Malformations of cortical development: clinical spectrum in a series of 101 patients and review of the literature (Part I)

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Patients with malformations of cortical development (MCD) present with a wide spectrum of clinical manifestations ranging from asymptomatic cases to those with epilepsy and neurodevelopmental problems. Thorough clinical delineation of patients with MCD may provide clues for future phenotype-genotype correlation studies. We studied clinical features of patients with MCD, including developmental risk factors and family history. We evaluated 101 patients with MCD at Hacettepe University Children's Hospital, Department of Pediatric Neurology. All patients underwent neurological evaluation with detailed medical and family history, and neuropsychological evaluation. Routine EEG and MRI were obtained. The patients were between 1 month and 19 years of age (mean: 6.1 ± 4.4 years). Fifty-four patients were diagnosed with polymicrogyria (PMG), 23 patients with lissencephaly, 12 patients with schizencephaly, and 12 patients with heterotopia. Parents were relatives in 31.7% of the cases; consanguinity was most common in patients with lissencephaly and other MCDs with diffuse/bilateral involvement. Initial clinical presentation was seizures in 61.4% of the cases, developmental delays in 12.9%, and microcephaly in 9.9%. Neurological evaluation revealed most severe abnormalities in patients with lissencephaly, and relatively better outcome in patients with heterotopias. Cognitive functions were better in patients with heterotopias compared to other groups. Overall, 71.3% of patients had epilepsy. In conclusion, initial presentation and clinical course of patients with MCD are variable and seem to be correlated with the extent of cortical involvement. Epilepsy and mental retardation are the most common problems. The most severe clinical outcome was seen in patients with lissencephaly.

Key words: malformations of cortical development, lissencephaly, heterotopia, polymicrogyria, schizencephaly, clinical course, epilepsy.

Malformations of the cerebral cortex in childhood mainly cause growth retardation, epilepsy and motor retardation. Clinical and electrophysiological findings are frequently not specific and depend on the function of the affected region. While severe malformations can manifest with prominent developmental retardation and early-onset repetitious seizures, mild malformations are usually identified at any age, mostly during evaluation following a seizure[1-3].

With the help of high resolution neuro-radiological imaging techniques, there has been an increase in the number of cortical developmental lesions that were previously classified as cryptogenic, identified as the cause of

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epilepsy. However, despite all neuroradiological and molecular advances, classification of cortical developmental disorders remains an obstacle for clinicians[1,3-5]. Alterations during neuronal proliferation, migration and organization stages of the developing brain constitute the basis of these malformations[1,4,6-9,11,12]. These developmental stages are intertwined, and cannot be differentiated with clear-cut terms. It is generally accepted that the proliferation stage starts at 5-6 and ends at 16-20 weeks of gestation; migration runs from 6-7 weeks through 20-24 weeks; and the organization stage covers 16 to 24 weeks of gestation[13]. During the developmental stages, intervening genetic and prenatal environmental factors may contribute to the development of malformations. Nevertheless, in the majority of cases, the cause is unknown.

The aim of this study was to determine a phenotypic definition in the light of clinical findings, developmental risk factors and familial factors in malformations of cortical development (MCD).

Material and Methods

The study was carried out between 2002 and 2004 at the Pediatric Neurology Unit of İhsan Doğramacı Children's Hospital, Hacettepe University Faculty of Medicine, on 101 cases (51 males and 50 females) with MCD confirmed by cranial magnetic resonance imaging (MRI). Our unit is a tertiary referral center and the largest children's hospital in Turkey.

Neuroimaging: Neuroradiological examinations carried out elsewhere were re-assessed by two pediatric neurologists and two neuroradiologists. T1- and T2-weighted MR images at two planes were considered sufficient for radiological evaluation. MR images were obtained by a 0.5T Philips Intera, 1.5T Siemens Symphony or 3T Siemens Allegra scanner available at our center. Image data set included thin coronal images obtained using T2-weighted and inversion recovery (IR) sequences, as well as T1-weighted volumetric images. MR images were classified according to the severity, site, and extent of the malformation. Based on the findings, cases were grouped into agyria-pachygyria complex, polymicrogyria (PMG), schizencephaly and heterotopia.

