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A case of early neonatal diagnosis of familial tuberos sclerosis

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ABSTRACT

Background. Tuberous Sclerosis Complex (TSC) is a multisystemic neurocutaneous genetic condition with autosomal dominant inheritance. It is characterized by hamartomas that affect multiple organs, in particular skin, central nervous system, heart, lungs and kidney.
Case presentation. Here we report a case of early post-natal diagnosis of familial TSC.
Conclusions. TSC is a quite rare genetic disease and early diagnosis is very uncommon, given few cases published in literature. In our patients, early diagnosis has been performed by using early postnatal ultrasound screening, without a prenatal diagnosis.

INTRODUCTION

Tuberous Sclerosis Complex (TSC) is a multisystemic neurocutaneous genetic condition with autosomal dominant inheritance. It is characterized by hamartomas that affect multiple organs, in particular skin, central nervous system (CNS), heart, lungs and kidney [1-4].
There are several genes involved in the aetiology of this disease in particular the tumour suppressor genes TCS1 and TCS2 respectively located on chromosome 9 and 16 that codify for the proteins hamartin and tuberin [3, 5].
The role of this protein complex is to control cellular growth, by suppressing mTOR (mechanistic target of rapamycin) pathway, involved in the proliferation and inhibition of cellular apoptosis. Inactivating mutation or deletion leads to a permanent mTOR pathway activation and so to the development of hamartomas in multiple organs [6].

Skin manifestations (hypopigmented macule, "confetti lesions", angiofibroma, cephalic plaque, shagreen patches, ungual fibroma) are the most common and overall, they affect 90% of patients [4, 5, 7, 8].
The main neurological manifestation is epilepsy (70-90%) that starts usually in the first three years of life; in addition, TSC patients have a high risk of neurocognitive impairment (autism, mental retardation, movement disturbance). Notably, neuroimaging shows cortical and subcortical tubers, subependymal nodules in the lateral ventricles, subependymal giant astrocytomas (SEGA) [4, 10, 11].
Whilst, cardiological manifestations are represented by rhabdomyomas, diagnosed in the foetus and new-born, usually in the ventricular wall. These are mostly asymptomatic, even though they can cause cardiomegaly, arrythmias and even death [9].
Other manifestations are renal (80% of cases) as angiomyolipoma [10, 12], pulmonary (lymphangioleiomyomatosis) [10], ophthalmological (retinal hamartoma) and hepatic (angiomyolipoma) [7, 13].
Importantly first diagnostic criteria of 1998 have been reviewed in 2012 in the second International Tuberous Sclerosis Complex Consensus Conference, by including genetic tests. Based on the new criteria, a pathogenic mutation in TSC1 or TSC2, is sufficient to assess the diagnosis, regardless clinical manifestations [7]. Nevertheless, 10% to 25% of patients could not have a pathogenic mutation in conventional genetic testing. Therefore, a normal molecular test cannot exclude a diagnosis of TSC.
Clinical criteria are divided into major: hypopigmented macules (≥ 3, with at least 5 mm diameter), angiofibroma (≥ 3) or fibrous cephalic plaque, ungual fibromas (≥ 2), shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, angiomyolipoma (≥ 2); and minor: "confetti" lesion, enamel pits (> 3), intraoral fibroma (≥ 2), retinal hypopigmented macule, multiple renal cysts and nonrenal hamartomas. If two major criteria or one major and two minor criteria are all meet diagnosis can be definitive. While it can be probable with one major criterion or two or more minor.
The diagnostic suspect comes usually from prenatal individuation of cardiac rhabdomyomas; in the post-natal period, the identification of hypopigmented macules on the skin has been observed; in childhood the seizures are the most common clinical manifestation followed by cognitive impairment.
Here we report a case of early post-natal diagnosis of familial TSC.

