Correlation between Incomplete Hippocampal Inversions (IHI) with Incidence of Seizure Based on MRI Findings: A Systematic Review

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**Abstract**

**Introduction:** Incomplete Hippocampal Inversions (IHI) is considered as leading cause of several neurological complications including epilepsy. This paper provides a systematic literature review about the possible causative role of incomplete hippocampal inversions in patient with epilepsy based on findings of Magnetic Resonance Imaging (MRI).

**Materials and Methods:** The incomplete inversion of hippocampus with MRI imaging in patient with epilepsy was searched in PubMed and Scopus with the following search strategy ((incomplete hippocampal inversion or hippocampal malrotations) and epilepsy) and (magnetic resonance imaging or MRI). Then, data including the number of patients, and concluded results were extracted and compared between the groups.

All types of articles including case series, clinical trials and cohort studies in English language with no time limit were included. All searches, selection of articles and the data extraction were performed by two independent reviewers.

**Results:** Only 11 papers met the inclusion criteria. Data were extracted and compared between two groups of patients and healthy controls. Results of this review showed that among 854 healthy controls and 1402 patients with verified temporal lobe epilepsy or hippocampal abnormalities, 59 cases with Hippocampal Malrotation (HIMAL) were in control groups, and 165 cases were in patients with epilepsy.

**Conclusions:** The results showed that incomplete hippocampal inversion can be considered as an important cause of seizure. But still, studies with large sample size and equal number of cases and controls should be conducted to strongly confirm this association.

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**Introduction**

Epilepsy is among the most common chronic neurological disease and one of the major health problems in developing countries with the incidence of almost (7.5%) (1). Magnetic Resonance Imaging (MRI) is typically used as a noninvasive medical test for the evaluation of patients with epilepsy. After the diagnosis of epilepsy, in order to find the cause of seizures, prognostic, and treatment plans, brain structure should be evaluated with MRI (2).

Previously, the relationship between the hippocampus and epilepsy has been studied. Temporal lobe epilepsy is the most common form of partial epilepsy in which the hippocampal sclerosis is the most common radiologic findings (1). It is suggested that developmental abnormalities of the hippocampus may lead to seizures or may be the main cause of epilepsy (2). Hippocampal folding in temporal lobe occurs at 18 weeks of fetal development, and in week 21, the folding pattern is similar to those in adults (3, 4).

Because hippocampus has many role in cognition and memory processes (5); hence, every malrotation during hippocampal folding may be responsible for most of hippocampus related complications including cardiac and respiratory dysfunction (6), loss of cognitive function, learning and memory impairment (7) and other complications such as incidence of seizure (8). Incomplete Hippocampal Inversion (IHI) which is traditionally known as Hippocampal Malrotation (HIMAL) is the incomplete inversion of the hippocampus to abnormally round shape (9). In other word, the shape of hippocampus in malrotated form is round or pyramidal than oval. Incomplete
rotation rate of the hippocampus in both healthy subjects and patients with epilepsy are not clear. In addition, there are different estimations on the relationship between incomplete rotation of hippocampus and partial seizures. But, it is not yet clear whether this partial rotation as a structural disorder is the underlying cause for seizure, or it is a common finding in asymptomatic population.

Although the role of hippocampus anomalies in onset of seizures is accepted (6); yet, the exact role of incomplete hippocampus inversion in patients with epilepsy is not fully understood. Hence, finding relationship between incomplete inversion of hippocampus and epilepsy can help to predict the incidence of seizures or other structural abnormalities in the fetus. This study aimed to systematically review the frequency of reported incomplete rotation of the hippocampus in epilepsy patients compared to healthy individuals based on MRI findings.

