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Pupillary response in adults with Marfan syndrome and its effect on straylight

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ABSTRACT.

Purpose: **The main objective of this study was to examine the pupillary response in patients with Marfan syndrome (MFS) and secondarily to determine whether changes in the pupillary response are associated with the increased disability glare previously shown in the same patient population.**

Methods: **This study included 60 eyes of 34 patients with MFS diagnosed in accordance with the Ghent-2 criteria and 81 eyes of 44 controls. Pupillary response was measured with a pupillograph and disability glare with a straylight meter.**

Results: **The patients with MFS had a significantly smaller maximum pupil size than the control group, 4.87 (4.50–5.23) mm versus 5.58 (5.25–5.90) mm ($p = 0.01$). In addition, they exhibited slower contraction velocities ($p = 0.03$) and longer re-dilation times ($p = 0.01$) compared with the control group. The mean straylight value was higher in patients with MFS than controls, even when including pupillary parameters together with lens surgery, cataract, iris colour, axial length and corneal curvature as possible explanatory variables in the analysis. However, when including data from both groups, a significant negative correlation was seen between maximum pupillary diameter and straylight value ($p = 0.01$). The other pupillary parameters did not correlate with straylight.**

Conclusion: **Patients with MFS had a smaller maximum pupil diameter, slower pupillary contraction and longer re-dilation time than the controls. Despite the correlation between pupil size and straylight value, the pupillary response demonstrated in MFS eyes could not explain the increased straylight in these patients.**

Key words: glare – Marfan syndrome – ocular straylight – pupil size – pupillary response

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Introduction

Marfan syndrome (MFS) is a connective tissue disorder affecting multiple organs, including the eyes, the skeletal system, the cardiovascular system and dura mater (De Paepe et al. 1996). A presumed disease giving variant in *FBN1* is thought to cause MFS (Dietz 2001). However, *FBN1* variants are also found in other conditions. Therefore, a list of criteria

is used for diagnosis (Loeys et al. 2010).

Several parts of the eye are typically affected in MFS. Ocular features included in the Ghent-2 diagnostic criteria from 2010 are ectopia lentis (EL) and myopia over three dioptres (D) (Loeys et al. 2010). Other typical characteristics in MFS eyes are increased axial length, flattened corneal curvature, early cataract and increased risk of retinal detachment (De Paepe et al. 1996; Konradsen et al. 2012; Konradsen & Zetterstrom 2013; Drolsum et al. 2015; Sandvik et al. 2019). Studies have demonstrated poorly developed iris sphincter and dilator muscles, contributing to a miotic pupil that is difficult to dilate (Maumenee 1981; Wheatley et al. 1995). We have only found one previous report specifically investigating the pupillary response in patients with MFS. That study found a slower average dilation velocity in adults and a slower average and maximum constriction velocity in children compared with a matched control group (Shah et al. 2018).

In a recent paper, we demonstrated more disability glare in patients with MFS compared with controls, 1.29 log (s) versus 1.01 log(s) respectively ($p < 0.001$) (Sandvik et al. 2021). This difference was statistically significant even after adjusting for cataract, spherical equivalent, iris colour, axial length and corneal curvature. Furthermore, subgroup analysis revealed no obvious association with EL. Thus, the underlying cause of the increased disability glare in MFS remains unknown. One could speculate that patients with MFS experience visual disturbances with glare due to an abnormal pupillary response caused by structural changes in the iris.

The primary aim of the present study was to investigate the pupillary response in adult patients with MFS compared with a control group. The secondary aim was to elucidate whether any changes in the pupillary response are associated with the increased disability glare experienced by these patients.

