CONGENITAL CARDIAC RHABDOMYOMA AND EPILEPSY IN A PATIENT WITH TUBEROUS SCLEROSIS: A CASE REPORT

Danilo Nonkulovski[1], Ljelja Muaremoska-Kanzoska[1], Teodora Spasovska[1], Ilija Kirovski[1], Natasha Damjanovska[1]

[1]Department of Pediatric Neurology, University Children's Hospital in Skopje, North Macedonia

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ABSTRACT

Introduction: Tuberous Sclerosis Complex (TSC) is a rare disease with autosomal dominant inheritance pattern. Mutations on either of the two genes Tuberous Sclerosis Complex 1 (TSC1) or Tuberous Sclerosis Complex 2 (TSC2) play an important role in the pathogenesis and results in forming tubers, affecting organs like the brain, heart, kidneys, skin, lungs, and liver.

Purpose: This review highlights the importance of genetic analysis that provides early diagnosing and adequate multidisciplinary therapeutic approach in order to improve life's quality of the children with TSC.

Materials and Methods: Blood samples were taken from the patient and the parents for genetic analysis for eventual pathogenic variants in TSC1 and TSC2 gene, neurological examination, laboratory analysis and imaging diagnostic records were also taken in consideration.

Results: We present a case of a 16 months old female child diagnosed with epilepsy and treated with AED. Delivered from well monitored pregnancy, by caesarean section at 39 weeks gestation, APGAR score 6/8, with olygohydramnion and prenatally noted tuberous formations in the right ventricle, suspect for tuberous sclerosis. Postnatal genetic analyses confirmed the diagnosis Tuberous Sclerosis, inherited from the father.

Conclusion: Early diagnosis allows careful genetic counselling in the context of variable clinical expressivity and helps the physicians to arrive to their decisions for early and further treatment. Multidisciplinary team approach to management is essential to maximize the prognosis of this condition.

Keywords: tuberous sclerosis, cardiac rhabdomyoma, epilepsy, TSC1, TSC2

INTRODUCTION

Tuberous sclerosis complex (TSC) is multisystemic genetic disorderaffecting approximately 1 in 6000 to 1 in 10,000 live births, with an overall prevalence of 1 in 20,000. 1 The inheritance pattern autosomal dominantand males and females are equally affected. TSCis characterized by an increased predisposition for hamartoma formation. The disease is result of mutations in the genesTSC1 (9q34) and TSC2(16p13.3) that are responsible for the production of proteins that regulate cell division and growth in the body, hamartin and tuberin, respectively. The frequency of mutation is higher in TSC2 gene compared to TSC1 gene, but also approximately 15% of the patients with a typical clinical presentation for TSC have no identifiable genetic mutations. 1,2,6

The diagnosis is established either by satisfying criteria that are mentioned in the Table 1, or by genetic analysis with targeted sequencing for TSC1and TSC2 genes. 5

Diagnostic criteria for tuberous sclerosis include the following major and minor features:	
MAJOR FEATURES	MINOR FEATURES
Hypomelanotic macules (more than 2, and at least 5 mm in diameter) Angiofibromas (more than 2) or fibrous cephalic plaque Ungual fibromas (more than 1) Shagreen patch Multiple retinal hamartomas Cortical dysplasias Subependymal nodules Subependymal giant cell astrocytoma Cardiac rhabdomyoma Lymphangioleiomyomatosis Angiomyolipomas (more than 1)	•Confetti skin lesions •Dental enamel pits (more than 3) •Intraoral fibromas (more than 1) •Retinal achromic patch •Multiple renal cysts •Nonrenal hamartomas
*Definitive diagnosis is established in patients with two major features or one major feature with at least 2 minor features, while "possible diagnosis" is recognized in patients with one major feature or at least 2 minor features.	

Table 1.

