A neonatal case of tuberous sclerosis presenting two types of tubers on cranial ultrasound images

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We report a neonatal case of tuberous sclerosis (TS) presenting two types of tubers on cranial ultrasound (US) images. Multiple cardiac rhabdomyomas (CRs) were detected at 36 weeks’ gestation by intrauterine US. Postnatally, the patient had no heart problems. On her second day after birth, she experienced generalized tonic clonic seizures. On the same day, tubers, white matter lesions, and subependymal nodules were recognized on her brain magnetic resonance imaging (MRI) scan. In addition, cranial US showed multiple brain lesions. The patient fulfilled the diagnostic criteria for TS. Two types of tubers were detected on US: an incomplete ring resembling a half-eaten doughnut and a solid mass. These could be observed more clearly with a 12-MHz linear probe than with a 7-MHz sector probe. If the fetal US examination had been performed with suitable probes, her brain lesions could have been prenatally detected. When CRs can be detected on fetal US, neuroimaging enables a rapid diagnosis of TS. In addition to genetic testing and the morphology of tubers as seen on MRI, it is likely that the types of tubers seen on US facilitate forecasting of the postnatal severity of the neuronal manifestations of TS.

Keywords: tuberous sclerosis, cardiac rhabdomyoma, cortical tuber, US, MRI

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Fig. 1  Postnatal heart US scan confirming cardiac rhabdomyomas
(a) A large rhabdomyoma in the right ventricle apex measured 20 mm × 15 mm. (b) The other rhabdomyomas, each about 5 mm in diameter, were recognized at the tricuspid valve, left ventricle.

Fig. 2  MRI scan on infant’s second day after birth
Axial T1-W images: (a-d) demonstrate multiple tubers (small arrows: appearing as half-eaten doughnut tuber on US; large arrows: appearing as solid tuber on US), white matter lesions (small arrowheads), and subependymal nodules (large arrowheads) to be hyperintense. T2-W images: (e-h) demonstrate all the lesions as hypointense. FLAIR images: (i-l) are more difficult to differentiate with respect to all types of lesions than other images.
was flat, and the neurological examination was normal. No heart murmur was detected. An electrocardiogram revealed incomplete right bundle branch block and no arrhythmia. Her cardiac US confirmed multiple CRs. A large rhabdomyoma in the right ventricle apex measured 20 mm × 15 mm, and the other rhabdomyomas, which each measured around 5 mm in diameter, were seen at the tricuspid valve and in the left ventricle (Fig. 1).

On the infant’s first day of life, no abnormality could be detected on routine renal or head US. The next day, the infant experienced many generalized tonic clonic seizures. Her EEG showed sporadic sharp waves in the left central area. Treatment with phenobarbital produced a substantial improvement in the number of seizure episodes. On the same day, multiple tubers, white matter lesions, and subependymal nodules (SENs) were observed on her brain MRI scan. All the lesions were detected as hyperintense on T1-weighted images and hypointense on T2-weighted images. Fluid-attenuated inversion recovery (FLAIR) images are more difficult to differentiate with respect to all types of lesions than other images (Fig. 2). The patient fulfilled three major symptoms of the diagnostic criteria of TS. We carefully performed her cranial US examination again. We re-confirmed her brain lesions on US as well as on MRI. We visualized all the findings with a 12-MHz linear probe more easily than with a 7-MHz sector probe (Fig. 3 and Fig. 4). We observed two types of tubers on the US images. One type appeared as a half-eaten doughnut (Fig. 3a,e and Fig. 4d), and the other type appeared as a solid mass (Fig. 3b,c,f and Fig. 4c).

At age 2 months, the patient presented with new onset of infantile spasms. Currently, at age 7 months, her motor development is delayed and her epileptic movements are intractable, despite the administration of many anticonvul-

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**Fig. 3** Cranial US images using a 12-MHz linear probe: coronal view (a-d) and sagittal view images (e,f)

We detected two types of tubers: an incomplete ring resembling a half-eaten doughnut (small arrow) and a solid mass (large arrow). We noted the presence of white matter lesions (small arrowheads) and subependymal nodules (large arrowheads).
sive medications. The large rhabdomyoma in the right ventricle apex appears to be regressing. We did not perform the patient’s genetic analysis until her present age of 7 months.

