

Spectrum of Malformation of Cortical Development with Clinico-radiological Correlation

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Abstract

Introduction: Malformations of cortical development (MCD) are one of the recognized causes of childhood epilepsy presenting as epilepsy, development delay, and other neurological manifestations.

Purpose: Purpose of the study was for emphasis on the clinical and radiological spectrum of MCD.

Materials and Methods: We evaluated 14 patients of MCD who were diagnosed on structural neuroimaging. Retrospective and prospective reviewing of magnetic resonance imaging (MRI) and computed tomography (CT) of the brain were done in our department of radiology from January 2013 to July 2015, including outside scan films. Assessment of clinical details was done in coordination with the department of pediatrics and medicine.

Result: Out of 14 patients 8 were male and 6 were female with age ranging from 2.5 months to 22 years with mean age of 7.3 years. Epilepsy and developmental delay were main clinical presentation in most of the cases. On structural neuroimaging, multiple abnormalities were noted in 50% cases. Heterotopias and lissencephaly-pachygyria complex were most common among MCDs, seen overall in 42.8% and 21.4% cases respectively (including cases with multiple abnormalities).

Conclusion: MRI of the brain has a definitive role in the diagnosis of most cases of MCD aided by CT for initial evolution. Most cases of MCD present with a different spectrum of epilepsy or developmental delay.

Key words: Computed tomography, Epilepsy, Malformations of cortical development, Magnetic resonance imaging

INTRODUCTION

Malformation of cortical development (MCD) is structural abnormality of the cortex of brain parenchyma caused by derangement of the normal developmental process due to various underlying factors. It can be genetic mutations, environmental insults¹ seen during antenatal, perinatal, or postnatal period, during corticogenesis or after corticogenesis.²

MCD is classified based on earliest disruption of development,^{2,3} which includes neural stem cell

proliferation, migration, and finally neuronal differentiation. Malformation resulting from abnormalities of cell proliferation is microcephaly, megalencephaly, and cortical dysplasia. Disorders of neuronal migration may cause heterotopia and classical lissencephaly. Disorders of neuronal arrest can result in cobblestone lissencephaly. An abnormal cortical organization may result in schizencephaly and polymicrogyria. Although cortical development has been separated into these stages, there is significant overlap between the stages and many abnormalities may cause dysfunction at more than one level.³ Malformations of the proliferative stage seen from ventricles to the piamater while those resulting from abnormal cellular migration are located in the white matter and/or the cortex, and those caused by abnormal organization are limited to the cortex.⁴⁻⁶

MCD clinically presents as one of the important cause of epilepsy, refractory to treatment and many of previously considered idiopathic or cryptogenic epilepsy has

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developmental malformations of the cortex on imaging.⁷ Structural imaging findings of brain, especially magnetic resonance imaging (MRI) findings are most important noninvasive technique for its diagnosis, which has greatly improved with the progress in contemporary imaging techniques.⁸

Many studies have found underlying MCD in 23-26% cases of refractory epilepsies in children and young adults.^{9,10} So, MCD should be ruled out in every case of epilepsy or developmental delay by neuroimaging.

The objective of this study was an analysis of clinical details along with an emphasis on neuroimaging findings critical for its diagnosis.

Microcephaly is small brain with head circumference below two standard deviations of population mean with correction for age and sex.³

Hemimegalencephaly is characterized by overgrowth of part or all of the cerebral hemisphere. It may be isolated anomaly or seen in association with other syndromes such as epidermal nevus syndrome, Proteus syndrome, unilateral hypomelanosis of Ito, neurofibromatosis Type I, Klippel-Trenaunay syndrome, and tuberous sclerosis. MRI shows variable blurring of gray-white matter differentiation with variable abnormal prolongation of T1 and T2 of the white matter due to underlying heterotopia and astrocytosis. MRI shows associated enlargement and elongation of ipsilateral lateral ventricle with a characteristic shape of the frontal horns that appears straight and pointed anteriorly and superiorly.¹¹⁻¹⁵

Focal cortical dysplasia (FCD) is characterized by the abnormal focal presence of neurons and glial cells within the cerebral cortex. MRI typically shows blurring of gray-white matter differentiation with localized area of cortical thickening and abnormal signal such as subtle T2 hyperintensity within adjacent white matter.¹⁵⁻¹⁷

