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Quantifying Health Status and Function in Marfan Syndrome

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ABSTRACT (132 words; max 150)

To evaluate quality of life and function in patients with Marfan syndrome, 230 were prospectively enrolled in this study and completed various portions of the Short Form 36 and study specific questionnaire (visual analog scale 1 to 10, comprising three separate questionnaires). The two greatest health concerns were cardiac (high in 70% of patients), followed by spine and generalized fatigue (both high, in 53%). The most severe reported pain involved the back: 105 (46%) rated pain as 6 to 10. Of 72 responding to work life, work hours were reduced because of treatment (59, 82%) or directly because of Marfan syndrome (29, 40%). Across all Short Form 36 domains, patients scored significantly lower than United States population norms ($p < 0.05$); physical health scores were considerably lower than mental health scores.

Key words: Marfan syndrome; Health; SF-36; Pain; Questionnaire

INTRODUCTION

Marfan syndrome (MFS) is a disorder that affects two to three of 10,000 people (1, 2) and is caused by mutations in the fibrillin-1 gene located on chromosome 15 (3-10). Fibrillin microfibrils are widely distributed in the extracellular matrix. Improper production of fibrillin leads to structural disruption of connective tissue, resulting in multiorgan involvement and subsequently a wide array of clinical symptoms (1, 11-16). The diagnosis of MFS is based on the modified Ghent nosology (17). Based on these criteria, the syndrome involves multiple organ systems, including, but not limited to, the ocular system (e.g., ectopia lentis) (1, 18-21), cardiovascular system (e.g., aortic dilatation, aneurysm, and dissection) (22-24), pulmonary system (e.g., spontaneous pneumothorax) (25-27), and skeletal system (e.g., dural ectasia, pectus excavatum/carinatum, scoliosis, medially displaced medial malleoli, pes planus, and acetabular protrusion) (28-31).The physical and mental toll of MFS on each individual patient is profound, and because the systemic involvement varies, it potentially results in different areas of concern for each patient.

To our knowledge, there are only a few published studies on the quality of life in patients with MFS (32-35). However, although these studies used questionnaires to understand patients' psychosocial and physical problems, specific major health concerns by organ system, from the patients' perspective, are yet to be understood. In addition, these studies evaluated some aspects of the quality of life and work place problems, but no previous study has objectively evaluated the quality of life and its domains in patients with MFS by using study specific questionnaires in conjunction with the Short Form 36 (SF-36) questionnaire. Such information can help professionals to anticipate problems and place individual patients in perspective. The main goal

of our study was to understand the self-perception of physical and mental well-being in patients with MFS compared with that of the general United States population. We wanted to quantitate quality of life and the physical function experienced by the patients and focus on the levels and location of pain they experience. We also specifically aimed to document the effects of MFS on employment.

MATERIALS AND METHODS

The study design, patient recruitment, creation and dissemination of the specific questionnaire, and data gathering were all approved by our institutional review board.

Patients with a diagnosis of MFS confirmed by a geneticist in accordance with the modified Ghent criteria, as identified via the Annual Meeting of the Marfan Foundation, and who were 14 years old or older were invited to participate in this study. Of the 265 patients invited, 230 completed the forms and formed our study group. Of those 230 patients, slightly more than half were females (Table 1). Their mean age was 44 ± 14 years (range, 14 – 82).

We created a study-specific questionnaire designed to identify the main problems as perceived by the patients, with a specific focus on medical and psychosocial concerns.

The questionnaire was designed using a visual analogue scale (VAS), with a scale of 0 to 10 for any specific question. The section on personal health concerns inquired into several categories/organ systems: spine and back, ribs and thorax, hip, feet, vision, cardiac, pulmonary, skin, hernia, dural ectasia, fatigue, depression, and difficulty in concentrating and learning. The section on pain inquired into several anatomic regions: head, neck, shoulder, elbow, back, hip, knee, and ankle. The selection of these specific categories was designed to be broad and

inclusive of most of the disease burden experienced by patients with MFS. The section on work life inquired into hours worked per week, if MFS resulted in change in hours worked per week, the retirement age and if MFS affected age of retirement, if time from work was lost because of health effect from MFS or treatment associated with MFS, and if time was lost because of treatment, then specifically because of which treatment. Questions regarding work life were included for the last 72 patients enrolled in the study. The average age of this subgroup was 46.4 ± 14.9 years (range, 19 – 72).

Data collected through the questionnaire were: demographics, concerns about the specific health problems in MFS, anatomic areas where patients experienced pain, severity of the pain, and how work lives were affected and to what degree.

The SF-36, a questionnaire designed to assess the physical and mental aspects of a disease (with additional subdivisions, Fig. 1), was used to determine the levels of the patients' physical and mental health well-being and to allow comparison with a predefined and evaluated "healthy" population, i.e., United States population norms. Physical health evaluation includes: physical function (ability to partake in activities of daily living), role physical (effectiveness in performing tasks), bodily pain (pain magnitude and general interference), and general health (general sense of well-being). Mental health evaluation includes: (energy level), social function (extent and time able and willing to be allocated to social activities), role emotional (effectiveness with daily activities or work based on mental health), and mental health (mood).