History: Presenting complaints and history including prenatal, natal and postnatal periods were obtained from the parents. Gestational risk factors, such as vaginal bleeding, trauma, medications, infection, radiological examinations, and low blood pressure, were addressed. Regarding birth and postnatal period, the following were questioned: birth weight and head circumference at birth, dysmorphic facies/features, convulsion, metabolic disorders, consanguinity between parents, mental retardation, congenital anomalies, and epilepsy.

Physical and Neurological Examination: Neurological and other physical examinations were carried out by at least two consultant pediatricians, one of whom was a pediatric neurologist. Cases were defined as microcephaly if head circumference was 3SD below the mean[14].

Neuropsychological Evaluation: Bayley's test (for subjects aged between 16 days and 30 months) and Wechsler Intelligence Scale for Children (WISC-R), or the Stanford-Binet intelligence test were used as a measure of mental and motor development. Intelligence quotients (IQ) of over 80, between 50-79, between 40-50, and less than 40 were considered as normal, mild, moderate and severe mental retardation, respectively[15].

Statistical Analyses: Kruskal-Wallis test, Mann-Whitney U test with Bonferroni correction, one-way analysis of variance (ANOVA), Tukey HSD and chi-square tests were utilized for statistical analyses.

Results

Neuroimaging studies revealed that of 101 cases, 54 had PMG, 23 had agyria-pachygyria (lissencephaly), 12 had heterotopia and 12 had schizencephaly.

1. Demographic Features: Fifty-one of the cases were males and 50 females. The ratio of females was higher in schizencephaly cases, though the difference between males and females was not statistically significant ($P>0.05$) (Table I).

Ages of our cases ranged between 1 month and 19 years, with a mean of 6.1 ± 4.4 years at the time of evaluation (Table I). ANOVA revealed significant age differences among groups ($F=5.305$, $P=0.002$) and pair wise comparisons showed a significant difference between lissencephaly and heterotopia groups ($P<0.001$).

Table I. Demographic Features of Patients

Group	n	%	Sex M/F	Age (year)	Age of the diagnosis (year)
PMG	54	53.5	28/26	6.3±4.2 1 month-17 years	4.8±3.9 10 months-14 years
Lissencephaly	23	22.8	12/11	3.6±3.5 2 months-12 years	2.0±2.5 2 months-10 years
Heterotopia	12	11.9	7/5	9.4±5.2 1.1-19 years	6.9±5.0 1.1-19 years
Schizencephaly	12	11.9	4/8	6.9±3.8 1.3-14 years	2.8±2.8 1 month-9 years
Total	101	100	51/50	6.1±4.4 1 month-19 years	4.3±4.0 1 month-19 years

PMG: Polymicrogyria. M: Male. F: Female.

Mean age of all cases at diagnosis was 4.3±4.0 years (Table I). There were significant differences between PMG and lissencephaly ($P<0.01$) and between heterotopia and lissencephaly groups ($P<0.005$). Age at diagnosis was lowest in lissencephaly and highest in the heterotopia groups. Generally, 34.2% of cortical dysplasia, 31% of PMG, and 25% of schizencephaly cases received a diagnosis at around 1 year of age, while 62.5% of lissencephaly and only 10% of heterotopia cases were diagnosed within the first year of life.

2. Neurological problems/impairment: The most common complaints among our cases were seizure (62/101, 61.4%), motor-mental retardation (13/101, 12.9%), microcephaly (10/101, 9.9%), hemiparesis (8/101, 7.9%), and speech disorder (6/101, 5.9%). One case was diagnosed with heterotopia coincidentally during neuroimaging after head trauma. Clinical seizure at first presentation was identified in 64.9% (35/54), 47.8% (11/23), 66.7% (8/12) and 66.7% (8/12) of PMG, lissencephaly, heterotopia and schizencephaly cases, respectively. Lissencephaly comprised 88.9% (8/10) of cases who presented with microcephaly. Febrile convulsion was the chief complaint in 6.9% (7/101) of the cases.