Heterotopia is the presence of normal neurons in abnormal location. On MRI, they appear isointense to the normal gray matter on all sequences with no enhancement on the post-contrast study. Periventricular heterotopia (PVH) or subependymal heterotopia is gray matter nodules seen along the ventricular wall of the lateral ventricles.^{4,5,18-20}

Subcortical band heterotopia is seen as band of gray matter neurons and is located between the ventricles and the cerebral cortex with contiguity to either cortex or ventricular region.¹⁸⁻²⁰

Classic or Type I lissencephaly patients have either completely smooth brain surface (seen in complete

form) with complete loss of the normal gyri and sulci, or smooth surface with few small gyral formation in the region of inferior frontal and temporal lobes (incomplete form). These are caused by arrest of the migration process.^{21,22}

Type II lissencephaly also known as cobblestone lissencephaly is characterized by nodular surface of the cerebral cortex, ocular anomalies, and congenital muscular disorders caused by over migration of the neuronal cells beyond the external glial limitations into the subarachnoid space.²¹⁻²³

Polymicrogyria refers to an excessive number of small fine gyri separated by shallow sulci not detectable on imaging. On imaging, overall cortical thickness may be normal

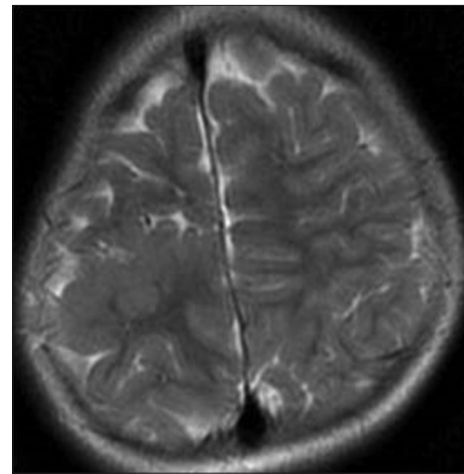


Figure 1: Axial T2-weighted magnetic resonance image of 17-year-old male patient showing localized cortical thickening in right superior frontoparietal region suggesting focal cortical dysplasia

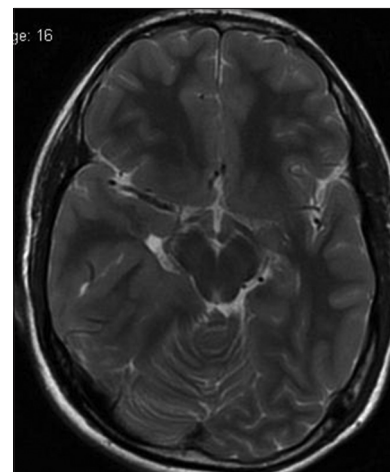


Figure 2: Axial T2-weighted magnetic resonance image of 12-year-old female patient shows subtle cortical thickening in right temporal lobe region with relative enlargement of left cerebral hemisphere suggesting focal cortical dysplasia with hemimegalencephaly

or increased seen in age <12 months and >18 months, respectively. Imaging mostly shows lumpy appearance with thickened cortex (5-7 mm) with an abnormal T2 prolongation of the underlying white matter noted in approximately 25% of cases.^{5,24}

Schizencephaly refers to cerebrospinal fluid (CSF) filled cleft lined by gray matter seen extending from subarachnoid CSF space to the ventricular system. Schizencephaly results from injury involving the entire thickness of the developing hemisphere during cortical organization. Schizencephaly is divided into Type I

(Closed-lip schizencephaly) and Type II (Open-lip schizencephaly) based on visualization of CSF cleft with closed lip schizencephaly showing approximation of gray matter-lined lips.^{25,26}

MATERIALS AND METHODS

Case series was done in those 14 patients who presented to an outer institution with variable neurological abnormalities and were diagnosed to have MCD on structural neuroimaging. Retrospective and prospective analysis of MRI and CT of brain findings were done in our department of radiology from Jan 2013 to July 2015 with the categorization of anomalies. Detailed correlation with clinical history and physical examination (mainly neurological) was done in coordination with the department of pediatrics and medicine.

RESULTS

During the retrospective and prospective study, we came across about 14 cases of MCD.

The mean age of study was 7.3 years with the youngest age of study being 2.5 months and oldest age 22 years (Table 1). There was no significant statistical difference between males and females with 8 (57%) being males and 6 (43%) being female. There was no history of drug intake (other than iron or folic acid) or maternal infection or radiation exposure during the antenatal period. In all cases, delivery was uneventful with delayed cry in one of the case. History of consanguineous marriage was noted in four cases.

