Tuberous sclerosis in a term newborn with opisthotonus – The value of ultrasound

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KEYWORDS

Tuberous sclerosis;
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Abstract *Purpose:* We describe the clinical findings and the results of cerebral imaging studies [ultrasound (US), magnetic resonance imaging (MRI)] in a full-term newborn with tuberous sclerosis (TS) complex. This condition is inherited as an autosomal dominant trait and characterized by hamartomas involving multiple organs. Diagnosis is based on physical examination together with imaging support.

Methods: Since the TS complex can result in numerous CNS abnormalities, cerebral US should be used to further characterize this malformation.

Conclusion: Sonography is a useful modality for evaluation of the full-term neonatal brain.

Sommario *Introduzione:* Vengono descritti il caso clinico e le anomalie ecografiche cerebrali di un neonato affetto da sclerosi tuberosa complessa, quadro malformativo raro con interessamento neurocutaneo e implicazioni genetiche. La diagnosi si basa sull'esame clinico, sulle indagini per imaging.

Metodi: Vengono confrontati i risultati ottenuti con le metodiche di indagine di riferimento (RM e US). Gli autori enfatizzano il fatto che, in assenza di una segnalazione ecografica prenatale, è importante fare affidamento sui segni clinici e impostare un corretto completamento diagnostico in epoca neonatale.

Conclusioni: L'ecografia transfontanellare occupa un ruolo importante anche nel neonato a termine.

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Introduction

Tuberous sclerosis (TS) is a hereditary disease transmitted as an autosomal dominant trait. It is characterized by the growth of benign hamartomatous masses involving multiple organs. The prevalence is approximately 1:6000 individuals. The molecular basis of the syndrome is known. The most disabling lesions are the cortical tubers that involve nerve

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structures: they vary widely in size, number, and location, and these variables determine the neurological manifestations of the disease, which consist primarily in seizures, mental retardation, and autism. Cardiac involvement consists in the presence of rhabdomyomatous tumors that develop mainly during the fetal period and tend to regress spontaneously during the first years of life (unlike the cerebral lesions, which tend to increase in number and size after birth) [1]. In the early stages of life, rhabdomyomas may be the only manifestation of TS. In fact, the manifestations that are considered highly specific for this disease are evident only at later stages. We describe the case of a newborn male who was being evaluated for asphyxia. During this work-up, typical cardiac lesions were incidentally observed, prompting a full instrumental evaluation. The purpose of this report is to describe the US features of the cerebral lesions and to compare these findings with those observed on MR studies.

Case report

The patient was a male newborn delivered at term with a vacuum extractor due to slowing of the fetal heart rate. The birth weight was 2830 g, and the 1-min Apgar score was 5. The family history was noncontributory, and prenatal studies were negative. The infant recovered rapidly after primary resuscitation. The finding of elevated muscle enzyme levels led the infant's physicians to order an echocardiogram, which reveals hyperechoic masses within the walls of both ventricles and sessile masses within the ventricular cavities that did not obstruct blood flow; the aortic arch was normal (Fig. 1). A diagnosis of multiple cardiac rhabdomyomas was made, and a cerebral US was obtained

Fig. 1 Echocardiogram reveals the presence of multiple cardiac rhabdomyomas.

with negative results. During the first 3 days of life, the newborn's condition improved; no skin lesions were noted, and negative findings emerged from an ophthalmologic evaluation and renal US. On the 10th day of life, MRI of the brain was performed with T1, T2 and FLAIR axial sections and T1-dependent coronal and sagittal sections: nodules with diameters ranging from 2 to 5 mm were noted at the subependymal level along with hyperintense foci within the cortical and subcortical white matter. The cerebral cortex appeared thickened and presented increased signal intensity in T1-dependent sequences (Fig. 2). The infant met the diagnostic criteria for TS complex established during the Tuberous Sclerosis Complex Consensus Conference in Annapolis in 1998 with subsequent recommendations. Molecular testing is underway to identify mutations of the *TSC1* and *TSC2* genes.

