Migraine, the heart and the brain

Koppen, H.

Chapter 5

Aortic root pathology in Marfan syndrome increases the risk of migraine with aura

H Koppen*, JC Vis*, DJ Gooiker, S Knudsen, BJ Bouma, JGP Tijssen, BAJM de Mol, BJM Mulder, MB Russell and MD Ferrari
* Shared first authors

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Abstract

Aim

To assess the lifetime prevalence of migraine in patients with Marfan syndrome (MFS) and to investigate a history of aortic root replacement (AR) as a possible risk factor.

Methods

In a multicentre study 123 MFS patients (n = 52 with AR, n = 71 without AR), 82 age and sex-matched controls and 51 patients with AR but without MFS, were interviewed using a semi-structured headache questionnaire. A multinomial logistic regression model was used to investigate risk factors for migraine with and without aura, adjusting for age and gender.

Results

Lifetime migraine prevalence was increased in female MFS patients (51%) compared to healthy female controls (29%), p = 0.017. In males lifetime migraine prevalence among MFS patients was only numerically increased. Lifetime prevalence of migraine with aura was increased among MFS patients compared to healthy controls both in males (19% vs.3%, p = 0.048) and females (30% vs. 14%, p = 0.049). A history of AR, independently from MFS, gender and age, increased the lifetime prevalence of migraine with aura (OR 3.1 [1.2–8.0]). In all but one patient migraine started before the AR.

Conclusions

The lifetime prevalence of migraine with aura, but not migraine without aura, is increased in patients with MFS. This association is driven by a history of AR. The replacement procedure itself is unlikely to be causally associated with migraine as in nearly all subjects, migraine started before the procedure. However this study adds to the evidence that underlying vessel wall pathology may be involved in migraine with aura.

Introduction

Migraine is a disabling neurovascular disorder with a lifetime prevalence of 13% in men and 33% in women (1). Approximately 70% of migraineurs suffer from migraine without aura and 30% from migraine with aura (1). The aetiology of migraine with and without aura are considered to be multifactorial due to a combination of genetic and environmental factors (2,3). Migraine with aura has been associated with cardiac shunts (4,5), non-shunting congenital heart defects (6,7), congenital abnormalities of the aorta (8), pulmonary arteriovenous malformation (9) and connective tissue disorders such as Ehlers–Danlos and Marfan syndrome (10,11). Marfan syndrome (MFS) is an autosomal-dominant multisystem disorder with specific cardiovascular, ocular and skeletal symptoms caused by a mutation in the fibrillin-1 gene (12). Aortic root dilatation or aortic dissection are considered major criteria for the diagnosis of MFS (13) and can be found in approximately half of patients (14). Aortic root replacement (AR) is a common procedure in severe MFS. In the present study we investigated (i) whether migraine prevalence is increased in patients with MFS, (ii) whether the effect is stronger in MFS patients who had severe aorta root dilatation requiring AR as a measure of disease severity, (iii) whether migraine prevalence is increased in non-MFS patients who underwent AR.

Materials and methods

Patients and procedures

MFS patients were recruited from two sites. MFS diagnosis on both sites was made according to the Ghent nosology (13). Danish recruitment took place in 2000 among members of the Danish Marfan patients' organisation (Landsforeningen of Marfan's syndrome) with re-interviewing in 2009 to register the specific history of AR.

The second site was the cardiology outpatient clinic of the Academic Medical Centre in 2008 (Amsterdam, the Netherlands). All eligible MFS patients were invited to participate. History of aortic root pathology was obtained from the database of the cardiology outpatient clinic. When AR had been performed, the indication was registered, which could either be prophylactic because of progressive aortic root dilatation, or acute following acute type-A aortic dissection. Two types of AR could have been performed and were registered, a Bentall procedure or a valve-sparing AR (David procedure).

All control subjects were recruited among acquaintances of Dutch MFS patients, specifically excluding family members. Patients were asked to supply the name of an acquaintance in the same age range and of the same gender as the patient who could serve as a control, before specifying the study goal. By this means, specific selection according to headache history of controls and patients was minimised.

