Original Article

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Radiology Section

Incomplete Hippocampal Inversion in Normal Individuals- A Retrospective Observational Study using Magnetic Resonance Imaging

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ABSTRACT

Introduction: Hippocampal inversion is a normal process that happens between 11 and 21 weeks of gestation. In some individuals the process is incomplete and is termed as Incomplete Hippocampal Inversion (IHI). There are differing observations recorded, of its incidence in normal individuals- from as high as 17% to nil making it difficult to come to a conclusion as to whether IHI is a normal anatomical variant or a marker of a wide spread disorder in brain.

Aim: To determine the incidence of IHI in the hippocampus of individuals who don't suffer from any form of epilepsy and for whom Magnetic Resonance Imaging (MRI) brain has been performed and seen to be normal.

Materials and Methods: A retrospective observational study was conducted in a tertiary centre using T1fl 3D, check globally isovoxel 0.86 mm images of the brain and incidence of IHI in normal individuals without seizures for whom MRI brain was normal otherwise was calculated. The MRI images of a total of 197 individuals qualified for the study. Analysis was done by four Radiologists using subjective visual criteria.

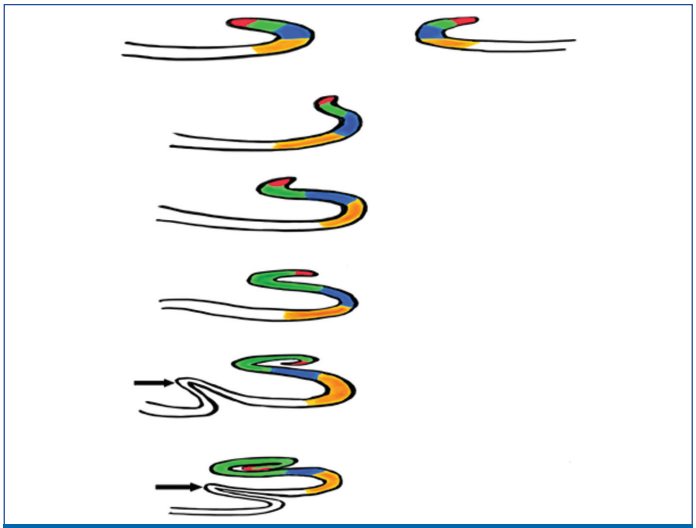
Results: It was seen that 1.015-1.52% was the incidence of IHI in otherwise normal MRI brain in present study. A 1.52% is the incidence placing a study classified as partial IHI under IHI and 1.015% not placing it under IHI. All were unilateral, on left side.

Conclusion: The results of present study point that there was very less incidence of IHI in normal individuals. Such a less incidence will make it difficult to suggest that IHI is a normal anatomical variant. Present study also encountered potential pitfalls with the use of T1 weighted 3 Dimensional (3D) images to determine of presence or absence of IHI.

Keywords: 1.5 Tesla, Hippocampal malrotation, Hippocampus, Stratum radiatum lacunosum moleculare, T1 Fast low angle shot 3 dimensional

INTRODUCTION

At 13-14 weeks of gestation hippocampus remains almost flat without any folding with widely open hippocampal sulcus. Hippocampal inversion/rotation begins with infolding at the Dentate Gyrus (DG)-Cornua Ammonis (CA) region of the hippocampus at approximately 11 weeks of gestation [1]. The hippocampal sulcus becomes deep but remains open. The hippocampal infolding/inversion/rotation is complete by 21 weeks of gestation with hippocampal sulcus being obliterated completely [Table/Fig-1] [1].



[Table/Fig-1]: A diagrammatic expose of the infolding/rotation/inversion process that happens in the hippocampus during development. Red represents Dentate Gyrus (DG). Green represents Cornua Ammonis (CA) and blue represents subiculum of the hippocampus. Yellow represents parahippocampal gyrus. Arrows represent collateral sulcus

In some individuals the inversion/rotation process is incomplete and it is termed as IHI or Hippocampal Malrotation (HIMAL). Whether this incomplete inversion/malrotation is a disease-causing pathology or not is an area of ambiguity with some [2] describing this as a variant without any disease sequel/association perse and some disagreeing saying IHI is a rare finding in patients without seizures and that IHI is therefore likely to be a pathologic finding [3,4].

