2018). There are a number of conditions associated with photophobia, including ophthalmological, neurological, psychiatric, and drug-induced conditions (Digre & Brennan 2012). Measurement tools are sparse, and most studies that have included questionnaires have focused on patients with migraine (Choi et al. 2009; Wu & Hallett 2017).

As there were no validated questionnaires available on photophobia in eye diseases, we formulated a patient-reported measure that includes seven statements concerning photophobia. In our search for another valid method with high repeatability that could measure symptoms related to such patients' complaints, we explored different methods, and chose to evaluate whether "disability glare" is the problem or part of the problem.

The term "disability glare" is sometimes used as a synonym for photophobia. Disability glare is defined by the Commission Internationale de l'Eclairage (CIE) as "a loss of retinal image contrast as a result of intraocular light scatter or straylight" (Vos 1984). The light scatter causes a veil of bright light and may be experienced as photophobia (Lapid-Gortzak et al. 2011). Straylight occurs when there are changes in the ocular media, especially in the lens (van den Berg et al. 2013). Patients with MFS have increased risk of developing cataract and ectopia lentis (EL) (Maumenee 1981). Thus, we hypothesized that light scatter may explain the discomfort that patients with MFS experience.

Several tests are available for measuring straylight in the eye, ranging from a simple pen-torch glare assessment and brightness acuity tester to more advanced units for combined visual-function testing (Aslam et al. 2007). The C-Quant straylight meter (Oculus Optikgeräte GmbH, Wetzlar, Germany) is one of the most widely used methods and has been shown to be a valid instrument for measuring straylight across various ocular conditions (van Rijn et al. 2005).

Both photophobia and straylight may have several causes. In addition to conditions related to the lens, patients with MFS have other structural characteristics in the eye which may possibly contribute to these symptoms. The aim of the present study was to investigate photophobia and disability glare in MFS patients in comparison to a control group, using statements regarding photophobia and glare as well as a C-Quant straylight meter.

MATERIALS AND METHODS

Study population

The study group included 44 adults (87 eyes) with verified MFS according to the Ghent-2 criteria who were investigated in 2014 and 2015.The participants were recruited through the TRS, National Resource Centre for Rare Disorders, the Journal of the National Association for MFS and through the Department of Cardiothoracic Surgery at the University Hospital in Oslo. The patients underwent a comprehensive multi-disciplinary examination of relevant organ systems and of the 60 patients examined, 44 patients fulfilled the Ghent-2 and were included in the study. Of the 44 participants, 42 carried a presumed disease-causing *FBN1* variant (Sandvik et al. 2019; Vanem et al. 2019). Experienced ophthalmologists and an optometrist performed the eye examinations. One of the included MFS patients had a prosthetic eye, and this eye was excluded from the study.

The control group included 44 age- and sex-matched individuals (88 eyes) who were recruited both from the hospital staff at the Department of Ophthalmology at Oslo University Hospital and the local community. This group was investigated in 2017.

The research adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants. The study was approved by the Regional Committees for Medical and Health Research Ethics (registration number 2013/2109).

Ophthalmological examination

All participants underwent a comprehensive ophthalmological examination. The anterior segment was investigated by slit-lamp examination, and the status of the lens was evaluated after pupillary dilation with cyclopentolate (10 mg/mL) and phenylephrine (100 mg/mL) in the MFS group and with tropicamide (5 mg/mL) in the control group. We registered the presence of EL, cataract and if the eyes were phakic, pseudophakic or aphakic. All measurements were conducted on both eyes.

To evaluate photophobia, a patient-reported measure would be preferable. However, in the planning of the study, we did not identify any validated questionnaire of photophobia related to eye disease. Still, a validated questionnaire from Choi et al on migraine patients focused on several aspects we deemed as relevant (Choi et al. 2009). With inspiration from this questionnaire we constructed seven statements concerning photophobia and glare. The participants were asked to rate their subjective experience regarding each statement using a 10-cm visual analogue scale (VAS), which was marked with “never” at zero and “always” at 10-cm. The seven statements are presented in Table 2.

