The Turkish Journal of Pediatrics 1998; 40: 481-490

NEURONAL MIGRATION DISORDERS PART II: MAGNETIC RESONANCE IMAGING*

*Işıl Saatçi MD**, Güzide Turanlı MD***, Yavuz Renda MD*****

SUMMARY: Saatçi I, Turanlı G, Renda Y. (Department of Radiology and Neurology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neuronal migration disorders. Part II: magnetic resonance imaging. Turk J Pediatr 1998; 40: 481-490.

With the widespread use of magnetic resonance imaging (MRI), neuronal migration disorders (NMD), including lissencephaly, pachygyria, polymicrogyria, schizencephaly, unilateral hemimegalencephaly and gray matter heterotopia, are more frequently and easily diagnosed. When NMD is a diagnostic consideration, MRI should be the imaging method of choice with the high contrast between gray and white matter it provides and its high resolution multiplanar display of anatomy. Magnetic resonance imaging displays the size, configuration and distribution of cortical gyri and cortical thickness for the evaluation of possible lissencephaly, pachygyri and polymicrogyri. It will successfully demonstrate deposits of gray matter in abnormal locations when gray matter heterotopias are present. With its multiplanar imaging capability, MRI will demonstrate the cleft extending from the pial surface to the ventricular ependyma whether the lips of the cleft are fused or separate, thus providing the diagnosis of schizencephaly. *Key words: brain abnormalities, brain MRI studies, magnetic resonance imaging, neuronal migration anomalies, schizencephaly, heterotopia, focal cortical dysplasia.*

Neuronal migration disorders (NMD) are congenital malformations caused by insults to migrating neuroblasts during the 8th-24th gestational weeks. Until the advent of magnetic resonance imaging (MRI), computerized tomography (CT) has been of assistance in the diagnosis of this group of anomalies. Magnetic resonance imaging should be the imaging method of choice when NMD is a diagnostic consideration, since it is more sensitive and more specific than CT in detecting these anomalies. Furthermore, it better delineates the abnormality with its better contrast between gray and white matter and its high resolution multiplanar display of anatomy. However, recognition of NMD on images depends on awareness of the characteristic appearance of the entities and use of the proper imaging technique.

* From the Department of Radiology and Neurology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Associate Professor of Radiology, Hacettepe University Faculty of Medicine.

*** Pediatric Neurologist, Hacettepe University Faculty of Medicine.

**** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

Lissencephaly

The term lissencephaly refers to a paucity of gyral and sulcal development on the surface of the brain. Agyria is defined as the absence of gyri on the surface of the brain and is synonymous with "complete lissencephaly" (Figs. 1a,b). The term pachygyria designates a less marked abnormality with the presence of sulci delineating broad, abnormal brain convolutions[1]. Lissencephalies can be divided into a number of subcategories based upon the morphology of the smooth brain and the associated brain anomalies[2].

Type I lissencephaly (the agyria-pachygyria complex)

Most patients in this group have areas of both agyria and pachygyria (i.e. incomplete lissencephaly). the areas of agyria are most frequently parieto-occipital in location, whereas the pachygyric areas are most common in the frontal and temporal regions[1,2].

Imaging studies of type I lissencephaly reveal a smooth brain surface with diminished white matter and shallow, vertically oriented sylvian fissures (Figs 1a,b). A thin outer cortical layer is separated from a thick deeper cortical layer by a zone of white matter (the "cell-sparse zone") that seems to myelinate normally. The gross appearance of the brain resembles that of the fetus prior to 23rd-24th gestational weeks, when sulci normally begin to form. The cerebrum has "figure eight" appearance on transverse images as a result of the shallow, vertical sylvian fissures. In cases of severe agyria, sagittal images may show callosal hypogenesis. The ventricular trigones and occipital horns are enlarged, mostly because of the underdevelopment of the calcarine sulci; hypoplasia of the callosal splenium may play a role in some patients. The brain stem often