Also, if there is a disturbance causing IHI, it should have happened at 10th to 21th week of gestation and it is unlikely that such a disturbance results in a focal solitary event and there should have been other disorders of development in other parts of the brain that will contribute to diseased states- i.e., IHI is considered a sign of a more widespread disorder of cerebral development that may affect other parts of the brain [5].

Hence, studies have been conducted to see the prevalence of the IHI in normal non epileptic individuals. Again there are disagreeing results, with some studies observing the occurrence of the IHI as high as 17-19% in normal individuals [6,7] and some studies observing zero occurrence of IHI in individuals without any epilepsy [3]. A 44% of Rolandic epilepsy patients and 57% of cryptogenic generalised epilepsy patients had incomplete inversion of the hippocampus when compared to 25% of the normal individuals in a study conducted by Bajic D et al., [8].

Since, there are differing opinions regarding whether IHI is a normal variant or a marker of a pathological state and differing results in the incidence of IHI in normal individuals in the available literature, authors decided to check for the incidence of IHI in the hippocampus of individuals who don't suffer from any form of epilepsy for whom MRI brain has been performed and seen to be normal.

MATERIALS AND METHODS

The retrospective observational study was conducted in Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry, India, with 900 beds and fully equipped Radiology department using MRI images of Brain acquired using an 1.5 Tesla machine. The study duration was from 1/1/2018-12/03/2021. The analysis of the study was done in August and September 2021. Approval from local Ethical Committee was obtained for the study (approval no: 79/SVMCH/IEC-Cert/Jun21).

Inclusion criteria: Inclusion criteria were any MRI brain study with T1fl 3D (T1FLASH3d= T1 Fast low angle shot 3D (Siemens) 0.86 mm iso voxel images.

Exclusion criteria: Studies showing any other developmental pathology or pathologies that cause mass effect on hippocampus in the MRI brain were excluded in the study. Studies of the patients who have epilepsy of any form as per short history in the comments were excluded from the study. The MRI brain studies without T1fl 3D iso voxel (0.86 mm) images were excluded.

Study Procedure

The MRI studies from the sampling period were anonymised by a research coordinator deputed by the ethical committee. Name and hospital ID number of the patients were removed totally and replaced with random numbers as ID in the anonymisation process. Short history and reason for referral in comments section were retained with.

Horos (version 4.0.0 RC5)- an open source dicom image viewer for image analysis was used. Hard disks having the anonymised MRI studies were connected to a reporting system containing Horos software installed in it (any apple system with Mac-OS) and database from the hard disk was chosen in locations settings. Filter of 'Head' was applied under search box and modality filter was applied to MR and the studies were examined. If felt required to get additional details about the image acquisition parameters they were transferred back to the MRI acquisition console system and looked upon.

A total number of 1090 studies were examined of which 884 studies were excluded after applying exclusion criteria. Seven studies were excluded due to motion artefacts, two studies were excluded due to numerous hippocampal sulcal remnant cysts causing difficulty in interpretation. A total of 197 studies were included after applying the inclusion and the exclusion criteria and hippocampi in them were analysed for the presence/absence of IHI.

Authors have used the T1fl 3D images (0.86×0.86×0.86 mm, with Repetition time (TR)=15 ms, Time to echo (TE)=5 ms and flip angle=25°) of the brain for present study. The images were analysed with oblique coronal reformatting, with the oblique coronal plane being perpendicular to the long axis of the hippocampus that was examined. Perpendicularity was ascertained with sagittal reformatted images by the side.

The hippocampus was analysed at its body level in coronal plane perpendicular to the body. Slice localising with axial and sagittal reformatted images by the side, it was ascertained that the coronal plane is in body level. A guideline was followed that the part of the hippocampus that is anterior to mesencephalon can be taken as head and that to the side of the mesencephalon can be taken as body and that posterior to can be taken as tail region [5]. T2 coronal images if available in any study were observed only after finalisation of results from examinations of T1fl 3D images.