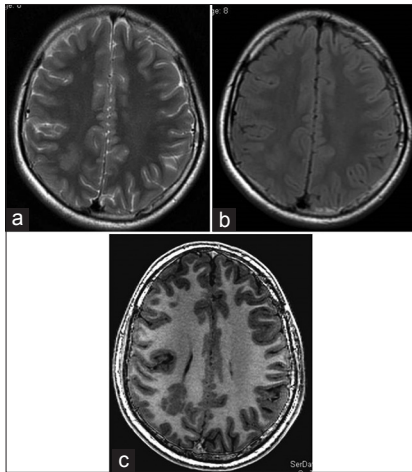


Figure 3: Axial T2 (a), Axial T1 (b) and Axial fluid attenuated inversion recovery (3c) weighted magnetic resonance image of brain of 11-year-old male child shows small nodular lesion in right parietal white matter region with isointense appearance on all sequences suggesting subcortical nodular heterotopia

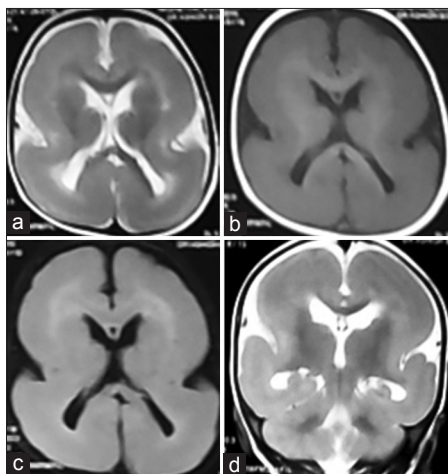


Figure 4: Axial T2 (a), Axial T1 (b) and Axial fluid attenuated inversion recovery (c) and coronal T2 (d) weighted magnetic resonance (MR) images of brain of 7-month-old female infant shows near complete absence of sulcal and gyral pattern with smooth outline with figure of '8' appearance with associated diffuse subcortical heterotopia with isointense appearance on all MR sequences s/o Type I lissencephaly

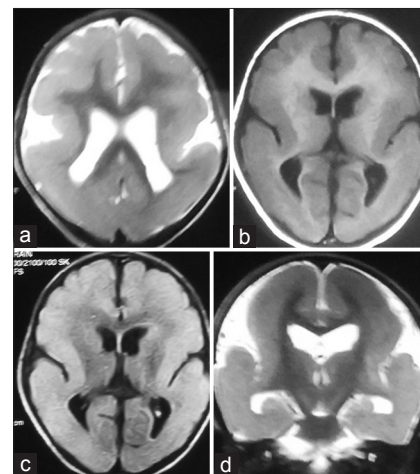


Figure 5: Axial T2 (a), Axial T1 (b) and Axial fluid attenuated inversion recovery (c) and coronal T2 (d) weighted magnetic resonance images of brain of 11-month old male infant shows significant paucity of sulcal spaces and gyral pattern with relatively smooth cortical with figure of '8' appearance with associated diffuse subcortical heterotopias s/o Type I lissencephaly-pachygyria complex (incomplete form)

Epilepsy was chief complaint in 42.8% of cases (Table 2). Overall seizure was noted in 71% of cases. On electroencephalogram, partial seizure (8/14, 57%) was most common seizure followed by generalized seizure (4/14, 28.5%). The complex partial seizure was a most common subtype. Mixed type of seizure was noted in 2 patients. Most patients had refractory type of epilepsy with frequent seizures noted even on medication. Variable delayed milestones were noted in 64% of cases.

Neurological examination was done in all cases. It was normal in four cases, variable motor disturbances in seven cases, microcephaly in two cases, left hemiparesis in one case, and hypotonia in three cases.

Only CT was available in two cases, only MRI scan was available in 5 cases, and both CT and MRI were available in rest of cases and with the establishment of diagnosis in all cases. In one case with only CT, polymicrogyria was suspected with underlying localized cortical thickening. Multiple abnormalities were noted in 7(50%) cases (Table 4) with polymicrogyria or heterotopia being a most common associated anomaly.

4 out of 14 patients (28.5%) had a bilateral or diffuse abnormality of the cortex. MCDs were localized to the right side in 6 patients (42.8%) and rest being localized to left cerebral hemisphere with multiple lobes of the same side was involved in 35.4% of total cases.

Heterotopias and lissencephaly-pachygyria complex were most common among MCDs, seen overall in 42.8% (isolated heterotopias in 28.5% cases) and 21.4% cases (Tables 3 and 4) respectively (including cases with multiple abnormalities).