3. Prenatal/Perinatal problems and neurological development: Review of medical history of the mothers revealed prenatal issues such as analgesic, antibiotic, L-thyroxine use (36/101, 35.6%), use of Ritodrine HCl for preterm labor (16/101, 15.8%), vaginal bleeding in the first trimester (12/101, 11.9%), frequent upper respiratory and urinary tract infections (9/101, 8.9%), low blood pressure (4/101), and exposure to X-ray (3/101). These problems were more common among lissencephaly and schizencephaly cases, though the differences between frequencies among groups were not significant ($P>0.05$). There were prenatal problems in 29.6% (16/54) of PMG, 47.8% (11/23) of lissencephaly, 25% (3/12) of heterotopia, and 50% (6/12) of schizencephaly cases. Prenatal problems were present in 40% (25/61) of bilateral and 27% (11/40) of unilateral malformations ($P>0.05$).

– **Natal history:** Thirty cases (29.7%) were delivered by caesarian section and 71 (70.3%) by normal vaginal delivery. There were no significant differences among groups with respect to the method of delivery ($P>0.05$). The most common indications for caesarian section were repeat caesarian section (8/101), failure to progress (6/101), macrocephaly and cephalopelvic disproportion (6/101).

– **Gestational age:** Ten percent of our cases had a history of premature birth. Prematurity was most common among schizencephaly cases (3/12, 25%); there was no history of premature birth among lissencephaly cases despite the presence of diffuse brain abnormalities.

– **Birth weight:** In 23.7% of our cases, history of low birth weight was noted, with 28.6% of lissencephaly, 27.5% of PMG, 10.0% of heterotopia and 9.1% of schizencephaly cases being affected. The frequency of low birth weight was highest in lissencephaly cases (28.6%) despite the lack of history of a premature birth. There was no significant difference between unilateral and bilateral cases with regard to birth weight ($P>0.05$).

– Microcephaly at birth: Microcephaly at birth was present in 21.8% (22/101) of cortical dysplasia and 17% (9/54) of PMG cases, and most commonly in lissencephaly cases (10/23, 43.5%) (P<0.01). Furthermore, it was more frequent in bilateral (18/61, 29.5%) compared to unilateral (4/40, 10%) (P<0.05) malformations.

– Development: There was global delay in all skills during the first year of life in 59.4% of our cases (60/101). Developmental delay was most common among lissencephaly cases (17/23, 73.9%), followed by schizencephaly (7/12, 58.3%), PMG (30/54, 55.5%), and heterotopia (6/12, 50%).

4. Family history: Family history in 40.6% (40/101) of cases revealed one or more problems: mental retardation (18.7%), epilepsy (17.8%), miscarriage (8.9%), similar anomalies (6%), and speech disorder (2%). Positive family history was relatively rare in the schizencephaly group (3/12, 25%), followed by PMG (40.7%), lissencephaly (43.5%), and heterotopia (50%). Among PMG cases, family histories of epilepsy (13/54, 24.1%) and mental retardation (11/101, 20.3%) were most common, whereas epilepsy alone was the most common among lissencephaly cases (5/23, 21.7%).

There was consanguinity between parents in 31.7% (32/101) of the cases. Consanguinity was most common among lissencephaly cases (11/23, 47.8%), in 33.3% of PMG, in 16.7% of heterotopia, and in 8.3% of schizencephaly cases (P<0.05). Cases with bilateral malformation (37.7%) did not differ significantly from those with unilateral malformation (22.5%) with respect to parental consanguinity (P>0.05).

5. Physical and neurological examination: Abnormal findings such as microcephaly (40/101, 39.6%), dysmorphic facial features (6/101, 6%), growth retardation, hypo-hyperpigmented skin lesions, macrocephaly and ptosis were observed during general physical examination in 49.5% (50/101) of the cases. Microcephaly was the most common finding in all groups, especially in patients with lissencephaly (13/23, 56.5%) and PMG (22/54, 40.8%) who had bilateral and diffuse involvement compared to the patients with heterotopia (25%) and schizencephaly (16.7%).

Neurological examination demonstrated abnormal findings in 73.3% (74/101) of our cases. Mental retardation, speech delay, motor retardation, hemiparesis, and tetraparesis were predominant findings; pyramidal, extrapyramidal and cerebellar abnormalities were also detected (Table II). Hemiparesis was more common in patients with schizencephaly and PMG, while speech delay was more common in patients with lissencephaly and PMG. Even though mental retardation was the most common in all four groups, it was relatively more frequent in patients with lissencephaly and PMG. Motor retardation was predominantly found in patients with lissencephaly and PMG (Table II).

