CASE REPORT



Everolimus as a possible prenatal treatment of in utero diagnosed subependymal lesions in tuberous sclerosis complex: a case report

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Abstract

Introduction The association between cardiac rhabdomyoma and intraventricular tumors and/or subcortical nodules is characteristic of tuberous sclerosis complex (TSC). Patients with TSC may have refractory seizures, autistic behavior, and cognitive decline. **Case report** The patient received the fetal diagnosis of TSC at the age of 19 weeks of gestations, where presented at prenatal ultrasound cardiac and brain tumors. Fetal MRI showed a lesion in the right and left lateral ventricles near the foramen of Monro associated with subependymal lesions along the entire ependyma of the lateral ventricles and several subcortical tubercles, and the fetal Doppler echocardiogram revealed three cardiac lesions. The fetus underwent intrauterine treatment with everolimus and presented regression and subsequent stabilization of the cardiac and brain lesions; additionally, the patient did not develop seizures or autism and presented good neuropsychomotor development.

Conclusion It is the first evidence that mTOR inhibitors may help to prevent neurological complications associated with TSC.

Keywords Fetal brain tumor · Tuberous sclerosis complex · Fetal chemotherapy

Introduction

Fetal brain tumors are rare, with a prevalence of 0.34 per million live births.[1] The presence of intraventricular brain tumors (subependymal giant cell astrocytomas) near the foramen of Monro (interventricular), subependymal lesions, subcortical tubercles, and cardiac tumors (rhabdomyomas) is highly suggestive of tuberous sclerosis complex (TSC). Targeted treatment with rapamycin derivatives for TSC has led to improvement in the quality of life of these patients, with a reduction in seizures, subependymal giant cell astrocytomas, and cardiac lesions. When to initiate chemotherapy is still controversial.[2, 3] Although intrauterine treatment with rapamycin derivatives for rhabdomyomas associated with TSC has been successful,[4–6] it

Marcos Devanir Silva da Costa marcoscostaneuro@gmail.com has not been applied in an attempt to avoid the neurological disorders caused by TSC. The objective of this study was to present a case of TSC diagnosed and treated during the fetal period.

Case report

A 30-year-old woman, primigravida, prenatal ultrasound at 19 weeks showed fetal cardiac and brain tumors. Fetal MRI (Fig. 1A and B) showed a lesion in the right and left lateral ventricles near the foramen of Monro associated with subependymal lesions along the entire ependyma of the lateral ventricles and several subcortical tubercles. The fetal Doppler echocardiogram (Fig. 1C and D) revealed three cardiac lesions: Two with defined edges measuring 10×7 mm and 6.7×3.7 mm adhering to the septum, and a third measuring 3.4×3.3 mm on the posterior wall of the left ventricle without hemodynamic repercussions. No other fetal lesions were identified. The diagnosis of TSC was made based on the appearance of the cardiac and brain lesions. With this diagnosis, the initiation of treatment during the fetal period was proposed and was immediately accepted by the family. Everolimus was introduced at a dose of 10 mg, and its serum concentration was 8.4 ng/ml (reference 3 to 15 ng/ml). The cardiac lesion progressively decreased, and the intracranial lesions

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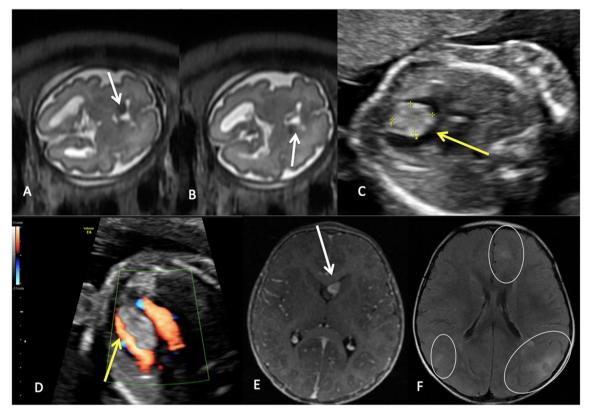


