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Malformations of cortical development (MCDs) and epilepsy: Experience from a tertiary care center in south India

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ABSTRACT

Introduction: Malformations of cortical development (MCDs) are increasingly recognized as important cause of epilepsy, especially refractory epilepsy. In developing countries like India, where the facilities for sophisticated imaging are not easily accessible to all, the prevalence and the types of cortical malformations are largely unknown. Hence this preliminary study has been undertaken to examine the relation between epilepsy and malformations of cortical development in a resource-limited setting.
Aims: To study various types of malformations of cortical development (MCDs) associated with epilepsy and to correlate with their clinical semiology.
Settings and design: The study was conducted in a tertiary care neurological center in south India. Cohort included all patients with epilepsy associated with cortical malformation on neuroimaging.
Methods and materials: Neuroimaging data of all patients with epilepsy were evaluated for a 5-year period from 1998 to 2003, for the presence of cortical malformations. The case records of those patients with cortical malformations were taken from the medical records department and the clinical and electrophysiological data were analyzed.
Results: We are reporting 34 cases of MCDs evaluated during the 5-year period. The mean age of the cohort was 15.1 (±12.2) years, with a range from 3 months to 45 years and 52.9% were males. Mean age at seizure onset was 7.2 years (±7.8), with a mean duration of seizure of 8.1 years (±7.7). Delayed motor and mental milestones were present in 15 patients (44.1%) and positive family history of seizure/epilepsy was seen in 9 patients (26.5%). Cortical malformations were most often associated with partial seizures (19/34, 55.9%). The most common type of seizure was complex partial seizure, seen in 12 patients (35.3%). Majority had very frequent, uncontrolled seizures with 16 (47.1%) patients having a seizure frequency of more than one per day. Heterotopias were seen in 14 patients (41.2%), in isolation in 5 (14.7%) patients and in combination with other malformations in 9 (26.5%) patients. Pachygyria was present as an isolated anomaly in five (14.7%) patients and combined with other abnormalities in eight (23.5%) patients. Cortical dysplasia was seen in 5 (14.7%) patients, hemimegalencephaly in two patients, polymicrogyria in two patients, lissencephaly and schizencephaly were seen in one patient each. EEG demonstrated focal epileptiform discharges in 59.1%, while generalized epileptiform discharges were seen in 22.7% of patients. Twenty-seven out of 34 (79.4%) patients had refractory/difficult to treat epilepsy.
Conclusions: Malformations of cortical development are a heterogenous group of disorders, associated with developmental delay and refractory seizures but seizures usually do not have pathognomonic semiologic features. Possibility of MCDs should be considered during the evaluation of refractory epilepsy cases.

1. Introduction

Malformations of cortical development (MCDs) are increasingly recognized as important cause of epilepsy, especially refractory epilepsy.[1] They were earlier identified only at postmortem examination of subjects with gross developmental disorders or with severe childhood epilepsy.[2] Now the scenario has changed due to the availability of newer and sophisticated imaging techniques such as computed tomography (CT) and high-resolution magnetic resonance imaging (MRI). Many of the cases initially considered as idiopathic or cryptogenic epilepsy are now found to be secondary to developmental malformations of the cortex.[3]

The true prevalence and incidence of cortical malformations associated with epilepsy is unknown, since MCDs causing easily treatable epilepsy may remain undiscovered unless all patients

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with epilepsy are subjected to neuroimaging (MRI) using appropriate techniques. In countries with limited resource settings like India, where the facilities for sophisticated imaging are not easily accessible to all, the prevalence and the types of cortical malformations are largely unknown. Hence this preliminary study has been undertaken to examine the relation between epilepsy and malformations of cortical development.

2. Subjects and methods

This study was conducted in a tertiary care neurological center (National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore), which caters to epilepsy patients, especially those from southern parts of India. Neuroimaging data of all epilepsy cases were analyzed over a 5-year period for the presence of MCDs. The case records of patients found to have cortical malformations on neuroimaging were taken for further analysis. Those with cortical malformations on imaging without any seizures, dysembryoplastic neuroectodermal tumors and patients with tuberous sclerosis were excluded from the study. Detailed clinical and electrophysiological data were prospectively collected from the patient/care giver with special reference to

1. The antenatal, perinatal and postnatal events.
2. Developmental milestones.
3. Family history of seizures.
4. Type and frequency of seizures.
5. The number of medications used (as a measure of refractoriness).