Disability glare was examined with a C-Quant straylight meter before pupillary dilation (Figure 1). An expected standard deviation (Esd) < 0.08 and a quality parameter $Q > 1$ were considered as indicating acceptable reliability. Measures not fulfilling these requirements were excluded. In addition, due to pain, one patient was unable to sit in the correct position to perform the test. Best corrected near visual acuity was determined, and the straylight test was performed with this refraction. One patient had reduced vision with spectacles because of excessive myopia and used contact lenses during the examination. Straylight was quantified by means of a straylight parameter *s* and is given logarithmically as log(s). A higher value indicates more straylight and more sensitivity to glare. Normal straylight values vary with age from around 0.9 log(s) for age below 40 years to 1.2 log(s) at 65 years of age (Van Den Berg et al. 2007).

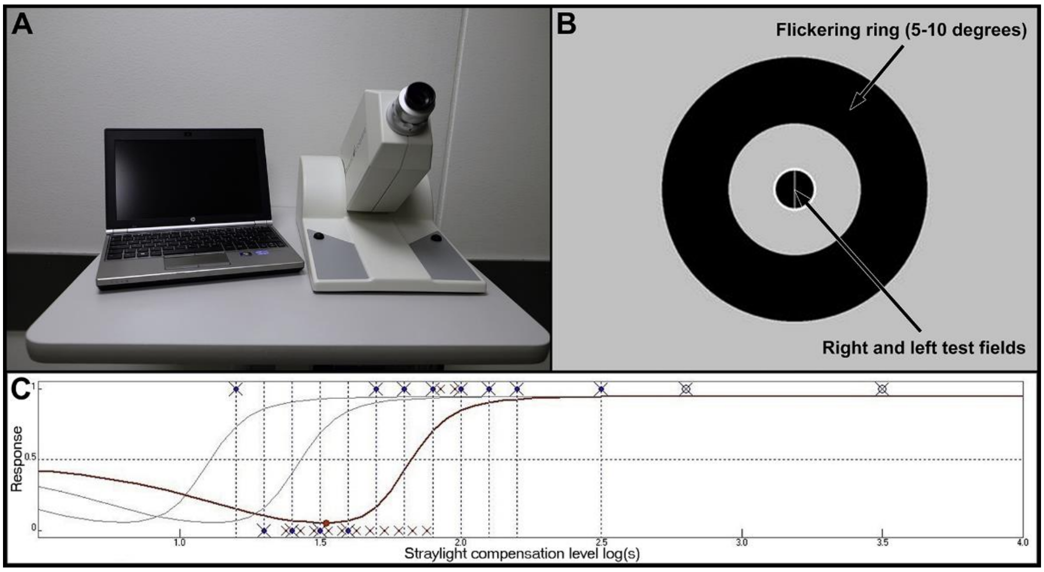

Figure 1: Straylight measurement using C-Quant (Oculus Optikgeräte GmbH, Wetzlar, Germany): The patient looks in the eyepiece (A) and fixates on the two half test fields in the centre (B). The straylight source is presenting a flickering ring with a radius of 5 to 10 degrees from the fixation area. Because of intraocular scatter, this flickering ring is causing a weak flicker in the test fields. In addition, one of the two test fields is giving a counterphase compensation flicker and the other test field is black. The patient is then asked to indicate which of the two test field flickers strongest. If the test field with the compensated light is chosen, this is scored as 1 (C). This is repeated with 25 different presentations and if the straylight flicker is exactly compensated there is no flicker in the test area and the response will be scored as 0 (C). The response chart (C) has a logarithmic scale, the straylight compensation level log (s), which is determined by the ratio between the compensated light (in one of the central test fields) and the intensity of the straylight source, and is given in the same unit as the straylight parameter “s”. In (C) the result of a Marfan syndrome patient is shown, and the straylight value for this patient is 1.5 (red dot).

Lens density was quantified using Scheimpflug imaging with a Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany). Using the software of this instrument, the density of the lens was measured by the linear analysis method as illustrated in Figure 2 (Weiner et al. 2014).

