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Title:
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Date:
2016-10-01

Citation:
Tsai, M. H., Vaughan, D. N., Perchyonok, Y., Fitt, G. J., Scheffer, I. E., Berkovic, S. F. & Jackson, G. D. (2016). Hippocampal malrotation is an anatomic variant and has no clinical significance in MRI-negative temporal lobe epilepsy. Epilepsia, 57 (10), pp.1719-1728. https://doi.org/10.1111/epi.13505.

Persistent Link:
https://hdl.handle.net/11343/291653

Accepted Date : 25-Jul-2016

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Hippocampal malrotation is an anatomic variant and has no clinical significance in MRI-negative temporal lobe epilepsy.

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Running title: HIMAL is a non-pathological variation in TLE

Keywords

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/epi.13505

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Incomplete hippocampal infolding, Lesion-negative epilepsy, hippocampal sclerosis, neuroimaging

Numbers of words, tables, figures and references: Abstract - 241, Text - 2379, Table -6, Figure -2, References -17

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Abstract

Objective: There is considerable difficulty in diagnosing hippocampal malrotation (HIMAL), with different criteria of variable reliability. Here we a) assess qualitative and quantitative criteria in HIMAL diagnosis and b) explore the role of HIMAL in MRI negative temporal lobe epilepsy (TLE).

Methods: We studied the MRI imaging of 155 adult MRI-negative temporal lobe epilepsy patients and 103 healthy volunteers and, asked 1) what are the qualitative and quantitative features that allow a reliable diagnosis of HIMAL, 2) how common is HIMAL in a normal control population and 3) is HIMAL congruent with the epileptogenic side in MRI negative temporal lobe epilepsy (TLE).

Results: We found that the features that are most correlated with the expert diagnosis of HIMAL are; hippocampal shape change with hippocampal diameter ratio > 0.8; Lack of normal lateral convex margin and a deep dominant inferior temporal sulcus (DITS) with DITS height ratio > 0.6.

In a blinded analysis, a consensus diagnosis of unilateral or bilateral HIMAL was made in 25/103 controls subjects (24.3% of people, 14.6% of hippocampi – 14 left, 6 right, 10 bilateral) which did not differ from 155 lesion-negative TLE patients where 25 had HIMAL (16.1% of patients, 11.6% of hippocampi - 12 left, 2 right, 11 bilateral). Of the 12 with left HIMAL only, 9 had seizures arising from the left temporal lobe while 3 had right-sided seizures. Of the 2 with right HIMAL only, both had seizures arising from the left temporal lobe.

Significance: HIMAL is an anatomic variant commonly found in controls. HIMAL is also an incidental non-pathological finding in adult MRI negative TLE and should not influence surgical decision-making.

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Introduction

Hippocampal malrotation (HIMAL) describes an atypical appearance of the hippocampus with abnormal medial location along the choroid fissure, round or pyramidal shape and/or verticalization of the collateral sulcus [1-3]. Because it resembles the fetal orientation, it is assumed that HIMAL is the consequence of incomplete infolding of medial temporal structures during embryonic brain development. HIMAL is reported in up to 18% of controls, which demonstrates that it can be a normal variant using the criteria of these studies [4-6]. However, diagnosis of HIMAL can be difficult as there is no "consensus criteria" or "gold standard". A variety of criteria have been used in different studies and often lack of scientifically validation to a "pathological diagnosis" as in hippocampal sclerosis [1, 3-5, 7-9].

As temporal lobe epilepsy (TLE) is the most common focal epilepsy in adults, whether HIMAL should be interpreted as a structural marker that informs epilepsy surgical management is important. In the absence of other identified structural pathology, the presence of HIMAL could be a developmental anomaly that predisposes to seizures, a normal variant of brain development without pathologic significance, or a marker of occult developmental abnormality [10].