Factors considered in analysis: A very high resolution of 7 Tesla MRI T2 oblique coronal image of the hippocampal body will show the anatomy of the various parts of the hippocampal body clearly and whether the hippocampus has fully inverted or not can be easily ascertained. But in preset study, with images from a 1.5 Tesla MRI machine, the study material was limited in resolution both spatial and contrast wise. The best image sequence to use for a retrospective study was T1fl 3D 0.86 mm isovoxel but it was not great in contrast resolution to reveal various parts of the hippocampus like CA and SRLM (Stratum radiatum lacunosum moleculare) layer separately. Even with an oblique coronal T2W image in a 1.5 Tesla machine, the differentiation was not guaranteed in all the studies in all the parts of body.

Hence, to analyse the images looking for presence of IHI indirectly taking help of various factors.

1. Collateral sulcus angle: The normal collateral sulcus is horizontal in left to right direction at the level of body of the hippocampus. When there is IHI and if the collateral sulcus is seen having a fair depth, the collateral sulcus will be more oblique or vertical. Flat horizontal normal hippocampus is what forces the collateral sulcus to be horizontal.

2. Roundedness and/or verticality of the hippocampal body: A properly rotated or inverted hippocampus has an oval appearance in coronal plane of the hippocampal body with long axis of the oval being in the left right direction. When there is incomplete inversion the hippocampus assumes more dimension in vertical direction due to any of the following factors: 1) Thickened subiculum; 2) Thickened DG. CA being vertical is a direct effect of incomplete inversion.

3. Medial positioning of the hippocampus: The lateral most portion of the fully inverted hippocampus body in coronal section is usually lateral to the lateral most reach of the collateral sulcus. In incomplete inversion, the hippocampal body loses its left to right length due to increase in verticality and hence collateral sulcus will be reaching more lateral than the hippocampal body.

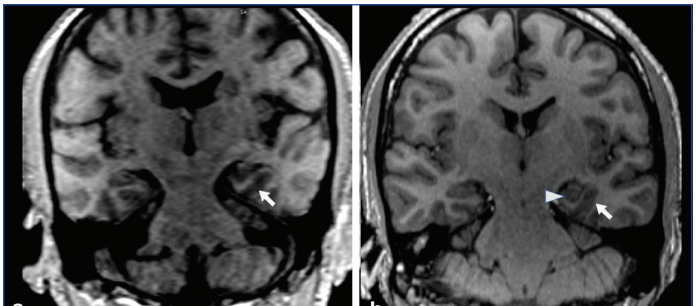
Subjective analysis using all the criteria described above was done separately by four National Medical Commission (NMC) registered radiologists. Joint analysis or consensus analyses were to be done only if there was variation among the interpretations. If no consensus was attained still, three interpretations favouring a result would be taken discarding one against the same. If there were two interpretations for and two interpretations against, that was classified as ambiguous and reported separately in the study. Anterior parts of the hippocampal body showing features of non inversion while the posterior parts of the body showing features of normal inversion is reported separately as partial IHI. Such appearance is seen described as partial IHI in literature [7].

STATISTICAL ANALYSIS

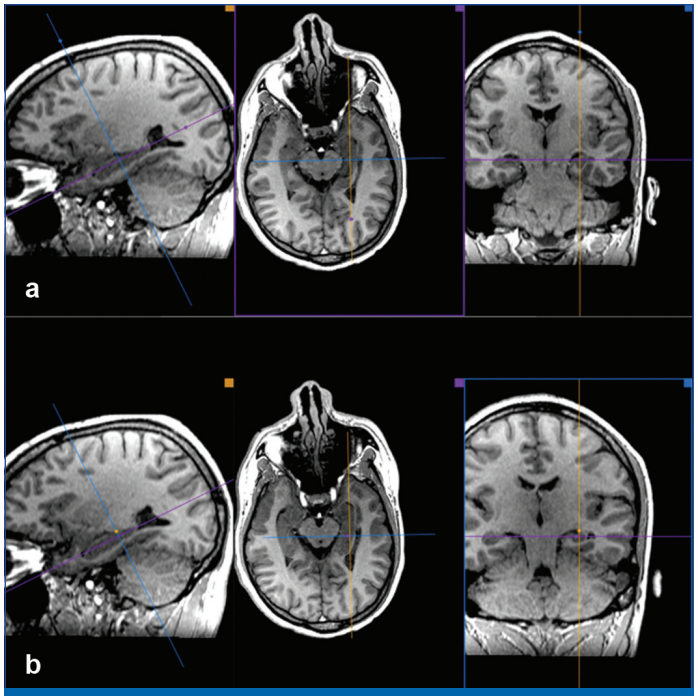
The incidence of IHI in normal individuals was calculated as total number of IHI observed divided by total normal MRI brain studies examined and was expressed in terms of frequency and percentage.

