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Cerebral MRI Findings in Neonatal Tuberos Sclerosis

Tuberos sclerosis (TS) is a developmental neuroectodermal disorder, affecting multiple organ systems. Most patients are diagnosed at the age of five years or later. Only recently, mutation analysis of TS Complex genes has enabled us make an early or even an antenatal diagnosis of the disease. Early onset with infantile seizures is mainly an ominous sign for an unfavorable outcome.

MRI findings in older children and adults are well-known; however, only limited publications illustrate brain MRI findings in newborns.

We present a female neonate with a positive family history, categorized as "definite TS." On MRI of the brain, white matter lesions were depicted. MRI findings were correlated with published data on neonatal TS.

Keywords: tuberos sclerosis, diagnosis, magnetic resonance imaging

Introduction

Tuberos sclerosis (TS), also known as TS complex (TSC), and Bourneville-Pringle's disease, belongs to the group of phakomatoses or neuroectodermal dysplasias which are developmental disorders, affecting multiple organ systems. The classical clinical presentation includes a triad of mental retardation, epilepsy, and facial adenoma sebaceum. Primary, secondary and tertiary criteria for confirmation of the diagnosis have been well defined.¹ Only recently, mutation analysis of two TSC-genes has enabled us make a precise early molecular diagnosis.²

Brain manifestations in TS have been postulated abnormalities in the development along the radial migration pathway of glia and neurons between the germinal matrix and the cortex so that anomalies may be present on the way from the subependymal region to the cortex.³⁻⁶ Extracerebral manifestations of TS include rhabdomyomas of the heart, angiomyolipomas of the kidney, and hamartomas of different organs.

In the majority of TS patients, seizures commence only at the age of five years. Earlier appearance indicates a greater risk of mental retardation, and a severe clinical course.^{5,7}

Our patient presented with seizures, clinically obvious facial angiofibromas, apparent hypomelanotic 'Confetti' skin lesions, and had a positive family history so that the diagnosis of definite TS was made clinically, according to the literature.¹ Magnetic resonance imaging (MRI) of the brain revealed cerebral white matter manifestations.

MRI findings are illustrated and compared to published data.

Case Presentation

The patient was a full-term newborn female who was delivered by cesarean section. On the fourth day, she developed neonatal seizures which were treated

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with phenobarbital. Family history revealed 'definite' neonatal TS in the patient's 9-year-old uncle. Dermatologic examination of the neonate depicted clinically obvious facial angiofibromas, and 'Confetti' skin lesions on the trunk. Electroencephalogram did not show any epileptiform discharges; echocardiography was normal; no cardiac rhabdomyoma was verifiable. Ultrasound (US) of the kidneys and abdomen was also normal with neither angiomyolipomas nor cystic renal disease.

Because of the clinical diagnosis of definite TS, MRI of the brain as well as cranial computed tomography (CT) (to rule out calcifications), were requested by the pediatric neurologist, and discussed with both parents who gave their informed consents.

MRI of the brain (Fig. 1A-D) was obtained on the seventh day of life; it included T1-weighted (W), T2-W spin echo (SE) sequences, T1-W and T2-W Fluid-Attenuated Inversion Recovery (FLAIR) sequences, and T1-W SE sequences after intravenous (IV) administration of a gadolinium (Gd)-based contrast medium in axial, coronal, and sagittal planes, with addi-

tional axial diffusion weighted SE echo planar imaging, and ADC mapping. Several lesions were detected in the periventricular white matter, most evident in the right centrum semiovale. The focal lesions were linear, semicircular, and circular in shape with hyperintense margins, isointense centers, and only minimal contrast enhancement. Neither subependymal nodules (candle guttering), nor typical transmantle dysplasia, nor cortical tubers were present. The lesions were best demonstrable on T1-W unenhanced SE-, and on T1-W FLAIR sequences. On corresponding T2-W images, the right sided lesions were not well visible; additionally diffuse increased signal intensity was depictable in the bi-frontal white matter, suggesting edema (Fig. 1D). The hippocampus formation appeared bilaterally normal. Parasitic or inflammatory diseases were excluded by serum and cerebrospinal fluid (CSF) laboratory workup.

