Pentalogy of Fallot

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INTRODUCTION

Tetralogy of Fallot (ToF) constitutes approximately 10% of all congenital heart disease, with a prevalence in the general population ranging from 0.03% to 2.8%. ToF is a heterogeneous condition, which may be associated with other rare anomalies (Supplementary material, *Table S1*) or occasionally may coexist with otherwise frequent anomalies or variants, such as the bicuspid aortic valve [1]. When ToF coexists with an atrial septal defect (ASD), it is referred to as pentalogy of Fallot (PoF). There is some variation in nomenclature when ToF coexists with a patent foramen ovale (PFO). Some authors include ToF with PFO in the PoF definition [2], while others do not [3–5]. An angiographic study by Dabizzi et al. [5] has shown that ToF is more frequently associated with ASD (23%) than with PFO (10%) [6]. Consequently, the calculated PoF prevalence in the general population depends on how it is defined and range from 0.006% to 0.84%.

Unlike ToF, which has been extensively described, PoF is less represented in the literature.

The aim of this study was to retrospectively describe the clinical and anatomical features of all identified adult PoF patients. We also aimed to compare group 1 (ToF + ASD) with group 2 (ToF + PFO).

METHODS

Briefly, we retrospectively screened patients' discharge diagnoses collected in an electronic database for the presence of PoF in consecutive patients, who were hospitalized from January 2008 to November 2020 for various reasons (mainly cardio-vascular). The patient charts and imaging data for all identified cases were reviewed (detailed description of methods and statistics can be found in the Supplementary material online). Follow-up was defined as time from the first hospitalization in our institution to the collection of data.

The primary end-point was re-interventions. The secondary end-point was cardio-vascular assessment by echocardiographic variables.

RESULTS AND DISCUSSION

In our institution, 63 PoF-patients were hospitalized, at a median age of 21 years; the interquartile range (IQR) was 19–32, and 34 were male (54.0%). Among the PoF patients, 25 (39.7%) presented with ASD type II, 27 (42.8%) had PFO, and PoF type (ASD or PFO) was not specified in 11 patients (17.5%) (group 3). Demographics and clinical profiles are presented in Table 1. Atrial fibrillation (AF) or atrial flutter (AFl) was the most commonly diagnosed arrhythmia (n = 10, 15.9%) and was more frequent in group 1 ($P = 0.02$). Cardiovascular imaging, performed in our center by cardiac computed tomography, cardiac magnetic resonance or both modalities, was available for 53 patients (84.1%). Imaging data are presented in Supplementary material, *Table S2*. The most common PoF-associated cardiovascular anomalies involved the aortic arch, with 15 patients (28.3%) having a right

Table 1. Demographics and clinical profile

	Type of PoF				*P*-value
	Total	ToF + ASD	ToF + PFO	PoF not specified	ToF + ASD vs. ToF + PFO
	n = 63	n = 25	n = 27	n = 10	
Age[a], years, median (IQR)	21 (19–32)	23 (19–32)	19 (18–23)	31 (24–35)	0.09
Male, n (%)	34 (54.0)	12 (48.0)	17 (63.0)	5 (45.4)	0.40
II–III NYHA class, n (%)	17 (27.0)	7 (28.0)	7 (25.9)	3 (27.3)	0.87
Arrhythmias, n (%)					
AF/AFl	10 (15.9)	7 (28.0)	1 (3.7)	2 (18.2)	0.02
Other supraventricular arrhythmias	2 (3.2)	1 (4.0)	1 (3.7)	0 (0)	1.00
Ventricular arrhythmias	5 (7.9)	3 (12.0)	1 (3.7)	1 (9.1)	0.34
Concomitant disorders, n (%)					
Hypothyroidism	9 (14.3)	5 (20.0)	3 (11.1)	1 (9.1)	0.46
HL	7 (11.1)	3 (12.0)	2 (7.4)	2 (18.2)	0.66
Stroke	6 (9.5)	3 (12.0)	2 (7.4)	1 (9.1)	0.66
Mental retardation	5 (7.9)	2 (8.0)	3 (11.1)	0 (0)	1.00
Epilepsy	4 (6.3)	1 (4.0)	2 (7.4)	1 (9.1)	1.00
HT	4 (6.3)	2 (8.0)	1 (3.7)	1 (9.1)	0.60
Obesity	3 (4.8)	2 (8.0)	1 (3.7)	0 (0)	0.60
Asthma	2 (3.2)	1 (4.0)	1 (3.7)	0 (0)	1.00
IGT	2 (3.2)	0 (0)	1 (3.7)	1 (9.1)	1.00
DiGeorge syndrome	2 (3.2)	1 (4.0)	1 (3.7)	0 (0)	1.00

[a]On first hospitalization in our institution

Abbreviations: AF, atrial fibrillation; AFl, atrial flutter; ASD, atrial septal defect; HL, hyperlipidemia; HT, hypertension; IGT, impaired glucose tolerance; IQR, interquartile range; NYHA, New York Heart Association; PFO, patent foramen ovale; PoF, pentalogy of Fallot; ToF, tetralogy of Fallot

aortic arch, 3 (5.7%) having a common origin of the carotid arteries, 3 (5.7%) having an anomalous right subclavian artery, 1 (1.9%) having an anomalous left subclavian artery, and 1 (1.9%) having an aberrant left vertebral artery.

