Diagn Interv Radiol 2017; 23:326–330

PEDIATRIC RADIOLOGY

ORIGINAL ARTICLE

Evaluation of hippocampal infolding angle and incomplete hippocampal inversion in pediatric patients with epilepsy and febrile seizures

Mehtap Beker-Acay
Reşit Köken
Ebru Ünlü
Emre Kaçar
Çınar Balçık

PURPOSE
We aimed to investigate the frequency of incomplete hippocampal inversion (IHI) and the hippocampal infolding angle (HIA) in pediatric patients with no additional abnormal findings in the brain.

METHODS
Pediatric brain magnetic resonance imaging (MRI) examinations conducted between September 2012 and February 2015 were screened and 83 patients with epilepsy, 49 patients with febrile convulsion, and 74 control patients were included in this retrospective study. Presence of IHI was evaluated and HIA was measured on MRI.

RESULTS
IHI was found in 23 patients in the epilepsy group (27.7%), 15 patients in the febrile convulsion group (30.6%), and 14 patients in the control group (19.0%), with no significant difference between the groups ($P = 0.27$). Compared with the epilepsy and febrile convulsion groups, HIA was significantly larger in the control group in sections of the right cerebral pedincule, the left cerebral pedincule, and the right superior cerebellar pedincule. No correlation was found between the laterality of the epileptogenic focus in the epilepsy group and existence of IHI, nor between age and HIA values among the groups.

CONCLUSION
Although IHI is not an uncommon abnormality in the normal pediatric population, decreased HIA is more frequently found in patients with epilepsy or febrile convulsions.

Hippocampal development is nearly complete between gestation weeks 8 and 21 (1). During this process, the dentate gyrus and cornu ammonis infold around the hippocampal sulcus, which is called hippocampal inversion (2–4). If this process fails, incomplete hippocampal inversion (IHI, also called hippocampal malrotation) occurs, which is characterized by a rounded hippocampus along with a vertically oriented hippocampal sulcus (2, 4–10). This condition has been described in epileptic populations at a higher frequency (11). Otherwise, it is an incidental finding on magnetic resonance imaging (MRI) in a small part of the population without seizures (2, 4, 5, 7). It has been stated that hippocampal developmental abnormalities may lead to or further epileptogenesis (2, 12, 13). However, studies in the literature have not proven whether this condition represents the visible part of a more distant disorder of brain development or an epileptogenic focus (2, 5, 8–12). Studies have focused on hippocampal infolding or the existence of IHI in different populations. The objective of this study was to sum up the existing knowledge on the relationship between hippocampal infolding angle (HIA) and the frequency of IHI among pediatric patients with epilepsy or febrile seizures, and to promote considerations of occult brain malformations in these patients by adding information on image evaluation.

Methods

Subjects

Reports of 1707 brain MRI examinations of patients 0–16 years of age performed from September 2012 through February 2015 were manually screened and reviewed to determine any

From the Departments of Radiology (M.B.A. ✉ *mehtapacay@gmail.com*, E.Ü., E.K., Ç.B.) and Pediatrics (R.K.), Afyon Kocatepe University School of Medicine, Afyonkarahisar, Turkey.

Received 23 February 2016; revision requested 2 April 2016; last revision received 2 January 2017; accepted 11 January 2017.

Published online 16 May 2017.
DOI 10.5152/dir.2017.160077

You may cite this article as: Beker-Acay M, Köken R, Ünlü E, Kaçar E, Balçık Ç. Evaluation of hippocampal infolding angle and incomplete hippocampal inversion in pediatric patients with epilepsy and febrile seizures. Diagn Interv Radiol 2017; 23:326–330.

abnormality related with epilepsy. A total of 83 patients with epilepsy, 49 patients with febrile convulsions, and 74 control patients were included in the study. None of the patients had a brain abnormality related with epilepsy. The number of patients and the demographic characteristics of the groups are summarized in Table 1. Medical records, including electroencephalography (EEG) of all patients, were examined by a pediatric neurologist to define the type of epilepsy. Epilepsy classification was made using the International League Against Epilepsy (ILAE) guidelines. The institutional ethics committee approved the study protocol (n:07-174).