Cranial CT without administration of IV contrast was performed on day 14 after informed consents of both parents to rule out calcified tubers (Fig. 2). Axial sections neither revealed calcification nor subepen-

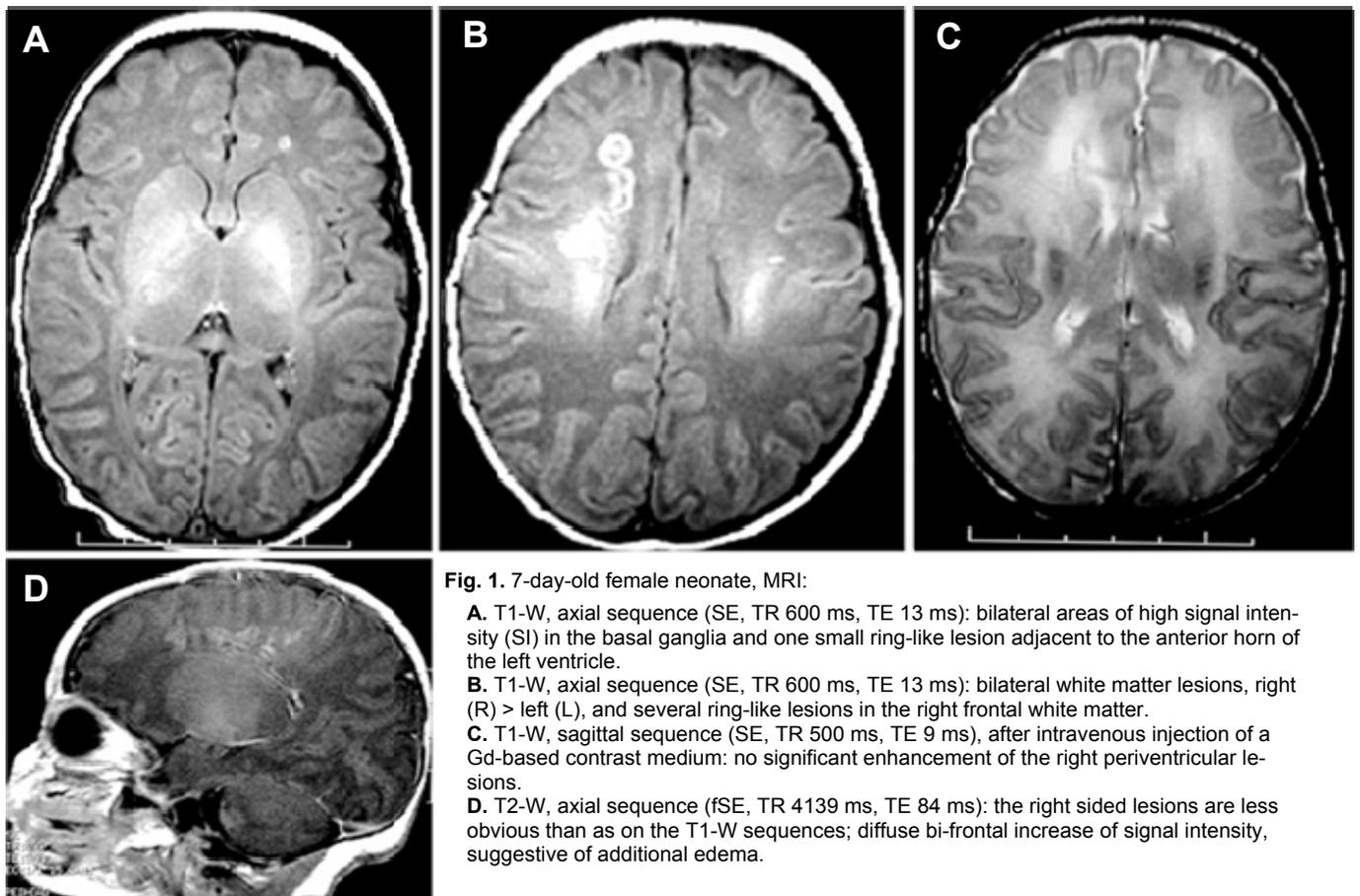


Fig. 1. 7-day-old female neonate, MRI:
A. T1-W, axial sequence (SE, TR 600 ms, TE 13 ms): bilateral areas of high signal intensity (SI) in the basal ganglia and one small ring-like lesion adjacent to the anterior horn of the left ventricle.
B. T1-W, axial sequence (SE, TR 600 ms, TE 13 ms): bilateral white matter lesions, right (R) > left (L), and several ring-like lesions in the right frontal white matter.
C. T1-W, sagittal sequence (SE, TR 500 ms, TE 9 ms), after intravenous injection of a Gd-based contrast medium: no significant enhancement of the right periventricular lesions.
D. T2-W, axial sequence (fSE, TR 4139 ms, TE 84 ms): the right sided lesions are less obvious than as on the T1-W sequences; diffuse bi-frontal increase of signal intensity, suggestive of additional edema.

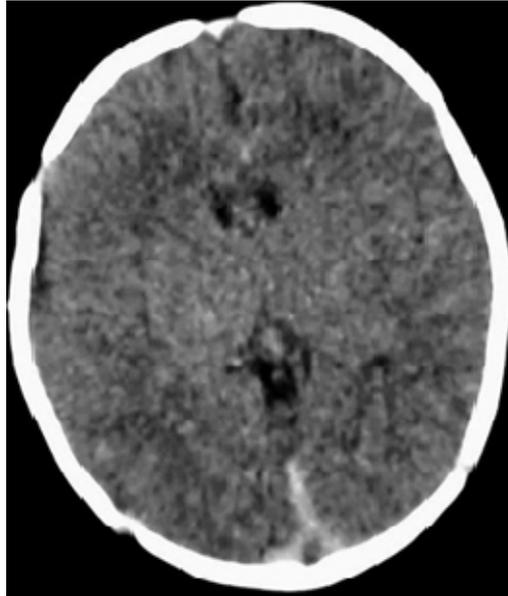