Fig. 1 A Fetal MRI with HASTE sequence at 19 weeks of gestation showing a subependymal tumor at the level of the foramen of Monro on the right side arrow). B Fetal MRI with HASTE sequence at 19 weeks of gestation showing a subependymal tumor at the level of the foramen of Monro on the left side (white arrow). C Image from fetal echocardiography performed at 21 weeks and 6/7 days showing an echogenic mass with defined edges measuring 10×7 mm. D Image from

remained stable. At 39 weeks of gestation, the patient underwent cesarean section. The NB was female, with Apgar scores of 8 and 9 at birth and weighing 3200 g. The postnatal echocardiogram showed a small atrial lesion, while the MRI (Fig. 1E and F) showed an unilateral lesion next to the foramen of Monro without signs of hydrocephalus but with several intracerebral tubers and subependymal lesions. At 4 days of life, the patient resumed everolimus treatment at a dose of 4.5 mg/m²/day, with serum levels maintained at 5 ng/ml. The patient was unvaccinated until the age of 5 months, when the necessary vaccinations were administered, and everolimus was reintroduced 3 months later and maintained continuously afterwards. The patient walked at 10 months of age and at her last follow-up at 36 months of age exhibited normal neuropsychomotor development. The patient's EEG was normal, and she never had a seizure.

Discussion

The presence of one or more cardiac rhabdomyomas associated with brain lesions is pathognomonic of TSC. It is known that 96% of infants with cardiac rhabdomyomas will

fetal echocardiography performed at 25 weeks and 6/7 days showing an echogenic mass with defined edges located in the interventricular septum. **E** Postnatal MRI with T1WI sequence and contrast enhancement showing a single subependymal lesion at the level of the foramen of Monro on the left side (white arrow), without signs of hydrocephalus. **F** Postnatal MRI with FLAIR sequence demonstrating hypersignaling in three different subcortical areas: left frontal and bilateral parietal (white ellipse)

ultimately be diagnosed with tuberous sclerosis. There are reports of treatments of fetal cardiac lesions and rhabdomyomas that compromise the ejection fraction of these patients.[4, 6, 7] Most rhabdomyomas regress spontaneously during the first 3 years of life, and few cases require surgery or even chemotherapy.[7] There are also reports of mothers who have undergone kidney transplant or have angiomyolipoma who maintained the use of rapamycin throughout pregnancy without compromising the fetus. Additionally, patients with TSC have continued their treatment with mTOR inhibitors during pregnancy without harm to the fetus.[5]

>Approximately 85% of patients with TSC will exhibit neurological symptoms, including seizures, learning deficits, behavioral disorders, and autism. The prevalence of mental retardation is 44%, and two-thirds of cases are severe (IQ < 20).[8] Despite the use of various types of anticonvulsants, many patients with TSC have seizures that are refractory to treatment. Epileptogenesis in TSC is caused by decreased neuronal inhibition secondary to molecular changes in Gamma aminobutyric acid (GABA) receptors in giant cells and dysplastic neurons and by increased excitability secondary to molecular changes in glutamate receptors in dysplastic neurons. GABAergic interneuron deficiency may explain the early onset and severity of seizures in TSC.[9] Velíšek and Moshé[9] have shown that the immature brain is more likely than a mature brain to generate seizures.

Jóźwiak et al.[10] proposed the administration of antiepileptic agents in infants at high risk of developing seizures, as in the case of TSC, before the onset of seizures to improve cognitive development and reduce the risk of refractory seizures. Seizures during the early stages of development may be associated with autistic behavior. The frequency of TSC in autistic children may be extremely high.[11, 12] Some studies have shown that rapamycin and its derivatives are effective for the control of seizures and autism symptoms. However, cases of pharmacoresistance are difficult to control, even with the use of mTOR inhibitors, and require surgical procedures.[8]

The diagnosis of TSC during the fetal period is difficult, but it seems logical to introduce chemotherapy during the fetal period because it can avoid triggering seizures and perhaps prevent the onset of autistic behavior. Chemotherapy with rapamycin and its derivatives may have adverse effects that cannot be ignored, such as stomatitis and diarrhea, and may increase vulnerability to opportunistic infections due to its immunosuppressive effect.[13] Special care should be taken with NBs who have been treated with rapamycin or its derivatives during the fetal period; contact with multiple people should be avoided during the neonatal period, and routine postnatal vaccines should be very well planned. A larger number of cases should be analyzed to prove the efficacy of this precision therapy at the early stages of life and to determine the possible long-term impairments that this type of drug may cause.

Conclusion

The fetal diagnosis of TSC with brain lesions is difficult however; patients with brain and heart tumors are candidates for harboring TSC1 or TSC2 mutations. The case presented raised an important question that we may start treating the TSC with brain tumors as soon as possible, including the fetal period that seems to be safe.

Declarations

Statement of ethics The parents signed the informed consent of the study.

Conflict of interest The authors have no conflicts of interest to declare.

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