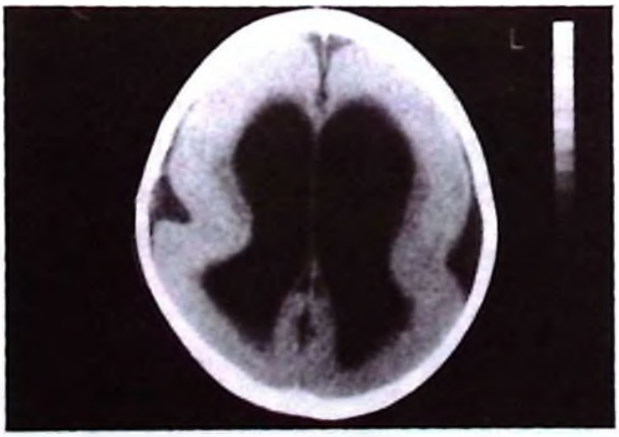

Fig. 1a

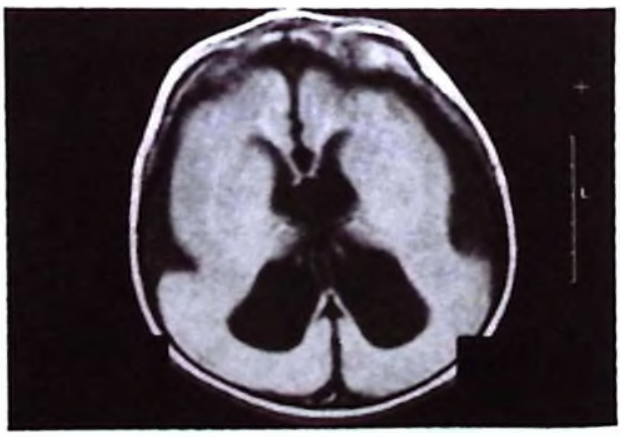

Fig. 1b

Figs. 1a,b: Type I lissencephaly
CT (a) and T1W (b) transverse MR images showing absence of cortical sulci (agyria or complete lissencephaly) with the exception of slyvian fissures, giving a "Figure eight" appearance to the brain. The lateral ventricles are enlarged, the cortex is thickened.

appears hypoplastic, probably because many of the corticospinal and corticobulbar tracts do not form[3].

Areas of pachygyria also have a thickened cortex, but broad gyri and shallow sulci are present. Pachygyria can be focal or diffuse. When focal, it can occur in any part of the brain. When diffuse, it is often associated with regions of agyria and tends to be more severe in the parieto-occipital region of the brain[4].

Type II lissencephaly (Walker-Warburg syndrome, Fukuyama's congenital muscular dystrophy, and related syndromes)

Type II lissencephaly is characterized pathologically by a thickened and severely disorganized unlayered cortex, which is disrupted by penetrating vessels and fibroglial bundles. Subcortical heterotopias are not rare. The meninges are thickened and densely adherent to the cortex, obliterating the subarachnoid space and resulting in hydrocephalus. The entirety of the cerebral hemispheres is involved[1,3].

On imaging studies, patients with type II lissencephaly have a thickened cortex with shallow sulci (which may appear intermediate between type I lissencephaly and diffuse polymicrogyria), microphthalmia and hypomyelination. More severe cases will have hydrocephalus, vermian hypogenesis, cerebellar polymicrogyria, dysgenesis of corpus callosum and, occasionally, an occipital cephalocele.

Diagnosis of microcephalia vera (type III lissencephaly) and *radial microbrain (type IV lissencephaly)* are solely based on histopathologic examination. *Microcephalia vera* is characterized by thin cortices, shallow sulci and markedly diminished callosal fibers (which originate and terminate in the outer cortical layers)[3] on pathologic examination of brain. The term *radial microbrain* has been used to describe a group of patients that were born at term with a markedly reduced brain size despite normal gyral patterns, absence of destruction or gliosis, normal cortical thickness and normal cortical lamination. The number of neocortical neurons was only 30 percent of normal. MRI scan may show microcephaly, delayed myelination and a slightly immature gyral pattern.