Methods

Subjects and ethical considerations

The present work was performed as part of a multi-disciplinary study where participants underwent an examination of all organ systems related to MFS. Patients with presumed MFS were recruited for a cross sectional study through TRS National Resource Centre for Rare Disorders, the Journal of the National Association for MFS and the Department of Cardiothoracic Surgery at Oslo University Hospital (Vanem et al. 2018). Of 60 patients investigated, 44 adults fulfilled the Ghent-2 criteria. The control group consisted of 44 age- and sex-matched participants (88 eyes) who were recruited from the staff at the Department of Ophthalmology at Oslo University Hospital and the local community. The patients who were not able to perform the pupillary measurements or cases who did not reach the accepted quality parameter, as determined by the software of the pupillograph, were excluded. Consequently, 28 eyes (both eyes in ten persons and one eye in eight persons) in the MFS group and seven eyes (one eye in seven persons) in the control group were excluded. Thus, 34 patients with MFS (60 eyes) and 44 controls (81 eyes) were included in this study. The MFS patients were examined in 2014 and 2015 and the control group in 2017. The eye examinations were similar for the two groups. None of the participants in the two groups had pseudoexfoliation syndrome, diabetes mellitus or used systemic alpha-agonists. One participant in the MFS group had glaucoma, but the pupillary measurement was missing in this patient; hence, none of the included participants were treated with topical glaucoma medications. The number of eyes in the straylight measurements in this paper were 45 MFS eyes and 78 control eyes, which is different from the previous publication (Sandvik et al. 2021) as some were excluded because of poor quality of the pupillary measurements.

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

Eye examination

The pupillary response was examined before administration of any eye drops and was performed with Compact Integrated Pupillograph (CIP) version 13.00 (AMTech Pupilknowlogy GmbH, Dossenheim, Germany). Prior to the measurements, patients underwent 5 min of dark adaptation. The pupillary light reflex (PLR) mode was used with a recording time of 2 seconds and a sampling rate of 250 Hz. The optical stimulus was presented by a yellow LED (585 nm) with an intensity of 784 cd/m^2 for 200 ms. Two infrared (880 nm) lights illuminated the test eye. Each eye was measured three times with 10–15 seconds in between in order to allow the pupil to re-dilate between the measurements. Recordings with artefacts were deleted manually, and the mean value was calculated (Fig. 1). Data were transferred to LoOK! software (AMTech Pupilknowlogy GmbH, Dossenheim, Germany) and analysed. The software LoOK! automatically calculates the pupillary parameters. Before the stimulus, the mean value of the initial dark adapted pupil diameter is calculated. Then, the stimulus is presented in 200 ms, and latency is defined as the time from start of the stimulus to the first sign of contraction. Further, the amplitude between maximum and minimum pupil size is calculated. In this interval, the contraction velocity is assumed to be linear. A straight line is fitted between the initial diameter and the minimum diameter, and its slope represents the contraction velocity in mm/s. A measurement was excluded if some part of the recording was deficient or if the measurement did not fulfil the quality evaluation of the software. Some measurements had to be excluded because the participants were not able to sit in the correct position or had to blink during the examination.

Disability glare was examined with C-Quant straylight meter (Oculus Optikgeräte GmbH, Wetzlar, Germany) before pupillary dilation, which provides a straylight value, log(s). An expected standard deviation (Esd) < 0.08 and a quality parameter $Q > 1$ was considered acceptable reliability. Best corrected near visual acuity was measured and used during the examination. Straylight was quantified by means of a straylight parameter s and is given logarithmically as log(s).

Corneal curvatures were measured with Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany),

