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Original Research Article

# A Prospective Study on Clinical Features of Anomalies of Cortical Development and Incomplete Hippocampal Inversion

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**Abstract**

**Objective:** To research the prevalence and clinical traits of incomplete hippocampal inversion (IHI) and malformation of cortical development (MCD) in persons with uncontrollable seizures.

**Materials and Methods:** 416 of the 3220 epileptic patients in our prospective study, who attended our epilepsy clinic between 2012 and 2014, experienced uncontrollable seizures. To determine whether MCD and IHI were present in any patients, a thorough clinical history, neurological examination, electroencephalography (EEG), computed tomography (CT) scan, magnetic resonance imaging (MRI) brain, and neuropsychological assessment were all carried out.

**Results:** 85 patients out of 416 with uncontrollable seizures had MCD and IHI verified (48 males, 37 females). 39 patients (9.37%) and 46 (11.05%) patients, respectively, had IHI and MCD, respectively. No statistically significant differences were found between the MCD and IHI groups among patients in various age groups, genders, seizure types, duration and onset, seizure frequency, clustering, status epilepticus, EEG, febrile seizures, and family history, according to the results of the chi-square test. Statistically significant differences ($P < 0.05$) were observed between the MCD and IHI groups for change in seizure semiology and in intelligence quotient (IQ) and memory quotient (MQ) scores obtained using Wechsler's adult intelligence scale III and Wechsler's memory scale. The IHI group showed higher IQ and MQ scores when compared to the MCD group. Furthermore, IHI occurred along with MCD in 6.52% ($N = 3$) of the population.

**Conclusion:** Patients with MCD and IHI frequently experience uncontrollable complicated partial seizures. Hippocampal volumetric tests should be used to examine people with intractable epilepsy who have normal intellect and MRI results in order to determine whether they have IHI. Due to the clinical similarities between isolated IHI and MCDs, isolated IHI can be thought of as a type of MCD.

**Keywords:** Focal Cortical Dysplasia, Hippocampal Volumetric Study, Incomplete Hippocampal Inversion, Intractable Epilepsy, Malformation of Cortical Development.



## Introduction:

Malformations of cortical development (MCD) are microscopic and macroscopic abnormalities of cerebral cortex development that result from genetic or environmental factors interfering with cortical development during foetal life. [1] Malformations caused by abnormal neural growth, abnormal neuronal immigration,

and abnormal cortical structure are the three categories into which MCDs fall under the Barkovich categorization. [2] The Barkovich classical classification has been expanded to include a fourth group of MCD (not otherwise categorised) as a result of advancements in magnetic resonance imaging (MRI) technologies utilised by epilepsy patients. [3]

In India, a meta-analysis of published and unpublished studies revealed an epilepsy prevalence incidence of 5.35 per 1000 people. [4] Adults are reported to have a prevalence of intractable epilepsy ranging from 15 to 20%. [5-7] There are very few studies reporting the prevalence of MCD in intractable epilepsy in the literature. According to reports, MCD occurs frequently in children with intractable epilepsy (between 25% and 40%). [7,8] Recent developments in radiological imaging methods have considerably improved MCD detection rates.

Most studies conducted on a group of patients with MCD reveal the most common types of MCD to be focal cortical dysplasia, polymicrogyria, lissencephaly, nodular heterotopias, dysembryonic neuroepithelial tumor, and hemimegalencephaly.[9-11] The clinical features of MCD are often heterogeneous. MCDs are generally reported to present with complex partial seizures more than any other form of seizures.[9] Thus, family history,[9] drug resistance and intractability,[10] change in semiology,[12] association with febrile seizures,[9] delayed motor or mental milestones,[9,11] cognitive defects, and learning disability should be recorded.[11] Approximately one-third of patients with MCD have hippocampal abnormalities such as hypoplastic hippocampus, hippocampal sclerosis, malrotated hippocampus, and enlarged hippocampus.[11]

Incomplete hippocampal inversion (IHI) is a failure of hippocampal inversion that occurs during normal fetal development. It can be diagnosed with MRI and is often reported to be pathological in patients with seizures.[13] Recent studies among patients with temporal lobe epilepsy (TLE) and MCD have reported that IHI can be found in a similar proportion of patients with MCD and TLE.[14] An excellent study by Bajic *et al*., showed that IHI are observed in 30% of patients with epilepsy, mostly on the left side, followed by bilateral and right-sided IHI.[15] The presence of IHI has been reported to be a marker of a more extensive disorder of brain development.[14,15]

The evidence that IHI is a deformity of brain development could suggest that this aberration is what is causing the patient's persistent epilepsy. The clinical characteristics of the IHI population have not been studied. We conducted a prospective study to look at the prevalence and clinical traits of MCD and IHI in intractable epilepsy because they can both occur alone and in combination.

