Localised neuronal migration disorder and intractable epilepsy: a prenatal vascular aetiology

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Abstract
Localised neuronal heterotopias are an increasingly recognised cause of intractable focal epilepsies. The aetiology of these circumscribed disorders of neuronal migration is often unknown although in some instances proximity to areas of prenatal infarction suggests that severe ischaemia was responsible. A patient is described with intractable complex partial seizures associated with heterotopic grey matter and cerebellar hypoplasia confined to the territory of the left posterior cerebral artery; the left hippocampus was spared. Angiography showed a normal left anterior choroidal artery but a hypoplastic left posterior cerebral artery, implicating prenatal ischaemia without frank infarction as the aetiology of the malformation.

Case report
A 25 year old woman was referred for evaluation of intractable complex partial seizures. The perinatal period had been uneventful but between the ages of 18 and 24 months the patient had 7 brief febrile convulsions without focal features. Early development was normal. There was no family history of epilepsy.

At the age of 15, typical complex partial seizures started. They were characterised by an initial motionless stare, an unusual epigastric sensation, gustatory hallucinations, dystonic posturing of the right arm and automatisms. Secondarily generalised tonic-clonic seizures were infrequent. The seizures occurred at least weekly despite treatment with several anti-convulsants including carbamazepine, phenytoin and primidone.

Neurological examination revealed an incongruous, homonymous, peripheral right sided field defect. She was left handed, of average intellectual capacity and detailed neuropsychological assessment of visuoperceptual, language and material specific recent memory function was normal.

MRI showed that the left occipital lobe was considerably smaller than the right (fig 1A).

Although circumscribed disturbances of neuronal migration have long been recognised in necropsy or surgical specimens, MRI has increased awareness of their importance as a cause of intractable focal epilepsies. In many cases the cause of the malformation is unknown. However, a vascular aetiology has been implicated when the disruption of histogenesis, most commonly polymicrogyria, lies adjacent to an area of putative infarction. We present evidence that nodular heterotopias may also result from ischaemia without frank infarction occurring early in gestation.

Fig 1 A) Axial cranial MRI scan showing marked hypoplasia of the left occipital lobe; B) Coronal T1-weighted cranial MRI scan showing areas of ectopic grey matter in the subcortical white matter of the left posterior temporal lobe (arrow).
Areas of ectopic grey matter were present in the white matter of the left occipital and posterior left temporal lobes (fig 1B); the anterior quarter of the temporal lobe appeared unaffected. The left hippocampus appeared normal in size.

Discussion

During fetal development, radial glial fibres span the telencephalon, guiding the migration of neurons from the ventricular and subventricular areas to their destinations in the cerebral cortex. Destruction of these fibres plays an important role in the pathogenesis of neuronal migration disorders. The majority of neurons migrate between 7 and 16 weeks gestational age making it likely that the developmental insult occurred in the early fetal period in this patient. Lack of glial scarring is further evidence for an early gestational lesion; during this period the cell bodies of astrocytes are restricted to the periventricular region.

We propose that the aetiology of the neuronal migration abnormality in this patient was intrauterine ischaemia in the territory of the left posterior cerebral artery. The artery was hypoplastic with an anomalous origin. The salient abnormalities in our patient, left occipital hypoplasia and occipitotemporal grey matter heterotopia, were limited to the artery's zone of perfusion. In keeping with the fetal pattern of arterial supply, hippocampal histology and thalamic morphology on MRI were unaffected. The developing hippocampus and diencephalon are supplied by the anterior and
posterior choroidal arteries, prominent branches of the primitive internal carotid artery. The peculiar distribution of abnormalities makes a primary vascular event far more plausible than a patchy, multifocal pathogenetic process affecting both neuronal and vascular structures. Furthermore, the presence of normal major cerebral vessels in other cases with substantial abnormalities of neuronal migration and peroxisomal disorders supports the case for a primary vascular event in this patient.  

Intrauterine cerebral ischaemia is a recognised cause of disordered neuronal migration. In most previously described cases, the ischaemia has been severe. For example, Dekaban, Levine et al and Ferrer described areas of polymicrogyria located at the borders of extensive forebrain defects and Norman described heterotopic clusters of neuroblasts and bilateral encephaloclastic lesions in a fetal brain following a putative hypoxic-ischaemic insult at about the third gestational month. Can abnormal histogenesis occur with ischaemia insufficient to produce frank infarction? Our case supports this possibility. Barth and van der Harten describe the product of parabiotic twin pregnancy with focal cerebral hypoplasia, microgyria and nodular heterotopias in the territories of bilateral hypoplastic posterior cerebral arteries. Richman et al and McBride and Kemper have also described cases of microgyria restricted to a vascular territory and unassociated with cavitation; however, the description of arterial supply was incomplete in both cases.

Our case provides clear evidence of an arterial abnormality in association with neuronal heterotopia and focal cerebral hypoplasia. It gives further support for a vascular aetiology in at least some instances of disordered neuronal migration. The spectrum of pathogenetic mechanisms responsible for these malformations has been extended to include reduced perfusion without frank infarction.