Table 1. Patient demographics

	Epilepsy	Febrile convulsion	Control
Age (years), mean±SD	7.1±4.5	3.9±2.8	7.8±4.7
Sex, n (%)			
Female	46 (55.4)	19 (38.8)	32 (43.2)
Male	37 (44.6)	30 (61.2)	42 (56.8)
Total, n	83	49	74

SD, standard deviation.

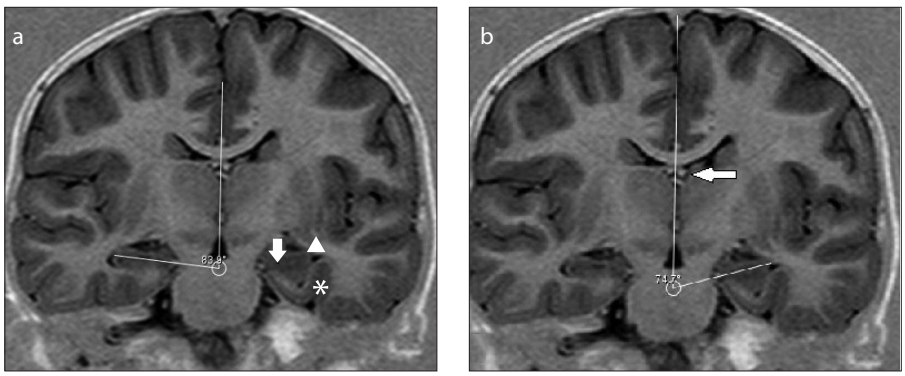

Figure 1. a, b. Oblique coronal T1-weighted inversion recovery image shows left-sided incomplete hippocampal inversion in a section of the cerebral peduncle in a 7-year-old male from the control group. Panel **(a)** shows the main points in measuring the hippocampal angle: cornu ammonis *(arrowhead)* and subiculum *(white arrow)*. A decreased hippocampal infolding angle, vertically positioned collateral sulcus *(asterisk)* and a low-lying fornix (**b**, *arrow*) was found on the left side.

MRI technique

All patients with epilepsy and febrile seizures underwent unenhanced brain MRI examination on a 1.5 Tesla scanner (Philips Medical Systems, Amsterdam, the Netherlands). A dedicated epilepsy protocol was employed as follows: In addition to routine brain MRI protocol, T1-weighted inversion recovery (TR, 4825 ms; TI, 350 ms; TE, 10 ms; slice thickness, 3 mm; gap, 0.6 mm; matrix, 256×256) and T2-weighted turbo spin-echo (TR, 4022 ms; TE, 100 ms; slice thickness, 4 mm; gap, 0.4 mm; matrix, 256×256) sequences on the oblique coronal plane perpendicular to the long axis of the hippocampus were added. The routine protocol included sagittal T1-weighted spin-echo, axial T2-weighted turbo spin-echo; axial fluid attenuation inversion recovery (FLAIR), coronal FLAIR sequences for all patients, and also axial T1-weighted spin-echo images obtained for patients under the age of 6 months to analyze the myelination pattern. Coronal sequences were added to the routine cranial MRI protocol by one of the radiologists (M.B.A.) prospectively for 2 weeks for all patients and subsequently, 35 of these with normal findings were selected randomly in order to establish the control group.

Main points

- Incomplete hippocampal inversion is not significantly higher in patients with epilepsy and febrile seizures.
- Incomplete hippocampal inversion is not an uncommon abnormality among normal pediatric population.
- Decreased hippocampal infolding angle may be a sign of some process that has affected the brain development.