Fig. 2. Female neonate, at the age of 14 days, unenhanced cranial CT: small lateral ventricles, no subependymal nodules, no calcifications; several questionable, tiny hyperdensities in the right occipital cortex without correlation to the pathologic MRI findings in Figure 1.

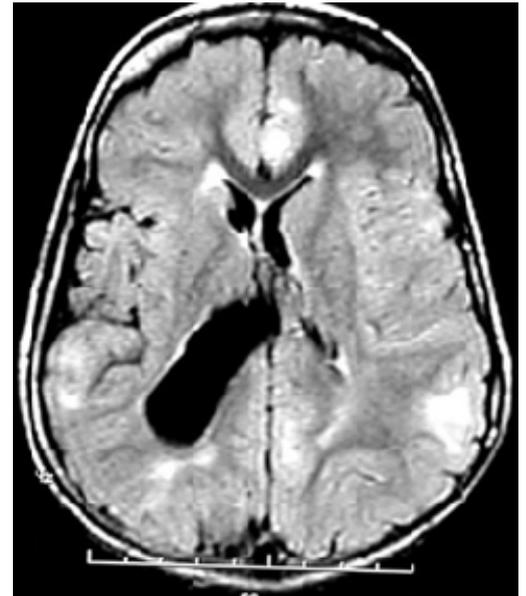


Fig. 3. Male infant, 9-year-old uncle of the present newborn, MRI brain: axial T2-W FLAIR sequence (TR 9002 ms, TE 133ms): status after SGCA operation, right ventriculomegaly, disseminated hyperdense white matter lesions, transmantle dysplasias, cortical tubers, tiny isointense subependymal nodules, and abnormal temporal gyri.

dymal nodule formation. Several uncertain tiny scattered hyperdense focal lesions were seen; however, those lesions had no obvious correlation with the pathologic MRI findings in Figure 1.

Clinically, the newborn developed normally so far without recurrence of seizures or neurologic deficit. On follow-up MRI at the age of two months, the bifrontal edema was no longer evident; the white matter lesions presented unchanged; there were no residual changes of a previous intracerebral bleeding.