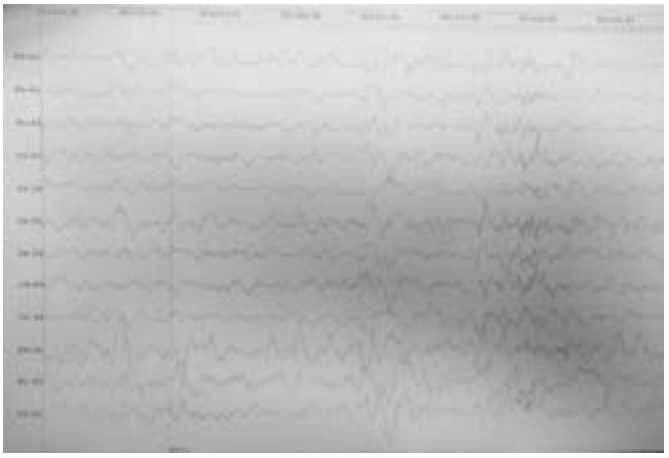
The disease most commonly causes neurological disorders including epilepsy and intellectual disability. In the most of the cases the disease is diagnosed in infancy or in early childhood, but in the milder forms it can be diagnosed later. Some of the manifestations like cortical tubers and cardiac rhabdomyomas can be noted on prenatal ultrasound and in such a cases it is highly indicative for performing further diagnostic procedures for TSC. The clinical presentation varies depending of the developmental stage of the individual and the wide range of phenotypic variability. 90% of the affected patients present skin lesions like hypopigmented macules in early childhood, while the appearance of ungual fibromas and facial angiofibromas is more common in adolescence. 1,3

CASE PRESENTATION

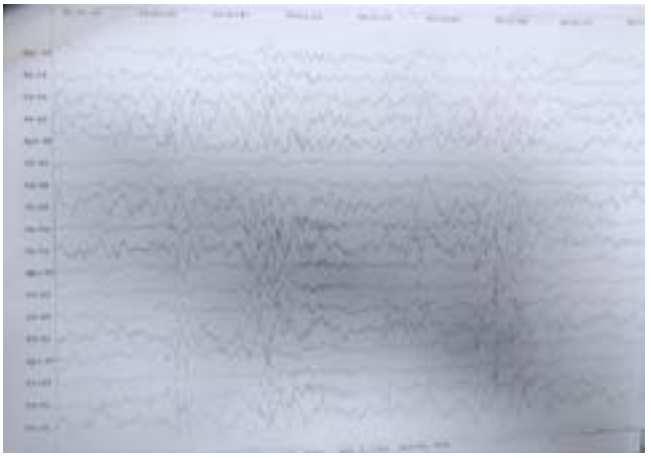
We present the case of a 15-month old Caucasian female patient, from a well monitoredpregnancy. The ultrasound examination at 20 weeks gestation revealed oligohydramnios and tumorous formation in the the right ventricle, highly suspicious for rhabdomyoma. The parents were informed and counselled about the further clinical implications. The baby was delivered by elective caesarean section at 39 weeks' gestation (weight 2530 g, body length 44 cm and APGAR score 6/8). Neurological examination revealed mild axial hypotonia, and the rest of the physical examination findings were unremarkable.

Postnatal head ultrasonographic examination didn't show any abnormalities and the brain MRI with FLAIR was also normal.Transthoracic echocardiography confirmed the presence of two tumorous formations in the apical part of the right ventricle, mild hypertrophy of the interventricular septum without obstructing the blood flow and adequate kinetics of the heart. The abdominal ultrasonography, renal MRim and MRim of the brain didn't reveal any abnormalities. Examination by an Ophtalmologist revealed only coloboma iridis dextra. Laboratory analyses were unremarkable.

Picture 1



Picture 2



Genetic testing using targeted sequencing for TSC1 and TSC2 identified pathogenic variant c.1734_1738delinsT (p.Ile580SerfsTer48)in the exon 15 from the TSC1 gene, inherited from her father. This particular variant is not previously described in literature and according to the criteria of American College of Medical Genetic (ACMG), this variant is interpreted as a likely pathogenic. Further testing for neurological development by the sixth month showedslight developmental delay, and retesting was required 6 months later. The patient started manifesting febrile seizures by the fifth month, and a month later continued with afebrile partial seizures resistant to antiepileptic monotherapy.