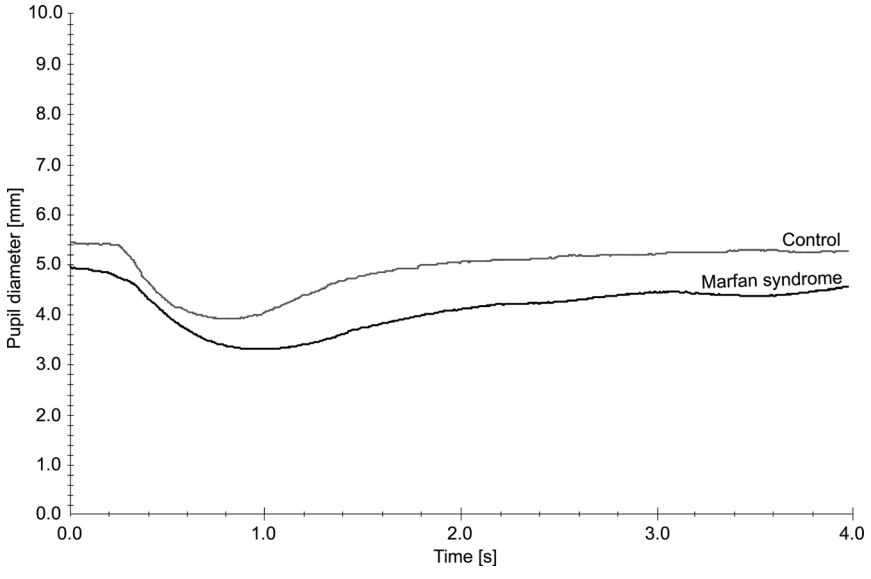

Fig. 1. Pupillogram of a typical measurement of an MFS eye and a control eye. The lines are the mean value of three recordings. The MFS eye had a smaller maximum pupil size, a slower contraction velocity and a longer re-dilation time compared with the control eye.

and axial length was measured with NIDEK Biometer AL-scan (NIDEK Co., Ltd, Gamagori, Japan). Iris colour was noted as light blue, blue-grey, brown-hazel or brown (Nischler et al. 2013).

After the pupillography and straylight measurements, all participants underwent a full ophthalmologic slit-lamp examination, and the status of the lens was examined 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.

Statistical analysis

Descriptive statistics are presented as mean ± standard deviation or frequency (%). Linear mixed-effect models were used to estimate the mean value of each parameter in the pupillary measurements and the mean log straylight value. The mixed model analysis of the difference in pupillary measurements included lens surgery and iris colour as fixed effects. The mixed model analysis of the difference in straylight value included pupillary response, cataract, lens surgery, iris colour, axial length and corneal curvature as fixed effects. All fixed effects were tested for multicollinearity. Due to the high multicollinearity between the pupillary parameters, only one of these could be included in each mixed model. Thus, we performed this analysis six times to test all the different pupillary parameters. As both eyes were included and the MFS cases were matched to the controls, random effects were included to take dependencies into account. Results from linear mixed model are presented as marginal means with 95% confidence interval.

The Pearson correlation method was used to analyse associations between pupillary response and the straylight value. The left eye was chosen for these analyses. Two sample *t*-*t*est was used to compare the ages, and mixed model was used to compare axial length and corneal curvature between the two groups. A chi-square test was used to compare proportions between the groups.

All the statistical analyses were conducted using Stata SE version 15. A *P* value less than 0.05 was considered statistically significant.

Results

Comparison between patients with MFS and controls

The two groups were successfully age- and sex-matched (Table 1). The MFS group had significantly longer axial length, flatter corneal curvature, more patients with cataract and a higher rate of previous lens surgery. All eyes with cataract had a mild degree of lens cloudiness without affecting the visual acuity and without indication for operation. As shown in Table 2, MFS pupils were significantly smaller at their maximum size than control pupils (4.87 (4.50–5.23) mm versus 5.58 (5.26–5.90) mm; p = 0.01). In addition, MFS pupils exhibited slower contraction velocities (p = 0.03) and longer re-dilation times (p = 0.01) relative to control eyes. There were no significant differences between the two groups in the other pupillary parameters.