Subjective refraction was measured with Reichert manual Phoropter (Reichert Technologies, Munich, Germany) by an experienced optometrist. Best corrected visual acuity was noted in logarithm of the minimal angle of resolution (logMAR). Spherical equivalent was calculated. Axial length and anterior chamber depth were measured with NIDEK Biometer AL-scan (NIDEK Co., Ltd, Gamagori, Japan) and the corneal curvatures were measured with Pentacam HR. Information regarding previous vitrectomy was collected from the medical records. Iris colour was noted as light blue, blue-grey, green-hazel or brown (Nischler et al. 2013). All participants were Caucasian.

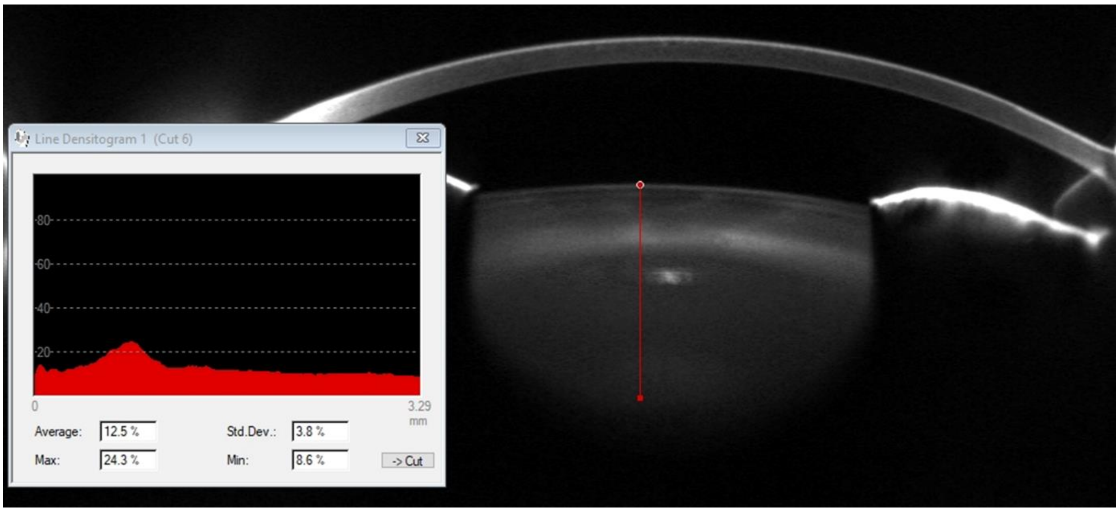

Figure 2: Example of densitometry analysis using the linear method in Pentacam HR software (Oculus Optikgeräte GmbH, Wetzlar, Germany). This method assesses the mean density of a vertical line drawn through the lens. The device rotates and takes 25 images in different degrees. To ensure comparability between patients, images in the same degrees for each patient were analysed. When the correct image is selected, a vertical line is drawn through the centre of the lens.

Statistics

Two-sample *t*-test was used to compare the self-reported photophobia between the groups. In addition, we performed linear regression analysis with relevant explanatory variables; cataracts, spherical equivalent, iris colour, axial length and corneal curvature. The difference in straylight between the two groups was analysed using linear mixed-effect models. The analyses were performed both with and without the same explanatory variables described above. These variables were included as fixed effects for the two groups. In addition, we performed analysis of straylight by replacing the value for cataract (yes/no) with the lens densitometry value, as well as excluding all patients with cataract. Only phakic cases were included in the analysis involving spherical equivalent.

Fixed effects were tested for multicollinearity. Since data from both eyes were used and since the MFS cases were matched to controls random effects were included to take into account dependencies. The Pearson correlation method was used to assess the correlation between the straylight value and the statements regarding photophobia. In these analyses, the highest straylight value of the two eyes was chosen. A two-sample *t*-test was used to compare age and spherical equivalent (when only phakic left eyes were included). A chi-square test was used to compare proportions between the groups. Mixed-model was used to compare spherical equivalent, visual acuity, axial length, and corneal curvature between the groups as both eyes were included in these analyses.