Interventional data are presented in Supplementary material: *Table S3* and *Figure S1*.

- Total surgical correction (TSC) was performed in 60 patients (95.2%), with 37 of them (61.7%) undergoing it as the initial approach, 21 patients (35.0%) after a previous Blalock–Taussig shunt, and 2 patients (3.3%) after percutaneous balloon pulmonary valvuloplasty. The median patient age during TSC was 4 years. In group 1, TSC was performed in 24 patients (96.0%), in group 2 in 25 patients (92.6%), and in group 3 in 11 patients (100.0%).
- Due to the retrospective nature of our study, we lack data on the size and hemodynamic significance of ASD before its closure in childhood. Closure of ASD was performed in 24 patients (96.0%), with 16 of them (66.6%) undergoing closure simultaneously with TSC. Six patients (25.0%) had surgical closure of ASD during re-do operations, and two patients (8.3%) underwent percutaneous ASD closure. The median patient's age during ASD closure was 7 years (IQR 3.75–14.0). Finally, one patient from group 1 had no correction at all.
- Re-interventions after TSC were performed in 31 of the 60 patients (51.7%). The main cause of re-intervention was pulmonary valve disease (27 patients), with pulmonary regurgitation being the most common presentation (18 patients).

Patients from group 1 were significantly older on their first hospitalization in our institution and more frequently presented with AF/AFl compared to patients from group 2. Furthermore, patients from group 1 underwent more re-interventions (Supplementary material, *Table S3*). Echocardiographic variables, adjusted for the patient's age at the echocardiographic assessment and time since the last intervention, showed that patients from group 1 had significantly higher right ventricular systolic pressure compared to patients from group 2 (Supplementary material, *Table S4*). Finally, *Table S5* summarizes pharmacological agents prescribed during the last hospitalization. The median time interval taken into account when estimating the Kaplan–Meier curves (time counted from the moment of TSC of the defect to the present) was: 32 years (IQR 23.0–39.5).

Pentalogy of Fallot is a rare entity, and this study primarily serves as a descriptive report. Given the high prevalence of PFO as a distinct finding, it may not be entirely justified to include it as part of the PoF features. In our PoF cohort, approximately 40% of patients had ASD, 43% had a PFO, and 17% had an unspecified PFO type. Considering the respective prevalence of both anomalies in the general population, it appears that ASD, rather than PFO, is preferentially associated with other features of ToF.

Secondly, patients with PoF often have additional anomalies. Approximately one-third of our patients had an anomaly related to the aortic arch, with the right aortic arch being the most prevalent. This anomaly is known to occasionally coincide with ToF (see Supplementary material, *Table S2*), but its incidence in patients with PoF remains unclear.

Thirdly, patient treatment pathways depend on whether this complex anomaly can be fully corrected through

a single surgical procedure or if preliminary palliation is needed. This is often determined by the presence of additional anomalies, mainly related to the right ventricle outflow tract and the pulmonary vasculature that affect clinical presentation and the timing of the surgical procedure. In our cohort, about 60% of patients underwent a one-time full correction of the anomaly, while the rest required a preliminary procedure before full correction, most often a Blalock–Taussig shunt. Another significant challenge for PoF patients is that not all the effects of complete surgical correction of the anomaly prove durable over time, which is often more complex than in the case of ToF due to additional anomalies. Thus, additional procedures, most commonly related to the pulmonary valve [7], are required several years after TSC. In our cohort, over half of the patients developed pulmonary regurgitation, PS, or complex pulmonary valve disease, requiring interventional treatment. Some of these patients also required re-intervention due to recurrence of either a ventricular septal defect or an ASD. The main treatment and decision to opt for complete correction or staging is multifactorial and based on similar criteria as in ToF. Despite usually good surgical results, these patients require regular long-term follow-up, as many, perhaps even most of them, will over time develop secondary problems.

Fourthly, our results indicated that ToF patients with ASD have worse clinical outcomes (in terms of more frequent AF/AFl and the need for re-interventions) and worse echocardiographic results (higher right ventricular systolic pressure) compared to ToF with PFO. ASD closure may not necessarily reduce the incidence of AF [8], as other factors also matter. AF in patients with congenital heart disease likely appears much earlier than in the general population, especially in patients with Ebstein's anomaly, followed by ToF patients [9].

Limitations

The first limitation of this study is its retrospective design and the fact that the cohort is from a single referral center. Secondly, it cannot be ruled out that some PoF patients died before reaching adulthood. Thirdly, as the data were collected retrospectively and spanned 12 years, not all data were available for all patients. The sample size does not allow for some statistical comparisons, and there is no control group.

Conclusions

We do not claim to finally resolve the nomenclatural question of whether ToF coexisting with PFO should or should not be classified as PoF. In our cohort, however, ToF patients with ASD-II had more cardiovascular comorbidities and underwent more re-interventions compared to ToF patients with PFO. Thus, PFO seems to be rather an "innocent bystander" to ToF.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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