The patient's nine-year-old uncle was also diagnosed with neonatal definite TS, presenting with an antenatally-detected cardiac tumor, multiple brain lesions, including a subependymal giant cell astrocytoma (SGCA), and a typical hypomelanotic skin lesions at birth. The patient underwent brain surgery twice with the result of subtotal SGCA resection. Figure 3 demonstrates his brain MRI after the second operation with characteristic TS findings and consecutive post-operative changes.

Discussion

TS belongs to the developmental disorders of neuroectodermal dysplasias with seizures and hamartomas of the brain, eyes, skin, heart and kidneys.

The estimated prevalence ranges from 1/6,000 to 1/12,000 live births.^{8,9}

Most articles published focus on TS features in older children or adults.¹⁰⁻¹² Only few publications exist about imaging findings in neonatal TS.^{5,13-15} In the majority of cases, TS was diagnosed in children older than five years⁷, unless a mutation analysis of TSC-genes was conducted antenatally.² A poorer prognosis is obviously present, when seizures start in the neonatal or early infancy period. Mental retardation develops in >80% of patients with TS plus infantile spasms. A large tuber load combined with infantile spasm is also a threatening sign for an unfavorable prognosis.⁵

In 1999, Baron reported on seven patients aged less than three months old; six presented clinically with severe TS symptoms and one was asymptomatic.⁵

Our newborn baby, as well as her nine-year-old uncle, presented also with neonatal TS and antenatally-diagnosed TS, respectively.

MRI and CT findings of brain involvement in TS vary over time.^{5,12} Baron described hyperintense white matter lesions on T1-W SE sequences in all neonates;⁵ these lesions are supposedly better detectable on T1-W images due to immaturity of the neonatal white matter. Their typical radial ventricofugal

pattern can be explained by the embryologic development so that white matter anomalies represent abnormal migration of neurons and glia.^{3,4} In Baron's newborn population, more than half of the white matter anomalies, visible on T1-W SE sequences, were missed or less obvious on T2-W SE images, like in our neonate. Tubers and subependymal nodules in neonates were likewise hyperintense on T1-W SE sequences, but were iso- or hypo-intense on T2-W images. After six months of age, lesions became hypointense on T1-W and hyperintense on T2-W sequences.⁵ According to MRI findings in the published literature, and as confirmed in our patient, T1-weighted SE images and also T1-W FLAIR sequences are best suited for the detection of white matter lesions. T2-W SE and T2-W FLAIR images are of limited value in newborns, however, they are good for patients older than six months. Tuber calcifications—which were absent in our two cases—have also been described in few neonates.⁵

An antenatally-diagnosed SGCA was present in our first-born patient corresponding to a case published by Mirkin in 1999.¹⁶ Baron also reported that two out of seven patients had SGCA (17%), and indicated a more severe affliction in those with early SGCA appearance.⁵ Menor described an 80% association of SGCA with myocardial rhabdomyoma.¹⁷

In our present neonate, MRI revealed white matter anomalies with radial ventriculofugal linear and semicircular lesions. These abnormalities—which have not been reported yet—appeared like tiny 'targets' with hyperintense rims and isointense centers, are better viewed on T1-W than T2-W sequences. Subependymal nodules and cortical tubers were not detectable on MRI.

Hippocampal developmental anomalies have been described in patients with TS by Sato in almost 2/3 of his patients.¹⁸ Such anomalies were not seen on coronal T1-W sequences with thin slices in our newborn.

Cerebral TS in neonates and small infants is generally quite characteristic, but the presence of solitary or few hyperintense lesions can create a diagnostic problem. The most important differential diagnosis in cases, not fulfilling the clinical criteria of definite TS, include subacute hemorrhage and congenital infection—both disease groups were excluded in our new-

born by laboratory findings and follow-up examinations.

In accordance with Baron⁵, early MRI before the age of six months and follow-up MRI examinations are recommended. As myelination proceeds, the signal intensities of gray and white matter start to reverse at approximately six months, which may cause a lower detection rate for white matter lesions, transmantle dysplasias, and cortical tubers. The value of diffusion-weighted images (DWI) and ADC maps is still a matter of debate¹⁹ so that they should not be routinely included in MRI protocols for patients with TS. T1-W coronal SE sequences with thin slices for adequate assessment of hippocampal developmental abnormalities, as recommended by Sato¹⁸, are deemed advantageous for assessment of TS patients.

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