The majority of patients with lissencephaly (95.7%) and PMG (72.2%) had abnormal neurological findings, and they presented with more severe clinical picture compared to other patient groups. Clinical findings in heterotopia cases were mild; only 50% (6/12) of the cases showed mild mental and speech retardation. Abnormal neurological findings were present

Table II. Major Findings on Neurologic Examination

	PMG	Lissencephaly	Heterotopia	Schizencephaly	Total
Mental retardation	29/54 53%	19/23 82%	4/12 33.3%	4/12 33.3%	56/101 55.4%
Speech retardation	24/54 44.4%	15/23 65%	2/12 16.6%	2/12 16.6%	43/101 42.5%
Motor retardation	21/54 38%	15/23 65%	1/12 8.3%	3/12 25%	40/101 39.6%
Hemiparesis	7/54 12.9%	2/23 8.6%	–	2/12 16.6%	12/101 11.8%
Tetraparesis	8/54 14.8%	2/23 8.6%	–	2/72 16.3%	12/101 11.8%

PMG: Polymicrogyria.

in 77.1% of cases with bilateral malformation and in 67.5% of unilateral cases (P>0.05). Hemiparesis occurred more commonly in cases with unilateral malformation compared to those with bilateral malformation (20% and 3.2%, respectively, P<0.05). Compared to patients with unilateral malformations, patients with bilateral malformations had higher rates of speech delay (50.8%, 27.5%), mental retardation (67.2%, 37.5%) and motor retardation (45.9%, 30%).

6. Neuropsychological evaluation: The neuropsychological tests showed that 68% (68/101) of the cases had mental retardation (Table III). Mental retardation was more common among patients with lissencephaly, with severe retardation most prevalent in this group as well. Cognitive function was highest in patients with heterotopia, with only mild retardation. Cognitive dysfunction was more common in bilateral (80%) compared to unilateral malformations (51.3%) (P<0.005), and mental retardation was more severe in bilateral malformations. We found no significant relationship between abnormalities with respect to cognitive function and the presence of clinical seizures (P>0.05). Of note, cases with moderate and severe retardation had more seizures compared to patients with mild mental retardation and normal IQ (P<0.05).

The mean IQ in cortical dysplasia cases was 65.4±25.0, with significant differences between groups (F=5.073, P=0.003). IQ was higher in patients with heterotopia whose malformations were more localized, whereas it was lowest in patients with lissencephaly who had diffuse malformations. Pair wise group comparisons showed significant differences between lissencephaly-heterotopia (P<0.005) and PMG-heterotopia groups (P<0.05).

Discussion

Anomalies of neuronal migration are characterized by ectopic localization of neurons in the cerebral cortex[16]. Clinically, these malformations are usually associated with neurodevelopmental anomalies and epilepsy of varying severity[1,4,17]. Our knowledge on the frequency of MCD is limited and its true incidence is unknown. The prevalence of lissencephaly has been reported as 11.7 per million live births. More than half of the patients referred to epilepsy surgery centers for intractable epilepsy had some developmental anomalies and almost 25% of children with partial seizures had focal cortical dysplasia[1]. The etiology in many MCDs is unknown. Disruption of the placental perfusion due to intrauterine disorders is one of the major causes of MCD[1,11,18-23].

Lissencephalies: Mean age of lissencephaly cases at diagnosis in this study was 2.0 years, youngest at the time of diagnosis, compared to the other malformations. Of these cases, 67.5% were diagnosed within the first year of life. The onset of findings in lissencephaly cases has been reported to be at 22 months[5], though Dobyns[25] and Barkovich[26] reported that diagnosis was established before the age of one in 70-80% and 60% of the cases, respectively,

Table III. Cognitive Function in Patients with Malformations of Cortical Development

