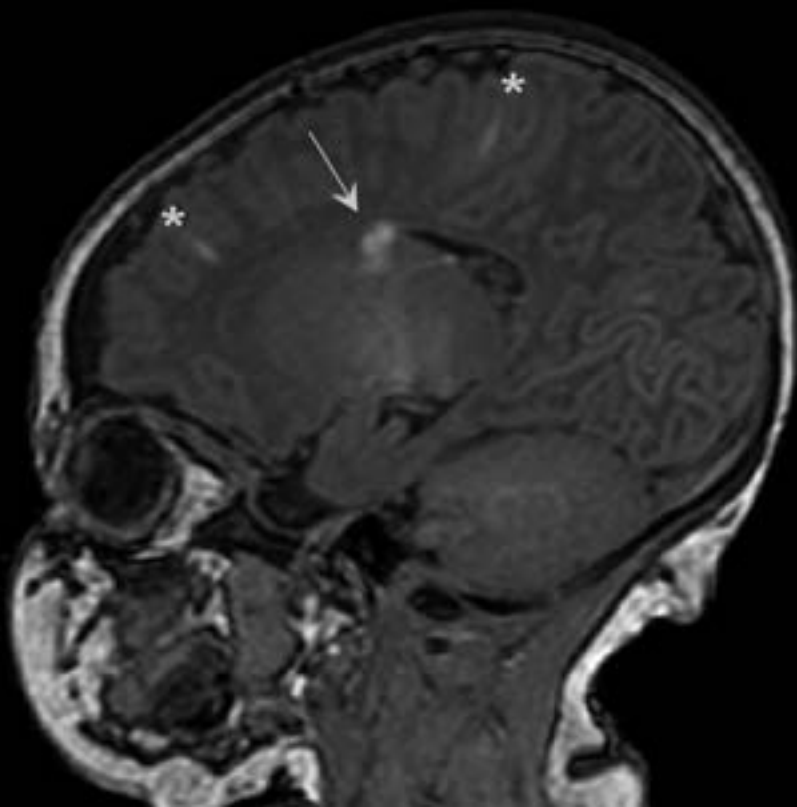# A rare cause of neonatal seizures

Hagmann C, Robertson NJ, Centre for Perinatal Brain Research, Institute for Women's Health, University College London, London WC1E 6HX

Seizures are more common in the neonatal period than during any other time throughout life. The incidence of seizures in infants born at term is 1.5-3.0 per 1000 live births; the incidence is even higher in preterm infants, ranging from 50-150 per 1000 live births (1). These figures are probably underestimations as they only include clinical and electroclinical seizures. The exact incidence of electrographic, clinically silent seizures is as yet unknown. The vast majority of neonatal seizures occur on the first day, and 70% of all cases eventually recognised are diagnosed by the fourth day. There are many varied causes of neonatal seizures (Table 1); the seizures themselves can be subtle, tonic, clonic or myoclonic (Table 2).

A female term infant (41 week's gestational age) was born by emergency Caesarean Section because of an abnormal cardiotocograph and failure to progress following induction. An artificial rupture of membranes was performed 5 hours prior to delivery and meconium stained liquor was noted. At delivery the infant was in good condition with Apgar scores of 9 at 1 minute and 10 at 5 minutes. The birthweight was 3.96 kg and head circumference 38 cm. The baby was transferred to the postnatal ward where breastfeeding was established. The mother and baby were discharged home on day 2 of life.

Causes of neonatal Seizures	Frequency (%)
Hypoxic ischaemic encephalopathy	30-55
Intracranial hemorrhage	7-17
Cerebral malformation	3-17
Infection	2-15
Hypoglycaemia	0.1-5
Hypocalcaemia, hypomagnesemia	4-22
Pyridoxine dependency	3-4
Maternal drug withdrawal	4
Idiopathic	2
Benign idiopathic neonatal seizures	1

Table 1

Causes of neonatal seizures (1,2).

Classification of seizures in the newborn (1).

