Cardiology in the Young

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Everolimus treatment in a 3-month-old infant with tuberous sclerosis complex cardiac rhabdomyoma, severe left ventricular outflow tract obstruction, and hearing loss

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Brief Report

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Abstract

Tuberous sclerosis complex is a rare multisystem genetic disorder characterised by the growth of numerous tumour-like malformations in many parts of the body including skin, kidneys, brain, lung, eyes, liver, and heart. Mutations in the *TSC1* or *TSC2* genes have been reported to cause disruption in the TSC1–TSC2 intracellular protein complex, causing over-activation of the mammalian target of rapamycin protein complex. In this study, we present a 3-month-old male infant diagnosed with tuberous sclerosis, bilateral neurosensorial hearing loss, Wolff–Parkinson–White syndrome on electrocardiography, multiple cardiac rhabdomyomas with severe stenosis in the left ventricular outflow tract, who responded well to the Everolimus therapy.

Tuberous sclerosis (also known as tuberous sclerosis complex) is a rare autosomal-dominant inherited multisystem disorder with a birth incidence of approximately 1 per 5000–10,000 live births. This syndrome is characterised by numerous tumour-like malformations on many parts of the body such as the skin, kidneys, brain, lung, eyes, liver, and heart.[1] We present a case of 3-month-old male infant diagnosed with tuberous sclerosis, bilateral neurosensorial hearing loss, Wolff–Parkinson–White syndrome on electrocardiography, multiple cardiac rhabdomyomas with severe stenosis in the left ventricular outflow tract who responded well to the Everolimus therapy.

Case

A 3-month-old male infant who was born at home presented with complaints of contraction and bruising all over his body. This occurred for a total of four times in 15 days, at an interval of 3–4 days, each lasting for approximately 1–2 minutes. The 33-year-old mother reported not visiting a health centre during the entire term of pregnancy, and that she and her husband were related by blood. A physical examination of the patient was done to determine his body weight (7000 g [68p]), height (63 cm [65p]), and the presence of 3/6 systolic murmur in the mesocardial focus. The heart rate was reported as 110/min and the arterial blood pressure as 80/60 mmHg. Although the neurological examination of the patient showed no bilateral response to audible stimuli, the skin examination revealed numerous hypopigmented macules, measuring 3 × 2 cm in the left eye lateral, 3 × 5 cm in the periumbilical region, 2 × 1 cm in the lower inner surface of the right leg, and a few millimetres on both feet (Fig 1 a). Other system examinations were normal. The laboratory examination showed a haemoglobin level of 10.8 g/dl, haematocrit 32%, white blood cell 12,300/mm^3, platelet count 361,000/mm^3, and the biochemical values, coagulation panel, and urine test were reported as normal.

While the electrocardiography was compatible with WPW syndrome (short PR, delta wave, and wide QRS) (Fig 1b), the transthoracic echocardiography showed round, smooth-edged, hyperechogenic masses in the left atrium (10.2 × 10.1 mm adherent to the mitral anterior leaflet), the left ventricular outflow tract obstruction (7.9 × 6.1 mm), the left ventricular midcavitary region (2–3 smaller), and the right ventricular apex (9.1 × 5 mm). The mass in the left ventricular outflow tract obstruction had caused severe stenosis (peak gradient 65 mmHg), and the left ventricle and interventricular septum were hypertrophic (secondary to left ventricular outflow tract obstruction) (Fig 2a). In addition, multiple subependymal nodules were observed in the T1 A sections at the caudate nucleus level (Fig 2c) and in the Sagittal T2 A section at the lateral ventricular frontal horn level (Fig 2d). Although abdominal and urinary ultrasonography and eye examination were all normal, a positive TSC2 mutation was revealed by the genetic examination and a bilateral neurosensory hearing loss by a neonatal hearing screening test.

