Ascertainment and severity of Marfan syndrome in a Scottish population

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Abstract

This study in north east Scotland has shown that Marfan syndrome has a minimal birth incidence of 1:9802 live births, a minimal prevalence of 1:14217, and that 8/30 (26.7%) of cases in our series are new mutations. The calculated mutation rate is $15 \pm 6.7 \times 10^{-6}$ and there is evidence of reduced reproductive fitness.

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The connective tissue disorder Marfan syndrome was described for the first time in 1896¹ and then defined over the next 50 years as a genetically inherited, autosomal dominant disorder of near complete penetrance but wide variability in clinical expression. The classical syndrome consists of abnormalities in the cardiovascular, skeletal, and ocular systems, the cardiovascular features being responsible for the significant mortality. Lynas² performed the only previous population study of Marfan syndrome in 1958. Although a very detailed study for the time, it was recognised by the author that the prevalence figure of 1.459 per 100 000 population (and equally the given mutation rate of between 4.2 and 5.8×10^{-6} per generation) was certain to be an underestimate. In more recent times the prevalence figure has been estimated at between 4 and 6 per 100 000³ climbing to the widely quoted 1 in 10 000⁴ with no differences detected in any racial or ethnic group or indeed any difference between males and females. This study set out to determine the prevalence of Marfan syndrome in our local, well demarcated, and relatively static population in north-east Scotland. A major difficulty in accurately assessing the prevalence of the disorder lies in the difficulties of clinical diagnosis. The spectrum of the disorder may extend from the limits of normality to the more classical picture, and there are a large number of varied and often clinically overlapping differential diagnoses.

Before a diagnosis of Marfan syndrome can be made at least four other clinical conditions must be considered, and if possible excluded. These include homocystinuria, congenital contractual arachnodactyly, variants of Ehlers-Danlos syndrome, and the autosomal dominant mitral valve prolapse syndrome. As detailed by previous workers⁵ a large number of other disorders share one or more clinical features with Marfan syndrome and may also enter the differential diagnosis on occasion.

In an attempt to overcome these diagnostic dilemmas classifications of increasing rigour have been developed. In the 1950s Lynas²

suggested the criteria of acceptance were persons showing two or more of the characteristic cardiovascular, ocular, or skeletal features or persons with one of the triad plus a definitely affected sib/parent/cousin/grandchild. Pyeritz and McKusick³ produced a more extensive diagnostic classification in 1979 and this became the definitive work until currently agreed criteria were laid down in the Berlin Nosology⁶ in 1986. The Berlin Nosology further defined the diagnostic criteria to obtain diagnostic specificity and allow accurate linkage studies. It is these guidelines that we have used in this ascertainment study.

Patients and methods

RECRUITMENT

The study was carried out between August 1991 and February 1993 in Tayside and north-east Fife with a population of approximately 441 000. A Marfan syndrome clinic was established and widely publicised both within the hospital and in the community. All hospital specialists likely to be involved in the management of Marfan syndrome patients, all GPs, and all community physicians were contacted by letter both individually and within their regular newsletters. Information on Marfan syndrome, the aims of the clinic, and the benefits to the patients of accurate diagnosis and counselling was provided. A search of all genetic and cardiology notes in the regional hospital was undertaken. Any patient identified through the records was contacted, after permission was obtained from the appropriate General Practitioner. An advertisement in the local newspaper publicised an open meeting held with the help of the British Marfan Syndrome Association, and over 80 interested persons attended. The Clinical Genetics departments in Edinburgh and Aberdeen allowed us to examine their patient records and in the process we discovered two families with affected members resident in our study area. All patients who agreed to participate were seen at the routine weekly Marfan syndrome clinic.

CLINICAL DATA COLLECTION

Two clinicians (JRG and ABB) evaluated all patients with reference to the diagnostic criteria laid out in the Berlin Nosology.⁶ A family history was taken and all patients received a physical examination.

Skeletal evaluation

Various skeletal indices were measured. Dolichostenomelia was assessed partly on a

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subjective scale and partly as a function of span being at least 7.5 cm greater than height,⁷ and an upper segment to lower segment ratio less than 0.85 was regarded as abnormal.

Ophthalmology

Slit lamp and fundal examination, through dilated pupils, were performed by one ophthalmologist familiar with Marfan syndrome. Myopia was marked as positive if severe (greater than 6 diopters).

Echocardiography

All echocardiograms were performed by the same cardiologist familiar with Marfan syndrome. Recordings were made using a Hewlett Packard Sonus 1000. The following indices were determined: (1) aortic diameter, assessed by M mode, was considered increased in adults when greater than 37 mm and in patients under 16 years of age it was related to body surface area⁸; (2) valvular function, in particular aortic and mitral regurgitation, was assessed both by colour flow and doppler; (3) the presence of mitral valve prolapse.⁹

Pedigree analysis

A full family history was obtained with details of any characteristic clinical findings. First and second degree relatives of affected subjects were traced and all those who consented were examined. Death certificates and clinical documentation were examined when available.