Table 2

Type	%	Clinical signs	Ictal EEG abnormalities
Subtle	50	Ocular, oral, autonomic, limb posturing and movements	+/-; ++ if prolonged EEG monitoring
Tonic	5	Stiffening, decerebrate posturing	+ if focal, - if generalised, but then abnormal background
Clonic	25-30	Repetitive jerking, distinct from jittering, unifocal or focal	+++
Myoclonic	15-20	Rapid, isolated jerky, usually bilateral	+ if generalised, - if focal

From day 4 after birth the mother noted jerky movements of the limbs with deviation of the eyes to the right; these episodes lasted up to 2 minutes. She was initially reassured by the midwife, but when the midwife observed the movements herself she referred the infant to the paediatric ward for further investigations. During the admission examination, a 2-minute-episode consisting of deviation of the eyes to the right and limb posturing without cyanosis or apnoea was observed. All laboratory investigations were within normal limits including normal echocardiography and kidney sonography.

A loading dose of phenobarbitone was given and no further seizures occurred during this admission. An EEG showed normal background for age except for some runs of high frequency activity lasting about ten seconds over the right central region (Fig.1). If clinically there would be no correlate then these runs of high activity could be brief ictal rhythmic discharges (BIRDS).The cranial ultrasound showed a hypoechogenic area in the periventricular white matter extending to the cortex (Fig. 2). The brain MRI, which was performed on day 10 following birth, was diagnostic. Multiple sub-ependymal nodules (Fig. 3) were observed in the caudo-thalamic notch (Fig. 4), cortex and white matter on both sides (Fig. 3, 5, 6). The largest lesion was observed in the left frontal lobe with signal abnormality extending down the ventricular margin (Fig. 6, 7). These findings were consistent with a diagnosis of tuberous sclerosis.
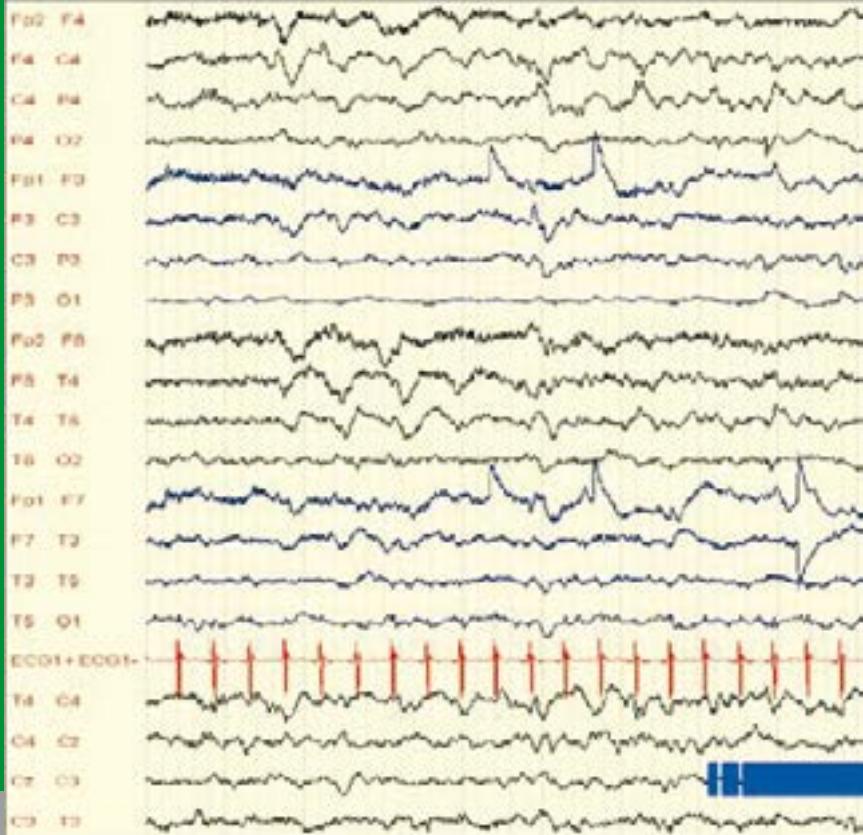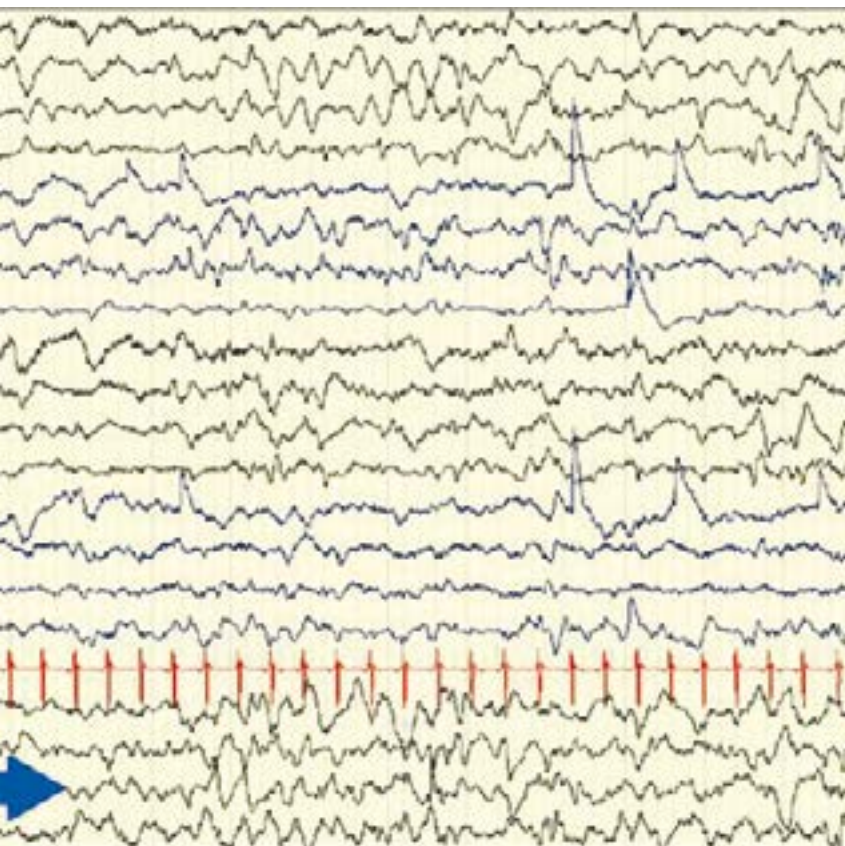
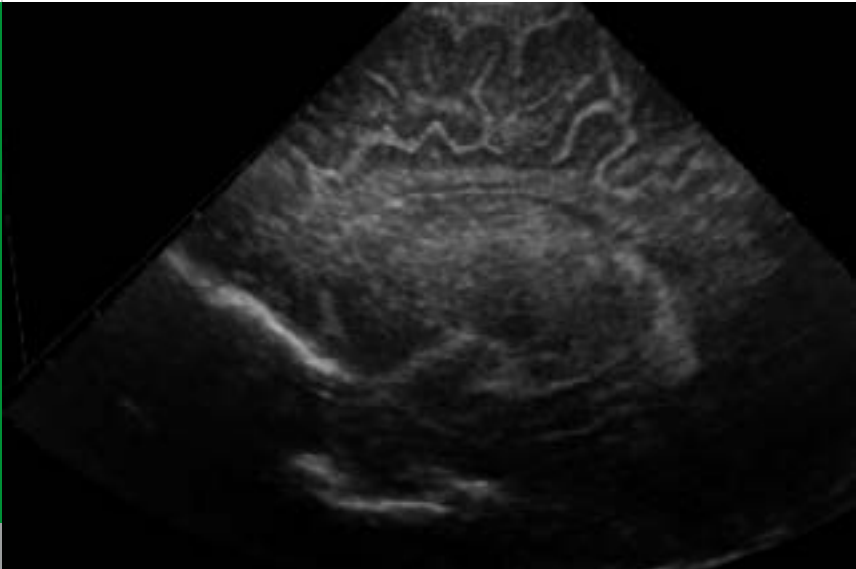*EEG recording showing short runs of rhythmic activity (mainly over C3 and F7, arrow).*

