Hippocampal Malrotation

Subjects: Neuroimaging

Contributor: Meng-Han Tsai

Hippocampal malrotation (HIMAL) is an increasingly recognized neuroimaging feature but the clinical correlation and significance in epilepsies remain under debate.

Hippocampal malrotation epilepsy

1. Introduction

Hippocampal malrotation (HIMAL), also termed incomplete inversion of the hippocampus or hippocampal "malformation," is an increasingly recognized neuroimaging finding of undetermined clinical significance. HIMAL was initially identified in patients with malformations of cortical development (MCD) and/or agenesis of the corpus callosum [1][2]. Subsequently, isolated HIMAL was also found in patients without an obvious brain malformation [3]. Since the hippocampus is one of the most important brain structures associated with epilepsy, HIMAL has been implicated in the development of epilepsy; however, the relationship is not clear cut.

2. Mechanisms of HIMAL Development

The resemblance of HIMAL to the fetal hippocampus leads to the hypothesis that HIMAL results from the failure of the normal infolding process during development. The two possible mechanisms for incomplete infolding are as follows:

- Lack of infolding drive: The hippocampal infolding process is passively driven by the development of the neocortex, which pushes the hippocampus deeper into the temporal lobe forming the "Swiss roll" appearance. If there was a problem with neocortical development, the hippocampus would assume its prenatal position. This is likely the explanation for HIMAL associated with diffuse cortical malformations, for instance, periventricular heterotopia, polymicrogyria, and lissencephaly;

- Local blockage or tectonic effect: The maldevelopment or disorganization of the CA1/Subiculum forms a "blockade" or "tectonic plate," which impedes or disrupts the infolding process of the hippocampus [4][5]. This would explain why the neocortex appears normal in isolated HIMAL.

The exact cause of the failure is unknown. Acquired factors, such as toxins, metabolism derangement, or ischemia, in combination with genetic factors occurring during this critical stage of brain development, are likely contributing to the pathogenesis of HIMAL.

3. The Role of HIMAL on Pre-Surgical Decision

Temporal lobe epilepsy (TLE) is a more common focal epilepsy in adults. These patients are good surgical candidates if not responding to antiseizure medications (ASMs). The possibility of HIMAL being epileptogenic raised an important clinical question as to whether HIMAL should be considered as an imaging marker (such as HS) to inform epilepsy surgery. We performed a study on 155 lesion-negative TLE patients and identified 25 patients with HIMAL (11 bilateral, 12 left, and 2 right). There was no correlation between the side of seizure onset and the side of HIMAL [6]. This suggests that the presence of HIMAL in medication refractory TLE patients should not influence the decision of epilepsy surgery. Leech et al. also studied a smaller cohort (n = 48) of surgically treated pediatric patients and found that HIMAL did not predict the surgical side and outcome [7]. In conclusion, there is insufficient evidence to use HIMAL for guiding epilepsy surgery in both adult and childhood TLE or other epilepsy syndromes.

4. Relationship between HIMAL and HS

Another unresolved matter is the relationship between HIMAL and HS. Fernadez et al. reported two families with febrile seizures (FS) in which the probands had temporal lobe epilepsy and HS. Some affected individuals with FS and asymptomatic relatives had hippocampal malformation [8]. However, the “malformation” in this paper refers to asymmetric small hippocampi rather than the abnormal shape and orientation that typify HIMAL. Depondt et al. also reported a family with temporal lobe epilepsy and febrile seizures linked to chromosome 12q22-23.3, in which some affected and unaffected individuals had HIMAL [9]. Bernasconi et al. also found no association between the side of HIMAL and the side of hippocampal atrophy [10]. However, it is arguable whether analyzing the shape and position of the hippocampus is reliable when hippocampal atrophy exists. It has been hypothesized that HIMAL may increase susceptibility to febrile seizures, leading to the formation of HS and subsequent epilepsy. On the contrary, Sen et al. reported two patients with MCD and long-standing epilepsy who had HIMAL on MRI but did not develop HS on pathological examination. They concluded that HIMAL may not necessarily develop into HS, although they also could not exclude this could happen in other patients [11]. Recently, the large prospective Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study found that HIMAL is more commonly seen in patients with febrile status epilepticus than in patients with simple febrile seizures [12]. They concluded that HIMAL indicates an abnormality during brain development that predisposes to febrile seizures. Although febrile status epilepticus is a well-known risk factor for the development of HS, no robust evidence shows that HIMAL evolves into HS in humans.

5. Genetics of HIMAL

How genes are involved in the development of the hippocampus or HIMAL is still obscure. Some families with HIMAL or case reports associated with genetic variations have been reported. Families with predominantly febrile seizures may include some family members with HIMAL [8][9]. Kobayashi et al. described a family with two brothers presenting with 15q trisomy, both with minor dysmorphic features, mental retardation, epilepsy, and bilateral HIMAL

on MRI [13]. Pramparo et al. reported a patient with a 22q13 duplication who presented with bipolar disorder, dysmorphic features, and unilateral HIMAL, but other intracranial MRI abnormalities were also described, including high signal in the periventricular white matter, hippocampal atrophy (on the other side), and hypoplastic corpus callosum [14]. Andrade et al. reported a high prevalence (64%) of unilateral HIMAL in 19 consecutive cases with 22q11.2 microdeletion. However, the presence of HIMAL in patients both with and without epilepsy argues against its contribution to epileptogenesis in this cohort [15]. Sisodiya et al. reported four patients with de novo heterozygous *SOX2* mutations who presented with anophthalmia and bilateral HIMAL; two had seizures [16]. *SOX2* is a good candidate gene for HIMAL since it is vital to the developing brain and eye. However, screening of patients with a variety of different epilepsy syndromes failed to show any variants. Additionally, no genes have been associated with “isolated” HIMAL thus far. The recent JME study has provided further insight into the genetics of HIMAL [2]. Both JME patients and unaffected siblings were significantly more likely to have HIMAL than controls, suggesting that HIMAL is a heritable imaging trait that contributes to the polygenic composition of JME.