Materials and Methods

Literature search strategy

PubMed and Scopus were searched for evaluation of incomplete hippocampal inversion with magnetic resonance imaging in patient with epilepsy on words in the title, keywords, and abstract. First these databases searched for complete inversion of hippocampus or hippocampal malrotation. Then the search was limited to patients with epilepsy, and finally the results were restricted to those in which MRI has been used for brain structural evaluation. Relevant articles with the following search terms: (incomplete hippocampal inversion or hippocampal malrotations) and epilepsy and MRI were selected and reviewed with the last update on February 2015.

Nonrelevant articles were omitted as we reviewed the abstract of the articles. Subsequently, the full text of the relevant papers was studied. To minimize the possibility of missing relevant data, and in order to find further potentially relevant studies, the reference list of related articles was also scanned.

Study selection

There was no time limitation for the included articles, but we excluded the articles to those in English language. All types of the articles including the case series, clinical trials and cohort studies in which the study has been conducted on at least two patients were selected. But, we did not include review articles, meta-analysis and book chapters. Inclusion criteria for study selection were patients with verified hippocampal malrotation with or without epilepsy. Those papers with duplicated data were omitted. Exclusion criteria for this review were articles in which the patients with epilepsy had not been studied for incomplete inversion of hippocampus, or studies in which the incidence of seizure was due to hippocampal sclerosis or neuropathology of the temporal lobe. In order to avoid selection bias, we included all studies in which the incomplete hippocampal inversion had been investigated in patients with or without epilepsy, or studies in which the patients with epilepsy were studied for the presence of hippocampal abnormalities.

Data extraction

Data about authors, country of origin, publication date, study design and the concluded results were extracted. The data regarding hippocampal malrotation obtained in each study were compared. Total number of patients and controls were identified and structural features of hippocampus were compared between the groups. All information from included articles were tabulated. Results were organized based on the association between hippocampal abnormalities, specifically incomplete hippocampal inversion with the incidence of epilepsy. The quality assessment of selected papers was performed based on recommendations of CONSORT checklist 2010 by two independent reviewers (10).

Results

From overall 645 article found in PubMed and 12 in Scopus, only 33 articles seemed to be relevant to the purpose of this study in the first step. After carefully reviewing the articles, only 11 papers met the inclusion criteria for further assessment. Therefore, full texts of these articles were collected and the data were extracted based on the main purpose of this study.

Figure 1 shows step by step selection process of articles.
The number of patients and healthy individuals studied for evaluation the relationship between incomplete hippocampal inversion with the incidence of seizure varied from 2 patients in a case report to 527 participants among the studies. The age of studied patients or healthy controls also varied from one month old neonates (11) to a patient with 101 year old (12) among the included studies. Among all the individuals, 854 people were healthy controls and 1402 were patients with verified temporal lobe epilepsy or hippocampal abnormalities. Of these cases, 59 hippocampal malrotation had been reported in control groups, while 165 had been observed in patients with epilepsy. The findings show that the rate of incomplete hippocampal inversion is almost double in patients with epilepsy compared to controls. Analysis of extracted data showed that incomplete hippocampal inversion occurs with high frequency unilaterally on the left side. According to documented data reported in reviewed papers, only minority of hippocampus malrotations with almost (20%) are bilaterally, while the frequency for left and right sided malrotations are (71% and 9%), respectively. Although the data regarding demographic information including sex and age were limited, but most of the included papers have concluded that HIMAL is more frequent in men than in women.

