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ABSTRACT

The Marfan syndrome (MFS) is strongly associated with aortic disease causing a high prevalence of prophylactic aortic surgery, aortic dissection, and sudden death. The aim of the present study was to evaluate mortality in a nationwide Danish MFS population diagnosed by the Ghent II criteria. In a register-based setting, we identified all Danish patients with MFS (n=412, male n=215) by assessment of their medical records. We established a gender and age matched control cohort based on 41,000 control persons (male n=21,500). MFS cases risk time was 6,669 persons years. We applied Cox regression using each case and his/her control as one stratum, adjusting for age and calendar time. We found a significantly decreased lifespan of 50 years compared to 60 years among controls. The mortality hazard ratio (HR) among MFS compared to controls was significantly increased to 3.6 (CI 2.8–4.7, p<0.001); males 4.0 (CI 2.8–5.7, p<0.001); females 3.2 (CI 2.1-4.8, p<0.001). Aorta disease represented the main reason for the overall increased mortality with a HR of 194.6 (CI 67.4-561.7, p<0.0001); males 208.7 (CI 53.8–809.1, p<0.001); females 173.4 (CI 31.5–954.5, p<0.001). In addition, an unexplained mortality due to respiratory illness was not attributed to pneumothorax. Excluding cardiovascular and respiratory causes of death, we found no indication that MFS is associated with increased mortality for other reasons.

Key words

Epidemiology, rare diseases, aortic aneurism, aortic dissection, sudden death

BACKGROUND

Marfan syndrome (MFS) is a dominant hereditary connective tissue disease with a prevalence of 6.5/100,000[1]. It is a multiorgan disease affecting the spine, the musculoskeletal system, the eyes and lungs. Among the many phenotypic traits of MFS, aortic disease is the most detrimental, causing a high prevalence of early aortic events of both prophylactic surgery and aortic dissection[2]. It is not clear how high the mortality rates are in MFS. The latest survival study in MFS done by Silverman et al., used older diagnostic criteria and was published more than 20 years ago, but reported a mean age of death of only 41 years[3], possibly driven partly by a young cohort of MFS patients. Assumptions are a better survival today, supported by the very low mortality from aortic events observed in MFS patients if managed according to guidelines in a specialist center[4]. However, in real life MFS patients are still diagnosed late and not all patients achieve specialist care before they develop aortic disease, so unfortunately a post aortic dissection diagnose is not a rare phnomenon[1,2]. The aim of the present study was to evaluate mortality rates in a nationwide Danish MFS population diagnosed by the Ghent II criteria.

METHODS

We retrieved unique personal identification numbers (id-numbers) from all persons recorded in either *The Danish National Patient Registry* (DNPR) [5] or *The Cause of Death Register* (CDR) [6] with the ICD-10 diagnosis Q87.4 "Marfan Syndrome" or ICD-8 759.80 "Arachnodactylia (Syndroma Marfan)" during 1977 to 2014 and evaluated all medical records as described in a previous study [1]. In total, we identified 412 persons (215 men) with MFS, diagnosed according to the Ghent II criteria.

In Denmark, there is a central authority on national statistics. For each MFS patient we provided the id-number and the individual date of the MFS diagnosis. Statistics Denmark built a control cohort based on 100 individuals per MFS patient matched on sex, birth year and the residing municipality. Further, all controls were alive on the date their relevant MFS patient was diagnosed. For each patient and his or her controls, time at risk started the year of diagnosis. Time at risk ended on the last date of the study period (by end of 2016), first date of emigration or on date of death, which ever came first.

The study was approved by the Scientific Ethical Committee (31422) and the Danish Data Protection Agency (2011-41-6986). We retrieved data on *date of death* until the end of 2016 and registered 1819 deaths (58 cases and 1761 controls). We retrieved data on causes of death on 1612 controls and 51 cases until the end of 2016. Causes of death was not registered for 7 deceased cases and 149 deceased controls mainly due to reporting delay for 2016 deaths (7 cases and 134 controls). We sorted causes of death according to the ICD 10-chapter system. ICD 8 codes were translated into ICD 10 codes (supplementary table S1).