IQ	PMG n=53	Lissencephaly n=23	Heterotopia n=12	Schizencephaly n=12	Total n=100
Normal	18 34%	3 13%	6 50%	5 41.7%	32 32%
Mild mental retardation	13 24.5%	3 13%	5 41.7%	4 33.3%	25 25%
Moderate mental retardation	17 32.1%	8 34.8%	1 8.3%	3 25%	29 29%
Severe mental retardation	5 9.4%	9 39.1%	–	–	14 14%
IQ Min-max	61.9±22.7 20-120	51.1±30.5 20-94	86.3±21.3 55-129	71.1±20.9 40-107	65.4±25.0 20-129

PMG: Polymicrogyria. IQ: Intelligence quotient.

and that they had severe malformations. Kurul et al.[5] argued that generalized or bilateral gyral malformations displayed symptoms often in the first year of life. The presence of severe and easily identifiable clinical findings such as microcephaly, motor and mental retardation and seizures seems to lead to earlier diagnosis in patients with lissencephaly.

In 47.8% of lissencephaly cases, there were prenatal problems such as vaginal bleeding (21.7%), history of medication (17.4%) and infection. Dobyns[25] reported prolonged or serious bleeding between 2-4 months of gestation in 12% of cases with isolated lissencephaly. Kurul et al.[5] also reported vaginal bleeding and severe febrile disease in the first trimester of gestation. Dobyns[25] identified and reported flu-like syndrome, and methimazole, propyl thiouracil, and beta-blocker use in 12% of lissencephalic patients. These findings collectively suggest that maternal problems in early pregnancy may result in severe malformations such as lissencephaly.

There was no history of premature birth among lissencephaly cases. Compared to other groups, the low premature birth rate observed in lissencephaly cases with diffuse brain anomaly suggests that the severity and extent of the malformation do not correlate with prematurity. Literature data also confirm that the duration of the pregnancy and delivery are normal in lissencephaly cases[10,12]. However, birth weight corresponding to gestational age was low in 28.6% of lissencephaly cases. This is strikingly high, considering that the frequency of intrauterine growth retardation in Turkey is 8.9%[27]. Low birth weight in lissencephaly cases has also been reported by Dobyns[25] and Liang et al.[28] in 6.6% and 30% of cases, respectively. In addition to low birth weight, lissencephaly is usually accompanied by microcephaly. This proportional growth retardation may be interpreted as the fetus being affected in the early stages of pregnancy, or more severe and diffuse malformations developing following interactions during earlier stages.

The chief complaints in our cases were seizure (47%), microcephaly (34.8%), and motor and mental developmental delay (8.7%). Microcephaly was most common in lissencephaly cases, and in 88.9% of the cases microcephaly was the first sign. Also, global developmental delay within the first year of life was high (73.9%) in patients with lissencephaly. Literature review revealed seizure (67.5%), growth retardation (35%), microcephaly (24.3%) and motor dysfunction (10.8%) as the most frequently presenting symptoms in lissencephaly cases[5,28]. These findings help physicians and families in early identification of lissencephaly cases.

Microcephaly at birth, observed most commonly among lissencephaly cases, is an important diagnostic finding. Microcephaly is more frequent in diffuse bilateral malformations such as lissencephaly than in unilateral malformations. Microcephaly was the most common finding during general physical examination of lissencephaly cases. Microcephaly in lissencephaly cases has been reported to be present at birth or to occur later in the first year of life[10,12,29]. The frequencies of microcephaly at birth and at initial presentation have been reported as 29% and 71%, respectively, by Dobyns[25], and 24% and 51%, respectively, by Kurul[5]. In view of these findings, it is plausible that brain growth is delayed in the postnatal period in lissencephaly cases, i.e. neuronal migration and organization continued postnatally.

Family history in 43.5% of our cases revealed neurological problems including epilepsy (21.7%), mental retardation (13.3%) and miscarriage (13.3%). Kurul[5] reported that the incidence of family history of neurological disease in lissencephaly cases was 19%. Montenegro and colleagues[13], on the other hand, reported a family history of cortical dysplasia and mental retardation in 32% of the patients with agyria/pachygyria. There was no family history of lissencephaly among our cases. However, a high ratio of neurological problems and miscarriage in a family may be suggestive of the presence of structural abnormalities of the central nervous system that have not been fully uncovered, since we do not have access to detailed neuroradiological images of other members of the family.