Pupillary response and straylight

Within the MFS group, no significant correlations between the various pupillary parameters and the straylight values were identified (Table 3). When including patients from both groups, a negative correlation was revealed

Table 1. Characteristics of the Marfan syndrome (MFS) and the control groups (*n* = number of eyes)

	MFS (*n* = 60)	Control (*n* = 81)	p Value
Age (years)	50.3 ± 12.2 (32–80)	49.9 ± 11.6 (31–82)	0.89
Sex (female/male)	27 (79%)/7	33 (75%)/11	0.65
Axial length (mm)	25.3 ± 9.5 (21.0–38.5)	23.9 ± 3.1 (21.9–27.6)	0.02
Corneal curvature (D)	41.5 ± 4.6 (38.5–45.9)	43.4 ± 3.8 (40.9–47.8)	<0.001
Straylight value (log(s))	1.28 ± 0.6 (0.53–1.97)	1.03 ± 0.5 (0.65–1.78)	<0.001
Iris colour[a]			
Light blue	22 (37%)	35 (43%)	
Blue-grey	19 (32%)	28 (35%)	
Green-hazel	6 (10%)	10 (12%)	
Brown	2 (3%)	8 (10%)	
Lens status			
Phakic – with cataract	11 (18%)	1 (1%)	<0.001
Lens surgery	24 (40%)	5 (6%)	<0.001

Results are presented as mean ± standard deviation (range) or *n* (%).
D = dioptre.
[a] Iris colour not noted in 11 eyes.

Table 2. Comparison of pupillary response between the MFS group and the control group (n = number of eyes)

Pupillary parameters	MFS (n = 60)	Control (n = 81)	p Value
Maximum diameter (mm)	4.87 (4.50–5.23)	5.58 (5.26–5.90)	0.01
Latency (seconds)	0.26 (0.25–0.26)	0.26 (0.25–0.26)	0.83
Amplitude (mm)	1.56 (1.42–1.69)	1.66 (1.53–1.79)	0.34
Duration (seconds)	0.62 (0.58–0.65)	0.58 (0.58–0.61)	0.08
Contraction velocity (mm/s)	4.24 (3.96–4.52)	4.73 (4.44–5.02)	0.03
1/3 re-dilation time (seconds)	1.42 (1.34–1.49)	1.31 (1.26–1.36)	0.01

Results are presented as marginal mean (95% confidence interval).
Lens surgery and iris colour were included as a fixed effect.
1/3 re-dilation time = time from the minimum diameter until 1/3 of the amplitude is reached, Amplitude = difference between the initial pupil diameter and the minimum diameter, Contraction velocity = speed of pupil contraction, Duration = latency until minimum pupil diameter, Latency = time from stimulus onset until the reaction onset, Maximum diameter = maximum pupil size at the beginning of the measurement, MFS = Marfan syndrome.

Table 3. Correlation between pupillary response and straylight value within the MFS group and when both groups are included. (n = persons)

	Only MFS group (n = 23)		All patients in both groups (n = 61)	
Pupillary parameters	Correlation R Straylight value	p Value	Correlation R Straylight value	p Value
Maximum diameter (mm)	−0.12	0.57	−0.23	0.01
Latency (seconds)	−0.29	0.17	0.06	0.66
Amplitude (mm)	−0.07	0.75	−0.08	0.55
Duration (seconds)	−0.02	0.94	0.15	0.24
Contraction velocity (mm/s)	0.06	0.79	−0.17	0.18
1/3 re-dilation time (seconds)	−0.06	0.78	0.13	0.30

Missing values (n = 11) and (n = 17) are related to straylight value.
1/3 re-dilation time = time from the minimum diameter until 1/3 of the amplitude is reached, Amplitude = difference between the initial pupil diameter and the minimum diameter, Contraction velocity = speed of pupil contraction, Duration = latency until minimum pupil diameter, Latency = time from stimulus onset until the reaction onset, Maximum diameter = maximum pupil size at the beginning of the measurement.

between maximum pupil diameter and the straylight value (p = 0.01; Fig. 2). No significant correlations were detected concerning the other pupillary parameters.