**Aims:**

(a) In adults with medically intractable seizures, it is important to assess the prevalence of MCD and IHI;

b) prospectively investigate the clinical traits of MCD and IHI in adults with intractable seizures.

## Methods

Between 2016 and 2021, 3200 epileptic patients who were enrolled in the epilepsy clinic at Patna Medical College and Hospital, Patna, were examined for intractable epilepsy. Out of 3200 patients, 416 (239 men and 177 women) experienced intractable seizures, making up 13% of the overall population. They ranged in age from 10 to 65. All of the patients with uncontrollable seizures underwent a thorough clinical history and neurological evaluation. We noted their demographic information, educational and employment background, seizure onset and duration, and seizure semiology. All patients with

uncontrollable epilepsy underwent an interictal electroencephalography (EEG).

On a 1.5-Tesla, 48-channel system (Seimens, Germany) with a head coil (40 element), gradient strength of 45 mT, and flow rate of 200 m/s, all patients had a standard magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI). Axial T1-weighted, axial T2-weighted, and volumetric T1-weighted MRI (3D-SPGR; three-dimensional spoiled gradient echo) sequences made up the MRI procedure. Additionally, volumetric studies of the hippocampus were performed. These images were analyzed by experienced neuroradiologists who detected MCDs and hippocampal malformations. The criteria for IHI (malrotation of hippocampus) included incomplete rotation, abnormal rounded appearance of the head of hippocampus, blurry internal structure, changes in shape and size, and vertical orientation of the collateral sulcus. Patients fulfilling three of the several criteria were identified as having IHI.

The intelligence quotient (IQ) and memory quotient (MQ) were assessed by clinical neuropsychologists in patients presenting with MCDs and IHI using Wechsler's adult performance intelligence scale III and Wechsler's memory scale respectively. The Bender Gestalt test was also administered to assess the visual motor functions and simple visual recall. The prevalence, clinical features, and associations between all patients with MCD and IHI were estimated using descriptive and statistical analysis of the data (MCD as well as IHI).

## Results

Out of 416 patients with intractable seizures, 85 (48 male, 37 female) patients had MCD and IHI verified, making up 20.43% of the total population. 39 patients (9.37%) and 46 (11.05%) patients, respectively, had IHI and MCD, respectively. Different MCDs were seen in 46 MCD individuals, according to the Barkovich categorization. [5] Table 1 shows the grouping of 46 MCD patients into group I, II, and III abnormalities.

**Table 1: Various malformations observed in 46 patients with MCDs**

| MCD groups | No. of patients |
|---|---|
| **Group I: Malformations secondary to abnormal neuronal and glial proliferation or apoptosis** | |
| Hemimegalencephaly | 2.17% (*n*=1) |
| Agenesis of corpus callosum | 2.17% (*n*=1) |
| Dysembryonic neuroepithelial tumor | 4.34% (*n*=2) |
| **Group II: Malformations due to abnormal neuronal migration** | |
| Heterotopia | 2.17% (*n*=1) |
| Nodular heterotopia | 13.04% (*n*=6) |
| Lissencephaly | 4.34% (*n*=2) |
| **Group III: Malformations secondary to abnormal postmigrational development** | |
| Polymicrogyria | 13.04% (*n*=6) |
| Schizencephaly | 6.52% (*n*=3) |
| Focal cortical dysplasia (FCD) | 52.17% (*n*=24) |

The frontal lobe (N = 9), temporal lobe (N = 9), occipital lobe (N = 1), insular lobe (N = 1), amygdala (N = 1), opercular region (N = 1), peritrigonal area (N = 1), and anterior claustrum (N = 1) were all shown to have focal cortical dysplasia. In 39 patients with IHI, we found that IHI most frequently occurred on the left side in 87.17% (N =

34), compared to the right side in 12.82% (N = 5) of patients.