Consanguinity between parents was observed most commonly in lissencephaly cases (47.8%). In Turkey, the rate of consanguinity between parents varies considerably from one region to another, ranging between 10-20%[5]. The ratio of consanguinity between parents in lissencephaly cases was calculated as 27% and

4.61% by Kurul[5] and Dobyns[25], respectively. In a study carried out in Jordan, al-Qudah[31] found consanguinity between parents in 88.2% of the cases and family history of similar cases in 76.4%. Even though these findings show variability among nations, they support the notion that consanguinity between parents and therefore autosomal recessive trait are important in the etiology of cortical dysplasia. We believe that the high consanguinity rate in our cohort is partly a result of regional factors. The higher parental consanguinity rate than the mean consanguinity rate in Turkey demonstrates that genetic factors are very important in the etiology of lissencephaly, which are mostly in the form of bilateral diffuse malformations in our cases.

Severe mental-motor retardation and other neurological abnormalities may be present in lissencephaly cases[10,12,25,29]. The most frequent findings in our lissencephaly cases were mental, speech and severe motor retardation, hemiparesis and tetraparesis. It has been reported that the severity of lissencephaly correlates with severity of clinical findings[26]. Our findings are consistent with the previous report. In a series by Barkovich[26], seizure in all and speech retardation in 40% of the cases were reported at the initial examination. Liang[28] reported motor and mental retardation in 80% of lissencephaly cases and argued that the severity of psycho-motor retardation was related to the age of onset of the seizure rather than the severity of MRI abnormalities. Kurul[5] identified hemiparesis in 30%, quadriparesis in 35% and developmental and cognitive retardation in 95% of lissencephaly cases. In 56.5% of our cases, patients had seizures, most frequently generalized and secondarily generalized. The frequency of seizures in patients with lissencephaly varied between 76%[25] and 90%[3]. Severe mental retardation was also most frequent in lissencephaly cases. The frequency of mental retardation in lissencephaly cases reported by various studies in the literature has varied between 56%[25], 84%[13], and 92%[2]. These findings suggest that more severe clinical interactions can be expected depending on the extent of the lesion in bilateral diffuse malformations.

Polymicrogyrias: The mean age of diagnosis in patients with PMG was 4.8 years, and 31% of them received the diagnosis within the first year. The most frequent presenting complaints among our cases were seizure, motor-mental retardation, speech retardation, hemiparesis and microcephaly. Compared to other malformations, hemiparesis, speech retardation, and a history of febrile seizures were more common in patients with PMG. Guerrini[32] observed seizure as the first sign in all patients with bilateral parasagittal parieto-occipital PMG.

In 29.6% of PMG cases, there was a prenatal history of medication (16.6%), infection (7%), hypotension (5.5%), bleeding (5.5%), trauma and radiological examination. Guerrini et al.[32] reported maternal vaginal bleeding and use of bromocriptine in parieto-occipital PMG. In three PMG cases, clinical findings and calcifications observed in neuroradiological images led us to consider congenital cytomegalovirus (CMV) infection in the etiology. Serological tests were not helpful for diagnosis of congenital CMV infection at the time of the evaluation due to the ages of the patients. On the other hand, it has been argued that most viruses possibly caused the damage before the fetus produced a humoral antibody response, hence the negative serologic tests[25]. These findings indicate that even though the etiology is not definite in cerebral malformations, prenatal environmental and teratogenic factors as well as genetics play roles in the development of malformations. Among our PMG cases, 9.4% had a history of premature birth and this was comparable with the general population[33]. Birth weight with respect to gestational age was low in 27.5% of the cases. This rate is higher than that of the general population (8.9%)[27], and may be suggestive of intrauterine fetal development being affected by environmental factors, including viral infections.

In 40.7% of our cases we noted epilepsy (24.1%), mental retardation (20.3%) and other neurological problems in the family. In two families with diffuse PMG and bilateral perisylvian PMG, siblings had similar malformations. Montenegro and colleagues[13] reported family history of cortical dysplasia in 14% and mental and growth retardation in 22% of the cases with PMG or schizencephaly. These findings suggest that genetic factors play a role in the etiology of bilateral and/or diffuse cortical developmental disorders. The role of genetic factors in the etiology can be inferred by identification of consanguinity between parents in 33.3% of PMG cases. The frequency of consanguinity in bilateral frontal PMG cases is reported as 15% in the literature[34].

