Ventricular repolarization abnormalities: the electrocardiographic track of cardiac tumoural involvement in an infant with tuberous sclerosis complex. A case report

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Background

Primary cardiac tumours are rare in children. Against this backdrop, Doppler echocardiogram is the main diagnostic procedure, while electrocardiogram (ECG) usually plays a secondary role, by detecting tumoural consequences as cardiac arrhythmias and chambers overload. We describe a case where an electrocardiographic sign was the cornerstone to diagnosis and surveillance of an infant with a cardiac rhabdomyoma.

Case summary

A female infant was referred for cardiac evaluation to elucidate an electrocardiographic abnormality, detected during investigation of seizures. She had recently been diagnosed with epilepsy and was under three different anticonvulsants for appropriate control. Cardiovascular symptoms were absent. Skin inspection revealed hypochromic macules. Respiratory and cardiovascular examinations were normal, as well as laboratorial tests and chest radiography. Electrocardiogram (ECG) showed dome-shaped ST-segment elevation in V2 and V3. Transthoracic echocardiogram unveiled a single hyper-echogenic node (0.4 cm²) in the interventricular septum. Cardiac chambers had normal size and function and Doppler analysis was also normal. No specific medication was used to treat the tumour. During follow-up, she remained free of cardiac symptoms. Eighteen months after her first visit to the cardiologist, routine clinical assessment, ECG, and transthoracic Doppler echocardiogram normal results stated the spontaneous and complete involution of the tumoural lesion.

Discussion

Convex ST-segment elevation, generally related to myocardial injury, is unusual in paediatric patients. Once it occurs in asymptomatic individuals within this age bracket, exclusion of cardiac tumours is mandatory. However, data regarding the accuracy of such electrocardiographic marker in this clinical setting are still to be defined.

Keywords

Cardiac tumours • Rhabdomyoma • Tuberous sclerosis complex • Electrocardiogram • Case report

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**Learning points**

- Primary cardiac tumours are rare in children; the vast majority of them are benign. Rhabdomyoma, the most common histopathological finding, is often associated with tuberous sclerosis complex (TSC), a systemic genetic disorder. Cardiac rhabdomyomas (CRs) are multiple and usually silent in most TSC patients. Symptoms, when appearing, relate to the lesion number, size and location within the heart. Haemodynamic compromise is unlikely, but can occur as a consequence of big cardiac tumours or inflow/outflow tract obstruction. Heart rhythm disturbances are quite more common and a consequence of big cardiac tumours or inflow/outflow tract obstruction. Convex and localized ST-segment elevation is a promising marker for diagnosis and surveillance of primary cardiac tumours in infants. However, data regarding its accuracy in this clinical setting are still to be defined.

**Introduction**

Primary cardiac tumours are rare in the paediatric population and overall benign. Rhabdomyoma, the most common histopathological finding, is often associated with tuberous sclerosis complex (TSC), a systemic genetic disorder. Cardiac rhabdomyomas (CRs) are multiple and usually silent in most TSC patients. Symptoms, when appearing, relate to the lesion number, size and location within the heart. Haemodynamic compromise is unlikely, but can occur as a consequence of big cardiac tumours or inflow/outflow tract obstruction. Heart rhythm disturbances are quite more common and a lifelong concern. Cardiac evaluation is recommended in TSC patients at the time of diagnosis and every 3–5 years for surveillance. Doppler echocardiography is the imaging modality of choice to assess cardiac tumoral involvement in children with TSC. Standard 12-lead electrocardiogram (ECG) is also warranted, usually with the supporting role of detecting tumour consequences as arrhythmias and chambers overload. We describe a case of an infant where an electrocardiographic sign was the cornerstone to a CR diagnosis.