The statistical analyses were conducted using Stata SE version 15, and a P value < 0.05 was considered statistically significant.

RESULTS

The characteristics of the patients with MFS and the age- and sex-matched controls are summarized in Table 1. Previous lens surgery was more common in the MFS group than the control group ($p < 0.001$), and cataract was present to a significantly higher degree ($p < 0.001$). Patients with MFS had significantly longer axial length ($p = 0.003$) and flatter cornea ($p < 0.001$), but no significant difference was seen in spherical equivalent. No participants in either group had corneal cloudiness.

Table 1: Patient characteristics of the Marfan syndrome group (MFS) and the control group (*n* = number of eyes).

	MFS (*n* = 87)	Control (*n* = 88)	*P* Value
Age (years)	50.1 ± 1.8 (30 - 80)	50.0 ± 1.8 (31 - 82)	0.935
Sex (female/male)	33 (75%)/11	33 (75%)/11	---
Spherical equivalent (D) †	-0.38 ± 0.8 (-28.0 - 13.8)	-1.10 ± 0.3 (-8.5 - 3.3)	0.39
Spherical equivalent, adjusted (D) ‡	-0.71 ± 4.9 (-13.0 - 10.0)	-1.17 ± 2.2 (-7.4 - 2.0)	0.60
Visual acuity (logMAR)	0.18 ± 0.08 (-0.2 - 3.0)	-0.13 ± 0.01(- 0.3 - 0.7)	< 0.001
Axial length (mm) †	25.4 ± 0.5 (21.0 - 26.0)	23.9 ± 0.2 (22.0 - 26.1)	0.003
Corneal curvature (D) †	41.4 ± 0.2 (38.8 - 45.7)	43.4 ± 0.2 (40.9 - 46.0)	< 0.001
Anterior chamber depth (phakic eyes)	3.19 ± 0.06 (2.7 – 3.8)	3.35 ± 0.06 (2.5 – 4.2)	0.074
Glaucoma §	2 (2%)	0 (0%)	---
Iris colour			
Light-blue	31 (36%)	40 (45%)	
Blue-grey	24 (28%)	30 (34%)	
Green-Hazel	14 (16%)	10 (11%)	
Brown	6 (7%)	8 (9%)	
Lens status			
Phakic – with EL	16(18%)	0 (0%)	
Phakic – clear lens	29 (33%)	80 (91%)	< 0.001
Phakic – with cataract	16 (18%)	2 (2%)	< 0.001
Aphakic	16 (18%)	0 (0%)	---
Pseudophakic	26 (30%)	6 (7%)	< 0.001
Previous vitrectomy	26 (30%)	0 (0%)	< 0.001

Results are presented as mean ± standard error (range) or n (%).
D = diopter, logMAR: logarithm of the minimal angle of resolution, EL = ectopia lentis
†All eyes. Compared with mixed-models; results presented as mean ± standard error (range).
‡Left phakic eyes (n = 23/41)
§One patient with glaucoma in both eyes.

Photophobia

Patients with MFS reported significantly higher VAS scores on 4 of the 7 statements regarding photophobia and glare. When including cataract, spherical equivalent, iris colour, axial length and corneal curvature as explanatory variables, patients with MFS still reported significantly higher VAS scores on three of the seven statements and statement number 6 had a borderline significance (Table 2).

Table 2: Comparison of statements regarding photophobia and glare in Marfan syndrome (MFS) and controls. Visual analogue scales (0-10 cm) indicating "never" (0) and "always" (10) at the ends were used. (*n* = number of patients) Linear regression with explanatory variables included: cataract, spherical equivalent, iris colour, axial length and corneal curvature.