Age was not normal distributed and median values are presented. Risk time started at year of diagnosis and ended at year of death or at year of other censoring, whichever came first. Kaplan-Meier estimates were constructed for mortality. Hazard ratios (HR) and p-

values were calculated using Cox regression, where each patient and his or her matched controls were a stratum, hereby adjusting for gender, age and calendar timer. P values lower than 0.05 were considered statistically significant. Stata 12.1 for Windows (StataCorp LP, College Station, TX, USA) was used for all calculations.

RESULTS

Previously, we identified 412 MFS patients in Denmark (male n=215) [1]. Two female case patients were discarded from the cohort as we were unable to match 100 control persons to these cases. We established a control cohort based on 41,000 control persons. We identified 352 living cases and 58 diseased cases. In the control group, we identified 39,239 alive and 1,761 were deceased (*Table 1*). Median age of living cases by the end of 2016 was 38.5 years and for controls 40.0 years. The risk time for the MFS cases was 6,669 person years.

The annual death rate for MFS cases was 0.0087 deaths/year/person and for controls 0.0025 deaths/year/person. The median age at diagnosis was 38.5 years for deceased (range 0 to 75) and median age at death was 50 years for MFS cases (range 0 to 85 years) and 60 years (range 1 to 91 years) for controls. The difference in median age at death was 8 years for men (MFS cases 50 years (range 3 to 80) and controls 58 years (range 1 to 90)) and 13 years in women (MFS cases 50 years (range 0 to 85) and controls 63 years (range 1 to 91)). We found a significantly increased mortality HR of 3.6 (CI 2.8 – 4.7, p<0.001) (Figure 1); male 4.0 (CI 2.8 – 5.7, p<0.001); female 3.2 (CI 2.1-4.8, p<0.001) (Figure 2) among MFS compared to controls. Mortality due to cardiovascular diagnoses was significantly increased with a HR of 7.0 (CI 4.3-11.6, p<0.001); male 7.0 (CI 3.5 – 13.8, p<0.001), female 7.1 (CI 3.5 – 14.7, p<0.001). Eleven out of 17 cases with a primary cause of death due to cardiovascular disease died from aortic disease (ICD 10 codes I710-I719, ICD 8 codes 4410-

4412) compared to 6 out of 252 controls. MFS had a HR of 194.6 (CI 67.4-561.7, p<0.000); male 208.7 (CI 53.8 – 809.1, p<0.001); female MFS HR of 173.4 (CI 31.5 – 954.5, p<0.001) of dying from aortic disease. Except for abdominal dissection the location of the aortic disease was not specified (Cases ICD 10 codes: I710 (n=6), I711 (n=2), I718 (n=1), I719 (n=1), I713 (n=1). Controls ICD 10 codes: I710 (n=1), I713 (n=5)). Sub-analyzing this chapter, we found three female cases who died of non-aortic causes (heart failure (n=2) and AMI (n=1)) while all male cases died of aorta related causes. Furthermore, fourteen MFS cases were registered with a primary cause of death in the congenital chapter (ICD 10 Q874 or ICD 8 7598). Of these 14 cases, five cases were registered with another secondary code of aortic disease.

Only five controls were registered with a congenital cause of death and none had any registration with MFS or cause of death indicating aortic disease. Analyzing both primary and secondary causes of death from aortic disease we found 20 cases (11 primary cause of death) and 10 controls (6 primary cause of death) with aortic disease, which resulted in a HR of 223.7 (CI 98.4-508.9, p<0.001). When evaluating other diagnostic chapters than "Circulatory" only "Blood/immunology", "Respiratory", "Congenital" and "Other" stands out with significantly increased mortality rates among MFS. The Blood/Immunology chapter data is based on one case event and can be considered a chance finding (table 2). None of the 7 cases with a primary respiratory cause of death had pneumothorax as a cause of death (primary or secondary causes of death). Among controls, only one died of a pneumothorax. The number of cases (n=7) within the respiratory chapter is low and we did not find a pattern of causes of death in these cases indicating an explanation of the increased HR (among cases ICD 10 code: (n=2) "J960- Acute respiratory failure", (n=1) "J969 - Respiratory failure, unspecified", (n=1) "J158 - Pneumonia due to other specified bacteria", (n=1) "J151 - Pneumonia due to Pseudomonas", (n=1) "J189 - Pneumonia, unspecified organism", (n=1)