Diffuse polymicrogyria is sometimes referred to as *type V lissencephaly*[2]. The brain is diffusely smooth due to abnormal organization of cortical neurons, which results diffuse cortical dysplasia, or polymicrogyria. This is the type of lissencephaly seen in patients with cortical involvement from congenital cytomegalovirus infection[2].

Polymicrogyria (cortical dysplasia)

Polymicrogyria is a migration disorder in which the neurons reach the cortex but the normal six-layered lamination of the cortex is deranged. Thus, the term

cortical dysplasia may be more appropriate[2]. The results is formation of multiple small gyri. Small or large portions of the hemisphere can be involved. The most common location is around the sylvian fissure, particularly the posterior aspect of the fissure. However, any area, including the frontal, occipital and temporal lobes, can be affected.

Cortical dysplasia can have an irregularly bumpy surface or, paradoxically a smooth one, because the outer cortical layer fuses at the microsulci (Figs. 2a,b). It may have the appearance of pachygyria, with broad, thickened gyri, or it may look normal[4]. Cortical thickness in polymicrogyria is usually in the 5-7 mm range (normal 3 mm), whereas a cortical thickness of >8 mm is seen in almost all cases of pachygyria[3].

The dysplastic cortex can be flat and congruent to the arch of the normal cortex, or it may extend centripetally, appearing as if the cortex were buckled or folded inward (Figs. 3a,b and 4a,b). The character of the cortex in these regions of infolding is similar to that in superficial cortical dysplasia, with bumpy, irregular inner and outer cortical surfaces (Figs. 3a,b and 4a,b).

Typically, the dysplastic cortex is isointense to gray matter on all imaging sequences. T2 hyperintensity is present in the white matter subjacent to the dysplastic cortex in about 20 percent of patients, possibly caused by the same insult that resulted in the disorganization of the cortex (Fig. 2a). In less than five percent of the cases, calcification may be present[2]. Anomalous venous drainage is common in areas of the dysplastic cortex[5], particularly in regions where there is large infolding of the thickened cortex. In this instance, angiography is not indicated.

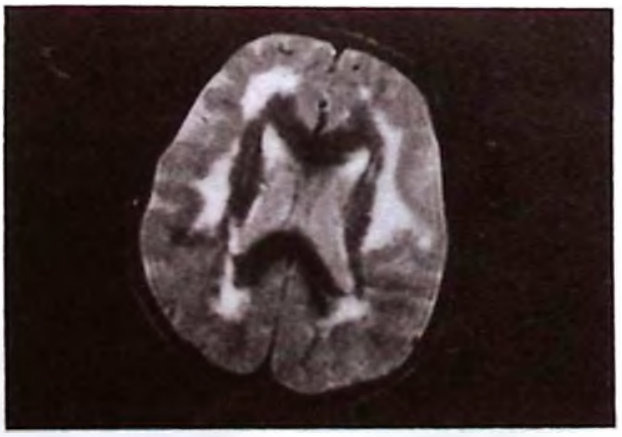

Fig. 2a

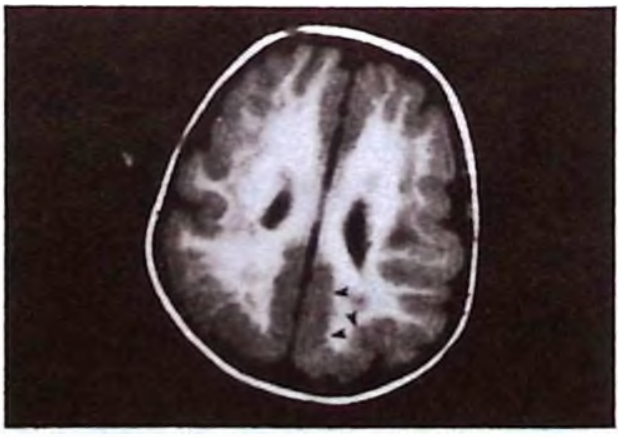

Fig. 2b

Figs. 2a,b: Polymicrogyria
T2W transverse images (a) demonstrates thickened cortex and abnormal high signal intensity in the hemispheric white matter. On T1W (b) image the microgyri can be identified (black arrowheads), particularly in the parietal region, leading to the diagnosis of polymicrogyria, in spite of the pachygyriclike appearance on T2W image.