To investigate the specific contribution of AR, non-MFS patients with a history of AR were recruited among patients attending the cardiothoracic surgery outpatient clinic of the Academic Medical Centre in 2008 (Amsterdam, the Netherlands). Indications for AR in this group were heterogeneous, ranging from aortic root or aortic ascendens dilatation with concomitant bicuspid aortic valve to aortic coarctation, aortic valve stenosis, severe aortic regurgitation, or systemic hypertension.

Subjects were asked to participate in a general health interview in order to reduce selection bias towards headache sufferers. The study was conducted in accordance with the revised Declaration of Helsinki (1998) and in agreement with the guidelines of the Danish and AMC Amsterdam ethics committees.

Migraine diagnosis

Danish MFS patients returned a questionnaire and then participated in a semi-structured telephone interview (10), migraine diagnosis was made according to ICHD-1 criteria (15). The Dutch participants (Marfan patients, non-Marfan patients with AR and controls) were interviewed in two stages. First three screening questions were asked. Screen positive for migraine headache was defined as those who had at least five moderate or severe headaches (excluding those due to hangover or sinus infection), or the participant was previously diagnosed with migraine by a physician. This first step screener was adapted from the GEM study and has a high sensitivity but a moderate specificity (1). Those fulfilling these screen-positive criteria proceeded in the same contact with a semi-structured telephone interview that focused on signs and symptoms of migraine headache and aura as outlined in ICHD-II (16). Those who screened negative did not proceed to the second stage of the interview, and were classified as having no migraine. An experienced headache neurologist, who was blinded to a subject's medical files and diagnoses, evaluated all the recorded individual interview results and made the migraine diagnosis, resulting in lifetime prevalence of migraine. No specific migraine diagnostic tool was used. A high lifetime attack frequency was defined as having had 4 or more attacks per months any time during life.

In one-third of initially screened positive subjects, final diagnosis was no migraine. These subjects were diagnosed with cluster headache, tension-type headache, and medication overuse headache.

Statistical analyses

Descriptive statistics were used to describe demographic and migraine characteristics. Comparisons between groups were analysed by a Student's t-test for continuous variables and the chi-square test for nominal variables. Multinomial logistic regression analysis was used to determine risk factors for migraine. Migraine with aura, migraine without aura and no migraine were used as dependent, no migraine was set as reference. As independent variables MFS, AR and gender were used, adjusting for age. P-values <0.05 were considered statistically significant. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL).

Results

Table 1. Demographic characteristics

	MFS N = 123	Healthy controls N = 82	Non-MFS with AR N = 51
Age, mean (SD)	42 (14)	43 (15)	53 (15)[a]
Male gender (%)	53 (43)	31 (38)	39 (77)[a]
Aortic root replacement (%)	52 (42)	0 (0)	51 (100)
Mean age at AR (SD)	30 (12), n = 52	Na	51 (15)[a]

AR: aortic root replacement; MFS: Marfan syndrome; Non-MFS with AR: non-Marfan syndrome with aortic root replacement; na: not applicable. Comparisons: Marfan syndrome vs. healthy controls and non MFS with AR vs. controls. Mean age at AR comparison Marfan syndrome vs. non MFS with AR.
[a] $p < 0.001$.

Table 2. Lifetime migraine prevalence for different diagnostic groups

	MFS		Healthy controls		Non-MFS with AR	
	Male	Female	Male	Female	Male	Female
	N = 53	N = 70	N = 31	N = 51	N = 39	N = 12
Migraine (%)	14 (26)	36 (51)[a]	6 (19)	15 (29)	7 (18)	6 (50)
Migraine without aura (%)	4 (8)	15 (21)	5 (16)	8 (16)	4 (10)	2 (17)
Migraine with aura (%)	10 (19)[a]	21 (30)[a]	1 (3)	7 (14)	4 (10)	4 (33)

MFS: Marfan syndrome; non-MFS with AR: non-Marfan syndrome with aortic root replacement. Comparisons: Marfan syndrome males vs. healthy male controls. Same comparisons for females separately. Comparison non-MFS with AR to controls, also stratified for gender.
Chi-square. [a] $p < 0.05$.