"J690 - Pneumonitis due to inhalation of food and vomit"). The increased HR in the congenital chapter was solely based on the MFS diagnosis among the cases as all 14 cases are registered with MFS as primary cause of death. A rather large proportion (5/14, 36%) had aortic disease as secondary cause of death and another five cases had other vascular secondary causes of death ("K55.0 Acute vascular disorder in the intestine", "I35.9 Aortic Valve Disorder, unspecified", "I69.4 Sequelae of stroke, not specified as hemorrhage or infarction", "Z95.2 Presence of prosthetic heart valve", "746.9 Unspecified anomalies of heart") while four were solely registered with MFS as the primary cause of death.

The "Other" chapter include "ill-defined and unknown causes of mortality". Among the 6 cases in this chapter two were "R989 - Unattended death" as primary cause of death and the secondary cause was "Q874 – Marfan Syndrome". Two cases were registered as "R092 – Respiratory arrest" and "Q874 – Marfan syndrome" as a secondary cause. One was "R99.1 - Other ill-defined and unspecified causes of mortality" as primary cause of death and secondary cause "Q874 – Marfan Syndrome". One was "R57.0 – Cardiogenic shock". No autopsy was performed in any of the six cases and all cases were registered as a death caused by "Natural causes". A speculative guess could be that the overrepresentation could be due to aortic rupture causing registration as sudden unattended death. Merging all ICD chapters except the circulatory chapter showed a non-significant mortality HR of 1.1 (CI 0.97 – 1.19, P=0.156) indicating that circulatory causes are the main reason for deaths among MFS.

DISCUSSION

Our study clearly indicates that the MFS diagnosis is associated with a significant increased all-cause mortality hazard ratio for both men and women at any time in life compared to the normal population. As expected, cardiovascular causes of death were the

major contributor with an overwhelming seven-fold increased HR and with an almost two hundred-fold increased HR of dying from aortic disease.

This study also shows that having MFS results in median age at death of 50 years. In the study by Silverman et al. the mean age at death was only 41 years, however, since there were no data on the age of the total cohort in Silverman's study, we cannot compare these two studies directly. Nevertheless, MFS cases still have a reduced median age at death of 8 to 13 years compared to the background population. Men and women had a similar lifespan which is in contradiction to previous studies that have shown that males with MFS are more likely to develop aortic disease including both prophylactic surgery and dissections[2,7].

In the present study, more than half of the MFS patients were not diagnosed until adult life[1]. In addition, a substantial part of MFS patients may also have died undiagnosed and are therefore not included in the present cohort. For the same reason, many patients were not diagnosed until after they had aortic dissection, which creates a much poorer outcome[2]. Therefore, it must be emphasized that identification of patients with MFS as early as possible is essential to provide the best possible care. An additional advance will be to identify MFS patients with a high risk of aortic dissection. A recent study indicated that MFS patients with aortic stiffness may have a higher risk of aortic dilatation and dissection which could mean that a subset of MFS patients should be followed more closely or have surgery at an earlier stage[8]. Until now, preventive pharmacological treatment has not shown a dramatic effect in preventing aortic dilatation and dissection[9,10] and it is still uncertain if any existing drug can do this[11]. It is difficult to argue convincingly either for the mechanobiological effects of betablockers or for inhibition of the TGFβ-system with Losartan[12]. Instead it seems that specialized follow-up and timely aortic surgery by dedicated surgical teams seem to be the most important factor for long-term survival[4].

The recommended aortic size limit is 5 cm and there is no evidence to support that aortic root replacement at smaller aortic diameters improves survival. However, there are specialized recommendations for women and pregnancy, where prophylactic surgery should be offered at 4.5 cm if the woman with MFS wishes to be pregnant[13]. We were unable to find any evidence in our data that indicated that pregnancy included a significantly increased mortality risk in this cohort, which is in contrast to previous observations[14].