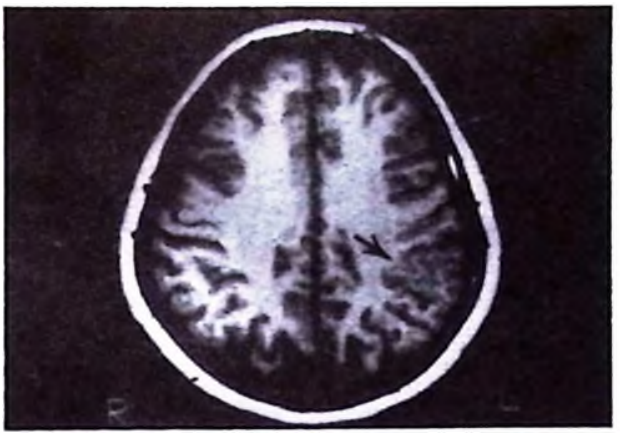

Fig. 3a

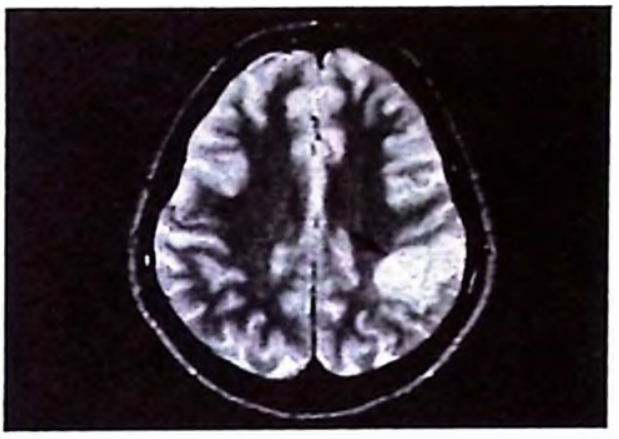

Fig. 3b

Figs. 3a,b: Focal cortical dysplasia
T1W (a) and T2W (b) transverse images showing a focal region of thickened cortex (black arrow) in the left parietal lobe with areas of trapped CSF in the infolding sulci (b).

