The diagnostic value of the facial features of Marfan syndrome

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Abstract

Purpose We examined the prevalence of known facial features of Marfan syndrome (MFS)—dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, and down-slanting palpebral fissures—and the diagnostic utility (sensitivity, specificity, accuracy, predictive values, and likelihood ratios) of using them for screening and diagnosis.

Methods Frontal and lateral photographs of 76 subjects with MFS (average age 18.3 years) and of 76 age- and gender-matched controls were obtained, randomized, and compiled into an online survey. Three physicians experienced with MFS rated each photograph for the presence of each feature and indicated whether each photograph triggered a suspicion for MFS. Eight non-expert orthopaedic surgeons reviewed a subset of those photographs and indicated if each triggered a suspicion for MFS. Half of the non-experts then received a brief diagnosis instructional sheet, and all non-experts were retested. The results were compared using Chi-square tests and *t*-tests with a significance level of $P < 0.05$.

Results Using facial features alone, the accuracy of experienced physicians in identifying individuals with MFS was 73%. Facial features had a 54% sensitivity, a 91% specificity, an 86% positive predictive value (PPV), a 67% negative predictive value (NPV), a 6.9% positive likelihood ratio (PLR), and a 50% negative likelihood ratio (NLR) for MFS. There was no significant difference in the

diagnostic accuracy between non-experts receiving and not receiving instructions.

Conclusions Facial features are more specific than sensitive for MFS. Therefore, the recognition of facial features of MFS can be used as an initial screening tool, but facial features do not have a high sensitivity for MFS.

Keywords Marfan syndrome · Diagnosis · Facial features

Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by inherited and de novo mutations in the fibrillin-1 gene; it has a prevalence of approximately 2–3 per 10,000 individuals [1, 2]. Early recognition and diagnosis is essential to avoid the life-threatening cardiovascular complications of MFS, including aortic dissection, congestive heart failure, and valvular disease [1].

Although genetic testing for fibrillin-1 mutations is available, the diagnosis of MFS still relies on the clinical evaluation of specific body systems, each of which has diagnostic criteria as outlined by the revised Ghent criteria [3, 4]. Among the minor criteria for the skeletal system are facial manifestations, i.e., dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, and down-slanting palpebral fissures. The reported incidence of these MFS-associated facial features varies widely [5–8], and although these features have been qualitatively described in several case series [5–8], to our knowledge, few studies have addressed them quantitatively [9–11]. This general lack of objective, well-defined criteria and simple methods of measurement make it difficult for physicians to reliably and objectively assess and report facial features in patients with MFS.

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Consequently, the importance of evaluating facial features cannot be overlooked [7, 8] because the recognition of commonly observed facial features could potentially be used as an outwardly evident and early screening tool for MFS.

Patients with MFS are often seen by orthopaedic surgeons because of the disease's many musculoskeletal manifestations, and, therefore, interventions to improve early recognition and referrals to appropriate specialists warrant attention [12]. Our goals were to determine: (1) the diagnostic utility (sensitivity, specificity, and accuracy) of using facial features to identify patients with MFS; (2) the variation in prevalence, if any, according to age; and (3) whether qualitative instructions could improve the accuracy of MFS diagnosis among orthopaedic surgeons inexperienced with MFS patients.

Participants and methods

This study was approved by our Institutional Review Board.

Participants

From April 2009 through January 2010, we recruited 76 patients from a genetics clinic, a paediatric orthopaedics clinic, and the Annual Conference on Marfan Syndrome and Related Disorders to form our subject group. The inclusion criterion was a diagnosis of MFS confirmed by a geneticist using the Ghent criteria [3]. The average age of the 36 male and 40 female subjects was 18.3 years (range 1.5–55).

We also recruited 76 age-matched (average 18 years; range 1.3–53) and gender-matched (36 males, 40 females) individuals without MFS from an orthopaedic surgery

clinic to serve as controls. These individuals had been referred for idiopathic scoliosis, developmental dysplasia of the hip, or traumatic fractures. Individuals with suspected or known genetic diseases, connective tissue disorders, or neurological disorders were excluded from the control population.

