

An excess of tetralogy of Fallot in Malta

V Grech

Abstract

Study objective—To estimate birth prevalence of tetralogy of Fallot (TF) in Malta.

Design—Retrospective data collection and analysis, and comparison with earlier epidemiological studies dealing with congenital heart disease.

Setting—Regional hospital providing exclusive diagnostic and follow up services for the entire country of Malta.

Patients—All Maltese live births diagnosed as having TF.

Main results—The birth prevalence of TF in Malta for the period 1980–1994 was 0.64/1000 live births (95% confidence intervals 0.48, 0.85/1000 live births). This was significantly higher than previously reported in the medical literature.

Conclusions—The Maltese gene pool seems to have a genetic predisposition towards live births with TF. Population genetic studies with emphasis on the prevalence of 22q11 microdeletion may yield clues regarding the cause of the high rate of this condition.

(J Epidemiol Community Health 1998;52:280–282)

Epidemiological studies dealing with malformations are important for several reasons. Quantification of birth prevalence and spectrum of malformations, along with analysis of past trends in management allow for planning of future provision of health services. In addition, clusters in time or space, or both, may provide clues as to aetiology, and recurrence risks for siblings and offspring can be calculated. Furthermore, outcome measures including survival rates and long term complications of disease and treatment can be assessed.

Certain conditions are essential for an epidemiological study dealing with congenital heart disease (CHD) to be valid and useful. The catchment area must be clearly defined with minimal population flux into and out of the region under study and there must be clearly identified referral routes for patients with suspected CHD. In addition, the methods used for reaching a diagnosis must be objective and reproducible. Moreover, accurate and retrievable records must be available and there must be precise registration of births and deaths with postmortem examinations carried out on all deaths without a known diagnosis. All of these conditions are satisfied in Malta, making this country an ideal location for epidemiological studies dealing with congenital malformations.

The aim of this study was to identify all cases diagnosed as having tetralogy of Fallot (TF) in Malta. This allows the calculation of birth

prevalence and allows comparison of birth prevalence with other studies.

Methods

DEFINITIONS

The usual definition of TF was used in that TF is caused by anterior aortic root displacement over a malaligned, outlet ventricular septal defect resulting in right ventricular outflow tract obstruction and hence, right ventricular hypertrophy.¹

Diagnosis of TF was only accepted if made by echocardiography, cardiac catheterisation, surgery or postmortem examination.

Patients with TF were identified for inclusion into the study in the following ways.

Malta has only one regional hospital (St Lukes), which caters for diagnosis and follow up of all patients with CHD. Sources included children being followed up at children's outpatients for CHD with or without other problems, copies of all paediatric echocardiogram reports, lists of locally performed elective cardiac catheters and operations and lists of patients sent abroad for urgent cardiac catheterisation or intervention not available in Malta. In addition, clinic registers of patients seen at visiting consultant paediatric cardiologist clinics (held 3–4 times a year) were examined, as were postmortem reports for the period under study.

Official Maltese publications were used to obtain total annual live births from 1945 to 1994.²

Patients with TF and a recognised syndrome were also identified.

STATISTICS

Excel was used to analyse rates and calculate 95% confidence intervals (CI) using the binomial distribution.³ The Astute Excel add-in was used to calculate significance levels by using χ^2 with Yates's continuity correction for 2 by 2 contingency tables. Graphs were plotted using Statistica. A p value <0.05 was taken to signify statistical significance.

Results

PATIENTS

A total 109 children born between 1922 and 1994 were diagnosed as having TF. Birth prevalences and 95% CI were calculated on a five yearly basis starting from 1945 (fig 1). These showed a steady increase in birth prevalence of diagnosed TF. The five yearly total live births with TF before 1980 suggest incomplete ascertainment with fewer cases being diagnosed. The period 1980–94 was therefore used to calculate baseline birth prevalence of TF along with 95% CI. There were 52 cases of TF with a birth prevalence of 0.64/1000 live births (95% CI 0.48, 0.85/1000 live births).

Paediatric
Department, St Lukes
Hospital,
Guardamangia, Malta
and Cardiothoracic
Unit, Great Ormond
Street Hospital for
Children NHS Trust,
London

Correspondence to:
Dr Grech, Paediatric
Department, St Lukes
Hospital, Malta.

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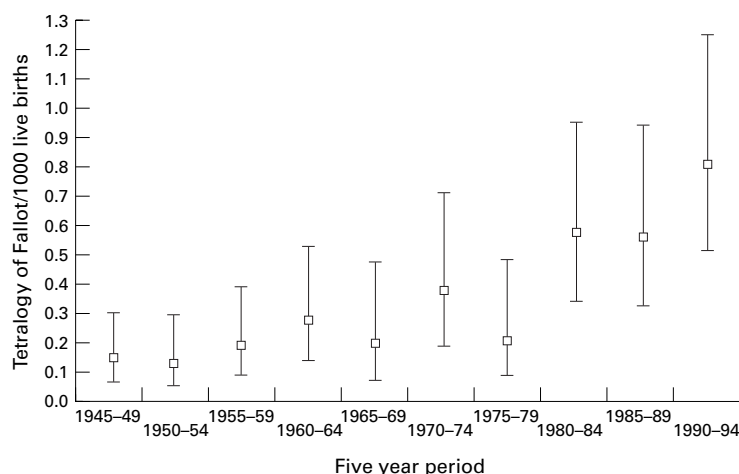