**Discussion**

Prenatal diagnosis of CRs often occurs during routine obstetrical US examination without other obvious features fulfilling the diagnostic criteria of TS. Bader et al.\(^2\) reported that among 19 patients noted as having fetal CRs, 15 were ultimately diagnosed with TS. These authors concluded that most cases of fetal CRs are diagnosed as TS. Yates et al.\(^3\) reported that out of 125 substantiated cases of TS, prenatal US examinations could be pointers to diagnosis for 18 (14%) of the cases, and only one of those patients could be documented as having a brain lesion. Worrmann et al.\(^4\) reviewed 20 cases of TS that demonstrated both CRs and CNS lesions by fetal imaging studies. In only two of those cases, CNS lesions were detected earlier than CRs. CNS lesions were observed between 21 and 32 weeks’ gestation. These authors implied that there was no difference in the time course of detection between different imaging methods (US and MRI).

Muhler et al.\(^5\) suggested that fetal MRI is a reliable diagnostic tool for demonstrating brain lesions in TS. These investigators presumed that US is not very sensitive in diagnosing cerebral lesions, except for large subependymal tumors. In our facilities, we routinely perform fetal US using a 3.5-MHz convex probe. We are convinced that by using fitting probes, for example, a 7-MHz convex one for conditions suitable for US diagnosis, we could have detected the present patient’s brain lesions antenatally as clearly as we did postnatally.

Serious attention must be given to the findings of neonatal brain MRI. All lesions, such as tubers, in infants under 3 months old are hyperintense on T1-weighted images and hypointense on T2-weighted images, as opposed to a reversed pattern of signal intensity in older persons. This is why the scarce myelination in neonates helps to identify white matter anomalies.\(^6\)

Recently, some authors have reported a correlation of tuber morphology on MRI with clinical manifestations,

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**Fig. 4 Cranial US images using a 7-MHz sector probe**

We perceived all findings with a 12-MHz linear probe more easily than with a 7-MHz sector probe. Use of the 7-MHz sector probe also showed the image of tuber resembling a half-eaten doughnut (small arrow), like a solid mass (large arrow), white matter lesions (small arrowhead), and subependymal nodules (large arrowhead).
including gene mutation. Chu-Shore et al. showed a strong association between cyst-like tubers and a TSC2 gene mutation, as well as a more aggressive seizure phenotype, such as that exhibited by a history of refractory epilepsy and infantile spasms. Gallagher et al. also found that patients presenting with the TSC2 mutation tended to have cyst-like tubers and the more severe seizure phenotype. We assume that a cortical tuber with the appearance of a half-eaten doughnut on neonatal cranial US correlates with a cyst-like cortical tuber seen on MRI imaging. Considering this, there is a good possibility that our patient had the TSC2 gene mutation because of early onset of infantile spasms and the potential for cyst-like tubers.

Cortical tubers are very common in TS and widely vary in size, appearance, and location. The pathogenesis and natural history of cyst-like changes in cortical tubers is unknown. Tubers are developmental abnormalities of the cerebral cortex characterized histologically by a loss of the normal six-layered structure of the cortex and dysmorphic neurons, large astrocytes, and a unique type of giant cell. Tubers can calcify or undergo cystic degeneration. Jurkiewicz et al. observed typical cyst-like tubers in 17 of 73 children with TS (aged 25 days to 12.3 years) on MR examinations. A hyperintense signal rim around a hypointense central part of these cortical tubers was seen on FLAIR images. The shape of the cystic part was categorized as expansile or shrunken. Those cyst-like tubers were detected in 14 (82%) of 17 patients below 7 years of age. Jurkiewicz et al. concluded that further investigation is necessary to discover whether solid tubers undergo cystic degeneration or whether cystic lesions shrink and remain in the cortex as solid tubers. Chu-Shore et al. also found that younger patients are more likely to have cyst-like cortical tubers than older patients, and postulated that these changes may be the result of accelerated apoptotic processes in altered neuronal and astroglial cells.

To the best of our knowledge, this is the first case report of two types of tubers seen on neonatal cranial US images. A better understanding of the association between tuber types and epileptogenicity could be beneficial in treating patients with TS. In the near future, the morphology of tubers classified by US and MR images could become a useful way of predicting the severity of the neurological manifestations and prognosis of patients with TS.

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