Result from linear mixed model analysis comparing straylight between the groups, adjusted for maximum pupil size, cataract, lens surgery, iris colour, axial length and corneal curvature still revealed a significantly higher straylight value in patients with MFS compared with the controls, 1.27 (1.17–1.36) log(s) versus 1.02 (0.97–1.08) log (s) respectively (p < 0.001). The same mixed model analyses were performed for the other five pupillary parameters with similar results (p ≤ 0.001).

Excluded eyes

We performed additional analyses related to the excluded eyes with missing values regarding pupillary response (n = 28). The straylight values were not significantly different between excluded and included eyes.

Discussion

In the present study, we investigated the pupillary response in patients with MFS and revealed that their pupils react differently than age- and sex-matched controls. Patients with MFS had smaller maximum pupil size and a slower contraction velocity in addition to a longer re-dilation time compared with controls. We have previously shown that patients with MFS experience more disability glare – not explained by the increased frequency of cataract and EL (Sandvik et al. 2021). The results of the present study indicate that small pupil size is associated with increased straylight when both groups were included in the analysis. However, within the MFS group, we found no correlation between increased straylight and the pupillary changes.

In the literature, reports describe miotic and 'poorly dilating' pupils in MFS (Maumenee 1981; Wheatley et al. 1995). However, we have only found one study measuring the pupillary response (Shah et al. 2018), in which adults and children with MFS were compared with a matched control group. That study reported a significantly slower dilation velocity in adult patients with MFS and a difference in contraction velocity in the children. In the present study, we showed both a slower contraction velocity and a longer re-dilation time in an adult population. In contrast, Shah et al. found that the difference in pupil size and contraction velocity had a non-significant tendency to be smaller and slower in the adult MFS group. One might speculate that their results did not reach significance due to the small sample size (11 patients, 22 eyes). Furthermore, they included both children and adults and used a different instrument than in our study, a hand-held NeurOptics PLR-2000 Pupillometer. In addition, in our study, the measurements were analysed for association with other ocular symptoms, and the lens status of the included patients was addressed, which is relevant because intraocular surgery can interfere with pupil size (Keuch & Bleckmann 2002; Kanellopoulos et al. 2015).

Knowledge about pupillary function in patients with MFS is important, especially when cataract surgery or surgery for EL is needed. In eyes with EL, the operation may be challenging due to weak or absent zonular support, and a poorly dilated pupil may further complicate the procedure, as pharmacological dilation also is reported to be affected (Maumenee 1981; Rosenthal & Venkateswaran 2016). This highlights the importance of detailed preoperative examinations, patient information and surgical planning, including tools that should be available to decrease the risk of complications (Goldman & Karp 2007).

The reason for the pupillary changes in MFS eyes is not known. One theory is related to the mutation in fibrillin-1. An abundance of fibrillin deposition