A total of 28.26% (N = 13) patients in the MCD group and 46.15% (N = 18) patients in the IHI group did not show clustering of seizures. Seizures were reported to be observed in clusters of 1 in 10.9%, clusters of 2 in 39.1%, and clusters of 3 in 19.6% in the MCD group. In the IHI group, seizure clustering was observed in clusters of 2 in 30.8%, clusters of 3 in 15.4%, and clusters of 4 in 5.1% of the population. Status epilepticus was present in 8.7% (N = 4) in the MCD group and 7.7% (N = 3) in the IHI group. No significant differences were observed in clustering (P = 0.135) and status epilepticus (P = 1.00) between the MCD and IHI groups.

A family history of seizures was present in 7 individuals (15.2%) in the MCD group and 1 patient (2.6%) in the IHI group. febrile seizures occurred in 23.9% (N = 11) of the MCD group's patients and 15.4% (N = 6) of the IHI group's patients. Neurocutaneous indicators, such as adenoma sebacium, were seen in 2 patients with MCD, while a patient with hemimeganencephaly had hypomelanosis of the skin. Two people in the IHI group had sebacium adenomas. Between the IHI and MCD groups, there was no statistically significant difference (P > 0.05) in regards to these traits.

## Discussion

To determine the incidence of MCD and IHI and its clinical features, we prospectively examined 416 patients with intractable seizures in the current study. 46 (11.05%) individuals with intractable epilepsy had MCDs, which is a relatively low number in our cohort when compared to other research. [7,8] This might be as a result of the sample subjects for the current study being adults. Additionally, the magnetic strength of the MRI employed in this investigation would have made it harder to detect MCDs and IHI. [16,17] We also saw a number of MCDs that were described in the literature. [5,9,18-21]

At present, only a few clinical features are known from the literature associated with IHI. Our study results correlate with the clinical features of IHI reported so far in the literature. [24,25] IHI is often associated with partial epilepsy,[25] does not have direct memory repercussions,[24] and mostly exhibits left hippocampal changes.[15] Interestingly, in our study, we found that MCDs and IHI have similar clinical features except the age of seizure onset, the prevalence of cognition disorders , and the changes in seizure semiology, which can distinguish MCDs from IHI.

Along with structural abnormalities of the brain, one of the indicators of intractable epilepsy is the age at which seizures first appear. [26] For the MCD group, the age at which seizures first appeared was under 5 years. However, according to other research, it was between 5 and 20 years in the IHI group. [9,22,26-28] MCDs ranged from single to numerous structural brain abnormalities that caused mild to severe levels of cognitive impairment. [26,27] Cognitive functions were fairly preserved in patients with IHI, which could be due to the noninvolvement of other brain structures. We also found that IHI can occur in isolation or in combination with MCD, occurring as forms of malformations secondary to the abnormal post-migrational gyral development.

We conclude from the current study that hippocampal volumetric studies should be performed on patients with intractable epilepsy who have normal intellect and MRI results in order to diagnose IHI. We suggest that hippocampal malrotation, often known as IHI, be classified as a type of MCD under group III since it is a gyrational developmental disorder.

## Conclusion

To determine the prevalence and clinical characteristics of MCD and IHI in individuals with intractable epilepsy, the

current investigation was conducted. We discovered that patients with intractable epilepsy, who could be identified using conventional MRI and volumetric T1-weighted MRI (3D-SPGR) sequences, can have similar amounts of MCD and IHI. Except for the age of seizure beginning, cognition, and the shift in seizure semiology, the clinical characteristics of MCD and IHI were frequently comparable. We draw the conclusion that IHI may be one of the factors contributing to these individuals' intractability of seizures. We emphasize that patients with intractable seizures of the complex partial type with normal cognition, having no change in the seizure semiology, should be investigated for the presence of IHI. Further histopathological studies may be performed in these patients to confirm IHI as a form of post-migrational gyral developmental malformation.

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