Results

During the study 40 families were referred to the Marfan syndrome clinic from areas both outside and within the Tayside Region. Twenty-one classically affected families were found, while in 16 families connective tissue abnormalities other than Marfan syndrome were observed. Three families were found to have no abnormality. Thirteen of the classically affected families were resident within the Tayside referral area and are used as the basis for the population analysis discussed in the rest of this paper. All families were tested for and shown not to have homocystinuria.

PEDIGREE ANALYSIS

Pedigree analysis was consistent with an autosomal dominant mode of inheritance of Marfan syndrome. There were frequent examples of male to male transmission and no departure from a 1:1 sex ratio among those affected (14 male:11 female). Using adult index cases where all offspring had been examined, segregation analysis showed no departure from the expected 1:1 ratio for an autosomal dominant condition (25/53 affected). Pedigrees showed two instances of three generation and one of four generation transmission of the disease. In all but one case the subjects in intervening generations showed appropriate manifestations of the disease. Eight cases were

identified giving no family history of Marfan syndrome in their sibs or in preceding generations. In three cases both parents were clinically assessed and in a further three cases the parents were not seen but hospital and general practitioner notes were examined. In two cases information on the parents was obtained from other family members. All eight cases were assumed to be new mutations of the Marfan syndrome gene. Four of these subjects currently have children, two of eight offspring being affected.

DISEASE PREVALENCE

Prevalence day was taken as 30 June 1991, and mid-year estimates published by the Registrar General for Scotland gave a population figure for the study area of 440 727. Identified Marfan syndrome patients alive on prevalence day numbered 30, giving an estimated prevalence of 1:14691 or 6.81 per 100 000 population.

Our methods of ascertainment may not have detected mildly affected cases, especially those children who are new mutations not yet showing characteristic features of the disease. To take account of this, the ratio of new mutations to familial cases at different ages was compared. One of 10 cases (10%) aged less than 20 years was a new mutation, compared with four of 20 (20%) cases aged 20 years or over. This implies that one new mutation aged less than 20 years was undetected, and correcting for this gives a prevalence of 1:14217 or 7.03 per 100 000.

INCIDENCE

The birth incidence of 1:9802 live births was estimated from the point prevalence of affected subjects who would have been aged between 15 and 39 on prevalence day (including two dead subjects), in comparison with the total population aged between 15 and 39 on that same day.

MUTATION RATE

Within the period 1953 to 1976 there were approximately 166 641 live births. Five sporadic cases were born during that period.

Estimated mutation rate¹⁰ ($\mu \pm 95\%$ confidence interval) was $5/2 \times 166\,641 = 15 \times 10^{-6}$, standard error = $\sqrt{pq/2N} = 6.7 \times 10^{-6}$. The mutation rate is $15 \pm 6.7 \times 10^{-6}$.

ESTIMATION OF FITNESS IN MARFAN SYNDROME

Estimation of fitness analysis^{10,11} was performed using the 13 index cases. Relative fitness = $w = A_p/A_o$

A_p = frequency of trait among parents of index case

A_o = frequency of trait among offspring of index case

$$A_p = 6/26 = 0.231$$

$$A_o = 5/14 = 0.357$$

$$w = 0.231/0.357$$

$$w = 0.647$$

The relative fitness of Marfan syndrome sufferers was 0.647 overall.

PARENTAL AGE EFFECTS

For six of the eight new mutations the age of both parents at their time of birth was known. The mean paternal age was 31.66 and mean maternal age was 29.17 compared with the expected ages of 30.35 and 27.45 years respectively as derived from the Registrar General's population data (table 1). Analysis of the data, as described by Emery,¹⁰ using Student's *t* test is shown in table 2. Differences are not significant.

Severity of cardiovascular manifestations

Assessing the cardiac features of the patients we constructed a graded index of severity as shown below.

CARDIOVASCULAR GRADING SYSTEM

Grade 1 (minimal): no aortic dilatation. (Aortic dilatation defined as greater than 37 mm in

adults. In patients under 16 years of age aortic root diameter is related to body surface area.⁸) Grade 2 (mild): aortic dilatation, not requiring surgical intervention, observed over the age of 40 years. Grade 3 (moderate): aortic dilatation observed between the ages of 20 and 40 years. Grade 4 (severe): aortic dilatation under 20 years of age or surgical treatment of aortic or mitral valve disease or aortic dissection.

Using the criteria shown the determinants of severity of cardiovascular features were assessed. Table 3 shows that neither gender nor parental source of the mutant gene has a significant effect on cardiovascular severity. Comparison of mean severity grades in all the analyses in this paper were by Student's *t* test.

Severity of skeletal manifestations

As with the cardiovascular features, it was possible to grade the skeletal manifestations exhibited by our Marfan population. One point is given for each of the characteristics shown below, and severity is determined by the number of features present.