Fig. 2A

Cranial ultrasound: parasagittal views of the right (A) and left (B) lateral ventricle showing hypoechogenic area in the left white paraventricular white matter extending to the cortex (arrow).
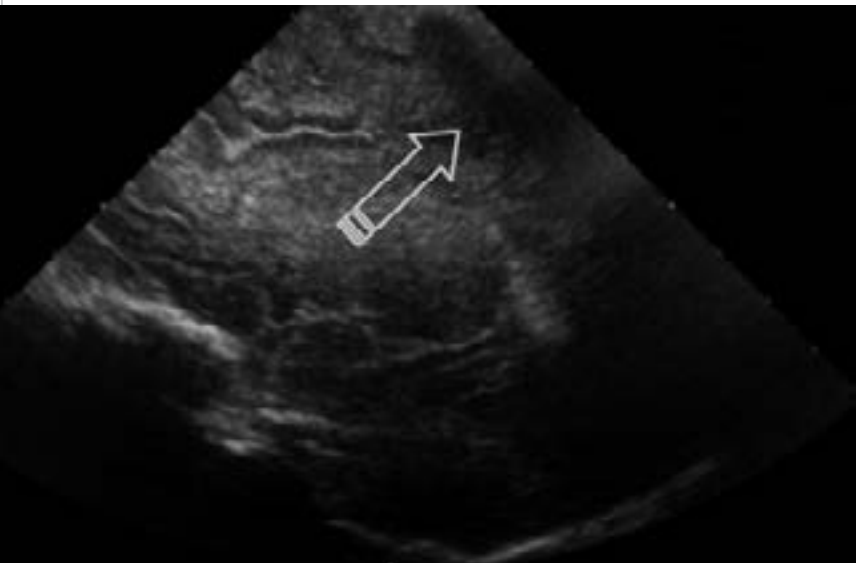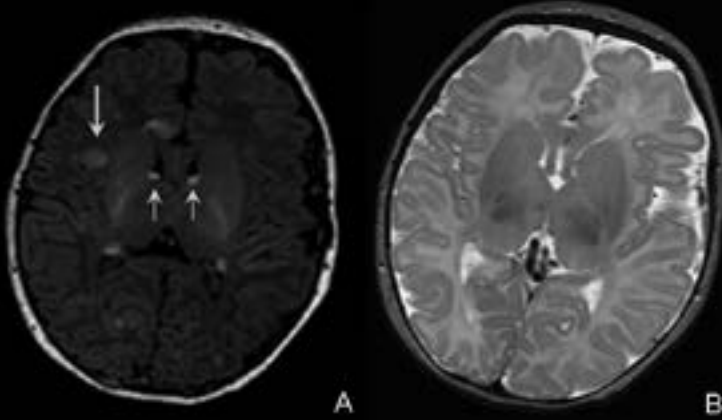
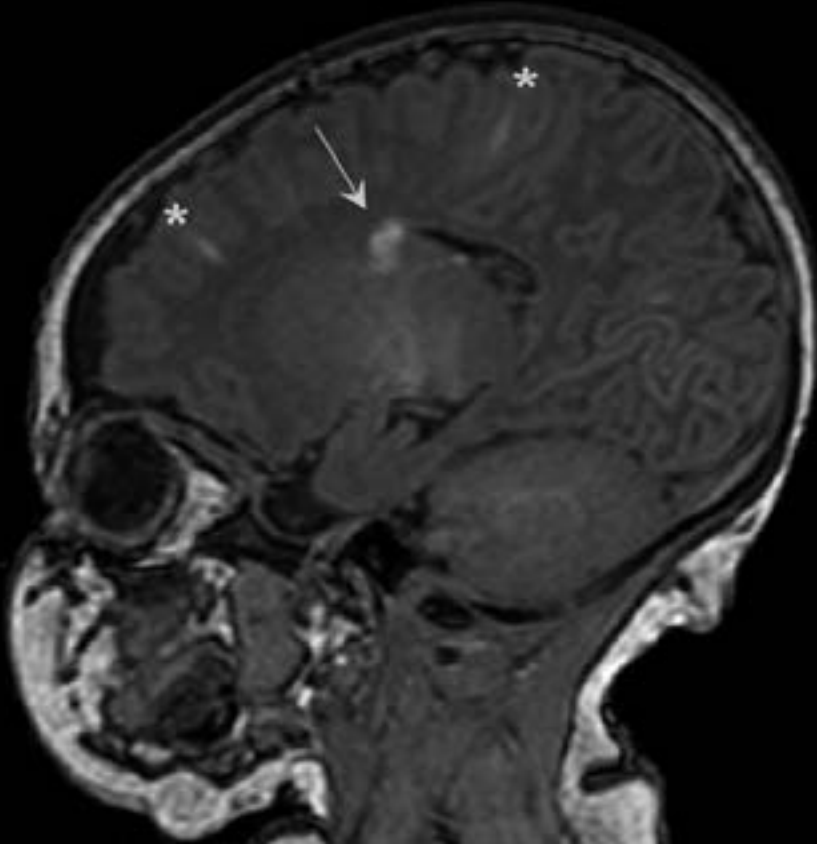**Fig. 2B**

