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Ventricularpre-excitationand Ebstein anomaly in a patient with Phelan Mc Dermid syndrome: A case report

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Abstract

Phelan-McDermid syndrome (PMS) or deletion 22q13 syndrome is a rare genetic syndrome resulting from loss of 22q13 region involving the SHANK3 gene. Main features are neonatal hypotonia, global developmental delay, absent to severely delayed speech and minor dysmorphic features. The true incidence remains unknown. The deletion can be detected by high resolution chromosome analysis, confirmed by fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (aCGH). Ebstein's anomaly (EA) is a rare congenital heart disease (1:20.000 live births) that consists in tricuspid valve's malformation: from minimal displacement of the septal and posterior leaflets to involvement of right ventricular outflow with functional pulmonary atresia and severe right ventricular dysfunction. This condition leads to a large spectrum of clinical presentations. EA patients have a large incidence of tachyarrhythmias, most of which can be attributed to accessory atrioventricular pathways that could be observed to electrocardiogram as ventricular pre-excitation. We describe a case of a child with PMS and accidental finding of ventricular pre-excitation to electrocardiogram that underlined the presence of EA.

Key words: ventricular pre-excitation, Ebstein's anomaly, congenital heart disease, genetic syndrome, phelan-mcdermid syndrome

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Introduction

Phelan-McDermid Syndrome (PMS) is a rare genetic condition caused by deletion or other structural change in the 22q13 region or a disease-causing mutation of the SHANK3 gene. The symptoms arise at birth or within the first six months of life, and often consist in hypotonia and developmental delay. Less frequently, children present with heart defects, kidney or other systemic problems, although these are usually not life-threatening malformations.

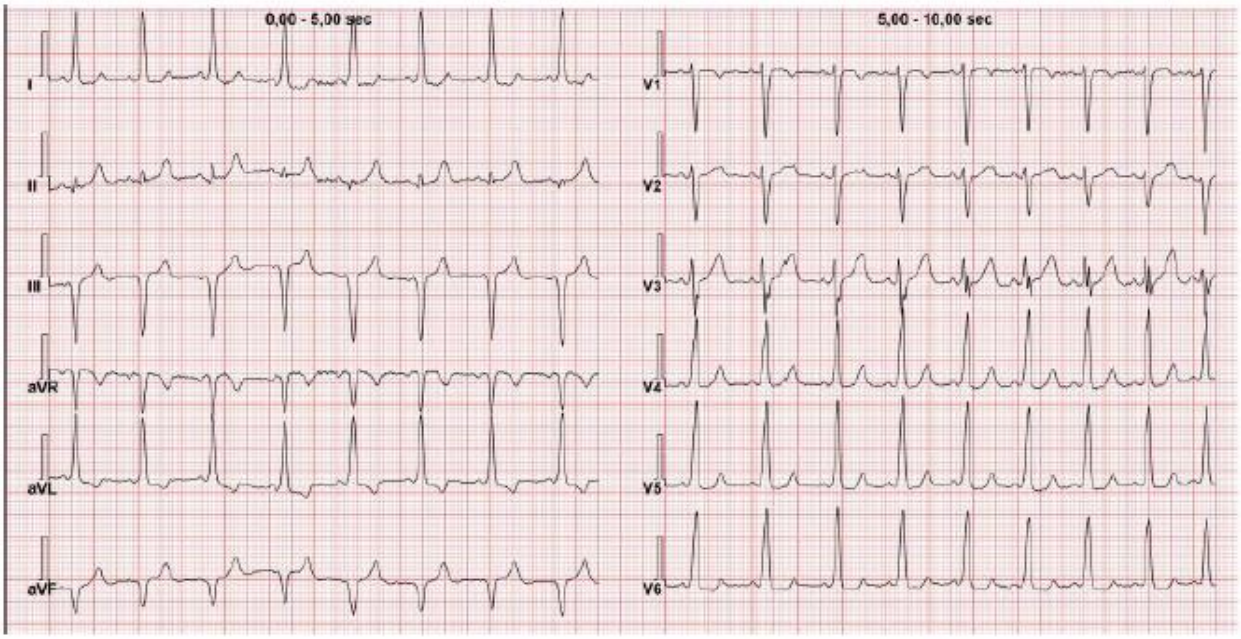
Ebstein's anomaly (EA) of tricuspid valve is a rare congenital heart disease that has long