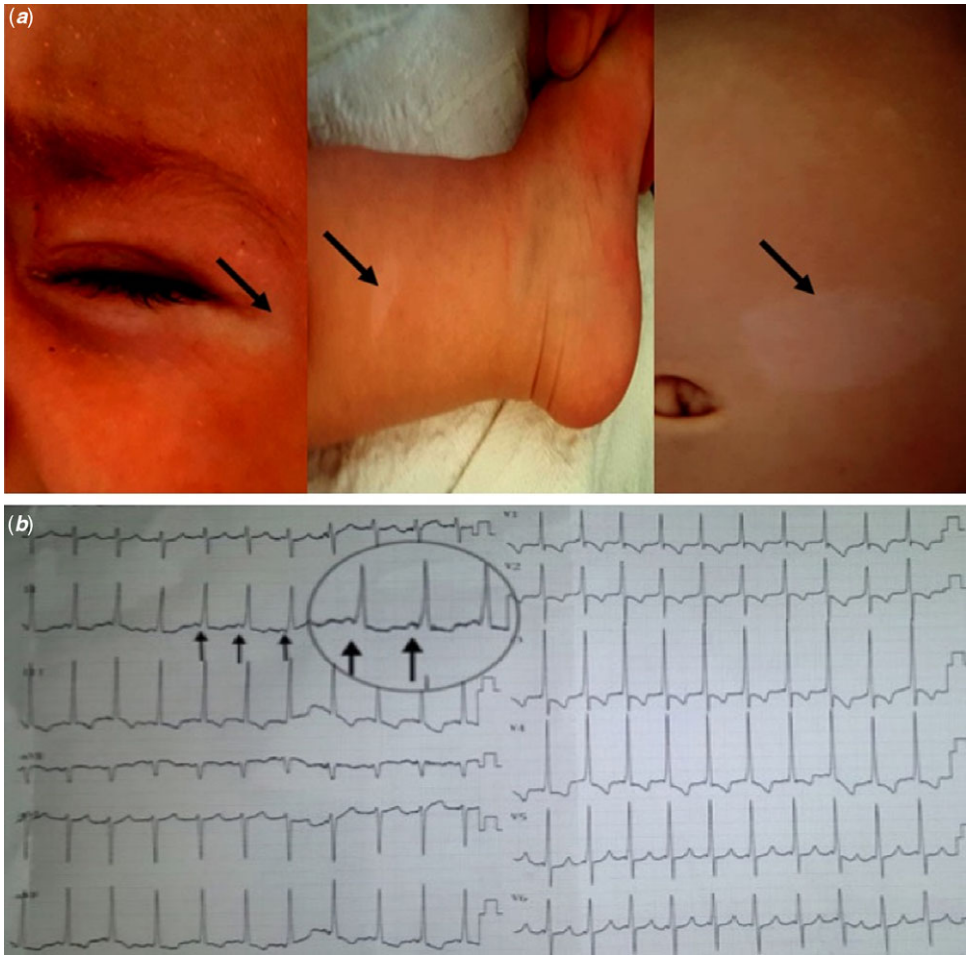

Figure 1. (***a***) Hypopigmented lesions of the patient on the skin (arrows). (***b***) Electrocardiogram of the patient (delta wave, broad QRS, and shortened PR).

At the time of hospitalisation, the patient was diagnosed with tuberous sclerosis, cardiac rhabdomyoma, and WPW syndrome. He was initially administrated with Levetiracetam for convulsions, and a prophylactic treatment (propranolol) was prescribed for the WPW syndrome. After Levetiracetam, the patient's convulsions and bruises did not recur and no tachycardia was ever reported in him. Thereafter, the treatment with Everolimus (4.5 mg/m^2 once a week, oral in two doses), a rapamycin analogue, was initiated for cardiac rhabdomyoma causing LV hypertrophy and severe left ventricular outflow tract stenosis. During follow-up, the patient's convulsions did not recur, the cardiac masses shrank significantly after 4 months of treatment (6.3 × 5.4 mm in the left atrium, 2.7 × 2.3 mm in the LVOT; Fig 2b), and the most recently measured peak pressure gradient at the left ventricular outflow tract was 18 mmHg. Although the Everolimus treatment of the patient was stopped at the end of the fourth month, the patient is still followed-up at regular intervals.

Discussion

As mentioned earlier, TSC can affect several parts of human body and the expression of the disease varies considerably. The diagnosis of TSC can be made clinically or through genetic testing, however, in approximately 25% of genetic tests, no mutation may be detected.[2] Therefore, a negative genetic test does not automatically rule out the diagnosis of TSC. Nevertheless, in our case, the genetic testing revealed a positive *TSC2* gene mutation.

In normal cells, the mTOR signalling cascade (also known as the phosphatidylinositol 3-kinase/protein kinase B/mTOR pathway) plays an important role in cell growth, proliferation, and survival. Inhibition of the TSC1–TSC2 complex results in the over-activation of mTOR, giving rise to cell growth and proliferation.[3] In addition, mTOR forms two distinct multiprotein complexes, mTORC1 and mTORC2, which are differentiated by their interaction partners, substrate selectivity, and sensitivity to rapamycin (sirolimus) and its analogues (e.g., Everolimus). Dysregulation of the mTOR pathway plays a role in the development of many tumours or hamartomatous lesions, including TSC and other neurological disorders.[3]