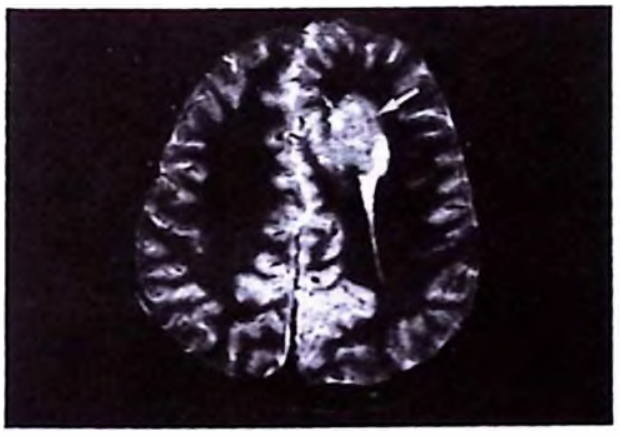

Fig. 4a

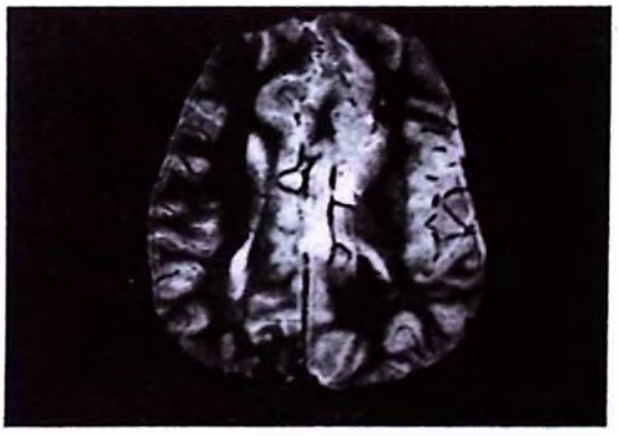

Fig. 4b

Figs. 4a,b: Gray matter heterotopia, focal cortical dysplasia
Consecutive T2W images (a,b) show the infolding of the cortex in the left frontal region, indenting on the lateral ventricle (large white arrow on figure a, black arrow on figure b). Areas of trapped CSF are seen within the heterotopic gray matter (small white arrow on figure a). Note that corpus callosum is absent, resulting in parallel configuration of the lateral ventricles and displacement of the pericallosal arteries.

A specific *syndrome of bilateral opercular cortical dysplasia (bilateral perisylvian dysplasia)* has been described, in which patients present with a syndrome of developmental pseudobulbar palsy (oropharyngeal dysfunction and dysarthria) and epilepsy[2,6]. Sectional imaging shows thick bands of gray matter in the sylvian and rolandic areas of both hemispheres; the cortical abnormality consists of polymicrogyria[7]. *Aicardi's syndrome* is another syndrome of cortical dysplasia with associated anomalies including interhemispheric cyst, gray matter

heterotopias, posterior fossa cysts, callosal anomaly, cerebellar hypoplasia, choroid plexus papillomas and microphthalmia. Myelination may be delayed[2].

Schizencephaly

Magnetic resonance imaging shows a gray matter lined cleft extending across the full thickness of the cerebral hemisphere, from the pial surface of the brain to the ventricular ependyma[8] (Figs. 5ab, 6a, 7). The cleft is commonly in the

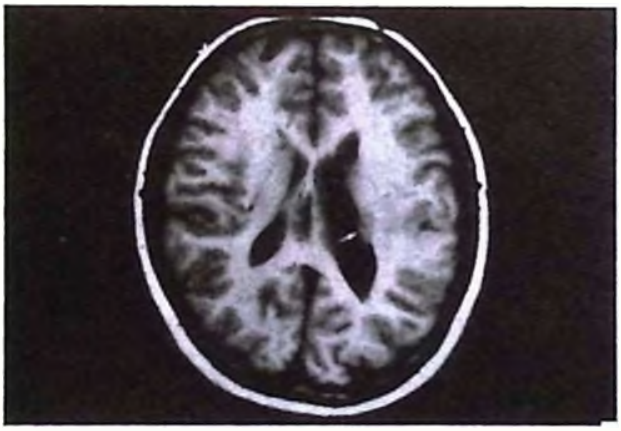

Fig. 5a

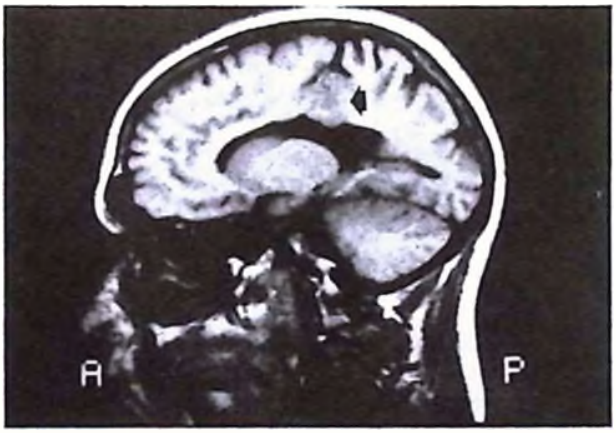

Fig. 5b

Figs. 5a,b: Unilateral closed-lip schizencephaly
a: T1W transverse image showing nodular gray matter (white arrow) at the wall of the slightly enlarged left lateral ventricle. The actual cleft of the schizencephaly could not easily be recognized on this particular image.
b: T1 weighed sagittal image demonstrating the cleft (black arrow) extending to the lateral ventricle completely fused medially with the gray matter lining. Note the dimple in the wall of the lateral ventricle indicating the continuity of the gray matter with the ventricle.