**Timeline**

| Time               | Events                                                                                           |
|--------------------|--------------------------------------------------------------------------------------------------|
| 18 January 2017    | Epilepsy diagnosis                                                                               |
| 30 March 2017      | Single cardiac rhabdomyoma (CR) detection                                                        |
| 19 June 2018       | Confirmation of TSC clinical diagnosis                                                          |
| 19 September 2018  | CR is no longer detected on echocardiography and ECG normalizes                                  |
| 31 October 2018    | Brain magnetic resonance imaging unveils tubers, cerebral white matter radial migration lines and ependymal nodules |

**Case presentation**

An eight-month-old female was referred for cardiac evaluation to elucidate an electrocardiographic abnormality detected during investigation of seizures. Cardiac symptoms were absent. She was undergoing routine neurological evaluations for epilepsy, controlled with Vigabatrin, Valproic Acid, and Clobazam. Family history was null regarding genetic syndromes. Prenatal, childbirth, and neonatal records were unremarkable. On examination, skin inspection revealed hypochromic macules (Figure 1). Respiratory and cardiovascular inquiries were normal, same as laboratory tests (Table 1) and chest radiography.

Her first ECG showed sinus rhythm, general parameters within normal range (heart rate: 125 b.p.m.; PR interval: 90 ms, SÅQRS: +50; QRS duration: 70 ms; QT: 260 ms; QTc: 375 ms, and a pronounced dome-shaped ST-segment elevation in V2/V3 (Figure 2A). The admission’s transthoracic echocardiogram detected a single hyper-echogenic regular node in the mid part and right face of the interventricular septum, with 0.4 cm² estimated area (Figure 2B–D). Cardiac chambers and Doppler analysis were normal without evidence of outflow tract obstruction.

**Table 1** Results and reference values, according to age and sex, of the most relevant laboratorial tests performed in our patient

| Labaratorial examination | Results  | Reference Value   |
|--------------------------|----------|-------------------|
| Haemoglobin              | 10.7 g/dL| 10.3–13.7 g/dL    |
| Creatinine               | 0.26 mg/dL| 0.17–0.42 mg/dL  |
| Potassium                | 4.3 mEq/L| 3.5–5.0 mEq/L     |
| Sodium                   | 137 mEq/L| 135–145 mEq/L     |
| Ionic serum calcium      | 5.39 mg/dL| 4.8–5.5 mg/dL    |
| Magnesium                | 2.07 mg/dL| 1.71–2.29 mg/dL  |
| Ammonia                  | 45 μmol/L| 21–50 μmol/L      |
| Glucose                  | 83 mg/dL | 60–110 mg/dL      |
| TSH                      | 8.27 μIU/mL| 0.27–10 μIU/mL   |
| Free T4                  | 1.12 ng/dL| 0.93–1.70 ng/dL  |
| CK-MB                    | 3.2 ng/mL| Until 3.8 ng/mL   |
| Troponin                 | <0.006 ng/mL| Until 0.04 ng/mL|

Figure 1 Hypochromic skin macules in our patient’s back (A) and left leg (B).
Ambulatory ECG 24 h-Holter monitoring displayed sinus rhythm, mean heart rate of 111 b.p.m., normal PR interval, and QRS duration. No arrhythmias were detected.

During follow-up, investigation of recurrent urinary tract infections revealed multiple bilateral renal cysts (Figure 3). Epilepsy, confirmed by electroencephalogram, was still controlled with the same medications. Seizures aetiology was elucidated, as brain magnetic resonance imaging unveiled cortical dysplasia and ependymal nodules (Figure 4).

Meanwhile, the patient remained free of cardiac symptoms. Given the benign course of the cardiac disease, no specific medication
(mTOR inhibitors) was used to treat the tumour. Cardiologic re-
evaluation was performed 18 months after. By then, ECG and echo-
cardiogram had become thoroughly normal (Figure 5) documenting
the total and spontaneous CR involution.

Discussion

Electrocardiogram was requested considering differential diagnosis of
seizures in children—given that complex ventricular arrhythmias can
manifest as convulsion and thus confound clinical investigation.
Moreover, primary neurological disorders—e.g. epilepsy, stroke, brain
tumours, cranio-cerebral trauma—may incur substantial autonomic
imbalance leading to cardiac alterations commonly disclosed on ECG,
such as sub-epicardial ischaemia, ST-segment elevation, and prolonged
QTc interval.8 When resulting from neurologic conditions, ventricular
repolarization abnormalities are overall displayed in multiple leads.8
Hence, although epilepsy diagnosis was beyond question, it could not
by itself explain the confined arrangement of ECG observations.