CASE PRESENTATION

A trigeminal pregnancy obtained through intracytoplasmic sperm injection technique delivered at 31+6 weeks of gestational age with an emergency C-section for preterm premature rupture of the membranes.
The mother had an history of epilepsy treated with Levetiracetam. She had a postoperative course uncomplicated, and she was discharged at day 3 after delivery.
The first twin was born without any complication and discharged day 3 after birth.
The second born, A., had an APGAR score of 2 and 7, at 1 and 5 minutes respectively; she received Cardio-Pulmonary Resuscitation and ventilated through endotracheal tube for severe cardiorespiratory depression. Neonatal birth weight was 1,458 grams (25-50° pct), length 40 cm (25-50° pct), cranial circumference 28.5 cm (25-50° pct). She received invasive respiratory assistance for 4 days, then she underwent non-invasive respiratory assistance until discharge. She received antibiotic therapy with Ampicillin and Gentamicin. Cultures were always negative. Echocardiography performed for neonatal screening showed multiple hyperechogenic formations considered as rhabdomyomas, furthermore a Patent Ductus Arteriosus with left-right shunt and thereby right hyperflux resistant to medical closure therapy. Therefore, she received surgical closure intervention with no complications. At physical examination, she also had a prominent skin lesion on the nape.
The third born, S., had an APGAR score of 2 and 7, at 1 and 5 minutes respectively; she received Cardio-Pulmonary Resuscitation and ventilated through endotracheal tube for severe cardiorespiratory depression. Neonatal birth weight was 1,393 grams (25° pct), length 38.5 cm (10-25° pct), cranial circumference 27.7 cm (10-25° pct). She received invasive respiratory assistance for the first 72 hours and administered endotracheal surfactant, then she received non-invasive respiratory assistance for 48 hours and underwent spontaneous breathing afterwards. Blood tests and cultures were al-

ways negative. She received a course of 24 hours phototherapy for neonatal hyperbilirubinemia. She received partial parenteral nutrition for 11 days and Minimal Enteral Feeding from first day of life, then completely full enteral feeding with good weight gain. At physical examination two prominent and rugous plaques on left forearm and left thigh were detected and suspected for skin fibromas. She started a diagnostic iter and performed complete ultrasound screening. Abdominal US showed a left renal hyperechogenic lesion with intralesional cysts compatible with renal angiomyolipoma. Echocardiography (**Figure 1**) showed multiple rounded endocardia hyperechogenic formations along Intra Atrial Septum and Intra Ventricular Septum considered as rhabdomyomas or hamartomas. Cerebral US showed right first grade Intra Ventricular Haemorrhage, bilateral rounded hyperechogenic > 1 cm nodules localized in the cortical-subcortical wall (**Figure 2**), considered as subependymal nodules. She was then transferred to the Pediatric Cardiologic Unit and monitored. After discharge, she experienced seizures and was admitted to Neurology Unit where she performed Electroencephalogram consistent for right centrotemporal epileptiform abnormalities and brain