Procedures

We took frontal and lateral photographs of each subject and control (without glasses, if worn). These 304 photographs were randomized and compiled into an online survey. Three attending physicians (two geneticists and one paediatric orthopaedic surgeon at academic institutions) who were experienced within the field of genetics and each of whom had seen >100 patients with MFS during his career (expert physicians) (Table 1) reviewed those photographs. After being informed that the photographs represented individuals with and without MFS, they used a four-point Likert-type scale (strongly disagree, disagree, agree, and strongly agree) to rate each photograph in terms of the degree to which they thought each of the MFS-associated facial features was present [13, 14] and indicated whether each photograph triggered a suspicion for MFS (yes or no). For photographs with divergent opinions (MFS versus non-MFS), the majority (two of three) ruled. Based on these expert ratings, we determined the overall and age-specific prevalence of each facial feature, the diagnostic utility of using facial features for the screening and diagnosis of MFS, and the association of facial features with correctly identifying a patient with MFS.

A small subset of 80 randomly selected photographs (40 from 20 subjects and 40 from 20 controls) was then used to survey how well eight orthopaedic surgeons less experienced with individuals with MFS (non-expert physicians) were able to recognize MFS-associated facial features

Table 1 Physician training and level of experience with Marfan syndrome (MFS)

Training and experience	Experts (<i>n</i>)	Non-experts	
		Intervention group (<i>n</i>)	Non-intervention group (<i>n</i>)
Academic practice (<i>n</i>)	3	4	4
Highest training level (<i>n</i>)	Attending (3)	Chief resident (1) Fellow (2) Attending (1)	Chief resident (3) Fellow (1)
Highest no. of years working in genetics field	6–10 (1) >20 (2)	0	0
Highest no. of patients with MFS seen during career	>100 (3)	1–5 (2) 6–10 (1) 11–20 (1)	1–5 (1) 6–10 (1) 11–20 (2)
Highest no. of patients with MFS seen annually	50–100 (2) >100 (1)	<1 (4)	<1 (4)

(Table 1). To evaluate their baseline knowledge of the facial features, all eight non-expert physicians completed a pre-test of those photographs in which they were asked only whether they had a suspicion for MFS based on the photographs (yes or no); these physicians were also informed that the photographs were of individuals with and without MFS. To avoid having the question stems themselves prompt physicians about facial features (i.e., to avoid providing clues about the specific facial features for which they were to search), we did not ask the physicians to rate the degree of each facial feature. Then, to determine whether a brief instructional sheet could improve the accuracy of diagnosis, we randomly divided the non-expert physicians into two groups (four each) and gave to only one group (intervention group) a brief instructional sheet with an example and description of each facial feature; the second group served as a non-intervention control group. Both groups then completed a post-test that repeated the initial 80 photographs and included an additional 80 randomly selected photographs (40 from 20 subjects and 40 from 20 controls). The post-test asked the physicians to rate each photograph in terms of the degree to which they believed each of the facial features was present (strongly disagree, disagree, agree, and strongly agree), in addition to whether they had a suspicion for MFS (yes or no).

Statistical analysis

Statistical analysis was performed using Stata 10.0 (College Station, TX).

The expert physicians' Likert ratings for each facial characteristic were converted to a numeric scale (strongly disagree = 0, disagree = 1, agree = 2, and strongly agree = 3) and averaged. The average scores for each characteristic for subjects and controls were then compared and dichotomized to determine the presence (average score > 1) or absence (average score ≤ 1) of each characteristic. The prevalence of each facial characteristic was compared between subjects and controls and, among subjects, in terms of arbitrarily designated age groups (1–10 years, 11–20 years, and >20 years) and gender. Univariate logistic regression was used to determine the contribution of each facial characteristic to identifying a photograph as a patient with MFS, and multivariate logistic regression was used to determine the independent effect of the presence of each characteristic.

The diagnostic utility (sensitivity, specificity, accuracy, positive predictive value [PPV], and negative predictive value [NPV]) of each expert physician's assessment of photographs as a subject or control was determined. Because our subjects did not reflect the true prevalence of MFS (that is, our result was 50% vs. the reported 2–3 per 10,000 individuals [1, 2]), we also determined the positive

likelihood ratio (PLR) and negative likelihood ratio (NLR), which may be more valuable than the predictive values.

The diagnostic accuracy (a combination of the accuracy, sensitivity, specificity, PPV, NPV, PLR, and NLR) of the non-expert physicians in the intervention and non-intervention groups was compared, as were their scores on the pre- and post-tests.