MRI-negative TLE is an important group where no epileptogenic lesion is visible on routine MRI. In this group, HIMAL is often reported and its role in the assessment of the patient for surgery is controversial as it is sometimes considered a candidate 'epileptogenic lesion' [4]. In this study we assess HIMAL in MRI-negative TLE patients and healthy controls using qualitative and quantitative methods. We ask 1) what are the qualitative and quantitative features that allow a reliable diagnosis of HIMAL equivalent to an expert neuro-radiologist, 2) what is the prevalence of HIMAL in a normal control population, and 3) is HIMAL congruent with the epileptogenic side in MRI-negative TLE, and thus likely to be relevant to seizure localization in the assessment of these patients.

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Methods

MRI acquisition: T1 weighted whole brain structural 3T MRI scans using an epilepsy protocol [11] and oblique coronal imaging perpendicular to hippocampal long axis were acquired in all subjects (MPRAGE, sagittal acquisition, TR= 1900 ms, TI= 900 ms, TE= 2.6 ms, flip angle=9 degrees). These images were acquired as part of routine clinical care and reviewed retrospectively as part of this study.

Study subjects: 103 healthy volunteers with no history of seizures and 155 lesion-negative TLE patients were recruited from the epilepsy program of the Austin Hospital, Melbourne, Australia. The diagnosis of TLE was made by experienced epileptologists based on both clinical semiology (either typical auras or seizures) and characteristic electrographic findings as reported previously[12, 13]. We excluded patients who had a clear epileptogenic lesion on MRI (e.g. hippocampal sclerosis, focal cortical dysplasia, malformation of cortical development, previous brain injury, cerebrovascular disease or other structural lesions).

Seizure lateralisation: Clinical semiology, EEG, video-EEG monitoring were reviewed blinded to the MRI findings to designate the side of seizure onset. MRI scans were separately reviewed blind to the clinical lateralization to determine the presence of HIMAL and the side of HIMAL.

Consensus determination of HIMAL as the reference diagnosis: The MRI scans were randomized and independently reviewed by two investigators blinded to the clinical diagnosis. A consensus opinion was determined on global impression with no emphasis on specific features and after discussion of :gruent findings. HIMAL was assessed as present, absent or borderline. For cases assessed as 'borderline', no diagnosis of HIMAL was made. Consensus opinion was subsequently used as the gold standard for diagnosis. The lesion-negative TLE cohort was subsequently assessed by a single investigator.

Qualitative analysis of specific features: Specific features associated with HIMAL were assessed, namely (Figure 1):

- Hippocampal shape (rounded/pyramidal, borderline, normal)
- Verticalization of the dominant inferior temporal sulcus (DITS - definite, borderline, normal). The DITS is the most prominent of the collateral sulcus or the occipital-temporal sulcus

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- Shape of the lateral aspect of the hippocampus (curved, borderline, flattened)
- Size of the temporal horn (enlarged, normal).

Quantitative analysis: We measured (Figure 2):

A. Hippocampal diameter ratio is the height divided by the width measured on the slice perpendicular to the hippocampal axis where the hippocampus looks most severely affected (either rounded or pyramidal in shape).
B. The DITS angle is the angle of the DITS (defined above) from the horizontal, measured on the slice where the sulcus is deepest.
C. DITS height ratio is the height from the inferior margin of the hippocampus to the superior limit of the DITS (a) divided by the total hippocampal height (b). If the DITS does not extend to the level of the hippocampus, the ratio is defined as zero.
D. Medial distance ratio is the distance of the medial border of the hippocampus from the midline, divided by the distance of the lateral border of temporal neocortex from the midline (at the level of the temporal horn). This is measured on the most anterior coronal slice that includes the hippocampal body.
E. Parahippocampal angle is measured between the ascending and descending white matter segments of the parahippocampal gyrus, on the most anterior coronal slice that includes the hippocampal body.

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Statistical analysis

Diagnosis of HIMAL

The inter-rater reliability was evaluated using percentage of agreement and Cohen's Kappa correlation for the qualitative assessments of specific features, and intra-class correlation coefficient (ICC) for the quantitative measures. To assess the diagnostic utility of specific features against the gold standard diagnosis of HIMAL, the Chi squared statistic was used for qualitative features, and Student's t test and Mann-Whitney test for parametric and non-parametric measurements.

A logistic regression model was used to predict the diagnosis of HIMAL, using all variables that reached significance on the above tests.