Table 1: Mean age of presentation in study

Type of MCD	Mean age of presentation
Isolated microcephaly	2.5 month
focal cortical dysplasia	17 year
hemimegalencephaly	2.7 year
heterotopias	10.2 year
Lissencephaly-pachygyria complex	7.5 month
Isolated polymicrogyria	9 year
Schizencephaly	11.5 year

MCD: Malformation of cortical development

Table 2: Chief clinical complaint in studied patients

Chief clinical complaint	Number (%)
Seizure	6 (42.8)
Microcephaly	1 (7.15)
Global developmental delay	4 (28.5)
Hemiparesis	1 (7.15)
Delayed motor development	2 (14.4)

Out of 14 cases two patients (isolated microcephaly in one case) had microcephaly with <3 standard deviation below normal for that age, presented after birth with poor feeding. MRI in one patient showed normal cortical thickness with a minimal paucity of sulcal spaces with normal ventricular size. Other patient had associated agyria suggestive of lissencephaly.

One patient had FCD presented at 17 years of age with recurrent refractory seizures with normal milestones. MRI showed localized thickening of cortex in the right superior fronto parietal region with subtle underlying white matter fluid attenuated inversion recovery hyperintensity suggestive of underlying subtle gliosis (Figure 1).

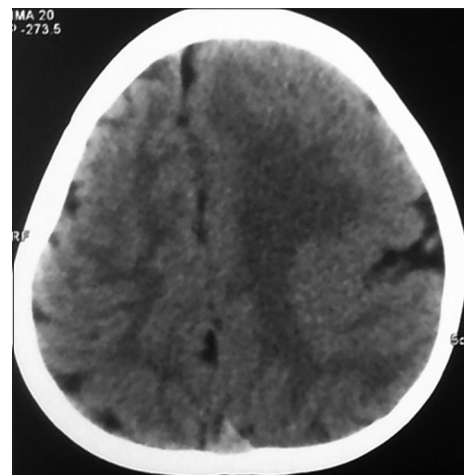


Figure 6: Axial non-contrast computed tomography of brain of 9-year-old child shows thickened cortex in left frontoparietal region with lumpy appearance s/o most likely polymicrogyria complex

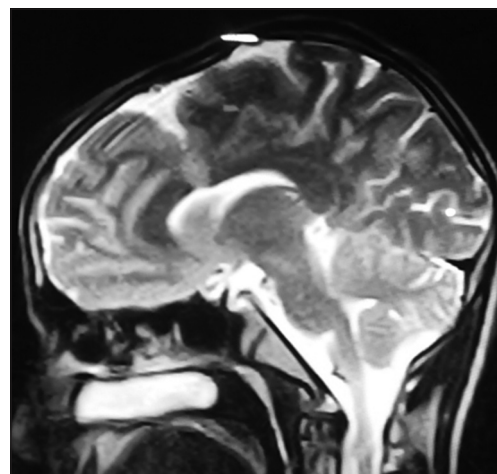


Figure 7: 16-year old male patient on sag T2-weighted magnetic resonance image showing cerebrospinal fluid (CSF) filled cleft in right parasagittal frontal region lined by gray matter seen extending from subarachnoid CSF space to the ventricular system with approximation of gray matter-lined lips towards ventricular end

Table 3: Incidence of various types of MCD with main clinical presentation

Type of MCD	Number (%)	Main clinical presentation
Isolated microcephaly	1 (7.15)	Small head with global developmental delay
Isolated focal cortical dysplasia	1 (7.15)	Convulsion
Hemimegalencephaly	2 (14.4)	Infantile spasm with delayed motor development with hemiparesis
Heterotopias	4 (28.5)	Convulsion
Lissencephaly-pachygyria complex	3 (21.4)	Global developmental delay
Isolated polymicrogyria	1 (7.15)	Convulsion
Closed lip schizencephaly	1 (7.15)	Convulsion
Open lip schizencephaly	1 (7.15)	Delayed milestones with recurrent seizures

MCD: Malformation of cortical development

Table 4: Number of patients with multiple abnormalities

Primary MCD	Associated MCD	Number
Hemimegalencephaly	Polymicrogyria	1
Hemimegalencephaly	Focal cortical dysplasia	1
Schizencephaly	Polymicrogyria	2
Lissencephaly-pachygyria complex	Diffuse band heterotopia	2
Lissencephaly-pachygyria complex	Microcephaly	1

MCD: Malformation of cortical development

Two patients had hemimegalencephaly. Both patients presented with recurrent infantile spasm and delayed milestones with first patient having partial hemiparesis toward the right side. Neck holding was also absent in the second patient.