Statements	MFS (*n* = 22)	Control (*n* = 40)	*P*
1: Bright light bothers me	4.1 ± 0.8 (0.0 – 9.9)	2.8 ± 0.5 (0.0 – 9.0)	0.21
2: I see a halo around light sources	2.6 ± 0.5 (0.0 – 10.0)	0.5 ± 0.3 (0.0 – 7.3)	0.003
3: I have to close the curtains to avoid bright light	2.9 ± 0.6 (0.0 – 8.5)	1.4 ± 0.4 (0.0 – 8.1)	0.04
4: I need to wear sunglasses in normal daylight	1.6 ± 0.6 (0.0 – 6.6)	1.5 ± 0.4 (0.0 – 9.4)	0.96
5: I have to wear sunglasses indoors	0.1 ± 0.0 (0.0 – 3.2)	0.1 ± 0.0 (0.0 – 0.4)	0.24
6: I feel dazzled by the headlights of oncoming cars	4.9 ± 0.8 (0.1 – 10.0)	3.0 ± 0.5 (0.0 – 10.0)	0.06
7: I see stars around light sources	2.1 ± 0.3 (0.0 – 9.9)	0.5 ± 0.2 (0.0 – 4.9)	<0.001
Results are presented in centimeter with mean ± standard error (range)			

Disability glare

The straylight value was significantly higher in the MFS group, 1.29 ± 0.03 log(s), compared to the control group, 1.01 ± 0.03 log(s) ($p < 0.001$). Similar results were found when patients with cataract were excluded ($p < 0.001$) or when densitometry was used as a fixed effect ($p < 0.001$). When including cataract, spherical equivalent, iris colour axial length and corneal curvature as fixed effects there was still a significantly higher straylight value in the MFS group compared to the control group, 1.29 ± 0.07 vs 1.00 ± 0.02, respectively ($p < 0.001$) (Figure 3). In the MFS group, 67% had EL or had undergone EL surgery. The number of patients with EL still present (phakic eyes) at the study examination was 16 (18%), as most patients with EL had previously had lens surgery. The analysis of straylight within the MFS group revealed no significant difference when comparing phakic eyes with EL (n = 12, measurements from 4 eyes were missing) to phakic eyes without EL (n = 17) ($p = 0.17$). In this analysis, lens densitometry was included as a fixed effect.

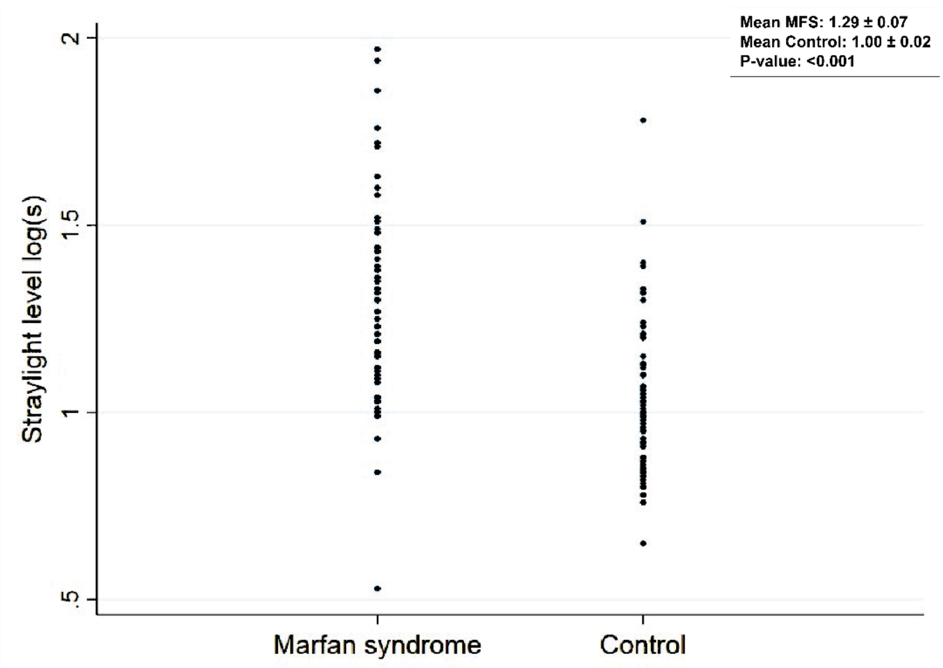

Figure 3: Scatter plot of straylight value (log(s)) of patients with Marfan syndrome and controls with cataract, spherical equivalent, iris colour, axial length and corneal curvature included as fixed effects in the mixed model.