Further electroencephalographic recordings revealed bihemispheral epileptiform discharges, with dominant left-sided foci and a tendency for generalisation.

The child became seizure free after antiepileptic drug therapy was ordinated with Levetiracetam and Vigabatrin. The child is brought for routine multidisciplinary follow ups at the University Children's Hospital, and has no further complications. As a next step for disease management, therapy with Everolimus is taken in consideration. The parents are advised to attend genetic counseling in order to adapt and manage the child's condition in the best possible outcome, and to provide help for the possible risk in the next pregnancies.

DISSCUSION

Cardiac rhabdomyomas are the most common pediatric primary tumor. Multiple cardiac rhabdomyomas are associated with TSC inaround 70% of the patients. 4 The presence of congenital cardiac rhabdomyomas, as one of the major criteria for TSC, should lead to high index of suspicion and should implicate performing further diagnostic procedures. 3,4 Cardiac rhabdomyomas typically are presented in the ventricular cavities or the outflow tracts and can cause inflow or outflow obstruction. Fortunately, in our case there was no obstruction in blood flow, neither on the initial transthoracic ultrasonographic examination, nor on the following check-ups. There is no indication for surgical treatment as long as there is no presence of inflow/ outflow tract obstruction causing heart failure and poorly controlled or intractable arrhythmias. Usually, congenital cardiac rhabdomyomas tend to regress by the age of 6 years. Despite the typical history of cardiac tumor regression, lifelong follow-up is necessary for the appropriate management of these patients.

	Initial Testing	Repeat Testing
Neurodevelopmental testing	At diagnosis & school entry	As indicated
Ophthalmic testing	At diagnosis	As indicated
Electroencephalography	If seizures occur	As indicated for seizure management
Electrocardiography	At diagnosis	As indicated
Echocardiography	If cardiac symptoms occur	If cardiac dysfunction
Renal ultrasonography	At diagnosis	Every 1–3 years
Chest CT	Adulthood (women only)	If respiratory dysfunction
Head CT	At diagnosis	Every 1–3 years in children
Head MRI	At diagnosis	Every 1–3 years in children

Table 2

Once the differential diagnosis is consistent of TS, the following diagnostic procedures are recommended at the moment of diagnosis and for future follow ups (Table 2). 5

Except for the cardiac rhabdomyomas, our patient is with Epilepsy eventhough there are no any abnormalities shown on the brain MRim. It is not excluded that some cortical tubers persist beyond current imaging resolution. Problems with central nervous system are more prevalent in patients with TS, but also more amenable to medicamentous therapy. Adrenocorticotropic hormone (ACTH) and vigabatrin (VGB) are considered mainstay therapies for the treatment of seizures in TSC patients. 7,8 Vigabatrin combined with levetiracetam gave satisfying response in our patient resulting with reduced, almost absent seizures. Because there are no other tuberous formations identified, therapy with mammalian target of rapamycin (mTOR) kinase inhibitor is not started yet. 7 It is not clear weather this therapy provokes regression for the cardiac tumors, even though it is proven to show successful regression in CNS lesions.

CONCLUSION

The severity of TSC can vary from patient to patient, but if often results in a wide range of physical and cognitive symptoms that can significantly impact a person's quality of life. While there is no curative treatment, there are

a variety of therapeutic interventions that can help improving the outcome. According to literature and experience, as a first drug of choice for experiencing seizures in this condition is Vigabatrin, which gave satisfying results combined with Levetiracetam in this case. Currently mTOR inhibitors (Sirolimus/ Everolimus) are effective in controlling TSC-associated tuber growths, implying a bright future for patients with TSC. Multidisciplinary approach is essential in order to achie the best outcome.

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