Image analysis

All images were analyzed in consensus by two radiologists (M.B.A. and E.U.) with 5 years of experience in pediatric neuroimaging, who were blinded to clinical information. The hippocampi of the patients were evaluated after recording the absence of additional brain abnormalities. A total of 8–10 coronal slices were evaluated through the hippocampi. Images were analyzed using a stand-alone personal computer for data analysis. All patients and the control group were evaluated for the presence of a rounded hippocampus with a vertically oriented hippocampal sulcus in coronal slices as the main sign of IHI. This morphologic evaluation for IHI included a hippocampus with an abnormally rounded shape but a normal size and signal intensity. Also, other features of IHI, including enlargement of the temporal horn tip, collateral sulcus orientation, collateral white matter position, and ipsilateral fornix position were analyzed according to relevant literature (2, 5, 6). Collateral white matter has a lateral position to the hippocampus and the ipsilateral fornix has a lower position in patients with IHI. The HIAs were measured twice, at the level of the cerebral peduncle (CP) and the level of the superior cerebellar peduncle (SCP). As previously described in the literature, HIA is the angle between the line connecting the medial superior margin of the subiculum with the lateral margin of the cornu ammonis and the vertical midline of the cerebral hemisphere (Figs. 1, 2) (3). HIA measurements of 50 randomly selected patients were repeated two weeks later by the same radiologist and the intraobserver reliability was found to be 0.8. Interobserver reliability for IHI detection among all patients was 0.97. Patient clinical records, including EEG, were evaluated by a pediatric neurologist with the aim of defining the type of epilepsy and the epileptogenic focus location.

Statistical analysis

SPSS statistical software (Version 20.0, IBM Corp.) was used for statistical analysis. Continuous variables were presented as mean and standard deviation, and categorical variables as percentage. Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Analysis of variance (ANOVA) test was used for determination of differences between three-group

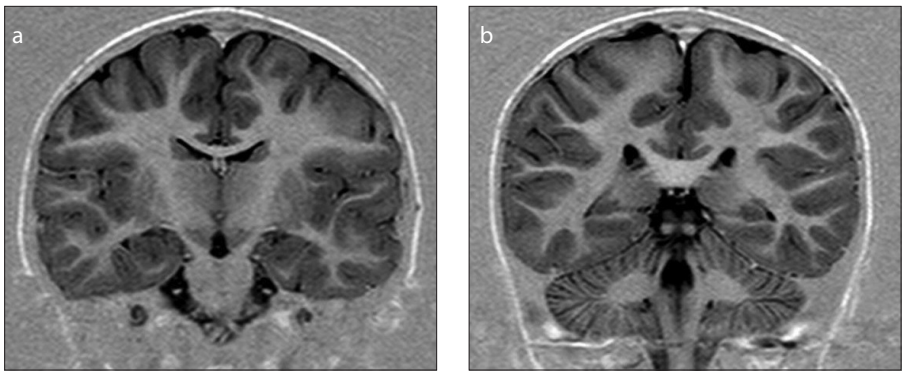

Figure 2. a, b. The hippocampal infolding angle is decreased in the cerebral pedincule section (**a**, right, 76°; left, 72°) compared with the section of the superior cerebellar pedincule (**b**, right, 85°; left, 83°) in a 9-year-old male with complex partial seizures.

Table 2. Existence of IHI among the study groups

	Right-sided IHI (%)	Left-sided IHI (%)	Bilateral IHI (%)	Total IHI (%)	No IHI (%)
Epilepsy (n=83)	2 (2.4)	17 (20.5)	4(4.8)	23 (27.7)	60 (72.3)
Febrile convulsion (n=49)	0	12 (24.5)	3 (6.1)	15 (30.6)	34 (69.4)
Control (n=74)	1 (1.4)	12 (16.2)	1 (1.4)	14 (19.0)	60 (81)
Total (n=206)	3 (1.5)	41 (19.9)	8 (3.9)	52 (25.2)	154 (74.8)

No statistical difference was found between the groups ($P = 0.27$).
IHI, incomplete hippocampal inversion.

Table 3. Hippocampal infolding angle in patient and control groups

	Epilepsy (n=83)	Febrile convulsion (n=49)	Control (n=74)	*P*
Right CP	76.65±5.79	76.63±5.96	79.86±4.55	0.001[a]
				0.002[b]
				0.008[c]
Left CP	75.14±5.49	75.27±5.94	77.54±6.45	0.01[a]
				0.015[b]
				0.05[c]
Right SCP	93.63±4.63	93.92±4.77	95.74±5.41	0.017[a]
				0.018[b]
				0.09[c]
Left SCP	91.86±4.91	91.16±6.5	93.56±5.32	0.076[a]
				0.2[b]
				0.07[c]

CP, cerebral pedincule; SCP, superior cerebellar pedincule.
[a]Comparison of all three groups by one-way Anova; [b]Epilepsy vs. control group, post hoc (Tukey) test; [c]Febrile convulsion vs. control group, post hoc (Tukey) test.

comparisons due to normal distribution of all data, and Tukey-b test results were interpreted. Independent sample t-test was used for evaluation of differences between two-group comparisons. Spearman's correlation analysis was used to evaluate correlation between age and HIA. Paired t-test was used in order to investigate the right and left side differences in HIA for CP and SCP. A *P* value of <0.05 was used for all tests.