HIMAL in lesion negative TLE

To assess the hypothesis that HIMAL is an epileptogenic lesion, the binominal exact test was used to compare the expected proportions of seizure onset side being ipsilateral or contralateral to unilateral HIMAL.

All statistical tests were performed on IBM SPSS Statistics 20.0 (New York, US).

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Results

HIMAL in healthy subjects

Consensus diagnosis of HIMAL

From 103 normal controls a consensus diagnosis of unilateral or bilateral HIMAL was made in 25 subjects (24.3%). Of the 206 hippocampi assessed, 30 had HIMAL (14.6% of hippocampi), with 14 left, 6 right, and 5 subjects (10 hippocampi) showing HIMAL bilaterally. Agreement between investigators for the diagnosis of HIMAL, before consensus discussion, was high (kappa=0.78).

Inter-rater reliability of qualitative and quantitative measures

Inter-rater reliability of qualitative features for HIMAL was high, with kappa values of at least 0.8, apart from verticalization of DITS (Table 1a). Quantitative measurements also had good agreement between the two neuroradiologists (ICC>0.64), except for DITS angle (Table 1b).

Comparison of qualitative and quantitative measures to consensus diagnosis

The qualitative features of rounded shape, verticalization of DITS and convex lateral aspect of the hippocampus were significantly associated with the consensus diagnosis of HIMAL ($p<0.05$). Verticalization of DITS was not specific to the diagnosis of HIMAL. An enlarged temporal horn had high inter-observer agreement but showed low sensitivity and was not significantly associated with HIMAL (Table 2). The quantitative measures of hippocampal diameter ratio, DITS height ratio and parahippocampal angle were significant correlated with the consensus diagnosis (Table 3). This corresponds to a more rounded shape, deeper DITS, and more acute parahippocampal angle in HIMAL.

Classification of HIMAL using qualitative and quantitative measurements

The logistic regression model for prediction of HIMAL using significant quantitative and qualitative features was:

$$\log\left(\frac{}{1-}\right) = 12.38 \times \textbf{Hippocampal diameter ratio} - 243.91 \times \textit{Normal shape} - 3.19 \times \textit{Convex lateral margin} + 5.13 \times \textbf{DITS height ratio} + 1.62 \times \textit{No DITS verticalization} + 0.04 \times \textbf{DITS angle}$$

Using a cut-off value of p=0.5, this model correctly classified 96.1% of hippocampi (172/176 normal hippocampi and 26/30 with HIMAL, with sensitivity 97.7% and specificity 86.7%). The most strongly weighted features were the quantitative

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hippocampal diameter ratio and qualitative assessment of hippocampal shape.

HIMAL in lesion-negative TLE

Of 155 lesion-negative TLE patients, 25 had HIMAL (16.1% of patients, versus 24.3% of the control cohort above). Clinical details are given in table 4. Fourteen patients had unilateral (left 12, right 2) and 11 had bilateral HIMAL. Of these 25, seizure localization was left temporal (n=20), right temporal (n=4), and bitemporal (n=1). Mean age of seizure onset was 26.2 years (range 1-68). 16 were female (64%).

Of the 12 with left HIMAL only, 9 had seizures arising from the left temporal lobe and 3 had right-sided seizure origin. Of the 2 with right HIMAL only, both had seizures arising from the left temporal lobe. For the 11 bilateral HIMAL patients, 9 had seizures originating from the left, 2 from the right (Table 6). In the subset of 5 bilateral cases where one side had more severe HIMAL (left>right 3, right>left 2), seizure origin was always on the left.

Using the exact binominal test, the observed seizure onset sides in patients with TLE did not differ from chance (p=1).

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Discussion

HIMAL is incomplete infolding of mesial temporal structures and its appearance is similar to the fetal hippocampus at gestation age 14-20 weeks, before tertiary gyration gives rise to the mature highly folded appearance of the cortical mantle. Because of this, it has been proposed that HIMAL might be an imaging marker of abnormal development of the temporal lobe that predisposes to epileptogenesis. In this study, we first determined what qualitative and quantitative features correlate with an expert neuroradiological diagnosis of HIMAL in order to enable standardization of the diagnosis in both epilepsy and controls. We then assessed how common this finding is in controls as a high incidence in controls would define this as an anatomic variant rather than a pathological feature in itself. Finally, if HIMAL has any pathogenic role in the focal epilepsy, we would expect that there would be concordance between the side of HIMAL and the side of seizure generation. We examined this in the clinical situation of MRI negative TLE where assigning significance of the finding of HIMAL is tempting.