been a challenge to electrophysiologists and cardiac surgeons. In addition to the hemodynamic burden of the valve defect, Ebstein's patients must also contend with a high incidence of tachyarrhythmias, most of which can be attributed to accessory atrioventricular pathways. We report a case of a 7-years-old girl affected by PMS with a pre-excitation syndromeconcomitant withEA. This is the first case in literature.

Case report

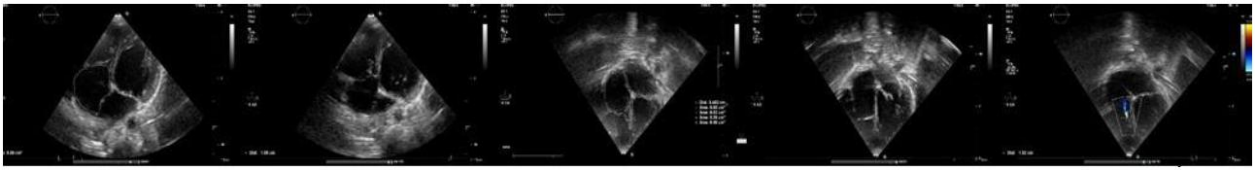
The patient was a 7-year-old girl affected by PMS caused by de novo heterozygous SHANK3 mutation diagnosed a year earlier. She showed dysmorphic (such as hypertelorism, bulbous nose, long eyelashes, epicanthal folds, pointed chin, wide nasal bridge) and neurological features (moderate autism spectrum disorder, mild intellectual disability, hyperkinetic and inattentive behavioural pattern and motor coordination deficit), hence she was followed by the Neuropsychiatric Infant Department of our Hospital. During a check, she performed an electrocardiogram (Fig. 1) that showed sinus rhythm, 97 bpm, PR interval of 0.10 s, QRS interval of 0.11 s and delta waves, more evident in the left precordial leads. Due to the shortening of PR interval and delta waves, we suspected a ventricular pre-excitation. According to the QRS vector's (negative in leads III, aVR, aVF, V1, V2, V3 and positive in I, II, aVL, V5, V6) we supposed aright lateral accessory pathway.

Fig.1 Patient's electrocardiogram (see text)



We performed 2D echocardiography (Fig. 2) that revealed features of EA: the tethering of septal tricuspid leaflet to the ventricular wall associated with mild tricuspid regurgitation jet. There were no other associated anomalies.

Fig.2 Patient's echocardiogram (see text)



We measure the distance between the septal tricuspid leaflet and the crux cordis (11 mm), increased in EA patients, and calculated the GOSE score (Great Ormond Street Echocardiography Score) to identify the severity of the malformation: Grade 2 (0,5; related to 10% of mortality). Reviewing patient's history we discovered that she has presented tachycardia episodes.

Discussion

Phelan-McDermid Syndrome (PMS) or 22q13 Deletion Syndrome is a rare microdeletion syndrome resulting from loss of 22q13 by simple deletion, unbalanced translocation, ring chromosome formation, or other unbalanced structural changes with involvement of at least part of SHANK3, or a heterozygous pathogenic variant in SHANK3. SHANK3 gene codes for a structural protein found in the post-synaptic density.

[1][2][3] PMS's incidence is indeterminate and it's under-diagnosed at both the laboratory and the clinical levels. The deletion occurs with equal frequency in males and females and has been reported in mosaic and non-mosaic forms. The structural abnormalities may be inherited in an autosomal dominant manner or de novo.

[2][4]Our patient showed a heterozygous, de novo, autosomal dominant deletion of SHANK3 gene (c.4102delG) identified by Next Generation Sequencing.