Chi-square tests were used to compare proportions and *t*-tests were used to compare continuous variables. A significance level of $P < 0.05$ was used for all tests.

Results

Overall, each of the five facial features (dolicocephaly, enophthalmos, down-slanting palpebral fissures, malar hypoplasia, and retrognathia) was significantly more prevalent among subjects than controls (Table 2). Analysis showed that there were statistical differences according to age with regard to two facial features: down-slanting palpebral fissures ($P = 0.002$) and retrognathia ($P = 0.02$). The highest rate of prevalence overall was for retrognathia in the age group 1–10 years (94%). The age groups 1–10 years and >21 years each had three of the highest prevalence rates (one duplicate at 88%); the 11–20 years group had none of the highest prevalences. There was no difference in the prevalence of facial features among men versus women.

Using facial features alone, experienced physicians correctly discriminated between subjects (patients with MFS) and controls with an overall 72.6% accuracy rate (Table 3). Overall, facial features had a sensitivity of 53.9%, a specificity of 91.2%, a PPV of 85.8%, an NPV of 67.2%, a PLR of 6.9%, and an NLR of 50% for MFS. In other words, an individual with facial features of MFS has a 6.9 times higher odds of having the disease than a person who truly does not have the disease, and an individual without facial features of MFS has 0.73 times the likelihood of having the disease (27% less likely to have it) than someone who truly does have the disease.

The odds of correctly identifying a patient with MFS increased by 11.4 times in the presence of dolicocephaly (Table 4). Multivariate logistic regression revealed that dolicocephaly, enophthalmos, and retrognathia were all significant identifiers for the presence of MFS. In addition, the presence of more than one facial characteristic increased the odds of correctly identifying the presence of MFS. For each additional facial characteristic, the odds of having MFS more than doubled, and although our analysis of specific combinations of facial characteristics was limited by the size of our subject group, we found that the odds of having MFS increased by 9.9 times in the presence of both down-slanting palpebral fissures and malar hypoplasia.

Table 2 Prevalence of Marfan syndrome (MFS) associated facial features in subjects and controls overall, and in subjects by age and gender

Facial characteristic	Overall prevalence		Prevalence in subjects by age				Prevalence in subjects by gender		
	Subjects (n = 76)	Controls (n = 76)	P-value	0–10 years (n = 17)	11–20 years (n = 43)	>21 years (n = 16)	P-value	Female (n = 40)	Male (n = 36)
Dolicocephaly	60% (46)	12% (9)	<0.001	50% (8)	57% (25)	81% (13)	0.14	54% (21)	68% (25)
Enophthalmos	71% (54)	36% (27)	<0.001	81% (13)	68% (30)	69% (11)	0.6	69% (27)	73% (27)
Down-slanting palpebral fissures	58% (44)	17% (13)	<0.001	75% (12)	41% (18)	88% (14)	0.002	51% (20)	65% (24)
Malar hypoplasia	78% (59)	58% (44)	0.01	88% (14)	70% (31)	88% (14)	0.21	77% (30)	78% (29)
Retrognathia	63% (48)	38% (29)	0.002	94% (15)	57% (25)	50% (8)	0.02	59% (23)	68% (25)

Table 3 Diagnostic utility of Marfan syndrome (MFS) associated facial features in subjects, as rated by expert physicians

Category	Utility rating in subjects			
	0–10 years old	11–20 years old	>20 years old	Overall
Accuracy (%)	82.8	68.6	72.9	72.6
Sensitivity (%)	70.9	46.2	58.3	53.9
Specificity (%)	94.1	91.5	87.5	91.2
PPV (%)	91.9	85.5	80.6	85.8
NPV (%)	77.5	63.5	69.2	67.2
PLR	12.1	9.1	4.7	6.9
NLR	0.31	0.58	0.47	0.50

PPV positive predictive value, NPV negative predictive value, PLR positive likelihood ratio, NLR negative likelihood ratio

Non-expert physicians in the intervention and non-intervention groups performed comparably on the pre-test (Table 5) and after administration of the instructional sheet to the intervention group. Furthermore, within each group, there was no significant improvement in the percentage of correct diagnoses on the pre- and post-tests.