Features that we found to correlate with an expert diagnosis of HIMAL: We examined the qualitative features suggested for the diagnosis of HIMAL and found that hippocampal shape change (rounded/pyramidal) is the most reliable feature for the diagnosis. Although a convex lateral margin of the hippocampus and verticalisation of the DITS were significantly correlated they were less sensitive and specific respectively. An enlarged temporal horn was not a useful diagnostic feature of HIMAL. We did not find medial positioning of the hippocampus as an overt qualitative requirement for the diagnosis of HIMAL, which might be the explanation of a higher frequency of HIMAL as compared to previously published studies [1, 4, 7].

We found that the “deep verticalized sulcus” is not always the collateral sulcus, sometimes it is the occipital-temporal sulcus. Thus we called it the dominant inferior

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temporal sulcus (DITS). We noted that the extension of the deep DITS to the lateral aspect of the hippocampus - that changes the lateral margin of hippocampus (from curved to flattened) - is a supportive feature for the diagnosis of HIMAL.

Similar to Bernasconi et al. [3] we quantified the features of HIMAL. The hippocampal diameter ratio represents the shape change of the hippocampus; an ovoid hippocampus has smaller height to width ratio compared to a rounded/pyramidal hippocampus. The DITS height ratio and DITS angle represents the deep and verticalized DITS. The DITS angle was not correlated with the consensus diagnosis, probably due to the difficulty of measuring the DITS as a consequence of variation in the sulcus, which may have a tortuous, shallow or bifurcated morphology.

We found that the following quantitative features are useful in the diagnosis of HIMAL:

1. Hippocampal shape change with hippocampal diameter ratio > 0.8
2. Lack of normal lateral convex margin
3. Deep DITS with DITS height ratio > 0.6

Prevalence of HIMAL in healthy controls: There is a wide range of prevalence of HIMAL reported in "normal" controls [4-6]. We found HIMAL was present in 24% of normal controls. Such high frequency would therefore mean that HIMAL is a common variant, rather than a pathological finding. It is unclear whether or not a higher overall frequency in diagnosis of HIMAL would disproportionately increase the frequency among controls as compared to MRI-negative TLE patients. The remaining question is whether this imaging variation is a vulnerability factor for seizures or focal epilepsy.

Correlation between HIMAL side and epileptogenic side in patients with TLE:

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Some case reports have suggested that HIMAL plays a role in epileptogenesis [9, 14], while others have provided evidence against this [3, 6]. The latter two reports were limited by studying a range of epilepsy syndromes including extra-temporal epilepsies, where seizures were unlikely to originate from the hippocampus. Therefore, we examined this issue in a cohort of MRI negative TLE patients.

We found that in 14 cases with unilateral HIMAL, 5 (36%) had contralateral seizure onset. This is consistent with previous reports [1, 3, 4] where in 25-50% of patients, seizure onset was contralateral to HIMAL, while in 15-50% cases, seizure onset was ipsilateral to HIMAL. The confirmation in multiple series that HIMAL is unrelated to the laterality of the seizure focus shows it is not a key epileptogenic lesion and should not have any significance in surgical assessment of such patients.

In our MRI negative TLE patients (and in our controls), HIMAL occurred more commonly on the left side and was more common in females. Left side predominance is consistent with previous imaging studies on both unselected epilepsy patients and controls [4-6]. The significance of this is not known, but may relate to development of the dominant temporal lobe and its specialized development to support language functions in humans.

Does HIMAL have any other significance? HIMAL had initially been suggested to be a developmental abnormality and precursor for epilepsy [15] but its frequency in normal controls makes this argument hard to justify.