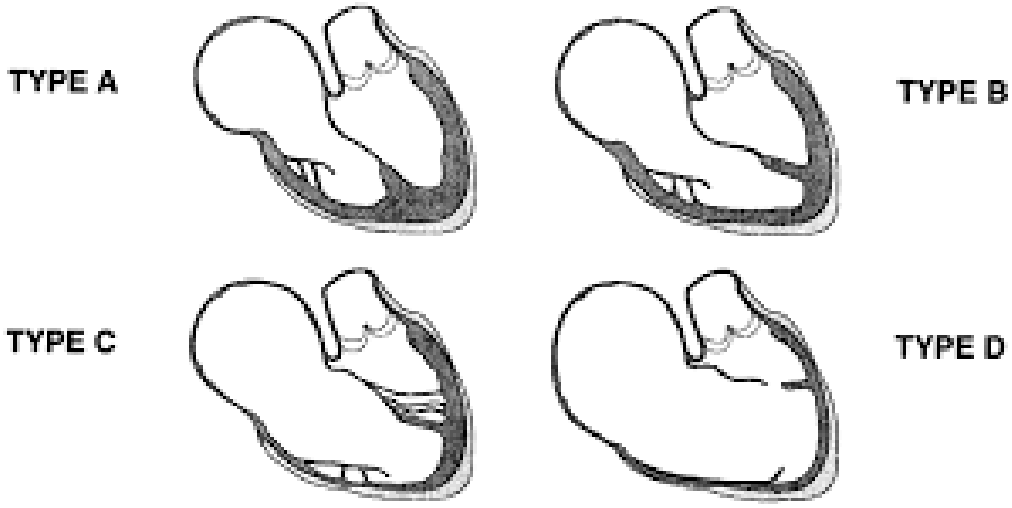
PMS is characterized by global developmental delay, severe deficits in or lack of expressive language, moderate to profound intellectual disability, behavioural manifestations frequently including autism, muscle hypotonia, seizures, abnormal brain Magnetic Resonance Imaging (MRI) [3][5] and minor dysmorphic features. Malformations and comorbidities found in sizable minorities of PMS patients include gastrointestinal symptoms, endocrine-metabolic disorders, immune dysfunctions, genitourinary abnormalities, heart defects (3% to 25%)including aortic regurgitation, patent ductus arteriosus, totally anomalous pulmonary venous return, atrial septal defect and tricuspid valve regurgitation [6][7].

The diagnosis is based on cytogenetic, molecular cytogenetic and/or molecular demonstration of loss or disruption of chromosome region 22q13.3 which contains the SHANK3 gene.

[8] FISH and aCGH have significantly enhanced the detection of this deletion. [9] In our

case, the patient showed mild to moderate neurological disorders without MRI or electroencephalography signs, while other listed comorbidities were absent

Fig.3 Carpentier Classification system. Type A adeguate volume of the true RV; Type B large atrialized portion of the RV with freely mobile anterior leaflet; Type C restrictive mobility of the anterior leaflet; Type D almost complete atrialization of the RV.



Ebstein's anomaly (EA) is a rare malformation of the tricuspid valve (TV) that has variable anatomic and pathophysiologic characteristics. The incidence is approximately 1:20,000 and occurs in less than 1% of patients with congenital heart disease but accounts for nearly half (40%) of all congenital malformations of the TV. [10][11] The anatomical hallmark is the apical displacement of the attachments of septal and posterior leaflets of the TV. Anatomical features include failure of TV leaflet delamination, apical descent of the functional tricuspid orifice, right ventricular (RV) dilation and "atrialization", anterior leaflet abnormal fenestrations and tethering, and right atrioventricular junction dilation.[12][13] The critical distinguishing feature of EA from other congenital regurgitant lesions is the degree of apical displacement of the septal leaflet (≥ 8 mm/m2 body surface area).[17] Most cases of EA are sporadic and familial incidence is rare. TV displacement is widely variable resulting in a range of valve pathology from little to no or severe regurgitation. Morphologic classification of the TV (types A to D) was based on a review of the echocardiographic images or the surgical/autopsy records according to the guidelines published in 1988 by Carpentier et al. (Fig. 3). Classification systems also include quantitative Celermajer (GOSE) score (Tab. 1 related with prognosis. [14][15]