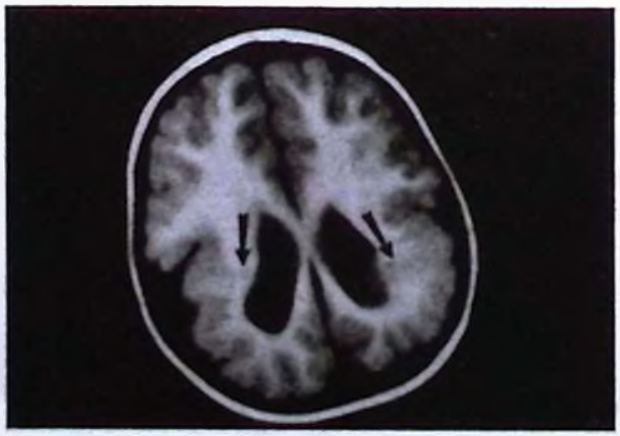

Fig. 6a

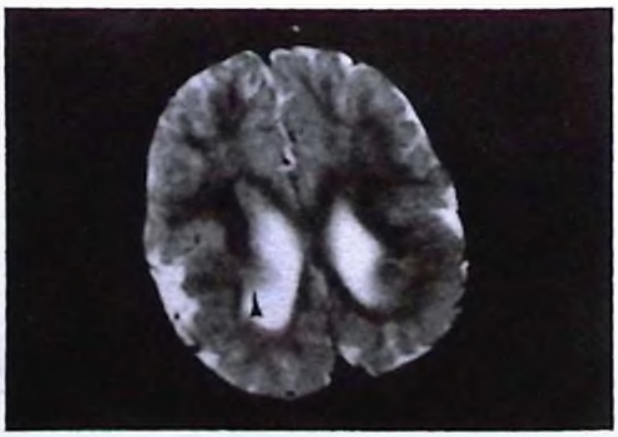

Fig. 6b

Figs. 6a,b: Bilateral open-lip schizencephaly
T1W transverse image demonstrating bilateral, symmetric, wide open clefts extending from the pial surface to the enlarged lateral ventricles. The cortex appears thickened with broad gyri and shallow sulci, giving the appearance of pachygyria.

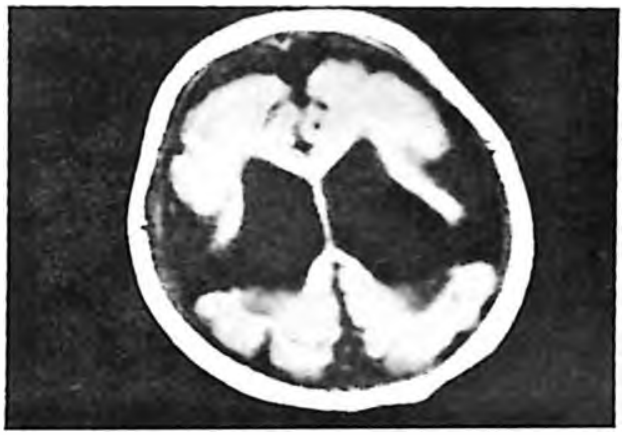

Fig. 7: Bilateral open-lip schizencephaly
T1W transverse image demonstrating bilateral, symmetric, wide open clefts extending from the pial surface to the enlarged lateral ventricles. The cortex appears thickened with broad gyri and shallow sulci, giving the appearance of pachygyria.