Results

Incomplete inversion of the hippocampus was found in 23 patients in the epilepsy group (27.7%), 15 patients in the febrile convulsion group (30.6%), and 14 patients in the control group (19.0%). Although there was an increase in the groups with seizures, there was no statistical significance between them ($P = 0.27$) (Table 2). The predominant findings in patients with IHI were vertically oriented collateral sulcus with deviating hippocampal shape and low-lying ipsilateral fornix. HIA was significantly larger in the control group in sections of the right CP ($P = 0.001$), left CP ($P = 0.01$) and right SCP ($P = 0.016$). Two-way comparisons revealed a significant decrease in the epilepsy and febrile seizure groups in the same sections compared with those of the control group. HIA was significantly increased on the right side than on the left for both SCP and CP sections ($P < 0.001$) (Table 3). With regard to the existence of IHI, the mean HIA was smaller on the same side compared with the control group. IHI and decrease in the angles were more prominent in the CP section (Table 4; Figs. 1, 2). Classification of epileptic patients according to their clinical history and EEG findings indicated that 59 (71.1%) had generalized and 24 (28.9%) had focal epilepsy syndromes. IHI laterality was crosschecked with the laterality of EEG findings: among 57 (69.7%) available EEG reports, 9 (10.8%) had right-sided abnormality, 4 (4.8%) had left-sided abnormality, 8 (9.6%) had undefined focus, and 36 (43.4%) had normal findings. There was no correlation between the laterality of abnormal EEG findings and existence of IHI. There was no correlation between the age and HIA values in SCP and CP cross-sections among the groups ($P > 0.05$).

Discussion

In this study, we investigated the frequency of IHI and conducted a comprehensive evaluation of HIA among different patient populations. We found that IHI and decreased HIA are not rare findings in pediatric patient groups with seizures. There are a number of studies evaluating hippocampal shape and development in the literature (1, 5, 13–16), which show that HIA increases gradually to a horizontal position from a vertical one over the course of hippocampal infolding. IHI was reported with a higher frequency in patients with epilepsy (2, 8, 11, 12) and, in a recent study, in prolonged febrile seizures (9). Nevertheless, the results of these studies are controversial concerning the prevalence of IHI in the normal population. In a study of 100 patients between the ages of 0 and 73 years, Bajic

Table 4. Hipocampal infolding angle according to the existence of IHI

	Right CP	Left CP	Right SCP	Left SCP
No IHI (n=154)	78.32±5.56	77.32±4.3	93.87±4.28	92.84±5.33
Right IHI (n=3)	74.33±2.08	81.33±3.51	94.67±4.61	93.33±3.05
Left IHI (n=41)	77.15±5.5	71.46±4.47	93.66±6.74	91.66±7.37
Bilateral IHI (n=8)	71.25±4.13	72.13±2.1	90.25±6.77	88.5±3.89

IHI, incomplete hippocampal inversion; CP, cerebellar pedincule; SCP, superior cerebral pedincule.

et al. (5) determined that IHI was present in 19% of the population and that the frequency was significantly higher in patients with epilepsy (30%). Our results are in line with this study, and a statistical significance could not be reached (27.7% in epilepsy group vs. 19% in control group, $P = 0.17$). We also demonstrated that in patients with IHI, the HIA of the ipsilateral hippocampus decreased, predominantly in the CP section. Since decreased angle is not the only criteria for IHI (as described in the methods section), we did not assign a cutoff value for this appearance. The occurrence of IHI on MRI examinations performed on children with prolonged febrile seizures has been previously reported (9). Pediatric patients with febrile seizures were examined in the present study; however, seizure duration could not be determined due to the retrospective design. Despite absence of a significant difference, the frequency of IHI was higher in these patients, mostly on the left side, when compared with the normal population (30.6% in febrile convulsion group vs. 19% in control group, $P = 0.1$).