RESULTS

A total of 197 MRI were included in the study, two MRI [Table/Fig-2a,b] were determined to be having IHI (1.015%). One MRI showed ambiguous appearance with anterior parts of the left hippocampal body showing features of non inversion while the posterior parts of the body showing features of normal inversion [Table/Fig-3]. Such appearance is seen described as partial IHI in literature. If this study is to be included as IHI then, the number



[Table/Fig-2]: T1fl 3D oblique coronal image reconstructions from two studies (a and b) show IHI on the left side. The collateral sulcus is more vertical on the left side (arrows) when compared to the right. The hippocampal body on the left side is more rounded (arrow head in b).



[Table/Fig-3]: T1fl 3D MPRs. Left hippocampus classified as partial IHI. Right-side hippocampus is normal. a) Oblique coronal section at proximal body of left hippocampus suggests the hippocampus to be incompletely inverted; and b) Oblique coronal section at distal body suggests the hippocampus to be normally inverted.

of individuals with IHI in present study was 3 (1.52%). All these three patients had unilateral IHI and in all of them it was on the left side. Number of individuals having bilateral hippocampal inversion in present study was zero.

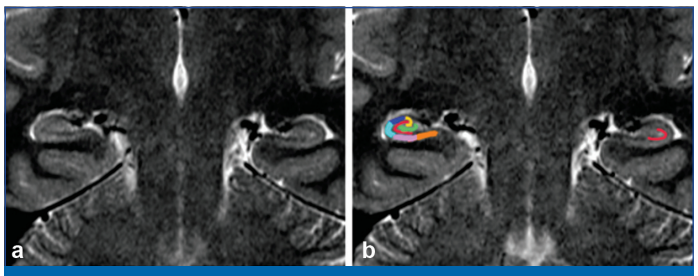
Total number of instances where there were discrepancies between interpretations of the four radiologists was zero. Total number of instances classified as ambiguous because of discrepancy between interpretations of the four radiologists was zero.