The recent FEBSTAT study reported HIMAL in 8.8% of children with febrile status epilepticus compared with 2.1% of children with simple febrile seizures. This suggests that HIMAL could be a risk factor or a 'bystander' marker of another process associated with prolonged febrile seizures. [7, 8] The lower prevalence of HIMAL in that study may relate to the different diagnostic criteria used and the significance of

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including blurring of the internal hippocampal architecture in the diagnosis.

There is also little evidence to suggest that HIMAL is a precursor to subsequent development of HS or TLE. Two reported patients with refractory temporal lobe epilepsy and HIMAL whose hippocampi were studied pathologically showed no HS decades after seizure onset [16]. In our previous study of relatives of patients with TLE and HS, we also found no changes in hippocampal volumes or T2 signal in HIMAL compared to non-malrotated hippocampus, which again suggests that HIMAL is not pathological [17].

Our study supports the concept that HIMAL is an incidental non-pathological finding that is an anatomic variant seen commonly in normal healthy adults. In MRI negative TLE there is no case that it serves any pathological role either directly or as a marker of abnormality of the temporal lobe in which it is found. It should not have any weighting in lateralization of the epileptogenic focus and therefore should not influence surgical decision-making in this common group with intractable focal epilepsy and no detected MRI lesions.

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Key point box

1. Rounded shape of hippocampus, verticalization of DITS, lack of normal lateral convex margin, DITS height ratio > 0.6 and hippocampal diameter ratio > 0.8 are useful in the diagnosis of HIMAL.
2. HIMAL is a common MR imaging finding in normal adult healthy controls.
3. The laterality of the seizure focus in MRI negative TLE is not concordance with the side of HIMAL.
4. HIMAL is an incidental non-pathological finding in MRI negative TLE and should not influence surgical decision-making.

Acknowledgements

This study was supported by the National Health and Medical Research Council (NHMRC) of Australia (program grant 628952; project grant 628725) and the Victorian Government Operational Infrastructure Support Program. G Jackson is supported by an NHMRC practitioner fellowship (1060312).

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest relevant to this research activity to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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Table 1 Inter-rater reliability of measurements for hippocampal malrotation (HIMAL)

(a)Qualitative measurements	Percentage of agreement	Kappa
HIMAL	93%	0.78
Shape	93%	0.8
Verticalization of DITS	45%	0.12
Lateral aspect of hippocampus	93%	0.8
Enlarged temporal horn	100%	1

(b) Quantitative measurements	ICC
Hippocampal diameter ratio	0.64
DITS angle	0.48
DITS height ratio	0.82
Medial distance	0.76
Parahippocampal angle	0.84

The interpretation of Kappa coefficient: 0-0.2 indicate slight agreement, 0.21-0.4 indicate fair agreement, 0.41-0.6 indicate moderate agreement, 0.61-0.8 indicate “substantial” agreement, and >0.8 indicate “almost perfect” agreement.

The interpretation of ICC: 0-0.2 indicate poor agreement, 0.21-0.4 indicate fair agreement, 0.41-0.6 indicate moderate, 0.61-0.8 indicate strong agreement, and >0.8 indicate almost perfect.

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Table 2 Comparison between consensus diagnosis and qualitative diagnostic criteria

Criteria	HIMAL (%)	Normal (%)	P value#	Sensitivity	Specificity	AUC
Shape	30/30 (100)	15/176 (8.5)	<0.0001	0.91	0.92	0.92
Convex lateral hippocampal margin	26/30 (86.7)	24/176 (13.6)	<0.0001	0.72	0.85	0.86
Verticalization of DITS	24/30(80)	92/176 (52.3)	0.007	0.86	0.35	0.66
Enlarged temporal horn	3/30 (10)	26/176 (14.8)	0.776	0.08	0.87	0.47

Chi square; AUC, area under curve

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Table 3 Comparison between consensus diagnosis and quantitative measurements

Measurements	HIMAL	Normal	P value
Hippocampal Diameter Ratio (%, mean±SD)	65±8	51±9	**<0.0001**
DITS Height Ratio (%, median, interquantile interval)	69.5(58-80)	45(27-60)	**<0.0001**
DITS Angle (◦, median, interquantile interval)	81.5(69.5-90)	77(60.25-90)	0.138
Medial distance ratio - MDR (%, mean±SD)	33.7±2.8	34.2±2.7	0.37
Parahippocampal angle - PHA (◦, mean±SD)	111±23	124±22	**0.002**