These data were entered on to a pre-designed clinical proforma.

2.1. MRI protocol

MR imaging was done using a 1.5 T, GE scanner. Protocol included SE (Spin Echo) T1W image, TSE (Turbo Spin Echo) T2W image and SPGR (Spoiled Gradient Recalled) sequence of brain in orthogonal planes. All scans were evaluated by an experienced neuroradiologist (SSG). Patient's clinical characteristics were correlated with neuroimaging findings.

2.2. Statistical analysis

Both clinical and neuroradiological data were entered into the SPSS 10, software package for descriptive statistics. Results of the study are expressed as mean with standard deviation and range, for continuous variables and as percentages for discrete variables.

3. Results

During the study period from 1998 to 2003, we encountered 34 cases of cortical malformations with epilepsy. In the year 2003, 220 MRI scans were done for patients with diagnosis of epilepsy/seizures, at NIMHANS and of this, 10 cases (4.5%) of cortical malformation and epilepsy were identified. Diagnosis of cortical malformation was made by either CT or MR imaging, in 30 out of 34 patients. Majority of the patients were diagnosed on the basis of MR imaging (79.4%). In two patients diagnosis was established postoperatively and in the other two at postmortem, by pathological examination.

3.1. Age and sex distribution

The mean age of the study group was 15.1 ± 12.2 years. The youngest of the cohort aged 3 months while the oldest was 45 years. Majority of the patients belonged to the second or third decade. Of the cohort, 18 (52.9%) were males and 16 (47.1%) were females.

3.2. Antenetal, perinatal events and milestones

There was no history of any antenatal maternal infection or drug exposure. Twenty-seven (79.4%) patients had normal vaginal delivery while remaining seven had lower segment caesarean section. Only three patients had history of delayed first cry. Delayed motor and mental milestones were noted in 15 patients (44.1%).

3.3. Family history

Family history of consanguinity was present in four patients and history of seizure/epilepsy was present in nine patients (26.5%). Among this cohort there was one pair of heterozygous twins with cortical malformation affecting both the twins.

3.4. Examination

General physical examination and neurological examination were normal in 22 out of 34 (64.7%) patients. Concomitant squint was noted in three patients, right hemiparesis in 2, microcephaly in 2, generalized hypertonia in 2, dysmorphic facies in 2 and paraparesis in 1.

3.5. Seizure type

Cortical malformations were most often associated with partial seizures (19/34, 55.9%). The most common type of seizure was complex partial seizure, which was seen in 12 patients (35.3%). In 10 patients with complex partial seizures there was history of secondary generalization. Seven (20.6%) patients had simple partial seizures. Of the seven patients who had generalized seizures, four were generalized tonic–clonic seizures, two were generalized tonic seizures and one had myoclonic seizure. Eight (23.5%) patients had multiple types of seizures. Median age of seizure onset was 5 years, with a range from 1 month to 27 years. Duration of seizures ranged from a minimum of 1 month to a maximum of 38 years. The mean duration of seizure was 8.1 years ($\pm$7.7 years).

3.6. Seizure frequency

Majority had very frequent, uncontrolled seizures with 16 (47.1%) patients having a seizure frequency of more than one per day. Two patients had seizure frequency of more than one per week, while eight patients had seizure frequency of one or more per month. Of the remaining eight patients, five had occasional seizures and data regarding seizure frequency were unavailable in three patients. Majority of them had refractory complex partial seizures.

3.7. Status epilepticus

Three (8.8%) patients had status epilepticus and all three expired. Partial autopsy was done in two patients. One patient had polymicrogyria in the occipital region and another one had heterotopia in the left parietooccipital region. Third patient had left frontal cortical dysplasia on neuroimaging.

4. Neuroimaging

4.1. Magnetic resonance imaging

MR imaging was available in 29 (85.3%) patients. Diagnosis of cortical malformation was established by brain MRI in 27 out of 29 subjects in whom it was done (93.1%). In other two patients though