DISCUSSION

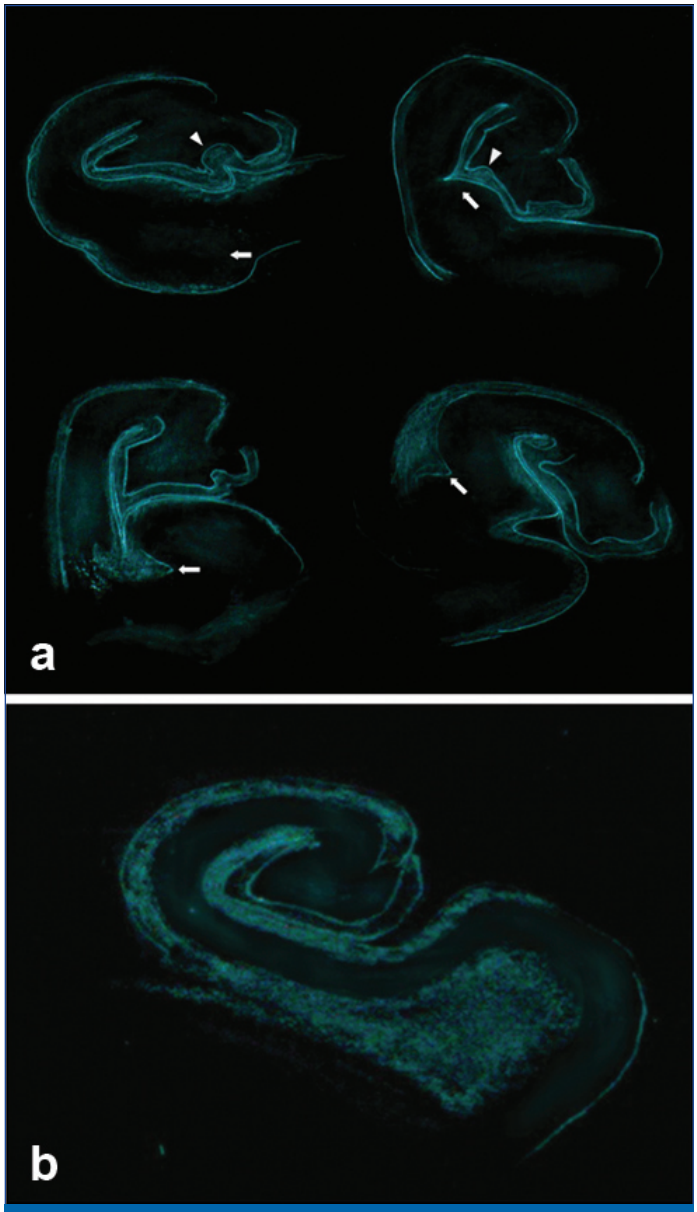
In present study, we found incomplete inversion of the hippocampus was found to be 1.015-1.52% of the normal individuals. Study done by Gamss RP et al., using 1.5 Tesla T2 weighted coronal images of the temporal lobe to examine the hippocampus reported non existence of IHI in patients referred for MRI for conditions other than seizures [3]. The images they used for examination were 3 mm or 4 mm in slice thickness. Study done by Cury C et al., using 3 Tesla 1 mm iso voxel T1 weighted 3D images and subjective visual criteria similar to present study, has reported high occurrence of IHI in normal individuals [6].

A review suggested that varied prevalence in different studies is likely due to variation in methodology used for examining the hippocampus [9].

In present study, only unilateral IHI and all were on the left side was observed in normal individuals. The left side dominance observed in present study was consistent with many other studies [6,8,10].



[Table/Fig-4]: a and b) Show the hippocampal body in the coronal plane in T2w images, without and with segment marking, respectively.
Red=SRLM layer (Stratum radiatum – lacunosummoleculare)
Green = DG (Dentate gyrus)
Yellow; Deep blue; Turquoise blue and Purple; subdivisions of Cornuaammonis (CA) - CA4,CA3, CA2, CA1, respectively; Orange=Subiculum

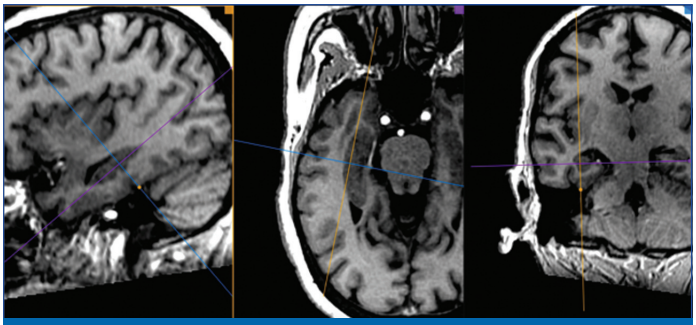


[Table/Fig-5]: a) Schematic diagrammatic representation exposing some of the various degrees and features of incomplete hippocampal rotation described in literature. Arrow heads represent invaginations in the DG. Arrows represent either thickened subiculum or infoldings in subiculum. Note: The colours and shades do not represent anything actual; b) For comparison, this is a drawing depicting the shape of a normally inverted hippocampus. Note: The colours and shades do not represent anything actual.