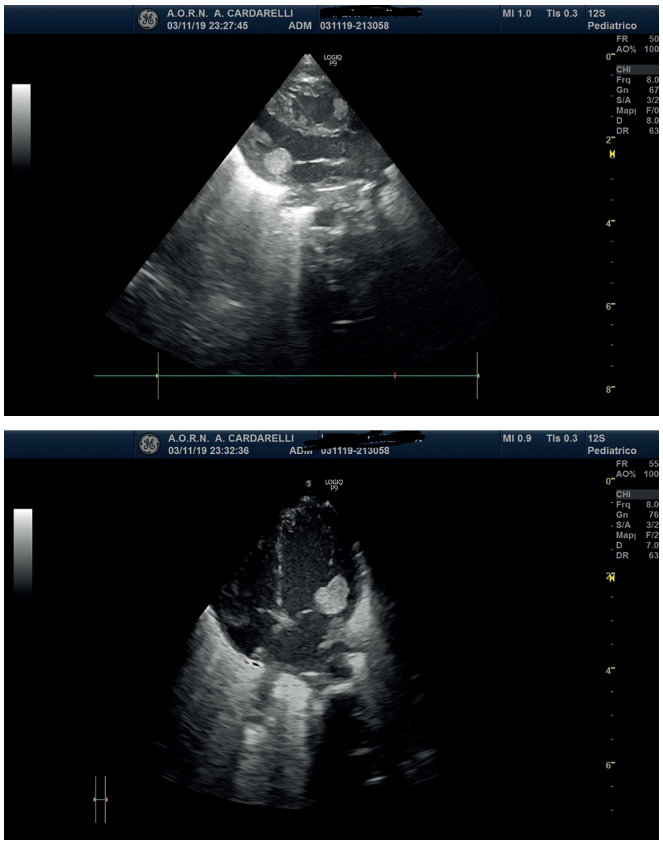

Figure 1. *Heart ultrasound.*

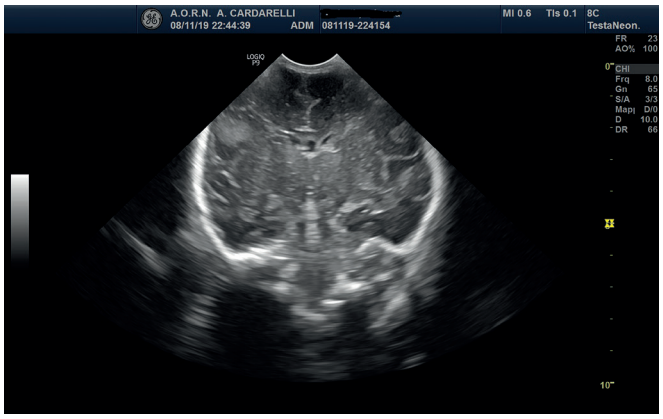

Figure 2. *Cerebral ultrasound.*

Magnetic Resonance Imaging with evidence of bilateral multiple cortical-subcortical and periventricular lesions consistent for hamartomas. She started antiepileptic therapy with phenobarbital and clonazepam, with good control.

Based on 2012 Criteria of second International Tuberous Sclerosis Complex Consensus Conference, the second twin had cardiac rhabdomyoma (major criterion) and one skin fibroma, thus a diagnosis of TSC was probable. The third twin had a cardiac rhabdomyoma (major criterion), subependymal nodules (major criterion), one renal angiomyolipoma, and two skin fibromas so a definitive diagnosis of TSC has been made.

In suspicious of hypothesis of familial Tuberous Sclerosis, a genetic panel was performed, that resulted negative for all the three children and both parents.

DISCUSSION

TCS is a multisystemic neurocutaneous genetic condition with autosomal dominant inheritance.

The first manifestation of TSC is a cardiac tumor assessed by using foetal ultrasound [14, 15]. With regards to clinical manifestation of TCS in the fetal period cardiac rhabdomyomas are often seen and these are, usually identified through US screening of second trimester. However, it remains challenging to detect these benign hamartomas in other organs such as the brain, the kidneys, the heart, and the skin. Notable, foetal magnetic resonance imaging (MRI) is useful in detecting extracardiac hamartomas but is difficult to use as a screening tool.

A family history of TSC is an important clue in the diagnosis of foetal TSC and it may require a target-

ed genomic sequencing of TSC1 and TSC2 genes, to improve the efficacy of prenatal detection of TSC and facilitate prognosis, counselling, and potential early intervention to improve the outcomes of these individuals [16].

In 2012, the Tuberous Sclerosis Consensus Conference updated diagnostic criteria and surveillance management of the disease [7]. In the recent years, relevant data on clinical and genetic came from the TOSCA (TuberOus SClerosis registry to increase disease Awareness) study, a long registry of patients with TSC [10]. In this registry the median age of diagnosis of TSC was one year, with central nervous system (CNS) involvement (most of the time seizures) as the main postnatal characteristic (73.3%) while cardiac rhabdomyoma detected in 22.1% of patients antenatally. In addition, genetic testing was available in 53.5% of patients, while no mutation identified in 19.6% of patients.

In the case we described there was no family history of TSC, but the mother of the three twins had a not defined history of epilepsy even though without a clear diagnosis and with no evidence of cardiac or skin abnormalities.

The early diagnosis of TSC has been assessed by using echocardiography and cerebral ultrasound performed in the early days of life for prematurity screening. In our twins the genetic test for TSC1 and TSC2 genes was negative.

Our epileptic patient in the follow up was treated with antiepileptic therapy but new studies have been made on mTOR inhibitors as a molecular target for the treatment of TSC manifestation including epilepsy, behaviour, TSC-related subependymal giant cell astrocytomas (SEGA) and renal angiomyolipoma [17].

This treatment is also safe and efficacious in TSC patients under 2 years of age. However, no prediction on long term safety under maintenance therapy can be made and further multicentre studies and registers with larger cohorts and longer follow-up periods are awaited.

In the last few years, noninvasive prenatal diagnosis (NIPD) based on cell-free DNA (cfDNA) has been introduced into the clinical application for some monogenic disorders but not for tuberous sclerosis (TSC) yet, which is an autosomal dominant disease caused by various variations in TSC1 or TSC2 gene. However, recently, Yang *et al*. showed that NIPD based on cfDNA is feasible for TSC, but required to be confirmed with more samples [18].

CONCLUSIONS

In summary, TSC is a quite rare genetic disease and early diagnosis is very uncommon, given few cases published in literature. In our patients, early diagnosis has been performed by using early postnatal ultrasound screening, without a prenatal diagnosis. In the next future a better knowledge of this disease, leads to an early diagnosis and treatment without requiring a genetic positive test or family history.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All authors contributed equally to this work.

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Disclosure of interests

The authors declare that they have no conflict of interests.

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Informed consent

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N/A.

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