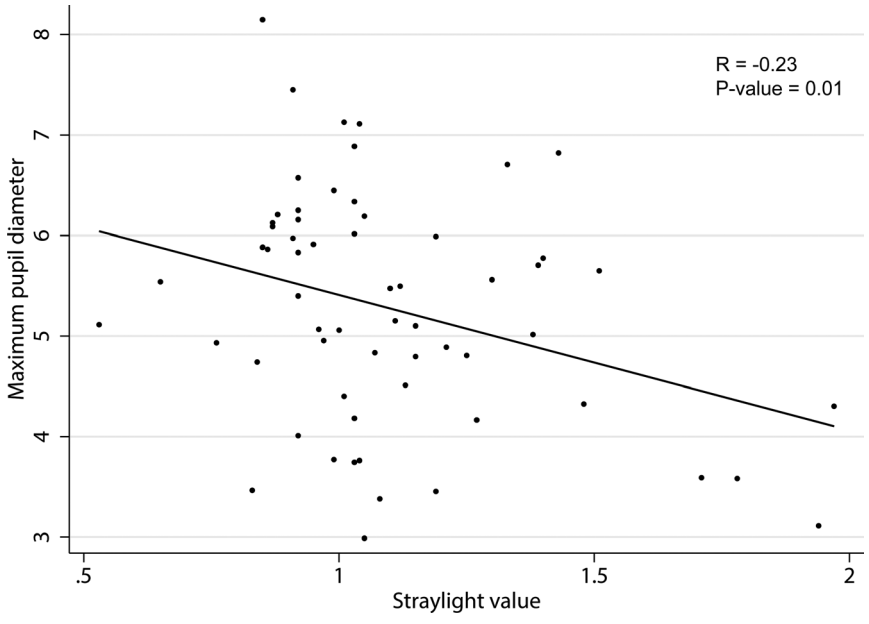

Fig. 2. Scatter plot of the correlation between maximum pupil diameter and straylight (participants from both groups included).

around the sphincter and dilator muscles has been described in healthy eyes (Wheatley et al. 1995). From studies of muscle biopsies of the vastus lateralis muscle, there is evidence that patients with MFS may suffer from myopathy due to defective fibrillin (Behan et al. 2003). Even though we are not aware of similar studies of the iris sphincter and dilator muscles, one may speculate that abnormal fibrillin in patients with MFS leads to changes in their pupillary responses.

Results from our recently published report demonstrated a higher straylight value in patients with MFS compared with controls (Sandvik et al. 2021). These group differences were present even after adjustments for ocular characteristics commonly seen in MFS eyes, such as cataract, myopia, increased axial length and flattened corneal curvature. Since the present study revealed a decreased pupillary response in patients with MFS, we hypothesized that pupillary response may correlate with the higher straylight values in these patients. Although we found that reduced maximum pupillary diameter correlated with a higher straylight value when participants from both groups were included, our results showed that the straylight values were still significantly more pronounced in the patients with MFS compared with the controls, even after adjusting for the pupillary measurements and other possible explanatory variables. For the other pupillary parameters, we found no correlations, neither within the MFS group, nor when including all participants. Other studies investigating pupil size and glare (independent of MFS) have shown that both small and large pupil sizes might be possible causes of glare; small pupils due to the translucency of the iris, while large pupils may expose peripheral lens opacities (Franssen et al. 2007; Gaurisankar et al. 2019). However, a study by Franssen et al. showed that the straylight value does not change much for pupil diameters between 2 and 8 mm (Franssen et al. 2007).

In our study, we included several features in the analysis that are commonly affected in MFS patients, such as axial length, corneal curvature and cataract. In theory, iris hypoplasia and absence of iris crypts may also explain the pupillary changes and increased straylight in MFS eyes (Dietz 2001; Nemet et al. 2006; Loeys et al. 2010). Therefore, further studies are needed to investigate this possible association.

A clinical implication of the present study is that an abnormal pupillary response must be assumed in patients with MFS. This is important knowledge when planning for cataract surgery in this patient group, which is often performed at an earlier age and for more challenging cases than usual as the lens might be dislocated. As part of the eye examination of patients with suspected MFS, a pupillary response measurement should be considered. Another clinical implication is that several of these patients may need information about what type of filter glasses that could help to decrease straylight. However, the reason(s) for increased disability glare in patients with MFS is still not fully understood; hence, more studies are needed to be able to consider more targeted treatments for this complaint.

The strengths of this study are that all patients with MFS were verified according to the Ghent-2 criteria, the study included an age- and sex-matched control group, and the pupillary parameters were objectively measured with a validated computerized instrument. Limitations include small sample size, due to the low prevalence of MFS, which reduces the statistical power of subanalysis. Further, the missing data related to the pupillary response measurements may introduce a potential source of bias. However, the participants failing the pupillary measurements did not have a significantly different straylight value compared to those with complete measurements.

In conclusion, our results indicate that patients with MFS have altered pupillary responses compared to the normal population. Furthermore, these patients experience disturbances related to straylight, which were present even if the changes in their pupillary response or other ocular features highly prevalent in MFS were included in the analysis. We recommend further studies designed to investigate the possible mechanism underlying disability glare in these patients.

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