Altered fluid hemodynamics after aortic root replacement[15] may be one among many reasons why MFS patients experience type B dissections late after prophylactic aortic root surgery[16]. It is therefore important also to observe the aortic arch and descending aorta meticulously when doing post-surgery follow-ups and offer treatment in due course[7].

Another major issue is reconstructive aortic surgery in MFS patients with chronic dissections[17]. Even though results seem excellent in highly specialized high-volume centers[18] the reality is that thoracoabdominal aortic repair of chronic dissections is a high-risk procedure also with considerable morbidity risk including spinal cord injury[19].

Our data do not indicate that MFS individuals present a higher risk of death by other causes of death than cardio vascular. As mitral valve prolapse is a common phenotypic manifestation in MFS[7] we expected to find an overrepresentation of mitral disease among cases. However, we did not find a single case with mitral disease as the primary cause of death indicating that mitral valve disease may be common but not fatal.

We assumed that pneumothorax would be the main cause of case representation in the "Respiratory" chapter. However, it is noteworthy that none of the cases with a respiratory cause of death had pneumothorax as a cause of death. We have no explanation of the overrepresentation of respiratory causes of death. An explanation could be respiratory complication in relation to aortic surgery. Obstructive sleep apnea is another major issue in

MFS but since this disorder is not registered systematically in Denmark, due to most treatment is managed in private hospital settings we cannot give an estimate of the influence from sleep apnea.

There are some limitations and possible bias due to the case-control study design. It is likely that we primarily included case patients with an obvious phenotype, and we cannot exclude that some cases are not yet diagnosed or have already died without being diagnosed. For these reasons, we may have overestimated the event rate. Diagnostic criteria for MFS have changed several times over the years but we recently showed that implementation new criteria [20-22] did not have a large impact on incidence and prevalence of MFS [1].

In conclusion, MFS has significantly increased overall mortality driven by death due to aortic disease with a HR of almost 200. In addition, an unexplained mortality due to respiratory illness was also observed. When excluding cardiovascular and respiratory causes of death, we found no indication that MFS is associated with increased mortality for other reasons.

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Figure 1: Kaplan-Meier survival curves for cases and controls with 95% confidence intervals. Time starts at diagnosis of case patient.

Figure 2: Kaplan-Meier survival curves for cases and controls divided on gender. Time starts at diagnosis of case patient.

Table 1

Data on cases and controls.

	Total cohort	Male	Female
Cases (MFS)	410	215 (52%)	195 (48%)
Cases alive	352	182 (52%)	170 (48%)
Cases diseased	58	33 (57%)	25 (43%)
Controls	41,000	21,500 (52%)	19,500 (48%)
Controls alive	39,239	20,504 (52%)	18,735 (48%)
Controls diseased	1,761	996 (57%)	765 (43%)

Table 2

Cause of death data divided by ICD chapter. HR: hazard ratio of death case compared with controls. Data only on causes of death data.

	Cases	Control	HR	Confidence interval	p-value
Combined	51	1612	3.4	2.6-4.5	<0.001
Infection	0	70	-	-	-
Neoplasm	3	390	0.8	0.3-2.6	0.771
Blood/ immunology	1	3	31.9	2.6-387.5	0.007
Endocrine	0	30	-	-	-
Mental	0	26	-	-	-
CNS	0	22	-	-	-
Eyes	0	0	-	-	-

Ears	0	0	-	-	-
Circulatory	17	252	7.0	4.3-11.6	<0.001
Respiratory	7	246	3.0	1.4-6.3	0.005
Digestive	0	82	-	-	-
Skin	0	0	-	-	-
Musculoskeletal	0	2	-	-	-
Genitourinary	0	14	-	-	-
Pregnancy	0	0	-	-	-
Perinatal	0	0	-	-	-
Congenital	14	5	274.8	99.0-763.2	<0.001
Other	6	265	2.4	1.1-5.5	0.031
Injury, poisoning & external	3	205	1.6	0.5-5.0	0.427
Unknown cause (no data)	7	134			

"-": HR's could not be calculated.