In their prenatal MRI study, Righini et al. (14) determined an increase in HIA between the gestational ages of 20 and 37 weeks. They noted no significant difference between the right and left HIA. In contrast, using the same method Okada et al. (3) determined that HIA was lower on the left side compared with the right and deduced that this may be an outcome of delayed formation of the left hippocampus. They also noticed that HIA increased slightly with age among 69 subjects aged 2–27 years that were evaluated in the study. Even though no correlation was determined between age and HIA in any of the subgroups, our results are compatible with the findings of right-left asymmetry.

Cranial ultrasound examinations of 156 newborns at <35 weeks of gestation were carried out in the study by Bajic et al. (1) which put forth that IHI was observed in 50% between the ages of 23–24 gestational weeks (GW) and 14% between the ages of 29–36 GW. Hippocampal inversion was not completed in about 50% of the neonates for up to 24 GW; but from 25 GW onwards, frequency and laterality of IHI were similar to that of the adult population. There was a diminished angle on the left side even though there was no relation between age and HIA. The higher frequency of IHI on the left side in our study was consistent with studies indicating a faster right side development of the hippocampus in comparison with the left (1, 3, 14). This also explains why IHI appears to be more on the left side rather than the right side. Cerebral development may have been disturbed when inversion has been completed in the right hippocampus but the left side has not yet reached that developmental stage (1). HIA was determined to be significantly higher at the SCP section in comparison with CP on both sides. This may be considered to support the theory that hippocampal infolding process develops from the tail to the head (3). Barsi et al. (6) determined IHI presence in 6% of 527 patients with suspected epilepsy. Peltier et al. (17) demonstrated hippocampal abnormalities in 14% of 97 epilepsy patients. Bernasconi et al. (12) found abnormal hippocampal forms in 43% of patients with temporal lobe epilepsy (13/30). It is still debated whether IHI contributes to the hippocampal insult, thus triggering the development of seizures or hippocampal sclerosis. Follow-up imaging of these children should help determine whether IHI predisposes them to temporal lobe epilepsy and mesial temporal sclerosis. Therefore, imaging findings of IHI may raise suspicion of an underlying potential for the presence of a seizure disorder (7). All patients with hippocampal atrophy were excluded from our study since their hippocampi were collapsed and they may not have preserved the original form. In addition, all patients with brain abnormalities were excluded because abnormal hippocampal shape is commonly seen in patients with obvious brain abnormalities. The incidence of IHI was found to be much higher in studies of patients with developmental brain anomalies (5). Bernasconi et al. (12) determined that 49% of patients with cortical development malformations, 43% of patients with temporal lobe epilepsy, and 10% of their control group had abnormal hippocampal shape and positioning. According to the aforementioned study, no association was found between the side of the morphologic hippocampal abnormalities and the side of the cortical malformation or the EEG focus. Likewise, hippocampal morphology abnormalities were not linked with the side of the EEG focus in temporal lobe epilepsy (12). There was no correlation between the laterality of IHI compared with the focus laterality on EEG (Table 4) among the 36 EEG findings in the present study. There are numerous morphologic studies of the fetal hippocampus, but most of them are microscopic examinations of limited numbers of formalin-fixed aborted fetuses. A major limitation of this type of approach is that anatomic shape and proportions usually change during these postmortem procedures (15, 16). Hence, brain evaluation inside the skull will provide more credible information with the aim of understanding the form and position of the brain structures. The hippocampal shape and infolding angle were assessed in a pediatric age group by minimizing the factors that might affect hippocampal development.

This study has some limitations, which have to be pointed out. We used a 1.5 T MRI unit, but we were not able to use more detailed and advanced brain imaging methods such as MPRAGE or brain segmentation. Therefore, we may have missed some of the pathologies that might be associated with epilepsy. To our knowledge, there is no existing literature indicating the prevalence of IHI combined with the HIA. We used a protocol similar to the one used by Bajic et al. (2) and evaluated the existence of IHI using a list of common radiologic features of IHI from their study. Potential bias may have existed because of the application of these criteria. We did not record the gestational ages and birth weights of the patients because of the design of the study.