Discussion

Many studies of the clinical features of MFS have discussed facial features without clearly defining them. One review of the literature summarized the reported prevalence of dolicocephaly (65%), retrognathism (37%), and prognathism (30%) among adult patients with MFS [5]. In the same year, another review reported vastly different results: distinctive facies (3/25 patients, 12%), dolicocephaly (6/25 patients, 24%), and micrognathia (2/25 patients, 8%) [6]. Of note, the latter study also reported significantly higher prevalence of facial features in a subpopulation of 22 patients diagnosed with MFS before 3 months of age. A third study reported features of malar hypoplasia, micrognathia, and down-sloping palpebral fissures in 33/40 (83%) patients with MFS less than 16 years old [7]. More recently, a study evaluating 320 paediatric patients (<18 years old) with fibrillin-1 mutations reported characteristic facial features in 58% of patients overall and reported the following prevalences based on age: neonates (82%), <10 years old (52%), and 10 to <18 years old (55%) [8]. To our knowledge, ours is the first study to focus on the prevalence and diagnostic utility of using the specific facial features outlined in the Ghent criteria to identify individuals with MFS. In our study, all participants were evaluated by three experienced physicians who have worked extensively with patients with MFS. The inter-rater agreement of the three expert physicians was moderate (kappa = 0.45) [15].

Table 4 Odds ratios for the correct diagnosis of Marfan syndrome (MFS) based on individual facial features

Facial characteristic	Univariate logistic regression		Multivariate logistic regression	
	Odds ratio [95% confidence interval]	<i>P</i> -value	Odds ratio [95% confidence interval]	<i>P</i> -value
Dolicocephaly	11.4 [5.0, 26.3]	<0.001	7.1 [2.8, 17.1]	<0.001
Enophthalmos	4.4 [2.2, 8.8]	<0.001	2.4 [1.1, 5.5]	0.04
Down-slanting palpebral fissures	6.7 [3.1, 14.1]	<0.001	2.5 [0.97, 6.4]	0.06
Malar hypoplasia	2.5 [1.2, 5.1]	0.01	0.82 [0.33, 2.0]	0.67
Retrognathia	2.8 [1.4, 5.4]	0.002	2.6 [1.2, 6.0]	0.02
Presence of each additional facial characteristic	2.4 [1.8, 3.2]	<0.001	N/A	N/A
Presence of dolicephaly and enophthalmos	8.8 [1.1, 72.4]	0.04	N/A	N/A
Presence of down-slanting palpebral fissures and malar hypoplasia	9.9 [2.2, 44.6]	0.003	N/A	N/A

N/A Not applicable

Table 5 Analysis of responses for non-expert physicians

Category (no. of questions)	Intervention group ^a	Non-intervention group ^a	<i>P</i> -value
Pre-test (<i>n</i> = 40)			
Number of correct responses	26.20 ± 3.60	26.00 ± 5.40	0.94
Accuracy (%)	66.00 ± 9.00	65.00 ± 13.00	0.94
Sensitivity (%)	38.00 ± 22.00	4.00 ± 32.00	0.90
Specificity (%)	94.00 ± 5.00	90.00 ± 9.00	0.49
Post-test repeated items (<i>n</i> = 40)			
Number of correct responses	28.50 ± 3.50	27.80 ± 5.40	0.82
Accuracy (%)	71.00 ± 9.00	69.00 ± 14.00	0.82
Sensitivity (%)	51.00 ± 19.00	55.00 ± 31.00	0.84
Specificity (%)	91.00 ± 6.00	84.00 ± 8.00	0.18
Post-test new items (<i>n</i> = 40)			
Correct responses	28.8 ± 1.20	27.80 ± 3.80	0.63
Post-test all items			
Number of correct responses	57.20 ± 4.10	55.50 ± 8.30	0.72
Accuracy (%)	72.00 ± 5.00	69.00 ± 10.00	0.72
Sensitivity (%)	52.00 ± 14.00	52.00 ± 26.00	0.97
Specificity (%)	91.00 ± 6.00	86.00 ± 9.00	0.39

^a Values are given as mean ± standard deviation (SD)

Our study has shown that there is a higher prevalence of all facial features in those with MFS than in healthy controls. Other studies have compared facial features in patients with MFS to those in non-MFS populations, but the latter populations were comprised of patients referred for suspected MFS and with fibrillin-1 mutations [8, 16]. In the study by Rybczynski et al. [16], facial appearance was shown to have a sensitivity of 28%, a specificity of 99%, a PLR of 13.47 (95% confidence interval [CI] 4.65–40.75), and an NLR of 0.73 (95% CI 0.71–0.79). Based on the high likelihood ratio (>10), the authors concluded that facial appearance is a highly useful clinical criteria. Our study yielded similar results, but, importantly, we used a control population of individuals with no known genetic,

neurologic, or connective tissue disorders who had been recruited from a paediatric orthopaedic surgery clinic.