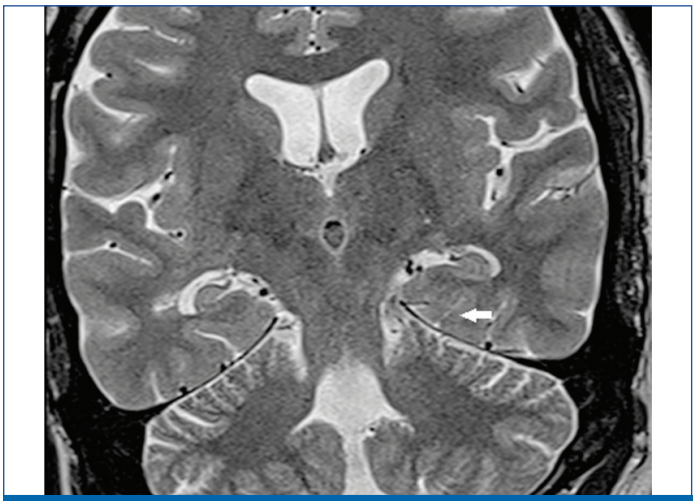
A revision of the anatomy of the hippocampus with high resolution T2 oblique coronal images [Table/Fig-4a,b] and appearance of various levels of IHI with diagrammatic representation [Table/Fig-5a] is given for a better understanding of the ensuing discussion.

The subiculum and CA are seen hyperintense. CA is divided into four parts- CA1 which is in continuum with subiculum and is horizontal, CA2 which is vertical and lateral most part of the body, CA3 which is again horizontal and CA4 which is seen in proximity to DG. In-between DG and CA1 and in-between DG and CA2 and in-between DG and part of CA3 is obliterated hippocampal sulcus. There can be sulcal remnant cysts formed during the obliteration process. The SRLM is seen as a thin hypointense C-shaped strip seen superior to CA1 medially to CA2 and inferior to CA3.

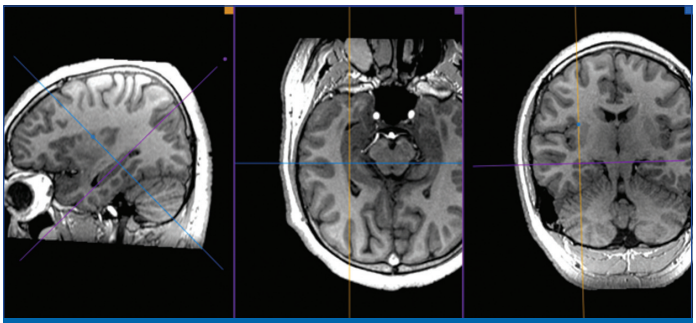
There were some difficulties experienced by us in the study for e.g., Hippocampal digitations can easily mimic IHI [Table/Fig-6] when indirect signs are being relied upon in T1w images to diagnose IHI. There were observations made by us of abnormal collateral sulcus angles/vertical collateral sulcus in a normal flat/oval hippocampus [Table/Fig-7,8] rising doubts on the credibility of the indirect signs



[Table/Fig-6]: T1 fl3D MPR from a study shows more rounded hippocampus on the right-side. That the roundedness is caused by digitations in the hippocampus is evident on comparison with the sagittal image. A high resolution T2tse oblique coronal image would have helped ascertaining the inversion status of the hippocampus easily and helped solve the ambiguity more easily in our opinion.



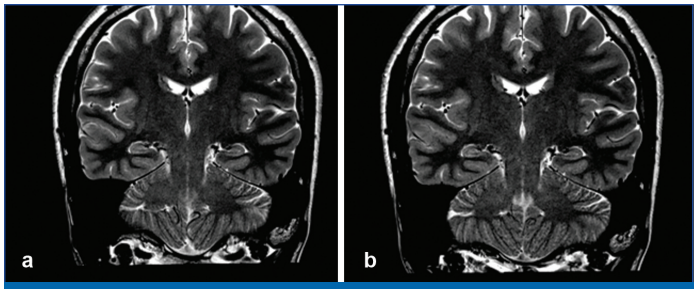
[Table/Fig-7]: T2 W coronal MR image from an excluded study (excluded as it was referred for seizures) shows more vertical collateral sulcus angle bilaterally (left side >right-side), however the hippocampus shows normal morphology as indicated by the shape of the T2 hypointense SRLM layers. Arrow points to left side collateral sulcus.