Typically, TSC is caused by a mutation in the *TSC1* or the *TSC2* gene. Loss of one of these genes triggers constitutive activation of the mTOR signalling pathway, giving rise to abnormal cell growth/proliferation and the subsequent formation of hamartomatous lesions.[3] The discovery of the relationship between TSC1–TSC2 and mTOR has led to significant clinical advances in the use of mTOR inhibitors, especially sirolimus and its analogue Everolimus, for the treatment of several TSC manifestations.[3,4] Recent studies have shown positive results of the use of rapamycin analogue in patients with TSC accompanied by cardiac rhabdomyoma, subependymal giant cell astrocytoma, renal angiomyolipoma, and epilepsy.[5]

The characteristic TSC central nervous system lesions include cortical tubers (also called glioneuronal hamartomas), subependymal nodules, giant cell astrocytoma, and radiologically detectable white matter abnormalities.[1] Cortical tubers are the distinguishing

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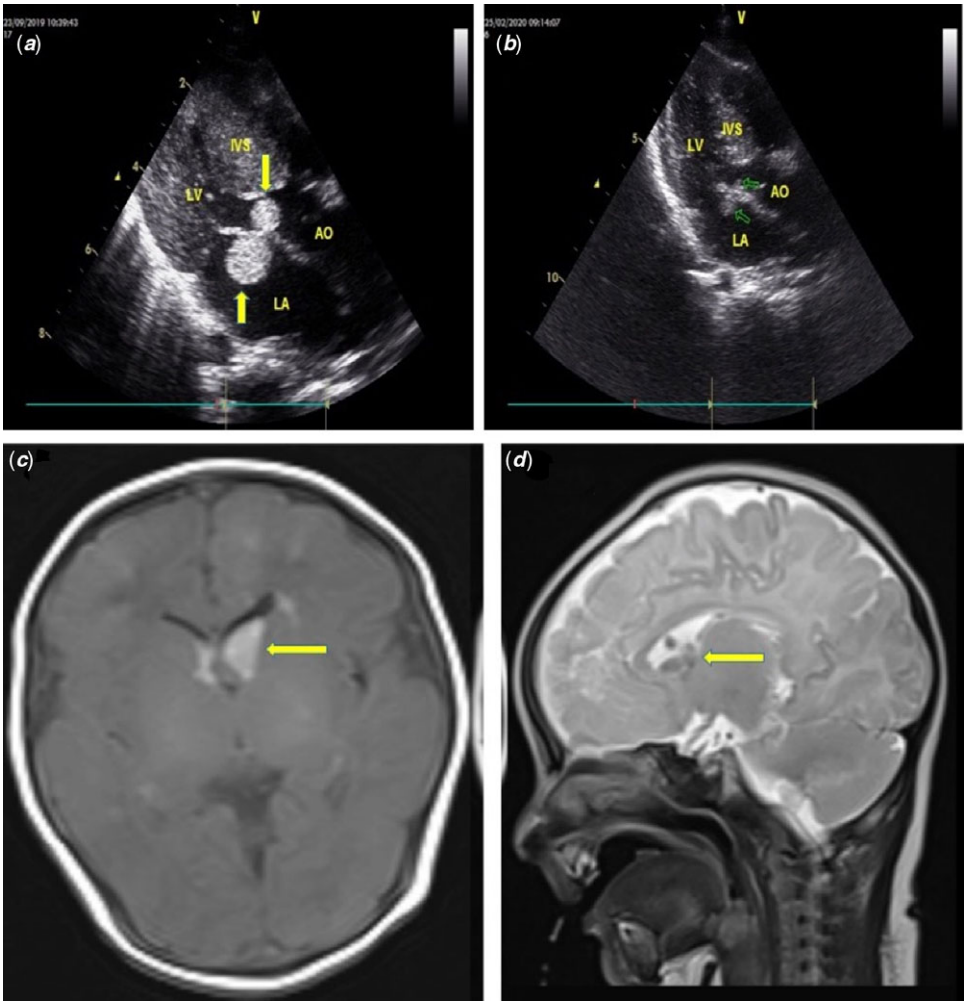

Figure 2. Echocardiographic images of cardiac rhabdomyomas located in ([***a***] pretreatment) the LA, measuring 10.2 × 10.1 mm and the outlet of the LV, measuring 9.1 × 5 mm, ([***b***] post-treatment) in the LA, measuring 6.3 × 5.4 mm and the outlet of the LV, measuring 2.7 × 2.3 mm. Arrow indicates the cardiac rhabomyomas. (***c*** and ***d***) Brain MR imaging of the patient. (***c***) Hyperintense subependymal nodule according to parenchyma in T1 A sections at caudate nucleus level. (***d***) Sagittal T2 A section, hypointense subependymal nodules are observed at the frontal horn level in the lateral ventricle. AO=aorta; IVS=interventricular septum; LA=left atrium; LV=left ventricle.