ST-segment elevation is an uncommon finding in infancy. Its most
common aetiology in this age bracket is pericarditis.9 However, the
absence of fever and cardiac symptoms, added to the localized ST-
segment elevation pattern without PR-segment depression, readily
dismissed this hypothesis. Normal laboratory tests, respectively,
rules out hydro-electrolytic disturbances and hypothyroidism. Sub-
epicardial injury—due to myocarditis, Kawasaki disease, or anomal-
ous left coronary artery—was also precluded, once cardiac size, func-
tion, and markers were all normal.9 The lack of J-waves testified
against Brugada syndrome,9 while literature search revealed that no
ventricular repolarization abnormalities had been reported so far in
association with any of the drugs our patient was taking.10,11

Figure 4 Brain magnetic resonance imaging of our infant patient
demonstrates cortical tubers (black arrow), cerebral white matter
radial migration lines (right arrows), and ependymal nodules (circled
with red-dashed line).

Figure 5 Electrocardiogram obtained almost 20 months after the rhabdomyoma diagnosis with normal findings, considering our patient’s age and
sex, showing the complete normalization of the ST-segment (A). Surveillance transthoracic echocardiogram—apical four-chamber view (B), apical
short-axis subcostal view (C), and long-axis view (D). The cardiac rhabdomyoma was no longer detected in our patient.
autopsies. Cardiac rhabdomyoma is the most common primary paediatric cardiac referral centres, and rare in clinical practice, occurring in 0.20% of children presenting to TSC patients. Although frequently silent, CRs have important implications: often the syndrome’s first sign, they can be detected early, are highly specific and a major feature for TSC clinical diagnosis (Table 2).

Next, cardiac imaging was performed to clarify the regional distribution of such electrocardiographic abnormalities. Apart from excluding chambers overload and blood flow obstacles, echocardiogram uncovered a small heart tumour, away from coronary courses. Cardiac tumours have been diagnosed more frequently after the advent of echocardiography. Still, primary cardiac neoplasms are uncovered a small heart tumour, away from coronary courses. Few case reports denoted specific ST-T changes in patients with CRs; however, spatiotemporal correlation between ECG and tumours prompted precocious and multidisciplinary assistance. Interestingly, the tumour spot correlated spatially to the leads displaying that unusual repolarization pattern—would it be a ‘fingerprint’?

Eighteen months after, echocardiogram documented the complete involution of the heart lesion—CRs actually tend towards spontaneous regression or even disappearance during the first 2 years of life. Electrocardiogram normalized concurrently. As drug therapy was unaltered, one could state that the first ECG pattern was not a pharmacologic effect.

The association between heart tumours and electrocardiographic abnormalities has been described in several publications, often case reports on metastatic lesions. Better evidence was provided by two studies demonstrating that, in patients with cancer, localized ST-segment elevation was the most specific electrocardiographic sign of myocardial malignant infiltration. Suggested pathophysiologic mechanisms include: (i) direct compression of coronary arteries, (ii) tumour extension/embolization to coronary lumen, (iii) neoplastic pericardium invasion, or (iv) myocardial injury by direct pressure or physiochemical action. Otherwise, literature regarding electrocardiographic features of primary cardiac tumours is scarce. Few case reports denoted specific ST-T changes in patients with CRs; however, spatiotemporal correlation between ECG and tumours could not be established by the authors. In our patient’s case, dome-shaped ST-segment elevation, spatial and timely related to the CR, was an important clue during clinical evaluation. More studies are needed to confirm this association.

| Table 2 | Revised clinical diagnostic criteria4 |
|---|---|
| **Tuberous sclerosis complex clinical diagnostic criteria** |
| **Genetic diagnostic criteria** | Identification of either TSC1 or TSC2 pathogenic mutations in DNA—note that in 10–25% of patients with TSC, no pathogenic mutation is identified by conventional genetic testing. Hence, a normal result does not exclude TSC diagnosis. |
| **Clinical diagnostic criteria** | 
| **Major features** | 
| 1. Hypomelanotic macules (≥3, at least 5 mm diameter) | 
| 2. Angiofibromas (≥3) or fibrous cephalic plaque | 
| 3. Ungual fibromas (≥2) | 
| 4. Shagreen patch | 
| 5. Multiple retinal hamartomas | 
| 6. Cortical dysplasiasa | 
| 7. Subependymal nodules | 
| 8. Subependymal giant cell astrocytoma | 
| 9. Cardiac rhabdomyoma | 
| 10. Lymphangioleiomyomatosis (LAM)b | 
| 11. Angiomyolipomas (≥2) | 