Student's t test, Mann-Whitney test

DITS - dominant inferior temporal sulcus

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Table 4 Clinical characteristics of patients with lesion-negative TLE and HIMAL

Pt	Age (Years)	Sex	Onset (Years)	HIMAL side	Seizure side	Seizure Semiology	EEG	SPECT/PET	Refractory
1	52	F	22	Left	Left	No aura, right side stiffening and jerking followed by FDS	Left temporal ictal onset	Nil	Yes
2	31	M	26	Left	Right	Fear, butterfly feeling in the abdomen and epigastric rising sensation, sense of falling off a cliff, then FDS and sometimes BCS	Right temporal T4-T6 ictal onset	Right hypometabolism on PET	Yes
3	57	F	52	Left	Right	Rising abdominal sensation followed by a sense of familiarity and déjà vu then FDS with oro-manual automatisms	Right temporal T4 ictal onset	Right hypometabolism on PET	Yes
4	15	F	9	Bilateral	Left predominant	No aura, FDS with blank stares and unresponsive with sometimes BCS	Left temporal ictal onset	Hypometabolism over left temporal and inferior frontal area on PET	Yes
5	23	F	8	Left	Right predominant	Butterfly in chest/abdomen, sour smell followed by FDS with hand rubbing and lip smacking, occasional BCS	Right temporal T6 ictal onset	Right temporal hypometabolism on PET	Yes
6	29	F	7	Left	Left	Déjà vu, aphasia then chewing movement, sometimes BCS	Left temporal ictal onset	Increase perfusion over left temporal region on SPECT	Yes
7	29	F	26	Bilateral	Right	Sense of detachment, déjà vu, fear and urge to urinate, sometimes burning smell then FDS, rare BCS	Right temporal ictal onset	Bilateral decreased metabolism (R>L) on PET and right temporal increase perfusion on SPECT	Yes

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8	30	M	19	Bilateral, Left>Right	Left predominant	Epigastric sensation, sense of body falling, stomach rising and hot flushes, tingling in fingers	Predominant left but also right temporal ictal onset	Increased perfusion in left during ictal	Yes
9	44	M	31	Bilateral	Right	No aura, FDS with blank stares and eye rolling	Right temporal EDs and slowing	Nil	No
10	20	M	17	Left	Left	Déjà vu followed by FDS	Left TIRDA	Nil	No
11	56	M	53	Bilateral	Left	Déjà vu, lightheadedness and funny feeling	Left ictal onset and left EDs	Nil	No
12	36	F	36	Bilateral, Left>Right	Left	Déjà vu and panic sensation	Left ictal onset and left interictal EDs	Nil	No
13	48	F	46	Right	Left	Déjà vu, feel disconnected from reality, followed by FDS, BCS	Left temporal slow	Nil	No
14	35	M	Teenage	Bilateral	Left	Lightheadedness feeling, epigastric sensation associated with a sense of familiarity	Left temporal EDs	Nil	No
15	29	M	1	Left	Left	Feel dizzy, confused and zone out, followed by awareness change, BCS	Left ictal onset and left inerictal temporal EDs	Left temporal decreased metabolism on PET	Yes
16	75	F	73	Right	Left	Abnormal smell, "closing-in" feeling ± aphasia, oral automatisms, FDS, BCS	Left temporal EDs	Nil	No
17	29	F	8	Left	Left	Epigastric sensation & disorientation; FDS with oro-manual automatisms	Left ictal onset and left inerictal temporal EDs	Left temporal ictal increased perfusion on SPECT and decreased metabolism on PET	Yes
18	22	F	21	Left	Left	Funny depressed feeling, followed by eye deviate to right, right arm elevated, ictal	Left ictal onset, left more than right interictal EDs	Nil	No