Table 1 Parental ages of new mutations of the Marfan syndrome

	Father	Mother
	33	33
	29	23
	42	40
	30	29
	25	24
	31	26
Mean	31.66	29.17
SD	5.7	6.43
Comparable population mean	30.35	27.45

Table 2 Comparison of parental ages for new mutations and the general population

	Mean paternal age	Mean maternal age
New mutations	31.66	29.17
General population	30.35	27.45
Difference	1.31	1.72
(Significance)	(<i>p</i> > 0.1)	(<i>p</i> > 0.1)

SKELETAL GRADING SYSTEM

- (1) Kyphosis.
- (2) Scoliosis.
- (3) US/LS ratio < 0.85.
- (4) Arachnodactyly.
- (5) Joint hypermobility.
- (6) Pectus deformity.
- (7) High arched palate.
- (8) Span > height > 7.5 cm.

Table 4 shows that no significant difference in severity grade was detected on the basis of parental transmission route, gender, or whether familial or a new mutation.

Discussion

In a population based study of Marfan syndrome in Tayside and north-east Fife we have derived a minimum prevalence figure of 1 in 14 217 (7.03 per 100 000 population). The figures calculated use the current guidelines for diagnosis and compare with the estimates of 4 to 6 per 100 000 in 1979³ and 1 in 10 000 in 1986⁴ quoted for the USA. The only previous reported comparable ascertainment study, looking at an entire population rather than just hospital referrals is that of Lynas² with a calculated prevalence figure of 1.459 per 100 000 population. The discrepancy between the studies may reflect the increasing awareness of genetic disorders in general and Marfan syndrome in particular. Also of relevance are the recent advances made in clinical diagnostic techniques, especially the development of non-invasive tests such as echocardiography, allowing screening for cardiological features of the disorder in large numbers of at risk subjects.

Segregation analysis is consistent with the expected autosomal dominant single gene

Table 3 Cardiovascular severity within Marfan syndrome subgroups

Factor	No	Mean grade of severity	Significance
Sex			
Male	19	2.84	NS
Female	15	2.13	<i>p</i> > 0.05
Parent affected			
Father	13	1.85	NS
Mother	13	2.8	<i>p</i> > 0.05 <i>p</i> < 0.1
Inheritance			
New mutation	8	3.25	NS
Familial	26	2.31	<i>p</i> > 0.05 <i>p</i> < 0.1

Numbers reflect all those cases, alive, dead, or newborn, diagnosed within the 13 families. Details on three subjects, who died before the study began, could not be traced.

Table 4 Skeletal severity within Marfan syndrome subgroups

Factor	No*	Mean grade of severity	Significance
Sex			
Male	14	4.5	
Female	14	4.36	NS <i>p</i> > 0.5
Parent affected			
Father	12	4.5	
Mother	12	4.25	NS <i>p</i> > 0.5
Inheritance			
New mutation	4	4.75	
Familial	24	4.2	NS <i>p</i> > 0.1

* Details on nine subjects could not be traced.

mode of transmission. In only one family was there evidence of an affected subject with an apparently normal but transmitting parent.

The calculated incidence of the disorder is 1 in 9802. The discrepancy between this figure and the prevalence rate may reflect childhood mortality. Previous studies^{12,13} have shown mortality and significant cardiac morbidity in infants and children afflicted with Marfan syndrome.

Marfan syndrome may cause death or severe handicap throughout adulthood and it may be anticipated to reduce reproductive fitness. We calculated a reproductive fitness of 0.647. There was no evidence of infertility in any of the couples in our study and we feel social factors such as voluntary family limitation may play a major part in reducing reproductive fitness, especially where a family has experienced severe manifestations of the condition. We are unaware of any similar studies on this disorder with which to compare this result.

The potential ascertainment difficulties have been mentioned, yet the estimate of mutation rate, at between $15 \pm 6.7 \times 10^{-6}$ and $18 \pm 7.3 \times 10^{-6}$ per haploid genome per generation is of the same order as estimated for tuberous sclerosis (2.5×10^{-5})¹⁴ and neurofibromatosis type 1 (3.1 to 10.4×10^{-5})¹⁵ and greater than other dominant disorders such as Apert's syndrome (3×10^{-6}).¹⁶ Our estimate for the mutation rate is greater than that calculated by Lynas for the population of Northern Ireland (between 4.2 and 5.8×10^{-6}), perhaps because of more complete ascertainment. The combination of the reduced reproductive fitness and the relatively high incidence of the disorder suggests that our higher mutation rate is likely to be in the correct range.

Eight of 30 cases in the prevalence study group are assumed to be new mutations. This figure agrees with other widely quoted estimates of between 25% and 35% of cases.⁴ Parental ages are given in table 1 and there is no evidence of an advanced paternal age effect as described by other workers.¹⁷ This may reflect our small sample size and continuing international studies using the current diagnostic criteria will be invaluable in addressing this question.

The severity of cardiovascular and skeletal components of the disorder was assessed using

graded scales. Cardiovascular and skeletal features showed no significant differences in severity when analysed according to sex, parental origin of the affected allele, or whether the cases were familial or new mutations. At present there are insufficient cases to address any suggestion that gene modification by imprinting could be involved in Marfan syndrome. This study provides preliminary data that will be useful in genetic counselling, there being no evidence for a more severe phenotype in either sex or evidence of maternal imprinting. The calculated incidence and prevalence figures, which are 10 times greater than previously reported for European populations, will allow assessment of the appropriate allocation of resources to this potentially fatal disease.

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