Axial T1 weighted image (A) and T2 weighted image (B): Hyperintense multiple subependymal nodules (short arrows) and white matter lesions (long arrow) are seen on the T1 weighted image; the subependymal nodules are less well seen on T2 weighted images at this age.

Fig. 4

Sagital T1 weighted image showing subependymal nodules at the thalamo-caudate notch (arrow). Note the thin hyperintensities in the white matter extending radially to the cortex (asterisks).

Fig. 5

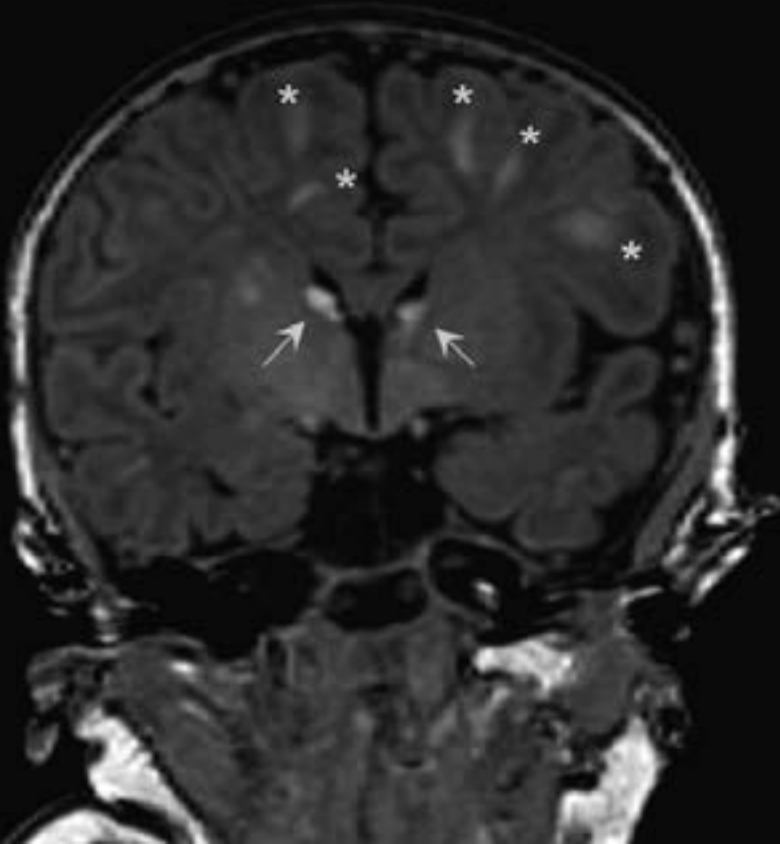*Coronal T1 weighted image showing subependymal nodules which are hyperintense at this age (arrows) and thin linear hyperintensities in the white matter (asterisks).*
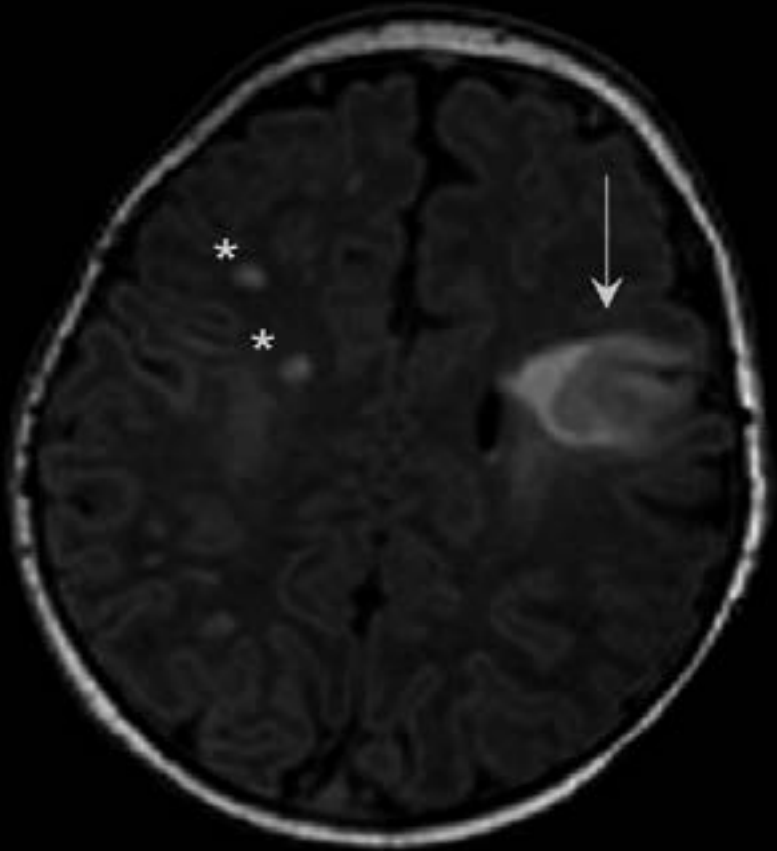
Fig. 6A