All gathered data and results were analyzed statistically by using SPSS version 13.0 statistical software (SPSS Inc., Chicago, Illinois). Mean values, percentages, standard deviations, and remaining statistics were calculated for personal health concern with regard to organ systems, pain based on anatomic regions, personal concern regarding the myriad of disease

effects of MFS, and results from the SF-36 questionnaire. NCSS 2004 statistical software (NCSS, LLC, Kaysville, Utah) was used to compare means of SF-36 domains between patients with MFS and general United States populations. Significance was set at $p = 0.05$.

RESULTS

Study Specific Questionnaire

Perception of Health Problems (Fig. 2) - Cardiac problems were the main health concerns: 70% (157 of 224) of respondents for this item rated cardiac concerns as 6 to 10 on the VAS. Only 4% (9 of 224) of the patients were not concerned about cardiac problems. Spine and fatigue problems ranked as the second highest concern; 53% (119 of 224) of patients rated them as 6 to 10 on the VAS.

Male patients were more concerned about vision and hernia associated problems, whereas female patients were more concerned about skin striae, dural ectasia, depression, and difficulty in concentrating (all $p < 0.05$).

Pain Levels by Anatomic Region - The most severe type of pain experienced by patients was back pain, followed by neck pain and headaches (Fig. 3). Back pain was rated as 6 to 10 (mean, 5.2 ± 3.1) on the VAS by 46% (105 of 229) of patients and also had the highest reported scores in patients between the ages of 25 to 45 years (Fig. 4). Neck pain and headaches were rated as 1 to 5 on VAS, respectively, by 68% (158 of 229) and 67% (153 of 229) of the patients,

respectively. Only 4% (9 of 229) of the patients did not experience back or neck pain and 5% (11 of 29) did not experience headaches.

Overall, the only statistically significant difference between genders with regard to pain was the severity of headaches, with female patients experiencing more severe headaches than their male counterparts ($p < 0.05$).

Work Life - The 72 work life responders were able to work 42.3 ± 12 hours per week. Of those responders, 89% (64) had to cut down their weekly work hours; 45% (32) stated this decrease was directly related to MFS. Additionally, 82% (59) patients lost, on average, 6.5 ± 7 months from work because of MFS related treatments. Of the 82% or 59 total patients who lost time, reasons were: aortic root surgery 53% (31 of 59); back surgery, 9.5% (6 of 59); and aortic valve replacement surgery, 6.3% (4 of 59). One patient has never been able to work full time because of his symptoms. Of the 72 patients, 26% (19 of 72) had retired at the time of the survey (average age, 48.5 ± 11.4 years), and of those 19, 58% (11) retired at age 50 or younger.

SF-36 Questionnaire

In all of the SF-36 domains, patients scored lower than the general United States population ($p < 0.05$).

Scores that were close to United States population norms, yet still significantly different, were the subdivisions of the mental health category. Scores that were lower than those of the United States population norms were all subdivisions of the physical health category.

In terms of gender differences, male patients with MFS scored higher than females in the vitality domain on the SF-36 (51.59 ± 20.83 *vs* 47.58 ± 24.67, respectively; $p < 0.05$). With the numbers available, no significant difference could be detected.

DISCUSSION

Although medical advances have succeeded in increasing life expectancy for individuals with MFS, and although many have productive roles in work and family, much remains to be learned about their disease burden, their ability to maintain these productive roles over time, and how their quality of life is affected. Our study goal was to quantitate quality of life and the physical function experienced by the patients and to focus on the levels and location of pain they experience. We found that the quality of life in this population is vastly lower than that of United States population norms, a finding attributable more to physical than mental effects.

Pain

The exact pathophysiology of pain in MFS has not been clearly elucidated; however, hypotheses are associated with muscular, ligamentous, and disc abnormality from mutations in the gene fibrillin-1 that encodes fibrillin and secondary elevations in transforming growth factor-β (TGF-β) levels. In our study, we found that patients rated back pain as the most severe type of pain they experienced, which substantiates the findings of other studies (33-35); it was their second most common concern. The definitive source of this back pain remains undetermined. Although back pain may be related to dural ectasia, some reports show that not all persons with

dural ectasia and MFS have associated back pain (34, 36-38). The high prevalence of scoliosis may also contribute to pain (33, 34). In addition, TGF-β interacts with several other cytokines that have roles in pain pathways, as seen in other pathologic states (39); therefore, the elevated circulating TGF-β and TGF-βR1 and TGF-βR2 loss of function mutation in MFS may be a link to another cause of back pain.

It is important to note that the most severe pain scores appear in patients between the ages of 25 and 45. The association is particularly interesting because this age range is arguably the most active period in an individual's life. If patients with MFS are more susceptible to injury because of the disruptions in their connective tissue, more physical strain may lead to increased perception and sensation of pain. Therefore, an individual's level of function may play a role in the development of back pain and explain the most severe pain levels for that particular age range.