We found the frequency of microcephaly to be 16.6% at birth and 40.8% at the time of diagnosis. This shows that microcephaly mostly appears later in the postnatal period in PMG cases. Head circumference can be within normal limits in parieto-occipital[32] and frontal PMG[34] cases. We observed abnormal neurological findings such as mental, speech and motor retardation, tetraparesis and hemiparesis among our PMG cases. Retardation in developmental stages has been observed in 44.4% of parieto-occipital PMG cases[32]. Guerrini and colleagues[34] reported developmental retardation and spastic quadriparesis (100%), speech retardation (92%), mental retardation (84.6%), and epilepsy (38%) in frontal PMG. Guerreiro et al.[36] demonstrated severe clinical findings and speech disorder in diffuse bilateral parietal PMG cases with an IQ score >70 and milder clinical and developmental speech disorders in bilateral posterior parietal PMG cases. These findings show that clinical features of PMG vary depending on localization and extent of the malformation. Unilateral PMG cases may present with congenital hemiplegia[35,37]. Seven percent of hemiparetic cerebral palsy cases have been reported to have unilateral PMG[37]. We found that 12% of PMG cases had hemiparesis. Six of these cases were unilateral perisylvian, and one was unilateral diffuse PMG. Caraballo[37] reported 12 cases of congenital hemiparesis with unilateral PMG involving the fronto-temporal and parieto-occipital regions in 75% and 25% of the cases, respectively. We observed seizures in 75.9% of PMG cases, with 40.7% generalized and 29.6% complex partial seizures. Kuzniecky and colleagues[4] reported the frequency of seizures in PMG cases as 50-85%.

There was mostly mild or moderate mental retardation (66%) in our PMG cases. Mild and moderate mental retardation were reported in 84.6% of bilateral frontal PMG cases[34]. Caraballo[37] reported mild mental retardation in 75% and moderate mental retardation in 25% of 12 unilateral PMG cases, while Montenegro[13] found mental retardation in 11% of cases. These different results may be related to the localization of the malformation.

Heterotopias: Patients with heterotopia were diagnosed at later ages compared to all other dysplasia cases in our series. The mean age at the time of diagnosis was 6.9 years. Only 10% of our cases received a diagnosis before the age of 1. Heterotopia cases usually had milder clinical signs and presented with late-onset seizures, therefore diagnosis was delayed. The most frequent presenting symptoms among our cases were seizure and motor and mental developmental delay. One of our cases was diagnosed with heterotopia incidentally. The most common presenting symptom in periventricular nodular heterotopia (PVNH) has been reported to be epileptic seizure that may occur at any age[1,17,24,38,39].

We noted prenatal history of vaginal bleeding, trauma, infection and medication in 25% of our heterotopia cases. Prenatal problems were reported by Palmini et al.[40] in 25% of focal neuronal migration disorders, and by Montenegro et al.[13] in 42% of heterotopia or agyria/pachygyria cases. We found preterm birth in 16.7% and low birth weight in 10% of our cases. These rates are similar to the rates calculated for the general population[27]. Developmental delay was present in 50% of heterotopia cases, which served as an early diagnostic warning. Developmental delay has been reported in 47% of cases with focal neuronal migration disorder[40]. Therefore, a close follow-up of children starting in infancy can help in early detection of patients with relatively mild MCD.

In 50% of our heterotopia cases, family history was positive for neurological problems such as epilepsy, mental retardation and miscarriage. In the literature, in 32% of cases in the heterotopia or agyria/pachygyria group, there was a family history of cortical dysplasia and mental retardation, and this was believed to be related to genetic predisposition[13]. We found consanguinity between parents in 16.7% of our cases. In band heterotopia, the risk of recurrence for carrier females is high. Among our cases, three siblings in a family had heterotopia (2 focal nodular heterotopia and 1 subependymal heterotopia-SEH) despite the fact that cranial MRIs of both parents were normal.