parietal and temporal areas of the brain, particularly involving the parasylvian region, and precentral and postcentral gyri[9,10]. Identification of the gray matter lining on the cleft is critical in differentiating schizencephaly from porencephaly. (This differentiation may be important for genetic counseling since the reported incidence of brain anomalies is five to 20 percent in subsequent siblings of children who have anomalies of cell migration)[11]. The clefts range from extremely narrow with actual fusion of the gray matter lined walls of the cleft (fused lips) (Figs. 5b, 6a) to quite large with wide separation of the walls (Fig. 7) and absence of large portions of the involved hemisphere. The gyral pattern of the cortex adjacent to the cleft is usually abnormal, demonstrating cortical dysplasia. The gray matter in the cleft may extend into the ventricle in the form of subependymal heterotopia (Fig. 5a). A dimple is usually seen in the wall of the lateral ventricle where the cleft communicates. The dimple is often a helpful sign of continuity of the cleft with the ventricle when the lips are fused[2] (Figs. 5b, 6a,b). There may be regional parenchymal volume loss and the sylvian vessels may be hypoplastic[12]. Ventricular diverticula may be present with or without lateral ventriculomegaly[12]. Cortical dysplasia may be present in the hemisphere contralateral to a unilateral schizencephaly. The septum pellucidum is absent in 80 to 90 percent of the patients with schizencephaly[2]. Approximately half of the patients with septooptic dysplasia may have accompanying schizencephaly[8,13].

Unilateral hemimegalencephaly

On CT and MRI, the involved hemisphere is moderately to markedly enlarged[2]. The cortex is typically dysplastic with broad gyri, shallow sulci and cortical

thickening. However, the gyral pattern may appear grossly normal or frankly agyric. In severely affected patients, the usually sharp border between the cortex and the subcortical white matter may blur or disappear altogether. The white matter may show areas of hypointensity on T1 and hyperintensity on T2 weighed (T1W, T2W) MR images, representing heterotopia and gliosis. The lateral ventricle on the affected side is enlarged in proportion to the affected hemisphere[7]. The frontal horn of the ipsilateral ventricle may have a characteristic configuration that is almost straight, pointing superiorly and anteriorly[2].

Gray matter heterotopia

For the purposes of clinical evaluation and prognostication, heterotopia may be divided into three groups[14]: 1-subependymal heterotopia 2-focal subcortical heterotopia 3-diffuse heterotopia. Heterotopias appear as nodular or broad regions in the subependymal, periventricular or subcortical areas that are isointense with gray matter on all imaging sequences. The most important features in distinguishing heterotopia from tumors are that heterotopias lack surrounding edema, remain isointense with gray matter on all imaging sequences (Figs, 8a,b) and with all imaging modalities, and do not enhance with contrast agents.

Subependymal heterotopias are smooth, ovoid masses that grow into the adjacent lateral ventricle, often causing the ventricle to appear compressed[14] (Figs. 8a,b). They are differentiated from the subependymal hamartomas of tuberous sclerosis by their shape (hamartomas of tuberous sclerosis are irregular and often elongated), their signal intensity (subependymal hamartomas of the tuberous sclerosis are usually iso-to hypointense compared to mature white