Axial T1 (A) and T2 (B) weghted images showing a large left cortical tuber (arrow), subependymal nodules (asterisks) and white matter lesions which are hyperintense on the T1 weighted image and hypointense on the T2 weighted image.
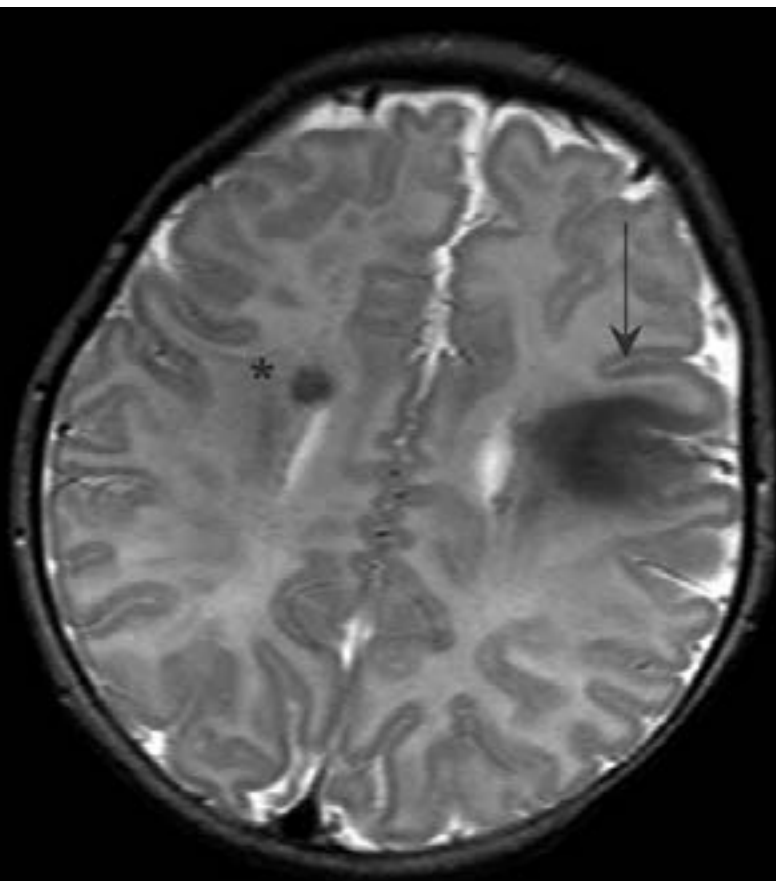
Major features	Minor features
Facial angiofibromas or forehead plaque	Multiple randomly distributed pits in dental enamel
	Hamartoma rectal polyps
Non-traumatic ungal or periungal fibroma	Bone cysts
	Cerebral white matter radial migration lines
Hypomelanotic patch	
Multiple retinal nodular hamartomas	Gingival fibromas
	Non-renal hamartoma
Cortical tuber	Retinal achromic patch
Subependymal nodules	"Confetti" skin lesions
Subependymal giant cell astro-cytoma	Multiple renal cysts
	Affected first degree relative
Cardiac rhabdomyoma, single or multiple	
Lymphangioleiomyomatosis	
Renal angiomyolipoma	

Table 3

Diagnostic criteria for Tuberous Sclerosis Sequence (TSC) (7).

Since the initial description of the cerebral abnormalities in 1882 (3), the diagnosis of tuberous sclerosis complex (TSC) has been based on the classic triad of mental retardation, epilepsy and the characteristic skin lesions. However, because intellectual deficits are seen only in 40% of patients and the cutaneous and intellectual deficits might not be apparent in the first 2-3 years of life, the radiologic manifestation has taken on considerable clinical importance in the diagnosis of TSC in infants (4). Characteristic abnormalities are present on neuroimaging studies in 95% of affected patients; brain and cardiac abnormalities may also be present before birth and can be detected with fetal imaging studies (5).

