The Hippocampus Does Not Swim Unscathed in the Sea of Cortical Malformations

Patterns of Hippocampal Abnormalities in Malformations of Cortical Development

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OBJECTIVE: To assess whether different types of malformation of cortical development (MCD) are associated with specific patterns of hippocampal abnormalities.

METHODS: A total of 122 consecutive patients with MRI diagnosis of MCD (53 males, age range 1–58 years) were included in the study. Hippocampal measurements were made on 1–3 mm coronal T1-weighted MRIs and compared with MRIs of normal controls.

RESULTS: A total of 39 patients had focal cortical dysplasia, 5 had hemimegalencephaly, 5 had lissencephaly-agyria-pachygyria, 11 had SLH, 11 had PNH, 12 had bilateral contiguous PNH, 5 had schizencephaly, and 34 had polymicrogyria. The frequency of hippocampal abnormalities in these patients with MCD was 29.5%. A small hippocampus was present in all types of MCD. Only patients with lissencephaly and SLH had an enlarged hippocampus. Abnormalities in hippocampal rotation and shape were present in all types of MCD; however, these predominated in PNH. None of the patients with lissencephaly-agyria-pachygyria or SLH had hyperintense signal on T2 or FLAIR images or abnormal hippocampal internal architecture.

CONCLUSION: A small hippocampus was present in all types of MCD; however, the classic MRI characteristics of hippocampal sclerosis were often lacking. Abnormal enlargement of the hippocampus was associated with only diffuse MCD due to abnormal neuronal migration (lissencephaly-agyria-pachygyria and SLH).

COMMENTARY

The cerebral cortex has three stages of development: neuronal and glial proliferation, neuronal migration, and cortical organization (1). Problems can happen in any of these different phases, causing a specific malformation, depending on the stage of development. Cortical dysplasia and other malformations of cortical development (MCDs) first were associated with epilepsy in 1971 (2), since then, MCDs have been increasingly recognized as important causes of epilepsy. The terms cortical dysplasia and MCD are used to describe a tissue that has failed to develop properly during embryonic or fetal life, as a result of a variety of genetic, environmental, and/or other unknown factors. The advent of high-resolution MRI has made it possible to detect MCDs and other brain dysgenesis in an increasing number of patients with intractable epilepsy who formerly had cryptogenic lesions.

MRI enables a detailed view of the fine structure of the living brain, which previously only had been possible by postmortem examination. The continuous development of this imaging technique has allowed more research in different areas of epileptology, in particular in the evaluation of MCDs and their associated findings. Pioneering work on this issue includes a report of developmental changes in the hippocampal formation in patients with lissencephaly, holoprosencephaly, agenesis of the corpus callosum, and detailed abnormalities of hippocampal formation, specifically in its vertical orientation and size (3). Later research determined that the shape of the hippocampus was important to the evaluation of the hippocampal formation in brains with MCDs (4), and subsequently a detailed quantitative analysis of shape and size was published (5). No specific associations among the different types of MCDs were found in any of these studies, only the fact that some of the patients do have abnormal (either in shape, orientation, or size) hippocampal formation. Montenegro et al. now has found an interesting association between hippocampal abnormalities and different types of MCDs. The most striking abnormalities, enlarged and abnormally rotated hippocampi, were found exclusively in MCDs that were due to abnormal neuronal migration, while abnormal internal architecture and T2 or fluid-attenuated inversion recovery (FLAIR) signal were present in the other types of MCDs. The results, although interesting, need

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to be carefully interpreted as the sample size for each group was small and random error could be an explanation for the findings.

Abnormal neuronal migration occurs when neurons migrate from their germinal matrices (either along specialized radial glial fibers or axons) to the cerebral cortex; there they disengage and extend neurites, which begins the process of cortical organization (1). The hippocampal formation is the first cortical area to differentiate, and it is closely associated with the development of other cortical areas. The hippocampal sulcus first appears in the human fetus at 10 weeks of gestation. At 13–14 weeks, on the medial surface of the temporal lobe, the unfolded hippocampus is surrounded by a widely open hippocampal sulcus, which remains open while the dentate gyrus and cornu ammonis start to infold. By weeks 18–20, theses structures have folded and the hippocampus resembles the adult hippocampus. Subsequently, the hippocampal formation fissure becomes reoriented from vertical to horizontal (6). The mechanisms behind the folding process are unknown. Different models have been proposed, including differential growth between cortical layers (7), tension-based mechanisms of the wiring (8), and an underlying genetic regulation (9). Also, it is important to consider that the most common type of extrahippocampal lesion found in patients with dual pathology is an MCD, suggesting a developmental relationship between the hippocampus and the neocortex or perhaps indicates that the hippocampal sclerosis is a secondary effect of the epileptogenic MCDs. Furthermore, hippocampal abnormalities are seen in some individuals without seizures who are close relatives of people with familial temporal lobe epilepsy (10), making the clinical picture more complex.

What are the clinical implications of these findings? Currently, the clinical implications are not clear. However, MRI research is moving forward and should be considered imperative to the evaluation of a patient with epilepsy. Whereas a discrete structural lesion reliably defines the epileptogenic region in epilepsy, focal lesions in MCD may be only the tip of the iceberg. Thus, although MRI can identify a specific cortical lesion in a patient with an MCD, the imaging may be more a marker of the epileptogenic zone, than a demarcation of its true extent.

The lack of large population studies using this technique does not allow strong conclusions to be made or a better understanding of the disease. Of much greater value would be the tailoring of the use of standard protocols to address the needs of individual patients and to provide more relevant information to the clinician. Trials correlating MRI findings with clinical, electrophysiological, functional imaging, and pathological data are essential for this purpose. Finally, improvement in methods of data acquisition and analysis will permit better localization and extension of MCDs and will decrease the number of patients who bear the generally unsatisfactory diagnosis of cryptogenic epilepsy.

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