In conclusion, we found that HIA is decreased in patients with epilepsy and febrile seizures. IHI may not be a direct cause of epilepsy, but decreased HIA may be a sign of some process that has affected brain development. In suspected cases of IHI, measuring HIA may contribute to characterize this

condition. A longitudinal large-scale study is required to detect the existence of mesial temporal sclerosis and epileptogenesis in patients with IHI.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Bajic D, Ewald U, Raininko R. Hippocampal development at gestation weeks 23 to 36. An ultrasound study on preterm neonates. Neuroradiology 2010; 52:489–494. [CrossRef]
2. Bajic D, Kumlien E, Mattsson P, Lundberg S, Wang C, Raininko R. Incomplete hippocampal inversion-is there a relation to epilepsy? Eur Radiol 2009; 19:2544–2550. [CrossRef]
3. Okada Y, Kato T, Iwai K, Iwasaki N, Ohto T, Matsui A. Evaluation of hippocampal infolding using magnetic resonance imaging. Neuroreport 2003; 14:1405–1409. [CrossRef]
4. Raininko R, Bajic D. "Hippocampal malrotation": no real malrotation and not rare. AJNR Am J Neuroradiol 2010; 31:E39–40. [CrossRef]
5. Bajic D, Wang C, Kumlien E, et al. Incomplete inversion of the hippocampus-a common developmental anomaly. Eur Radiol 2008; 18:138–142. [CrossRef]
6. Barsi P, Kenez J, Solymosi D, et al. Hippocampal malrotation with normal corpus callosum: a new entity? Neuroradiology 2000; 42:339–345. [CrossRef]
7. Gamss RP, Slasky SE, Bello JA, Miller TS, Shinnar S. Prevalence of hippocampal malrotation in a population without seizures. AJNR Am J Neuroradiol 2009; 30:1571–1573. [CrossRef]
8. Stiers P, Fonteyne A, Wouters H, D'Agostino E, Sunaert S, Lagae L. Hippocampal malrotation in pediatric patients with epilepsy associated with complex prefrontal dysfunction. Epilepsia 2010; 51:546–555. [CrossRef]
9. Chan S, Bello JA, Shinnar S, et al; FEBSTAT Study Team. Hippocampal malrotation is associated with prolonged febrile seizures: results of the FEBSTAT study. AJR Am J Roentgenol 2015; 205:1068–1074. [CrossRef]
10. Kim H, Chupin M, Colliot O, Bernhardt BC, Bernasconi N, Bernasconi A. Automatic hippocampal segmentation in temporal lobe epilepsy: impact of developmental abnormalities. Neuroimage 2012; 59:3178–3186. [CrossRef]
11. Baulac M, De Grissac N, Hasboun D, et al. Hippocampal developmental changes in patients with partial epilepsy: magnetic resonance imaging and clinical aspects. Ann Neurol 1998; 44:223–233. [CrossRef]
12. Bernasconi N, Kinay D, Andermann F, Antel S, Bernasconi A. Analysis of shape and positioning of the hippocampal formation: an MRI study inpatients with partial epilepsy and healthy controls. Brain 2005; 128:2442–2452. [CrossRef]
13. Bajic D, Canto Moreira N, Wikstrom J, Raininko R. Asymmetric development of the hippocampal region is common: a fetal MR imaging study. AJNR Am J Neuroradiol 2012; 33:513–518. [CrossRef]
14. Righini A, Zirpoli S, Parazzini C, et al. Hippocampal infolding angle changes during brain development assessed by prenatal MR imaging. AJNR Am J Neuroradiol 2006; 27:2093–2097.
15. Kier EL, Kim JH, Fulbright RK, Bronen RA. Embryology of the human fetal hippocampus: MR imaging, anatomy, and histology. AJNR Am J Neuroradiol 1997; 18:525–532.
16. Kier EL, Fulbright RK, Bronen RA. Limbic lobe embtyology and anatomy: dissection and MR of the medial surface of the fetal cerebral hemisphere. AJNR Am J Neuroradiol 1995; 16:1847–1853.
17. Peltier B, Hurtevent P, Trehan G, Derambure P, Pruvo JP, Soto-Ares G. MRI of hippocampal malformations in patients with intractable temporal lobe epilepsy. J Radiol 2005; 86:69–75. [CrossRef]