There were significant and positive associations between the statements and the straylight value for four statements when all study participants (both groups) were included in the analysis (Table 3).

Table 3: Analysis of correlation between the straylight value and the statements regarding photophobia. The highest straylight value for the two eyes was used in the analyses.

Statements	**Straylight value** Correlation R	***P* Value**
1: Bright light bothers me	0.31	< 0.001
2: I see a halo around light sources	0.31	< 0.001
3: I have to close the curtains to avoid bright light	0.17	0.13
4: I need to wear sunglasses in normal daylight	0.01	0.91
5: I have to wear sunglasses indoors	0.16	0.15
6: I feel dazzled by the headlights of oncoming cars	0.22	0.05
7: I see stars around light sources	0.38	< 0.001

Results are presented in Pearson correlation coefficient R.

For the C-Quant measurements, we had to exclude 25 eyes in the MFS group and 4 eyes in the control group due to patients not being able to fulfil the required quality parameters as a result of low visual acuity (n=17), technical problems (n=6), or difficulties in performing the test because of health issues (n=2). The cases in the MFS group with missing C-Quant measurements were compared with the MFS patients who managed the straylight test, and the mean result of the photophobia statements in these two groups were comparable; 2.3 ± 0.8 and 2.6 ± 0.5, respectively (p = 0.75). Further, there were no statistically significant differences concerning age, gender, proportion of cataract and axial length. However, the patients with missing straylight measurements had a slightly steeper corneal curvature; 42.2 ± 0.3 versus 41.7 ± 0.3 (p = 0.02).

DISCUSSION

In this study, we examined photophobia and disability glare in patients with MFS in comparison to a matched control group. The results revealed increased symptoms and a higher straylight value in these patients than the controls. Photophobia and disability glare may affect daily-life activities and add another burden to MFS patients, who are often affected by other medical conditions. To our knowledge, no previous studies have systematically investigated these aspects in patients with MFS. Therefore, we believe our findings are important in understanding patients with MFS and highlight the importance of advising these patients in what type of help is available to reduce their symptoms.

We included seven statements regarding photophobia that were evaluated by the study participants. These statements were chosen to reflect relevant situations in daily life, and were in line with a validated questionnaire of photophobia in migraine patients (Choi et al). The results of our patient-reported measures showed significant differences between patients with MFS and controls, reflecting more photophobia for the MFS group in three out of seven statements even after adjustments for cataract, myopia, axial length and corneal curvature. Thus, the results supported our clinical impression that MFS patients may complain more about photophobia and glare.

Some studies describe the terms "photophobia" and "disability glare" as representing the same symptoms (Lapid-Gortzak et al. 2011). It has been known since the early 20th century that disability glare is caused by the scattering of light in the eye (Vos 1984; van den Berg et al. 2013). Because glare has many manifestations and forms, it may be challenging to measure. In the present study, we chose a C-Quant straylight meter as it has been suggested as the most favourable method to measure this type of glare (Franssen et al. 2006; Aslam et al. 2007; van den Berg et al. 2013). When using this instrument, we found a significantly higher straylight value in MFS patients than the controls.