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						tachycardia and then BCS			
19	16	F	15	Bilateral, Left>Right	Left	funny feeling in abdomen, fear, associated with FDS ± BCS	Left temporal EDs	Nil	No
20	52	F	32	Left	Left	Tingling in abdomen, feel nausea	Right temporal ictal onset	Right temporal increased perfusion on SPECT; decreased metabolism on PET	Yes,
21	34	F	5	Bilateral	Left	No aura, FDS with prolonged confusion, "glassy eye" followed by BCS	Left interictal temporal EDs & slowing	Nil	Yes
22	79	F	68	Bilateral, Right>Left	Left	FDS, confused wondering followed by BCS	Left interictal temporal EDs	Nil	No
23	46	M	30	Left	Left	Confused and BCS	Left interictal temporal EDs	Nil	No
24	26	F	26	Bilateral, Right>Left	Left	Starring spells followed by BCS	Left interictal temporal EDs	Nil	Yes
25	27	M	10	Left	Left	Rising epigastric sensation and déjà vu; FDS and BCS	Interictal: Bilateral temporal EDs but left predominant	Nil	Yes

BCS, bilateral convulsive seizures; EDs, epileptiform discharges; FDS, focal dyscognitive seizures; HIMAL, hippocampal malrotation; PET, positron emission tomography; Pt, patient; SPECT, single photon emission computed tomography; TIRDA, temporal intermittent rhythmic delta activity

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Table 5 Comparison of seizure onset side and HIMAL side

Pt	HIMAL side	Seizure side	"HIMAL is epileptogenic"
1	Left	Left	Supportive
2	Left	Right	Against
3	Left	Right	Against
4	Bilateral	Predominant left	-*
5	Left	Predominant right	Against
6	Left	Left	Supportive
7	Bilateral	Right	-*
8	Bilateral, Left>Right	Predominant left	Supportive
9	Bilateral	Right	-*
10	Left	Left	Supportive
11	Bilateral	Left	-*
12	Bilateral, Left>Right	Left	Supportive
13	Right	Left	Against
14	Bilateral	Left	-*
15	Left	Left	Supportive
16	Right	Left	Against
17	Left	Left	Supportive
18	Left	Left	Supportive
19	Bilateral, Left>Right	Left	Supportive
20	Left	Left	Supportive
21	Bilateral	Left	-*
22	Bilateral, Right>Left	Left	Against
23	Left	Left	Supportive
24	Bilateral, Right>Left	Left	Against
25	Left	Left	Supportive

*Of patients with bilateral HIMAL, seizures originating from either the left or right would be consistent with the hypothesis that HIMAL is epileptogenic

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Figure 1 Qualitative features of hippocampal malrotation

Legend: Unilateral left hippocampal malrotation (HIMAL) shown on the right of the image. Note the rounded hippocampal shape and "flattened" lateral hippocampal border with a clearly increased radius of curvature (arrowhead at the top point of this). The arrow denotes the vertical orientation of the dominant inferior temporal sulcus (DITS). This can be compared to a normal right hippocampus as shown on the left of the image.

Figure 2 Quantitative measurements of hippocampal malrotation

Legend: Quantitative measurements of hippocampal malrotation were illustrated with normal hippocampi on the left side compared to unilateral malrotated left hippocampi HIMAL the right side. (A) Hippocampal diameter ratio=a/b, a=height, b=width; (B) Dominant inferior temporal sulcus (DITS) angle; (C) DITS height ratio=a/b, a=height of the highest level of DITS, b= total hippocampal height; (D) Medial distance ratio=a/b, a=distance from midline to medial hippocampus, b=distance from midline to temporal neocortex; (E) Parahippocampal angle.

Table 6: Laterality of Epilepsy versus Laterality of HIMAL in MRI-negative TLE

	Left HIMAL	Right HIMAL	Bilateral HIMAL	
Left Seizure	9	2	9	20
Right Seizure	3	0	2	5
	12	2	11	25

Correspondence of unilateral HIMAL to side of seizures was not significant using the

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binomial exact test (p=1).