Physiology depends on the severity of the RV outflow tract obstruction/pulmonary stenosis, degree of atrialized RV and RV dysfunction. Despite the absence of prograde flow across the pulmonary valve, there can be pulmonary regurgitation in "functional" pulmonary atresia. [17] EA is often associated with interatrial communication (patent foramen ovale/ostium secundum atrial septal defect) [15] and pulmonary valve stenosis or atresia

(30%).

A significant minority of patients are found to have left ventricular abnormalities: left ventricular noncompaction (18%), mitral valve prolapse (15%) or dysplasia (4%), and bicuspid aortic valve (8%)[16][17][18]. Baseline testing in patients with EA includes electrocardiogram, chest radiograph, 24-hour Holter monitor, echocardiography, cardiac magnetic resonance, and as-needed cardiopulmonary exercise testing. Electrocardiogram classically includes PR interval prolongation, tall P waves, and a degree of right bundle branch block [12]. Atrial tachycardia including atrial fibrillation, atrial flutter or ectopic atrial tachycardia is present in 25% to 65% of patients. Atrioventricular nodal re-entrant tachycardia is present in approximately 10% of patients and 10% to 45% of patients have accessory pathways leading to ventricular pre-excitation and Wolff-Parkinson-White syndrome [19][20] as in our patient.

Tab.1 "Celermajer" echocardiographic grading score-GOSE (Great Ormond Street Echocardiography Score).

GOSE score	Index (RA + RV): (RV + LA + LV)	Risk of mortality (%)
Grade 1	Ratio < 0.5	0
Grade 2	Ratio of 0.5 to 0.99	10
Grade 3	Ratio of 1 to 1.49	44 - 100
Grade 4	Ratio ≥ 1.5	100

Clinical presentation is variable due to the underlying heterogeneity of disease anatomy and physiology. Neonates with severe displacement of the TV and interatrial communication may present with heart failure and cyanosis and need for early intervention[21]. On the other hand, initial presentation due to new onset arrhythmias is common [22]. Accessory conduction pathways leading to atrioventricular re-entrant tachycardia are predominantly found in the septal and posterior areas of the TV suggesting an embryologic link between valve malformation and pathway occurrence.[23] EA patients need to be evaluated regularly by a cardiologist who has expertise in congenital heart disease and management must be specific for each patient. Observation alone is advised for asymptomatic patients with no right-to-left shunting and only mild cardiomegaly. Children who have survived infancy generally do well for several years and surgery can be postponed until symptoms appear. [10] Surgical repair is recommended for those cases with congestive heart failure or severe cyanosis and should be considered in case of progressive RV dilatation, heart hypertrophy on chest radiography, or appearance of premature ventricular contractions. [24] TV repair is the goal of operative intervention. [19] Patients with EA and cardiac failure who aren't candidates for surgery are treated with standard heart failure therapy. [12] Electrophysiological evaluation and

radiofrequency ablation of symptomatic accessory pathway(s) should be performed when feasible in patients with EA with a pre-excitation pathway. Most patients can be treated percutaneously with catheter ablation. in these patient mapping accessory pathways is often a challenge and fractionated ventricular electrograms may identify the true tricuspid annulus. [21][22] In our case report, the patient needn't neither surgery for EA nor ablation of the accessory pathway that is currently asymptomatic (only few episodes of tachycardia), so she undergoes clinical and echocardiographic follow-up.

Conclusion

EA is a rare congenital heart defect occurring in 1:20.000 live births. The spectrum of clinical presentations is variable due to the disease anatomy and physiology heterogeneity.EA has to be clinically suspected in presence of alteration of electrocardiogram as ventricular pre-excitation, like in our case.Thefindings of this peculiar case allowed a link between PMS andEA that wasn't yet reported in literature.

Conflicts of interest: The authors declare no conflict of interest.

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