Table 3. Risk factors for migraine

Variables	Migraine without aura OR (95% CI)	*p*-value	Migraine with aura OR (95% CI)	*p*-value	No migraine
Aortic root replacement (n = 103)	2.8 (0.9–8.5)	0.07	3.1 (1.2–8.0)	0.02	1.0 (referent)
Marfan syndrome (n = 123)	2.5 (0.7–8.8)	0.2	2.5 (0.9–7.1)	0.08	1.0 (referent)
Female gender (n = 133)	4.7 (1.7–13.3)	0.003	3.6 (1.6–8.2)	0.03	1.0 (referent)

The predictors for migraine without aura and migraine with aura, adjusted for age using a multinomial logistic regression model using aortic root replacement, Marfan syndrome and gender as independent variables. No migraine was set as referent.
OR: odds ratio, 95% CI: 95% confidence interval.

A total of 117 Dutch MFS patients were invited to participate in a general health interview and 47 MFS patients in Copenhagen were re-invited to participate in an interview on AR. A total of 123 of 164 invited MFS patients participated (response rate 75%, n = 33 Danish, n = 90 Dutch). A total of 60 non-MFS patients with AR were invited and of these 51 participated (response rate 85%). Eighty-two controls were provided by MFS patients and all 82 controls participated.
The demographic characteristics of the study population are summarised in Table 1. MFS patients with AR were slightly older than MFS patients without AR. Age when AR was performed was lower in MFS patients when compared to non-MFS patients.

Lifetime migraine prevalence was increased in female MFS patients (51%) compared to healthy female controls (29%), p = 0.017 (Table 2). In males lifetime migraine prevalence was only numerically increased. Lifetime migraine with aura prevalence was increased among MFS patients compared to healthy controls both in males (19% vs. 3%, p = 0.048) and females (30% vs. 14%, p = 0.049). Migraine without aura prevalence was not increased in Marfan patients. In non-MFS patients with AR, migraine prevalence compared to healthy controls was not significantly increased.

Table 4. Characteristics of migraineurs among groups, stratified for aortic root surgery

	Aortic root surgery		No aortic root surgery	
Variables	MFS (*n* = 27)	Non-MFS (n = 13)	MFS (*n* = 23)	Controls (*n* = 21)
Mean age at onset migraine (SD)	20 (11)	18 (17)	17 (6)	21 (12)
Mean age at onset migraine with aura (SD)	19 (10)	19 (18)	16 (5)	18 (5)
Visual aura duration, minutes (SD)	24 (8)	52 (46)	63 (105)	33 (22)
Lifetime high attack frequency (%)	8 (29)	4 (31)	11 (48)	10 (51)

MFS: Marfan syndrome; non-MFS: non-Marfan syndrome with aortic root replacement; SD: standard deviation. Values are presented as means (SD). Lifetime high attack frequency > 3 attacks/ month.

To analyze the effect of AR in MFS patients on the prevalence of different migraine types, and to be able to make necessary adjustments for age and gender, a multinomial logistic regression model was used. As expected female gender was a risk factor for both migraine with and without aura (Table 3). AR was a risk factor for migraine with aura (OR 3.1 [1.2–8.0]) but not for migraine without aura. Independent from AR, MFS was not significantly associated with migraine with aura.

As AR was the driver in the increased prevalence of migraine with aura, Table 4 shows migraine characteristics between the study groups stratified for AR. None of these migraine characteristics differed. In all but one of the MFS patients with migraine, onset of migraine was before AR. MFS patients without AR but with dilatation not yet requiring AR had no increased risk for migraine with aura.

Of only 41/123 (33%) of MFS patients the presence or absence of dural ectasias was known by spinal imaging. Migraine with aura was found in 24% of patients with dural ectasias compared to 13% of those without dural ectasias (OR 2.2 [0.2–21.1]).