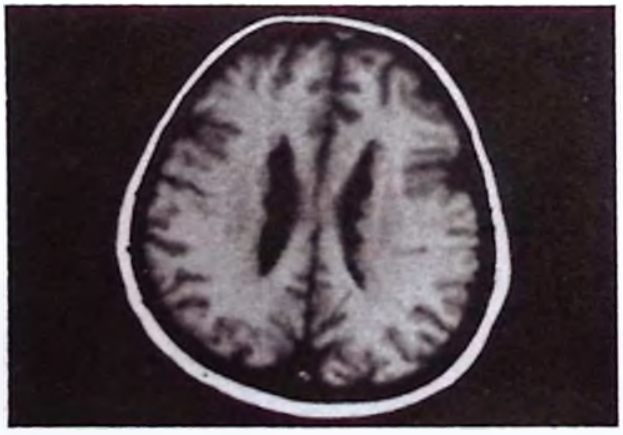

Fig. 8a

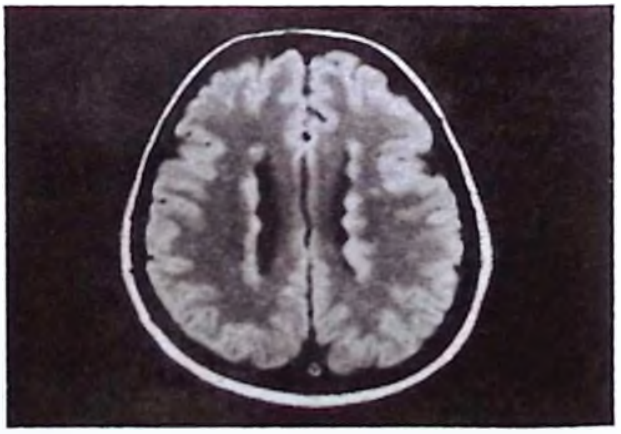

Fig. 8b

Figs. 8a,b: Subependymal heterotopia
T1W (a) and proton-density (b) transverse images showing nodules along the wall of lateral ventricles, bilaterally, isointense to gray matter on all imaging sequences. Note the indentation of the heterotopic gray matter on the ventricular wall.

matter), and the fact that they do not enhance after intravenous infusion of paramagnetic contrast[2].

Focal subcortical heterotopias will sometimes appear to contain vessels or cerebrospinal fluid, thereby mimicking tumors[14] (Fig. 4a). Closer examination will show that the vessels and cerebrospinal fluid are within infoldings of the cortex adjacent to the heterotopia. Patients with a large subcortical heterotopia may show thinning of the overlying cortex. The heterotopias may appear to exert mass effect on the adjacent ventricle or the interhemispheric fissure. The heterotopias can be differentiated from tumors, which enlarge the affected hemisphere, by the fact that the affected hemisphere is small and that the apparent mass effect is actually distortion of the hemisphere caused by the dysplasia[15].

Diffuse gray matter heterotopias include "band heterotopia" ("double cortex") and "laminar heterotopias"[14]. Laminar heterotopias are bilateral symmetrical ribbons of gray matter in the centrum semiovale[14]. Band heterotopias ("double cortex") appear as a circumferential band of gray matter that is deep in the cerebral cortex and separated from the cortex by a layer of normal appearing white matter[16] (Fig. 9). This band of gray matter has smooth inner and outer margins at its interface with adjacent white matter and the margins do not parallel the infolding of the overlying cerebral cortex[17]. The overlying cortex may appear normal, may have normal thickness with shallow sulci or may be pachygyric. The degree of cortical gyral dysplasia seems to be related to the thickness of the band heterotopia, i.e., the thicker the band of heterotopic gray matter, the more anomalous the overlying cortex[16].

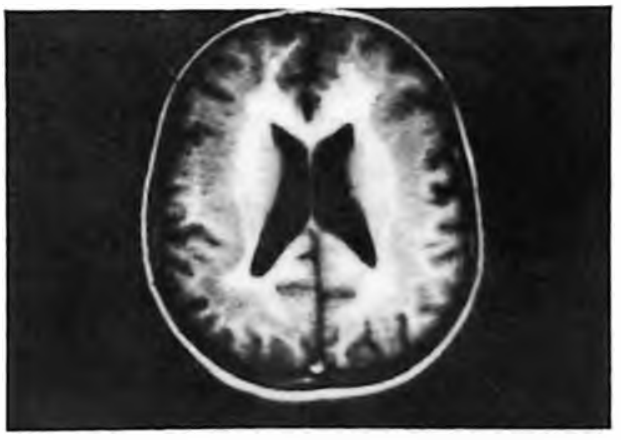

Fig. 9: "Double cortex" or band heterotopia
T1W transvers image revealing an inner layer of circumferential band of gray matter separated from the cortex by an intervening layer of white matter.

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