[Table/Fig-8]: T1fl 3D MPR in a patient shows vertical collateral sulcus angle on the right-side. However, the hippocampus appears normal in morphology.

used in the methodology to diagnose IHI. Relying upon indirect signs from T1w images was the method used by us and by Cury C et al., [6]. We felt that a high resolution T2tse coronal oblique sequence would have been much helpful in such situations for a better observation of hippocampal morphology.

In two of the studies, (which were excluded due to presence of seizures T2 coronal oblique with 2 mm slice thickness with increased spatial resolution (0.57×0.40 mm voxels) and increased contrast resolution (with averages to 4) were available and were seen to provide adequate spatial and contrast resolution to resolve clearly the T2 hypointense SRLM layer of the hippocampus [Table/Fig-2,9] -Observing the normal shape of the SRLM layer directly exposed whether the hippocampus is inverted completely or not, making it unnecessary to rely upon the indirect signs upon which we are forced to rely when we use T1fl 3D 0.86 mm isovoxel images to diagnose IHI. While in the high resolution T2 images [Table/Fig-2,9] the SRLM layer is clearly demarcated and is seen following the hippocampus foldings clearly (i.e., the degree of folding of the hippocampus is directly seen as degree offolding of the SRLM layer), in T1W images



[Table/Fig-9]: Shape of SRLM layer in a study exposing normal inversion of hippocampus. The sequence is T2tse oblique coronal 2 mm x 0.57 mm x 0.40 mm with average of 4. Image is from a study which was excluded as it was referred for seizures. a) MPR reconstruction of the T2tse coronal oblique image in mean mode- 3 mm thickness; b) MPR reconstruction of the T2tse coronal oblique image in Mean mode- 1 mm thickness.

no such differential internal morphology in the hippocampuscould be deciphered.

Considering these observations, authors think that probably the use of T2 oblique coronal sequence with high spatial and contrast resolution (for e.g., 0.57×0.40×2 mm with averages 4 in an 1.5 Tesla machine) would be simpler and easier and probably be better than a 3d T1w image for examining the hippocampus for IHI (we used 0.86 mm iso voxel in an 1.5 Tesla machine, Cury C et al., used T1w 1 mm isovoxel) [6]. T1fl 3D images were chosen by us because it is part of routine protocol in most of the MRI brain studies- while high resolution oblique coronal T2W images are obtained only for patients where temporal lobe is to be observed- the scenario in most such cases are seizures or observation of mass lesion in temporal lobe in routine sequences and they had to be excluded from present study. A prospective study to compare these two sequences would throw more light. Further studies to record the incidence of IHI with a larger sample size in different parts of the world, (preferably with high resolution T2tse oblique coronal images rather than T1 images) will help putting an end to the discussion as to if IHI is a normal variant or a marker of other disorders in brain.

Limitation(s)

A limitation in the study was that the individuals included in the study are not normal volunteers but people who have some or other complaints (other than seizures) for which they underwent MRI brain with MRI brain turning out to be normal. The authors doubt if the whole of the sample would truly belong the normal group of population. It would be better if the study group taken are normal volunteers. Authors feel that the usage of T1fl 3D 0.86 mm iso voxel sequence is another limitation. In many of the MRI brain examinations in present study, there were difficulties in evaluation of hippocampus with T1fl 3D sequence, especially when the hippocampus was small or when there were too many hippocampal digitations or if there were multiple hippocampal sulcal remnant cysts.

CONCLUSION(S)

The results of present study point that there was very less incidence of IHI in normal individuals. Auxiliary observations from two excluded studies which had oblique coronal T2w images with high spatial and contrast resolution 0.57×0.40 mm, slice thickness of 2 mm and averages 4) exposing the anatomy of the hippocampus in detail made us feel that using SRLM layer morphology as guideline to asses degree of hippocampal inversion is much simpler and probably better than relying on indirect signs from T1w images to diagnose IHI. A prospective study to compare these two sequences would throw more light.

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- iThenticate Software: Jan 29, 2022 (3%)

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