Discussion

In the present, largest ever, study on the association between migraine and MFS patients we confirmed earlier reports from two smaller cohorts (10,11) that MFS is associated with an increased lifetime migraine prevalence both compared to contemporary and historical controls (1,17). Thanks to the large number of participants, we could in addition determine that MFS only increased the risk of migraine with aura and not of migraine without aura. Moreover, we showed that aorta root pathology requiring AR was, independently from MFS, associated with an increased risk of migraine with aura, whereas MFS, independently from AR, was not significantly associated with migraine with aura. History of an AR thus was the main driver in the increased prevalence of migraine with aura. The underlying mechanism for this association is unknown but seems to point at systemic vessel wall pathology. Further research is warranted to unveil potential mechanisms.

There is increasing evidence that migraine is linked with impaired systemic endovascular function. Migraine has been associated with diseases considered to be related to extracellular matrix disorder like cervical artery dissection (18,19). The activity of elastases, enzymes capable of degrading elastic fibres and regulating enzymes of the extracellular matrix, has been associated with migraine with aura. A higher level of extracellular matrix degradation can explain both dissection as well as

atherosclerotic lesions (20). MFS is caused by mutations in the gene encoding for the extracellular matrix protein fibrillin-1. Contrary to diseases with vascular dilatation, recently it was found that the aortic rigidity measured by aortic pulse wave velocity in migraine is increased (21), whereas it has also been shown that compliance of brachial and femoral artery were decreased in migraineurs compared with controls (22).

A possible effect of these abnormalities found in the systemic blood vessels is a reaction from the endothelial cells, which secrete vasoactive mediators like vasodilator nitric oxide and vasoconstrictor endothelin-1. Several studies have found increased levels of these mediators to be present in migraineurs. These mediators are in turn thought to be able to produce cortical spreading depression. Another possibility is the presence of micro-emboli in the affected aortic root, which can act as a trigger for cortical spreading depression and was recently shown by Nozari et al. in mice (23). The use of specific vasoactive drugs in MFS patients with a dilating aortic root should also be considered, but was not investigated in this study. However most commonly used medications in MFS probably have a prophylactic rather than a migraine enhancing effect.

In our subjects the AR operation itself was not associated with the presence of migraine, as in all but one subject, migraine started many years before the operation. Surgical repair of the dilated aortic root/ ascending aorta for MFS patients to prevent a dissection, is usually performed at a threshold of an external aortic diameter of 50 mm (24). It is feasible to think that thus the dilatation would be associated with the increased migraine prevalence, however in MFS patients without AR but with dilatation not yet requiring operation no increased prevalence of migraine with aura was found. Possibly this non-operated MFS group is more benign and displays a different vascular phenotype.

Previously, one of us hypothesised that the dural ectasias frequently found in MFS could be an explanation for the increased headache prevalence (10). However, in the 42 patients in whom results of spinal imaging were known, we failed to find an association between migraine with aura and dural ectasias.

Strengths and limitations

As Marfan prevalence is low, numbers of migraineurs in the study are small, especially after gender stratification. The use of a telephone semi-structured interview aids diagnostic accuracy, whereas the study by Vis et al. (11) investigating partly the same

MFS patients only used filled in questionnaires by post, introducing possible diagnostic inaccuracy and response bias. For the Dutch study sample, a specially trained student who performed the telephone interviews was blinded for AR status (but not for MFS diagnosis); however the final migraine diagnosis was made by a headache neurologist blinded for all clinical characteristics. Migraine with aura prevalence could have been slightly underestimated, as the interview was only continued after the first screening step if participants had suffered at least five headache attacks. According to the ICHD-II criteria, for migraine without aura five attacks are needed, but only two attacks are necessary to fulfil migraine with aura criteria (16). Both MFS patients and aortic root patients without MFS were identified using hospital-based databases, whereas controls were not hospital based. Controls were selected by the Marfan patients, which could have introduced selection bias. This might have caused some disparity for unknown factors. If migraine activity altered due to the aortic root operation, this could not be investigated by this study, but a prospective study answering this question is highly interesting.

Aorta root pathology requiring AR was found to be a risk factor for migraine with aura. MFS independent from aortic root operation was no risk factor for migraine with aura. This study adds to the evidence that underlying vessel wall pathology might play a role in migraine with aura.

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