### Table 1: Characteristics of literatures included in this review.

<table>
<thead>
<tr>
<th>No</th>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Study design*</th>
<th>Number of participants</th>
<th>Study population</th>
<th>Inversion of the hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bajic D, (13)</td>
<td>2008</td>
<td>Sweden</td>
<td>PS</td>
<td>100</td>
<td>HI</td>
<td>19** 10 men 9 women</td>
</tr>
<tr>
<td>3</td>
<td>Henry T.R, (15)</td>
<td>2011</td>
<td>USA</td>
<td>CC</td>
<td>19</td>
<td>Case-Control</td>
<td>3.8 (37.5%) patient and 4/11 (36.6%) controls</td>
</tr>
<tr>
<td>4</td>
<td>Kuchukhidze G, (16)</td>
<td>2010</td>
<td>Austria</td>
<td>C-S</td>
<td>220</td>
<td>EP</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Gamss R.P, (12)</td>
<td>2009</td>
<td>USA</td>
<td>C-S</td>
<td>497</td>
<td>HI</td>
<td>6</td>
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<tr>
<td>6</td>
<td>Ramantani G, (17)</td>
<td>2013</td>
<td>Germany</td>
<td>C-S</td>
<td>4</td>
<td>EP</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Shinnar SH, (11)</td>
<td>2012</td>
<td>USA</td>
<td>PS</td>
<td>295</td>
<td>Case-Control</td>
<td>15.199 patients and 2.96 controls</td>
</tr>
<tr>
<td>8</td>
<td>Bajic D, (18)</td>
<td>2009</td>
<td>Sweden</td>
<td>PS</td>
<td>350</td>
<td>Case-Control</td>
<td>60.201 patient and 28.150 controls</td>
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<tr>
<td>9</td>
<td>Yeghiazaryan N.S, (19)</td>
<td>2010</td>
<td>Italy</td>
<td>Cs</td>
<td>2</td>
<td>Case Report</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>Baulac M(20)</td>
<td>1998</td>
<td>France</td>
<td>PS</td>
<td>19</td>
<td>EP</td>
<td>19</td>
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<tr>
<td>11</td>
<td>Lehericy S (21)</td>
<td>1995</td>
<td>France</td>
<td>C-S</td>
<td>222</td>
<td>EP</td>
<td>16</td>
</tr>
</tbody>
</table>

* HI: Healthy individuals, EP: Epileptic patients.

** Information about gender has only been reported in some studies.

# PS: Prospective study, CC: Case-Control, C-S: Cross-sectional, Cs: Case series

Some limitations in this study include the small number of enrolled patients in some studies, which could lead to insignificancy of the differences. Also in some studies, there was no distinction between morphological changes in the hippocampus and incomplete rotation, and may be incomplete rotation had been considered as part of the changes in the hippocampus.

### Discussion

Association between IHI and onset of epilepsy is a controversial issue. The results show that developmental abnormalities of the hippocampus on epileptic side are a common disorder in patients with epilepsy; moreover, there is sufficient data to support the role of incomplete hippocampal inversion in the incidence of seizure. But, some studies propose that temporal lobe epilepsy may be due to disturbance in hippocampal development, which may subsequently affect other parts of the brain leading to epilepsy.

Despite these conflicting results, data which suggest association between HIMAL and incidence of seizure are not negligible, and almost (11.3%) of temporal lobe epilepsy is due to HIMAL. Hence, it is suggested that incomplete inversion of hippocampus at least in some circumstances may be the most important cause of epilepsy. Hippocampal malrotation is also suggested to be associated with agenesis of the corpus callosum and complex prefrontal dysfunction leading to limbic system malformations (22) and attention and memory impairment and also unipolar depression (23, 24), respectively. As well, several studies have demonstrated the association between the changes in hippocampal shape and positioning and incidence of seizure (25).

On the other hand, the frequency of HIMAL in epileptic patients and non-epileptic population is also doubtful, and results do not firmly support any of the hypothesis. For example, the results of some studies show that IHI is a rare finding in non-epileptic population (12), while others show that it is a usual morphologic change in healthy people (13). In this systematic review, and based on extracted data, an association was found between incomplete inversion of hippocampus and incidence of seizure (11.3% compared to 6.9%). But, it should be noted that the number of patients and controls varied in different studies. Nonetheless, this association was significant in some results. Therefore, increasing sample size with
equal number of participants in case and control groups may help to clarify this association.

**Conclusion**

According to the results obtained in this study, incomplete hippocampal inversion can be considered as an important cause of seizure. And, many studies strongly support this association.

**References**