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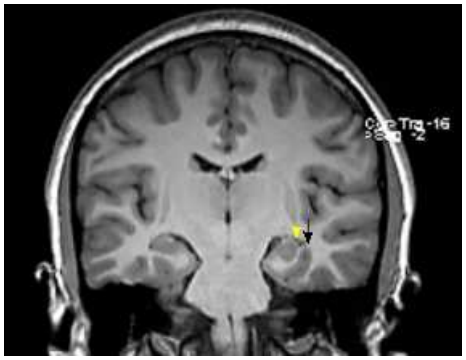

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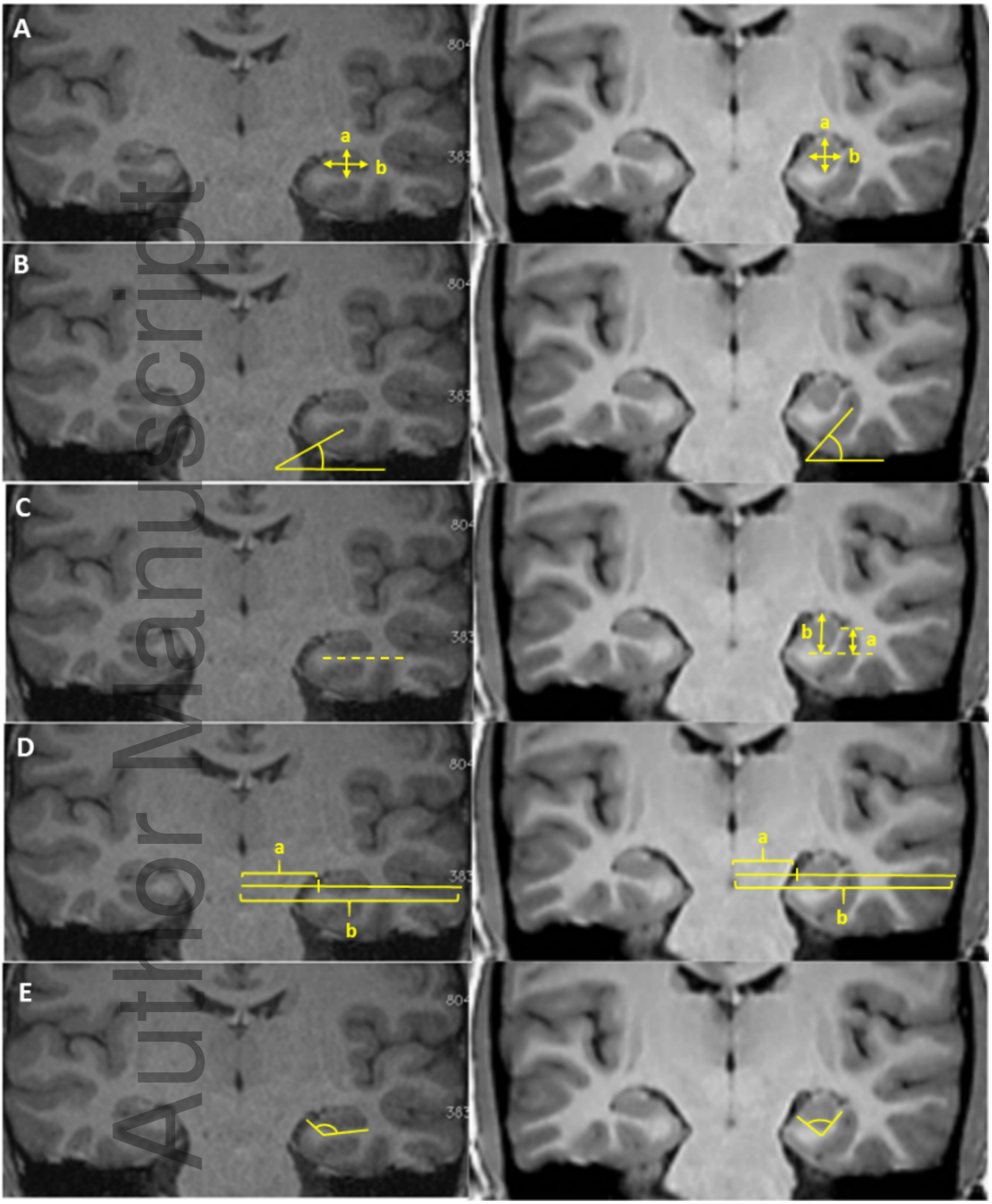

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