Figure 1 Five year birth prevalences and 95% confidence intervals for TF

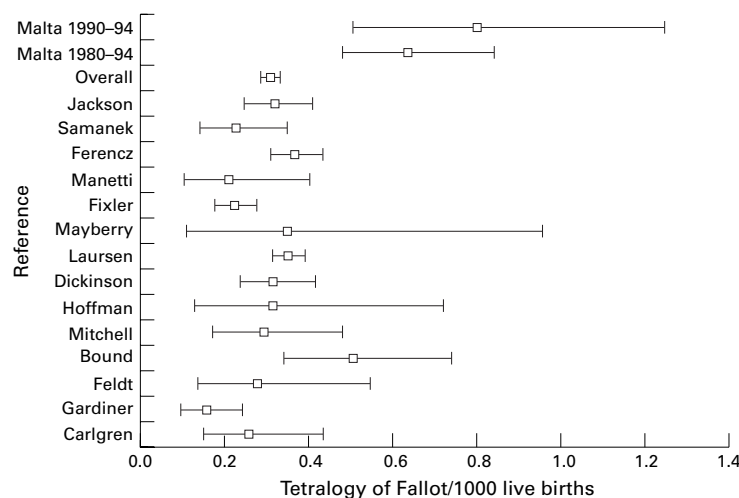


Figure 2 Birth prevalence and 95% confidence intervals for TF in previous and present studies. Overall includes all data except for the Maltese data.

Table 1 Comparison of birth prevalence of tetralogy of Fallot with two recent studies with similar methodology to this study

Reference	16	17	This study
Locality	Bohemia	Merseyside	Malta
Years studied	1980	1979-88	1990-94
Total live births	91 823	203 880	81250
With TF	21	66	52
Birth prevalence	0.23	0.32	0.80
Upper 95% CI	0.33	0.40	1.25
Lower 95% CI	0.13	0.25	0.51
p Value	0.0001	0.0003	

The birth prevalences of TF for this period and for 1980-94 were compared with historical data ranging from 1945-1996 (fig 2).⁴⁻¹⁷ The birth prevalence of TF in historical papers ranged between 0.16 and 0.51/1000 live births. The total live births and total cases of TF in the historical data were summated to obtain the overall rate of TF and compared with the Maltese results for 1980-94. The Maltese rate was significantly higher (p<0.0001).

Recent studies dealing with the epidemiology of CHD have only included cases of CHD diagnosed in infancy (that is, by 1 year of age) by echocardiography, cardiac catheterisation, surgery or postmortem examination. The five year period 1990-94 was used to compare the birth prevalence of TF in Malta with two

KEY POINTS

- Malta has a significant excess of live births with tetralogy of Fallot.
- This is the highest birth prevalence ever reported in the literature.
- The Maltese gene pool may have an inherent predisposition towards tetralogy of Fallot.
- Population genetic studies including prevalence of 22q11 microdeletion may yield clues as to the reason for this high prevalence.

recent studies with this methodology by χ^2 analysis.^{16 17} There were 21 cases of TF in Malta in this period and all cases were diagnosed in infancy. The Maltese prevalence was significantly higher than that reported in both studies (p<0.0001 and p<0.0003 respectively (table 1)).^{16 17}

There were seven cases of recognised syndromes born between 1971 and 1990, which comprised four Down's syndrome, one Noonan's syndrome, one Aarskog's syndrome, and one Killian-Pallister syndrome.

Discussion

The birth prevalence of TF in Malta was found to be significantly higher than that reported in previous studies.⁴⁻¹⁷ The rate was also significantly higher than that found in recent studies with similar methodologies.^{16 17} This may be because of one or more of several factors.

The finding of 0.64/1000 live births (95% CI 0.48, 0.85/1000 live births) may be the true birth prevalence of TF worldwide with under-ascertainment of cases of TF in previous studies. This is unlikely, particularly in recent studies with postmortem examinations undertaken in people dying of unknown causes. Furthermore, TF is a highly distinctive malformation that is easily distinguishable from other congenital cardiac malformations on visual inspection at postmortem examination or surgery. These features are equally unequivocal when diagnosis is established by cardiac catheterisation or echocardiography.

Alternatively, the increasing trends in birth prevalence of TF in Malta reported in this study may be true. This may reflect environmental teratogenic factors that have come into play in recent years, producing a significant excess of TF. However, there have not been any local reports of increasing birth prevalences in other types of malformations and the literature does not report any such type of environmental influence. Moreover, an environmental teratogen is unlikely to be so selective.

The most plausible explanation for the increasing number of cases of TF diagnosed is better ascertainment of the underlying birth prevalence of this condition resulting from better diagnostic and postmortem services. Diagnostic services include availability of cardiac catheterisation since the 1950s and the local introduction of echocardiography in the late 1980s.

The last theory implies that TF in Malta occurs in rates closer to 0.80/1000 live births (1990–1994) than 0.64/1000 live births (1980–1994), which would therefore make the birth prevalence of TF in Malta even higher than that in other countries. A genetic predisposition to TF in the Maltese population may be the cause of this higher birth prevalence of TF.

Further studies with genetic input may clarify the causes for the increased birth prevalence of TF in Malta.¹⁸

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