In the general United States population, back pain is a well-known cause of absence from work and results in substantial economic losses (40-43). Given this predisposition in the general population, back pain is likely to also impact MFS patients to the same or most likely a greater level of severity. In our study, patients' scores on the SF-36 role physical domain, which includes problems encountered with work or other daily activities as a result of physical health, is nearly half of those of the United States population norms, pointing to severe problems in the work environment. Our patients also had very low scores on the body pain domain. Given the findings of Peters et al. (32) and the results of our study, it appears there is a strong inverse relationship between pain and coping with work or functioning optimally within the work environment.

Fatigue

Fatigue is the second most common symptom associated with MFS after back pain in the literature (34, 35) and it is the third most common concern for this population in our study after cardiac and spine concerns. The cause of the fatigue is likely multifactorial: the multisystem organ involvement and high prevalence of specific and generalized pain all directly contribute to a lower energy level and sense of well-being.

Expanding on the findings of the our SF-36 questionnaire, fatigue also likely affects patients' ability to cope with daily activities, including integration into work and social life, preventing them from fully engaging in these activities. As a result, they may choose to modify their daily life and activities, as was supported by the study of Peters et al. (33) where nearly 80% of their patients chose to modify their physical activities because of MFS.

Work Life

Based on the SF-36 role physical and role emotional findings, patients with MFS function below the level of the general population because of physical problems and psychosocial limitations. It is apparent that MFS affects the ability to work continuously and efficiently, and although some of our patients stated that they never lost a day from their jobs, many were severely affected, losing months or even years from their jobs. Although the work life questionnaire was implemented midway through the study, the results point to an area that deserves further independent study given the sentiments expressed by patients and the stark contrast to the general population on multiple levels. On the study specific questionnaire,

patients also indicated issues with vision, difficulty with learning, and difficulty with concentrating as part of the study specific questionnaire. All of these factors, in addition to the findings in the SF-36 questionnaire, contribute to a decrease in work life productivity.

Patients with MFS also retire early because of chronic pain, fatigue, and/or the extensive treatments that they receive, especially aortic aneurysm or valve repairs contributing to physical and psychosocial deterioration. Most of the 19 patients who were retired at the time of the survey had retired several years before social security benefits are available.

Physical Function, General Health, and Quality of Life

Our patients scored lower in all SF-36 domains ($p < 0.05$) than general United States population norms. Their scores were especially lower in physical function, role physical, body pain, and general health domains, all of which subdivisions are part of the "physical health" assessment. It appears that the physical performance of the individuals with MFS is highly impacted by the multisystem and muscular involvement. Their overall quality of health is decreased mainly by the cardiovascular involvement, musculoskeletal involvement, and pain. Patients with MFS are affected in all facets of life, as is seen in the SF-36 questionnaire responses. The seemingly all-encompassing involvement of "mind and body" presents an especially challenging treatment dilemma. The results of our study, along with those of many others, have indicated that, above all else, additional investigation is needed to better understand the pathophysiology of MFS (4, 5, 10).

CONCLUSIONS

Patients with MFS view their disease as affecting them in multiple facets of life. They report being impacted in physical and psychosocial ways. Their sense of vitality and ability to function is severely impaired compared with that of the general population because of pain, cardiac and back involvement, and poor physical functioning.

Future Direction

The study helps to highlight some of the issues that will need further elucidation in the future to better treat patients with MFS by taking into account their perspectives and attitudes regarding their disease and how MFS affects their lives. It may also serve to direct future research efforts to improve the quality of life of patients with MFS by addressing the most important problems as perceived by the patients. Additionally, as we continue to build on our knowledge, it is evident that treatment will require a multidisciplinary approach focusing on medical, psychologic, and surgical interventions to assure optimal quality of life. This information will help physicians anticipate physical and psychosocial demands of the disease burden.

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TABLE 1 Patient participation

Group	N (%)
Total patients enrolled	230 (100)
Male	97 (42)
Female	133 (58)
Study specific questionnaire	
Perception of health	224 (97)
Pain levels by region	229 (99.5)
Work life[a]	72 (31)
Short Form 36 questionnaire[a]	214 (93)

[a]Last 72 patients enrolled. All were more than 18 years old.

FIGURE LEGENDS

FIGURE 1 Comparison of SF-36 scores from patients with MFS (MFS) and those of the general United States population (GUS). Error bars represent 95% confidence intervals

FIGURE 2 Main health concerns perceived by patients with MFS as indicated on a VAS. The greatest concern is cardiac problems. The error bars represent 95% confidence intervals.

FIGURE 3 Ranking of pain severity at various locations perceived by patients with MFS as indicated on a VAS. The error bars represent 95% confidence intervals.

FIGURE 4 The relation of back pain to age in patients with MFS. The black curve represents the mean values of back pain.