TSC is the second commonest phakomatosis affecting between 1 in 7000-10000 live births. It affects the brain (cortical and subcortical tubers, subependymal nodules, and giant astrocytoma), kidney (angiomyolipomas, cysts, carcinoma), skin (facial angiofibromas, periungal fibromas, hypomelanotic macules, shagreen patches), eye (retinal hamartomas) and heart (rhabdomyomas) (6). Diagnostic criteria for TSC are listed in Table 3 (7).

TSC is an autosomal dominant genetic disorder, although there is a high rate of spontaneous mutation in one of the TSC genes. Two separate mutated or deleted genes have been identified in patients with

periungal fibromas, hypomelanotic macules, shagreen patches), eye (retinal hamartomas) and heart (rhabdomyomas) (6). Diagnostic criteria for TSC are listed in Table 3 (7).

TSC is an autosomal dominant genetic disorder, although there is a high rate of spontaneous mutation in one of the TSC genes. Two separate mutated or deleted genes have been identified in patients with tuberous sclerosis. The TSC1 gene is localised to chromosome 9q34 and codes for a protein called hamartin, while the TSC2 gene has been localised to chromosome 16p13.3 and codes for a protein called tuberin. Hamartin and tuberin interact in vivo and that clarifies how mutations of these two different genes result in a common phenotype. It appears that mutations of these two genes make up the vast majority cases of tuberous sclerosis (5,7).

Neurological disturbances are often the presenting feature and cause morbidity/mortality. Infantile spasms or early childhood myoclonic seizures are presenting symptoms of TSC in approximately 80% of the patients. Any type of seizure can occur, our patient presented with subtle seizures on day 4 after birth. The incidence of mental retardation ranges from 45-82%. Patients with more than 10 cortical tubers seem to have a higher incidence of mental retardation, but this may be related to the higher incidence of epilepsy in this group.