Ocular structures that contribute to straylight include the cornea, lens, vitreous, translucency of the eye wall, and reflections from the retina (Vos 1984; van den Berg et al. 1991; Nischler et al. 2013). In the present study, the presence of opacities in the optical media would be an obvious explanation for the group difference, as cataract is expected to be more frequent in patients with MFS and is known to increase light scatter (Koch 1989). Vitreous floaters have also been associated with increased straylight (van den Berg et al. 2013). In our study, 30% of the MFS patients had undergone vitrectomy. Still, they had significantly higher straylight value than the control group, of whom none had undergone previous vitrectomy (Mura et al. 2011).In addition, it has been shown that increased axial length may affect straylight; a feature known to be highly prevalent in patients with MFS (Christaras et al. 2020). We could not find any studies investigating whether a flatter cornea might affect straylight. However, we identified one study reporting increased straylight in patients with steeper corneal curvature without corneal scars or cloudiness (Jinabhai et al. 2012). Regarding refraction, a subtle increase in straylight values has been reported when correction with high minus power was used (Gaurisankar et al. 2019). However, our analysis still revealed a highly significant difference between the groups, both when adjusting for cataract, spherical equivalent, iris colour axial length and corneal curvature, and when performing the analyses after excluding all patients with cataract. We also included lens densitometry measurements from Scheimpflug imaging as an effect variable to account for any low-level cloudiness of the lens, but we still found a higher straylight value in the patients with MFS.

In the MFS group, only 16 phakic eyes () had EL at the study examination, as most eyes with EL had previously undergone lens surgery. One could speculate that a tilt or displacement of the lens would induce an adverse effect of the light scattering and thus explain the increased straylight. We found no such relation among the patients with MFS, although it has to be emphasized that the study included only a few phakic eyes with EL. Thus, our findings should be interpreted with caution.

This study investigated photophobia and glare in patients with MFS, using both a patient-reported measure and a more objective measure. If these methods adequately capture the relevant symptoms, one would expect the measurements to be correlated. The analysis of correlation between the straylight value and the statements revealed a significant moderate positive association. The highest correlation was seen regarding the statements about halos and stars around light sources. This is comparable with symptoms normally related to glare problems (van den Berg et al. 2013).

Our study revealed that opacities in the ocular media (cataract), degree of myopia, axial length and corneal curvature were not significantly associated with the degree of photophobia and disability glare in patients with MFS. Further studies are needed to investigate other ocular explanations for the increased straylight and photophobia symptoms in these patients. Previous studies applying C-Quant measurements have reported an association between the degree of straylight and age, iris colour, axial length, spherical equivalent and cataract (van den Berg 1995; Rozema et al. 2010; Nischler et al. 2013; van den Berg et al. 2013; Labuz et al. 2015). However, we have not found any publications on EL and straylight. Patients with MFS are also known to have thinner sclera which might have contributed to the increased straylight value found in the MFS group (Maumenee 1981; Gehle et al. 2017). Several studies have also suggested that photophobia may be caused by impairments of the visual pathways. The intrinsically photosensitive retinal ganglion cells, also known as melanopsin cells, have been studied specifically, since they work as a transducer and transform bright light into painful sensations (Hattar et al. 2002). Thus, further studies are needed to elucidate the reason for photophobia in Marfan syndrome.

A clinical implication from the present study is that MFS patients should be asked about symptoms related to photophobia and glare, as they may not spontaneously report them. If not present, they need to be informed that such symptoms may appear and give guidance regarding how to handle them. This includes information about what type of filter glasses that could help to decrease symptoms related to photophobia, as well as possibly guidance about education and choice of occupation.

The strengths of the present study are that all patients underwent a comprehensive investigation of all organ systems related to MFS, and all included patients had verified MFS according to the Ghent-2 criteria. Furthermore, an age- and sex-matched control group was included. The study applied both a validated computerized instrument for measuring disability glare and a patient-reported measure of photophobia. Nevertheless, the limitations of the study include problems with missing data because of health issues and low vision which may bias the results. However, the structural changes in the eyes with missing data in the straylight analysis were quite comparable to the included cases. Further, we had a relatively low number of participants. However, since MFS is a rare disease, it is difficult to reach a sufficiently large sample size for subgroup analysis such as comparison between patients with and without EL. Furthermore, a validated questionnaire on photophobia and glare would have been preferable.

In conclusion, the present study revealed increased photophobia and a higher straylight value in patients with MFS even after adjustments for cataract and other features known to be prevalent in these patients. Awareness of this symptom in patients with MFS is important for providing information and advice to these patients. In the future, more research on this topic in MFS is needed, particularly to elucidate the prevalence and reasons for this photophobia and glare.

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Competing interests:

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