MRI in one patient with isolated hemimegalencephaly showed mild to moderate enlargement of the left cerebral hemisphere with elongated enlarged left lateral ventricle with relatively thickened cortex with evidence of polymicrogyria complex. Other patient showed moderate enlargement of the left cerebral hemisphere with FCD (Figure 2).

Four patients had isolated gray matter heterotopias. One patient had subependymal nodular heterotopia. Two patients had nodular subcortical heterotopias (Figure 3). One had mixed nodular and band type heterotopias.

All patients with heterotopias had history of recurrent partial seizure refractory to treatment. Associated delayed milestones were noted in two patients with mental retardation seen in one patient.

In the case of subependymal nodular heterotopia, MRI showed oval nodules in the subependymal region of lateral

part of both lateral ventricles with isointense appearance on all MR sequences.

Three patients had lissencephaly with all of them of classical type (Type I). In all patients with Type I, lissencephaly patients had significant hypotonia with poor feeding with significant motor developmental delay. MRI showed complete agyric pattern in one of the patients with rest of the patients showing poor formation sulcal spaces with band heterotopia noted in two patients (Figures 4 and 5).

One patient had an open lip and one had closed lip schizencephaly (Figure 7). Patient with open lip schizencephaly had significantly delayed motor milestones with closed lip type presenting with recurrent seizures. MRI showed gray matter lined cleft in both patients with isointense appearance on all MR sequences.

One patient had isolated polymicrogyria (Figure 6), presenting with recurrent partial seizures.

Six patients (42.8%) patients had multiple abnormalities of which polymicrogyria was most common associated abnormalities seen in two patients of schizencephaly and one patient of hemimegalencephaly. Diffuse band heterotopia was noted in two patients in association with lissencephaly-pachygyria complex.

DISCUSSION

MCD are important causes of developmental delay and epilepsy with variable neurological deficits. Progress in imaging techniques has made the possible initial establishment of diagnosis in most cases of MCD which is very helpful in increasing knowledge about the development of the cerebral cortex and the number and types of malformations reported.

Only CT was available in 2 cases, only MRI scan was available in 5 cases, and both CT and MRI were available in rest of cases and with the establishment of the diagnosis of MCD in all cases.

In present study, isolated heterotopias (28.5%) were most common followed by lissencephaly-pachygyria complex (21.4%) and polymicrogyria (21.4%). Multiple abnormalities were noted in 50 % of the cases. MRI had most important and definitive role in the diagnosis of MCDs.

In Sadek *et al.* study, a maximum number of the patients (42%) had lissencephaly followed by schizencephaly (28%), polymicrogyria (12%), FCDs (10%), and PVH (6%).²⁷ In

Güngör study, polymicrogyria were most common (53.5%) followed by lissencephaly (22.8%), schizencephaly (11.9%), and heterotopia (11.9%).²⁸ In Mathew *et al.* study, multiple abnormality was most common (31%), the most common being a combination of pachygyria and heterotopia.²⁹ In the study by Janszky *et al.*,³⁰ FCD was the most common MCD among cause of intractable focal epilepsy, followed by heterotopia and pachygyria. In the series of Brodtkorb *et al.*,³¹ schizencephaly were the most common abnormality. However, significant differences between different case series are probably due to selection bias rather than true frequencies.

In the present study, recurrent convulsions (42.8%) were the chief complaint followed by global development delay (28.5%) and motor disturbances. The overall seizure was noted in 71% of cases. Multiple symptoms were noted in most of the cases. It was comparable with other studies showing seizure as main clinical complaint. In Sadek *et al.* study, refractory seizures (42%) and global developmental delay were main chief complaint. In this study, overall seizures were noted in 82% of cases. Leventer *et al.*³² found seizures in 75% of patients with MCDs, and Güngör *et al.* found seizures in 71.3%.²⁷

CONCLUSION

MCD are a heterogeneous group of disorders during variable developmental stages of the brain. Recurrent refractory seizures with variable global developmental delay are main complaint with imaging having an important and definitive role (mainly MRI) in its diagnosis. So, it should be mandatory to do initial imaging in all cases of refractory epilepsy and global developmental delay whenever it is feasible. Imaging has also got a role in surgical cases where surgical planning has been done.

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