Intracranial manifestations include subependymal ha-
martomas, giant cell tumours, cerebral hamartomas,
white matter lesions, parenchymal cysts and cerebellar
lesions.

We discuss the intracranial lesions that have been
found in our patient.

Subependymal nodules

The most common of these are the subependymal
hamartomas, which differ histologically from the cor-
tical hamartomas (tubers) and therefore behave diffe-
rently on imaging studies. The subependymal nodules
tend to be located along the ventricular surface of the
caudate nucleus, most common on the lamina of the
sulcus thalamo-striatus immediately posterior to the
foramen of Munro. Giant cell tumour is given to the
enlarging subependymal nodules that are usually si-
tuated near the foramen of Munro. Their characteri-
stic location and tendency to enlarge usually result in
a clinical hydrocephalus. In neonates, subependymal
nodules can be detected by transfontanelle sonogra-
phy. On MRI, the hamartomas are relatively hyperin-
tensive on T1 weighted images and hypointensive on
T2 weighted images (Fig. 2, 5). They are most easily
visualised on T1 weighted images where they contrast
with low signal intensity of the CSF (Fig. 2, 4). If an
enlarging, contrast enhancing subependymal nodule is
seen in the subependymal region it should be consi-
dered a giant cell tumour (5, 8).

Cerebral hamartoma

Cerebral hamartoma or "tubers" are the most cha-racteristic lesions of tuberous sclerosis pathologically. They are most commonly supratentorial, although 8-15% of affected patients have cerebellar tubers. The MR appearance of cortical tuber change with age. In neonates, they appear hyperintense compared to the surrounding unmyelinated white matter on T1 weigh-ted images and hypointense to white matter on T2 weighted images. T1 and T2 shortening may extend through the cerebral mantle to the ventricle from the tuber (8).

White matter lesions

Isles consisting of a grouping of neurons and glial cells are invariably present in the white matter of patients with tuberous sclerosis. On MR, these white matter lesions have the same signal characteristics as corti-cal tubers and, if the proper imaging plane is used, are seen to course through the entire cerebral mantle from the cortex to the ventricular surface (Fig. 4) (5, 8). In summary, the large differential diagnosis following neonatal seizures prompts thorough investigations. The initial investigations should concentrate on the common aetiologies requiring prompt specific treat-ment. EEG can provide confirmation that any suspi-cious phenomena are seizures. Cranial ultrasound is readily available in most centres and useful as a first-line imaging. If ultrasound is reported as normal but the infant continues to have seizure or the ultrasound

is abnormal further neuroimaging studies such as MRI should be carried out.

1. Volpe JJ. Neonatal seizures. In: Neurology of the Newborn, WB Saunders Company, 2001 (4th edition), pp 178-214

2. Levene MI, Trounce JQ. Causes of neonatal convulsions. Arch Dis Child 1986;61:78-79 (Abstract)

3. Bourneville DM. Contribution à l'étude de l'idiote. Arch Neurol (Paris) 1882;1:81-89

4. Seidenwurm DJ, Barkovich AJ. Understanding Tuberous Sclerosis. Radiology 1992;183:23-24

5. Barkovich AJ. Pediatric Neuroimaging. The phakomatosis: tuberous sclerosis, Lippincott Williams & Wilkins, 2005 (4th edition), pp 463-476

6. Sparaganga SP, Barkovich AJ. Tuberous sclerosis complex. Curr Op Neurol 2000;13:115-119

7. Roach ES,Gomez MR, Northrup H. Tuberous sclerosis complex consenus conference: revised clinical diagnostic criteria. J Child Neurol 1998;13:624-628

8. Baron Y, Barkovich AJ. Mrimaging of tuberous sclerosis in neonates and young infants. Am J Neuroradiol 1999;20:907-916

SUPPORTED BY