**Minor features**

- 1. ‘Confetti’ skin lesions
- 2. Dental enamel pits (≥3)
- 3. Intraoral fibromas (≥2)
- 4. Retinal achromic patch
- 5. Multiple renal cysts
- 6. Non-renal hamartomas

Identification of either TSC1 or TSC2 pathogenic mutations in DNA—note that in 10–25% of patients with TSC, no pathogenic mutation is identified by conventional genetic testing. Hence, a normal result does not exclude TSC diagnosis.

*Includes tubers and cerebral white matter migration lines.

*A combination of the two major clinical features, LAM and angiomyolipomas, without other features does not meet criteria for a definite diagnosis.

For definite TSC diagnosis, either one major feature or ≥2 minor features are necessary: either one major feature or ≥2 minor features. Possible diagnostic criteria for TSC are satisfied by either one major feature or ≥2 minor features.

**Table 2** Revised clinical diagnostic criteria4

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According to some studies, 70–90% of children with CR have TSC, a multi-system autosomal dominant disorder. Tuberous sclerosis complex is reported in 1/6000 to 1/10 000 live births. Mutations in TSC1 and TSC2 genes (encoding for hamartin and tuberin, respectively) account for the majority of cases. Abnormal hamartin-tuberin tumour suppressor proteins imply in ubiquitous loss of control over cell cycle progression. Indeed, TSC most common findings are benign tumours (hamartomas) in the skin, brain, heart, lung, and kidneys. However, clinical spectrum is wide and syndrome’s recognition relies on diagnostic criteria (Table 2).

Heart involvement with benign tumours befalls in over one-half of TSC patients. Although frequently silent, CRs have important implications: often the syndrome’s first sign, they can be detected early, are highly specific and a major feature for TSC clinical diagnosis (Table 2). In this case, detection of a CR in a child with hypochromic skin macules not only certified TSC diagnosis, further endorsed by the unveiling of renal cysts and cerebral cortical dysplasia but also prompted precocious and multidisciplinary assistance. Interestingly, the tumour spot correlated spatially to the leads displaying that unusual repolarization pattern—would it be a ‘fingerprint’?

In this case, detection of a CR in a child with hypochromic skin macules not only certified TSC diagnosis, further endorsed by the unveiling of renal cysts and cerebral cortical dysplasia but also prompted precocious and multidisciplinary assistance. Interestingly, the tumour spot correlated spatially to the leads displaying that unusual repolarization pattern—would it be a ‘fingerprint’?

In this case, detection of a CR in a child with hypochromic skin macules not only certified TSC diagnosis, further endorsed by the unveiling of renal cysts and cerebral cortical dysplasia but also prompted precocious and multidisciplinary assistance. Interestingly, the tumour spot correlated spatially to the leads displaying that unusual repolarization pattern—would it be a ‘fingerprint’?
needed to explore the role of ECG concerning diagnosis and follow-up of primary cardiac tumours, especially in children presenting with other TSC characteristics.

Conclusion
Convex ST-segment elevation, generally related to myocardial injury, is unusual in paediatric patients. Once it occurs in asymptomatic individuals within this age bracket, exclusion of cardiac tumours is mandatory. However, the accuracy of such electrocardiographic marker in this clinical setting still needs definition.

Lead author biography
Mirella Facin graduated in Medicine at Universidade Federal do Paraná (UFPR), had residency training in Internal Medicine (Hospital de Clínicas—UFPR), Cardiology (Instituto Dante Pazzanese de Cardiologia de São Paulo), and Clinical Electrophysiology (Instituto do Coração—InCor-HCFMUSP). She is a specialist in Cardiology (Brazilian Society of Cardiology) and Clinical Electrophysiology (Brazilian Society of Cardiac Arrhythmias), and an ESC and AHA member. Currently, she works as an assistant physician at Instituto do Coração (InCor–HCFMUSP) and as a general physician at São Paulo State Court of Justice.

Supplementary material
Supplementary material is available at European Heart Journal - Case Reports online.

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IRB approval for this report has been obtained.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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