The infant remained asymptomatic until the 11th day of life, when he developed opisthotonus. Despite the negative findings on the transfontanellar sonogram, the decision was made to repeat the examination with the aid of the MRI study results. This time several hyperechoic spots were noted bilaterally, in the periventricular zones on the coronal and sagittal scans. In addition, the dimensions of the lateral ventricles appeared asymmetrical: the lumen of the left ventricle exhibited coarctation, and the lower border was irregular due to the presence of nodular formations that were hyperechoic with respect to the ependyma (Fig. 3a and b).

The infant is now 5 months old, asymptomatic, and is being closely followed.

Fig. 2 Sagittal T2-weighted MRI sequences without contrast enhancement demonstrate the extensive presence of hyperintense cortical lesions, which are typical of tuberous sclerosis, together with subependymal nodules.

Fig. 3 Transfontanellar ultrasonography. (a) Anterior coronal scan through the frontal horns of the lateral ventricles: hyperechoic nodules are present on the floor of the left lateral ventricle. (b) Scan in the left parasagittal plane shows irregularity of the floor of the ventricle with subependymal nodules bulging into its lumen.

Discussion

The results of most studies indicate that the majority of infants with multiple cardiac rhabdomyomas are ultimately found to have TS. Consequently, even if there are no specific clinical signs of the disease, a diagnosis of probable TS should be made in these cases, and the patient should undergo neuroradiologic, US, and molecular genetic testing [2].

The most characteristic manifestations of TS are the cerebral lesions, which include cortical tubers, subependymal nodules, and anomalies of the white matter. In 95% of TS patients, the tubers are detected radiologically, and they are located primarily at the cortical and subcortical levels. These tumors are responsible for the neurological disturbances associated with the disease. MRI is the diagnostic procedure of choice because it is capable of revealing the lesions and the altered neuronal migration, which typically develops perpendicular to the cortex [3]. Subependymal nodules are also found in most patients with TS. They can be identified in the early stages of the disease, and their number increases during the first decade of life. They are located on the floors of the lateral ventricles; in some cases, they undergo calcification over time and thus become visible on computed tomography (CT) as well. They can be seen in or near the head of the caudate nucleus, and they are considered the single most typical lesion found on CT: unfortunately, the examination may be negative during the first year of life, before the nodules have undergone calcification. In contrast, with transfontanelle US, the typical periventricular changes can be identified early, including the irregularity of the lower border of the lateral ventricles, differences in size, coarctation of one or both of the ventricles, and single or multiple nodules. Although the first reports of sonographic visualization of the cerebral changes associated with TS appeared in the 1980s [4], they are by no means numerous. The present report is also important because it highlights the importance of opisthotonus as a sign of TS [5]. (In this case, it was the only clinical manifestation of the disease.)

In the evaluation of brain structures in full-term newborns, one tends to consider US less effective than MRI. However, while the latter modality undoubtedly provides a more complete picture, US is still a highly useful tool for this purpose, particularly in settings where rapid access to MRI is limited. This would suggest, however, that sonographers themselves should have greater faith in the US examination; it also highlights the need to maximize the quality of the data obtained with US by using the latest generation scanners, transducers that provide high–very high resolution, and optimal visualization of the structure being examined, if necessary using an acoustic window other than the anterior fontanelle [6].

Given the autosomal dominant mode of transmission, there is a high risk of recurrence if one of the parents is affected, even with a subclinical form of TS. In those cases in which genetic testing is inconclusive, the physician should rely on the prenatal US examination (especially that of the fetal heart) and MRI, which can be performed after the 16th to 18th week of gestation. In our opinion, the US anomalies associated with TS can be identified during the neonatal period by means of a simple two-dimensional study. In the presence of clinical findings suggestive of TS, MRI imaging studies of the brain should be scheduled as soon as possible since this approach is the method of choice for identification of cortical/subcortical changes.

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