

Hippocampal Malrotation and Temporal Lobe Epilepsy: What is the Relationship?

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The importance of the hippocampus, in epileptic networks, which underpin temporal lobe epilepsy, have long been appreciated. Advances in MR imaging has facilitated the identification of structural lesions in the hippocampus. In the past few years, hippocampal malrotation or incomplete inversion of the hippocampus is increasingly reported in patients with and without epilepsy and the clinical significance of this imaging finding is unclear and controversial.

During fetal development the hippocampus undergoes folding, transforming it from a smooth structure to a complex folded one¹. The process of folding to the adult horizontal orientation is usually completed after 18 weeks gestation. In hippocampal malrotation, the folding is incomplete and the hippocampus has a vertically oriented, rounded appearance. This signifies a disruption of brain development and has been correlated with other markers of abnormal cortical development, such as increased cortical folding complexity and temporal lobe epilepsy².

Hippocampal malrotation is often seen in association with malformations of cortical development such as focal cortical dysplasia and polymicrogyria³ and nodular heterotopias⁴. Early pathological processes which affect hippocampal development may affect development of areas of the brain, either directly through hippocampal projections or through another common underlying pathological process. Hippocampal malrotation is thought to be a macroscopic marker of altered hippocampal development.

In a study of 527 patients suspected to have epilepsy who had MR studies, 32 had hippocampal malrotation and in 7 of 32 there were additional developmental brain abnormalities⁵. Bernasconi and colleagues, observed hippocampal malrotation in 49% of 76 patients with malformations of cortical development, and 43% of 30 patients with temporal lobe epilepsy and 10% of 50 healthy control patients³. In 497 patients without epilepsy who underwent MRI, no patients had all diagnostic features of hippocampal malrotation but six patients had two or more features⁶. In this issue of the journal, Andrade and colleagues reported hippocampal malrotation using 3 Tesla MRI in 9 of 14 adults with 22q11.2 deletion syndrome, a population with a 7 fold increased risk of developing epilepsy compared to the general population⁷. However, hippocampal malrotation was seen in six patients who did not have epilepsy. Three of four patients with epilepsy had hippocampal malrotation but also had polymicrogyria and periventricular nodular heterotopia.

Thus, while this study adds to the literature on the subject, it raises further questions about the clinical significance of hippocampal malrotation as it was more common in those without epilepsy in the study.

However, the prevalence of hippocampal malrotation in patients without epilepsy in Dr. Andrade's study suggests that other genetic or environmental factors may be important in

epileptogenesis⁷. The mechanism by which hippocampal malrotation leads to or is associated with epilepsy is poorly understood. It is postulated that it could be the "first hit" that in conjunction with other genetic or non-genetic factors may be involved in the development of epilepsy.

In the FEBSTAT study of 191 children, aged one month to five years, who had MR imaging performed within one week of febrile status epilepticus, 15 (7.9%) had hippocampal malrotation while only 2 (2.1%) of 96 controls has this finding⁸. The identification of hippocampal malrotation in MR studies particularly in children without any history of seizures raises questions about how to investigate and monitor such children and counsel families. Consultation with neuroradiology colleagues suggests that neuroradiologists often report this as a finding of uncertain clinical significance or may even not report the finding at all. Furthermore, this finding may be recognized on good quality, high resolution 1.5 T MRI and does not necessarily require 3T MRI.

From a clinical standpoint, it is going to be very important to prospectively follow children with hippocampal malrotation, in order to clarify the clinical significance of this imaging finding. In an individual who also has developmental delay or intellectual difficulties or epilepsy where the cause is unclear, detailed genetic studies may allow identification of subtle genetic abnormalities such as the 22q11.2 deletion or other microdeletion syndromes.

It should be possible in the next decade to gain a better understanding of the clinical significance of hippocampal malrotation. Similarly, in both children and adults who are found to have hippocampal malrotation, careful clinical and electrical phenotyping and genotyping should be undertaken. However, at this time, one cannot accurately counsel those with hippocampal malformations due to the prevalence in healthy controls.

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