Our study includes all ages of patients with MFS, instead of focusing on children or adults, and examines differences in facial manifestations across age groups. Facial features have been reported to usually appear by the age of 3–4 years, but they can be striking at birth in severe presentations. In contrast, related characteristics such as scoliosis and pectus deformities often become more prominent during pubertal growth [7, 8]. We found that the prevalence of retrognathia was significantly higher in the youngest age group (0–10 years) compared with the other age groups and that down-slanting palpebral fissures were most prevalent in children aged 0–10 years and patients

≥ 21 years of age. The reason behind these age-dependent differences is unclear; it is possible that younger patients with a more severe MFS are driving the observed results.

We found no difference in the prevalence of facial features among men and women.

There is no clear consensus on the diagnostic utility of using facial features to identify MFS [1]. Our results are consistent with those from recent research that reported facial features have a low sensitivity, but high specificity, for MFS [16]. We have also shown that facial features may have more clinical utility among young patients with MFS (0–10 years) based on the higher accuracy, sensitivity, specificity, and PLR for this age group. Of particular interest, we found that, for each additional facial characteristic identified as being present, the odds of having MFS more than doubled.

Our study highlights the need to increase awareness of the facial features of MFS among non-experienced physicians who are likely to encounter in their practice patients with MFS: only one of the eight surveyed non-experienced physicians mentioned facial features as a criterion for diagnosing MFS. Although the brief instructional sheet did not appear to significantly improve correct diagnosis, physicians reported feeling more confident in recognizing each facial feature after having read through the sheet. In response to an open-ended question about baseline knowledge of the Ghent criteria, facial features were mentioned only by one physician. When asked more specifically about each facial characteristic, physicians were most familiar with dolicocephaly (63%) and down-slanting palpebral fissures (63%), and least familiar with enophthalmos (25%). Of note, while they were equally confident in recognizing down-slanting palpebral fissures (63%), they were less confident in recognizing dolicocephaly (50%). Physicians were least confident in recognizing malar hypoplasia (25%). At the end of the survey, physicians in the non-expert intervention group were then asked whether they felt more confident or not in recognizing each facial feature. Subjectively, most of those physicians felt more confident in recognizing dolicocephaly (75%), down-slanting palpebral (75%), malar hypoplasia (100%), enophthalmos (75%), and retrognathia (75%). Because the brief instructional sheet included only one example image and a few brief bullet points describing each facial feature, there may be several ways to improve this teaching aid, such as providing opportunities for physicians to interactively test themselves on identifying each facial feature with feedback and providing guidance on ways to clinically assess each feature.

This study is limited by the size of the study population. We were unable to analyze several combinations of facial features due to inadequate sample size. Although our study shows that for each additional facial characteristic

identified as being present, the odds of having MFS more than doubled, there remains a need for more objectivity in the use of facial features for diagnostic purposes. For example, is there a certain number or combination of facial features that yields $>90\%$ specificity? A future study with a more robust study population would be beneficial. Furthermore, while using photographs provided the flexibility needed for several physicians to evaluate the same patients, some features that require an appreciation of depth (malar hypoplasia, enophthalmos, retrognathia) may be more easily evaluated with a physical examination. A future study that allows for the evaluation of facial features during a physical examination would be valuable.

Conclusions

In summary, facial features are more specific than they are sensitive for the presence of Marfan Syndrome (MFS). Therefore, although facial features of MFS can be used to prioritize patients for referral, for a more comprehensive evaluation, they cannot be relied upon as the sole metric for initial screening. To increase the likelihood that referrals to appropriate specialists are made as soon as possible, we must increase the awareness of, and confidence in recognizing, facial features of MFS among physicians who are likely to encounter in their practices patients with MFS.

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