feature of TSC and result from abnormal neuronal migration during early brain development. The increase in the number of tubers is associated with weaker cognitive functions, mental retardation, and resistant seizures. The treatment of epilepsy associated with TSC continues to be a major problem and more than 60% of the patients suffer from seizures.[6,7] In our patient, multiple subependymal nodules were observed in the T1 A sections at the caudate nucleus level (Fig 2c) and in the Sagittal T2 A section at the lateral ventricular frontal horn level (Fig 2d). Our patient had seizure attacks that developed as a result of brain involvement. These attacks, however, stopped after the Levetiracetam treatment was started.

Some studies claim that overactive mTOR signals may also cause neurosensory hearing loss, and that the treatments given to reduce mTOR activity may also act as a potential strategy to prevent hearing loss.[8] Our patient also had congenital bilateral neurosensory hearing loss, and to the best of our knowledge, this study is the first in the literature to report a child diagnosed with both tuberous sclerosis and hearing loss.

Moreover, a vast majority of the patient with TSC has characteristic skin lesions. The most common lesions are angiofibroma (formerly called adenoma sebaceum), hypopigmented macules (also known as ash-leaf spots), Shagreen patches, and a distinctive brown fibrous plaque on the forehead. Ash-leaf spots are very common in neonatal and infants[1], and it maybe the earliest noticeable sign of TSC after birth.[9] Our case also had hypomelanotic lesions around the eyes and umbilicus, and on lower extremities (Fig 1 a).

Cardiac rhabdomyomas, on the other hand, are benign tumours that may occur in any area of the heart, but mostly appear in the ventricle. Although the LV and the interventricular septum are the most common locations, as in our case, it may also appear in the atrial wall or the right ventricle in approximately 30% of the cases.[10] The masses are macroscopically hard, smooth-edged, unencapsulated, white–grey, and sizes may vary from millimetres to several centimetres. Cardiac rhabdomyomas occur in approximately 60% of the TSC cases, and therefore, in the presence of rhabdomyoma in echocardiography, the patient should be evaluated in terms of TSC.[11] Rhabdomyomas, which are generally detected in the foetal or neonatal period, tend to regress spontaneously in the first few years after birth.[12] Therefore, these masses in the heart do not require medical or surgical treatment, unless they have severe valve regurgitation, life-threatening dysrhythmia, or severe stenosis of the ventricular outflow tract in the early postnatal period.

Clinical findings in patients with rhabdomyoma largely depend on the location and mass effect of the tumour in the heart. As a result of haemodynamic instability due to the tumour's location, the risk of sudden death increase in such patients.[11] Surgical intervention is recommended only in the presence of life-threatening refractory dysrhythmia or severe haemodynamic disorder.[13] Therefore, in such cases, no delay must be caused in terms of

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medical or surgical intervention. In cases where the tumour is multifocal, infiltrative, or very large, surgical resection is quite difficult and unfortunately, the results are not very satisfactory.[14] Recent case reports and clinical trials have shown that the treatment of rapamycin analogues initiated in the early period can also effectively regress cardiac rhabdomyoma.[15] A rapamycin analogue (Everolimus) treatment was also started for our patient who had severe stenosis in the left ventricular outflow tract due to cardiac rhabdomyoma and developed secondary left ventricular hypertrophy. With the treatment of Everolimus, the masses in the patient's heart shrank, and the stenosis in the left ventricular outflow tract (latest 18 mmHg) and left ventricular hypertrophy also regressed. Our patient received a total of 4 months of Everolimus treatment. At the time of treatment discontinuation, the mass in the left ventricular outflow tract was 2.7×2.3 mm and the mass in the left atrium was 6.3×5.4 mm (Fig 2b). Therefore, it was found that our patient clearly benefitted from the Everolimus treatment that saved the patient from a possible surgery.

Conclusion

In conclusion, we report that patients with TSC may present with different cardiac conditions. Rapamycin analogues may be used in the treatment of cardiac rhabdomyomas with severe haemodynamic disorder and risk of sudden cardiac death. This medical treatment seems to be a good alternative to surgery in patients with high complications. In addition, infants with TSC may also present with neurosensory hearing loss, as in our case. Nevertheless, larger future studies are required to better understand this situation.

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

Ethical standards. The authors assert that this work complies with the ethical standards of the relevant national guidelines and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Ethical Review Committee at the University of Yuzuncu Yil, Turkey.

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