References

1. Baker, L.L.; Barkovich, A.J. The large temporal horn: MR analysis in developmental brain anomalies versus hydrocephalus. Am. J. Neuroradiol. 1992, 13, 115–122.
2. Atlas, S.W.; Zimmerman, R.A.; Bilaniuk, L.T.; Rorke, L.; Hackney, D.B.; Goldberg, H.I.; Grossman, R.I. Corpus callosum and limbic system: Neuroanatomic MR evaluation of developmental anomalies. Radiology 1986, 160, 355–362.
3. Baulac, M.; De Grissac, N.; Hasboun, D.; Oppenheim, C.; Adam, C.; Arzimanoglou, A.; Semah, F.; Lehéricy, S.; Clémenceau, S.; Berger, B. Hippocampal developmental changes in patients with partial epilepsy: Magnetic resonance imaging and clinical aspects. Ann. Neurol. 1998, 44, 223–233.
4. Thom, M.; Sisodiya, S.M.; Lin, W.R.; Mitchell, T.; Free, S.L.; Stevens, J.; Scaravilli, F. Bilateral isolated hippocampal malformation in temporal lobe epilepsy. Neurology 2002, 58, 1683–1686.
5. Sloviter, R.S.; Kudrimoti, H.S.; Laxer, K.D.; Barbaro, N.M.; Chan, S.; Hirsch, L.J.; Goodman, R.R.; Pedley, T.A. “Tectonic” hippocampal malformations in patients with temporal lobe epilepsy. Epilepsy Res. 2004, 59, 123–153.
6. Tsai, M.-H.; Vaughan, D.N.; Perchyonok, Y.; Fitt, G.J.; Scheffer, I.E.; Berkovic, S.F.; Jackson, G.D. Hippocampal malrotation is an anatomic variant and has no clinical significance in MRI-negative temporal lobe epilepsy. Epilepsia 2016, 57, 1719–1728.
7. Leach, J.L.; Awwad, R.; Greiner, H.M.; Vannest, J.J.; Miles, L.; Mangano, F.T. Mesial temporal lobe morphology in intractable pediatric epilepsy: So-called hippocampal malrotation, associated findings, and relevance to presurgical assessment. J. Neurosurgery Pediatr. 2016, 17, 683–693.

8. Fernandez, G.; Effenberger, O.; Vinz, B.; Steinlein, O.; Elger, C.E.; Dohring, W.; Heinze, H.J. Hippocampal malformation as a cause of familial febrile convulsions and subsequent hippocampal sclerosis. Neurology 1998, 50, 909–917.
9. Depondt, C.; Van Paesschen, W.; Matthijs, G.; Legius, E.; Martens, K.; Demaerel, P.; Wilms, G. Familial temporal lobe epilepsy with febrile seizures. Neurology 2002, 58, 1429–1433.
10. Bernasconi, N.; Kinay, D.; Andermann, F.; Antel, S. Analysis of shape and positioning of the hippocampal formation: An MRI study in patients with partial epilepsy and healthy controls. Brain 2005, 128, 2442–2452.
11. Sen, A.; Thom, M.; Martinian, L.; Dawodu, S.; Sisodiya, S.M. Hippocampal malformations do not necessarily evolve into hippocampal sclerosis. Epilepsia 2005, 46, 939–943.
12. Chan, S.; Bello, J.A.; Shinnar, S.; Hesdorffer, D.C.; Lewis, D.V.; MacFall, J.; Shinnar, R.C.; Gomes, W.; Litherland, C.; Xu, Y.; et al. Hippocampal malrotation is associated with prolonged febrile seizures: Results of the FEBSTAT study. Am. J. Roentgenol. 2015, 205, 1068–1074.
13. Kobayashi, E.; Facchin, D.; Steiner, C.E.; Leone, A.A.A.; Campos, N.L.V.; Cendes, F.; Lopes-Cendes, I. Mesial temporal lobe abnormalities in a family with 15q26qter trisomy. Arch. Neurol. 2002, 59, 1476–1479.
14. Pramparo, T.; De Gregori, M.; Gimelli, S.; Ciccone, R.; Frondizi, D.; Liehr, T.; Pellacani, S.; Masi, G.; Brovedani, P.; Zuffardi, O.; et al. A 7 Mb duplication at 22q13 in a girl with bipolar disorder and hippocampal malformation. Am. J. Med Genet. Part A 2008, 146A, 1754–1760.
15. Andrade, D.M.; Krings, T.; Chow, E.W.C.; Kiehl, T.-R.; Bassett, A.S. Hippocampal malrotation is associated with chromosome 22q11.2 microdeletion. Can. J. Neurol. Sci./J. Can. des Sci. Neurol. 2013, 40, 652–656.
16. Sisodiya, S.M.; Ragge, N.K.; Cavalleri, G.L.; Hever, A.; Lorenz, B.; Schneider, A.; Williamson, K.A.; Stevens, J.M.; Free, S.L.; Thompson, P.J.; et al. Role of SOX2 mutations in human hippocampal malformations and epilepsy. Epilepsia 2006, 47, 534–542.