In 50% of our heterotopia cases, neurological examination revealed mild mental retardation and delayed speech. None of the patients had microcephaly. Diffuse bilateral white matter heterotopias may co-exist with developmental retardation (78%) and normal or mildly abnormal motor functions[1,4]. Seizures were

present in 66.7% of our cases. Partial seizures, especially complex partial seizures, were most common (49.9%). In 80-90% of PVNH cases, partial seizures refractory to epileptic treatment could be seen[1,17,24,38,39]. Seizures have been reported in approximately 88% of periventricular and subcortical neuronal heterotopia cases[3]. Our heterotopia cases had only mild mental retardation. SEH cases have usually been reported as having normal intelligence, and mean IQ score was around 85[4]. Cognitive disorders can be seen in less than 20% of PVNH cases if unilateral and in more than 60% if diffuse bilateral[6].

Schizencephalies: Though the mean age at diagnosis in our schizencephaly cases was 2.8 years, 25% received the diagnosis within the first year. In the literature, neurological disorders were detected in the first year of life in 50% of all schizencephaly cases, and on average the diagnosis was established at 42 months by MRI[33]. Packard et al.[42] reported that neurological abnormalities were observed in the first year of life in 66% of cases. The relatively low percentage of cases diagnosed within the first year in our series may be due to the fact that our schizencephaly cases were unilateral closed-lip, thereby exhibiting milder clinical signs. Chief presenting complaints in our cases included frequent seizures, motor-mental developmental retardation, and hemiparesis. The most frequent presenting complaints reported in the literature are asymmetrical muscle tone in unilateral schizencephaly and developmental growth retardation in bilateral cases. Seizures are the first signs of abnormalities[33].

We noted prenatal problems including maternal drug use, bleeding, low blood pressure and infection in 50% of our schizencephaly cases. In a study by Montenegro and colleagues[13], the authors identified prenatal problems in 42% of cases comprising schizencephaly. There was a history of preterm birth in 25% of our cases. Denis et al.[33] reported that 20% of their cases had preterm birth despite the fact that the incidence of prematurity in the general population was 10%, and argued that prematurity was a non-specific risk factor in schizencephaly cases. High rate of prematurity among our schizencephaly cases is supportive of this argument. The low birth weight observed in schizencephaly cases is similar to that in the general population (9.1%).

A family history of epilepsy was present in 16.6% of cases. Montenegro[13] reported cortical dysplasia in the families in 14% and mental and developmental delay in 22% of cases in the PMG or schizencephaly group. The rate of consanguinity between parents was lowest among patients with schizencephaly (8.3%). This can be interpreted as a higher role of environmental factors in the etiology of schizencephaly than in the other dysplasia groups.

Unilateral closed-lip schizencephaly with mild clinical signs and symptoms comprised 83.1%. In 58.3% of our cases, abnormal neurological findings such as mental retardation, motor retardation, speech retardation and hemiparesis were observed. These findings are related to the localization and extent of the malformation. In 15 unilateral schizencephaly cases, hemiparesis and mental retardation were present in 80% and 27% of the cases, respectively[33]. In patients with schizencephaly, delay in motor coordination (38%), hydrocephaly (21%), seizures (13%), and speech retardation (68%) have been reported. In closed-lip schizencephaly, contralateral hemiparesis has been reported in 72% of cases and seizures in 22%[42]. In our cases, 83% of the cases had seizures, mostly generalized (33.3%), partial and secondarily generalized seizures. Denis[33], Packard[42] and Guerrini[3] observed epilepsy in 37%, 57% and 81% of schizencephaly cases, respectively. These differences are possibly due to the localization and extent of the malformation. 58.3% of our schizencephaly cases had mild and moderate mental retardation. Our cases were mostly unilateral and closed-lip schizencephaly and hence, their clinical presentation was milder. Among schizencephalics, 52% had severe, 32% had moderate, and 17% had mild or normal mental function. Unilateral schizencephaly has better prognosis than bilateral, and closed-lip has a better prognosis than open-lip[42]. Mental retardation in unilateral schizencephaly cases has been reported as 27%[33].

Conclusion

We conclude that clinical features and courses of cortical dysplasia cases vary considerably depending on the involved region and the extent of the lesion. Phenotypic signs specific to the type of the malformation seem to be limited. Lissencephalies are usually diagnosed in the first year of life. They often present before the age of one with generalized epileptic seizures

refractory to antiepileptic medications. Low birth weight, microcephaly at birth, dysmorphic face and retardation in developmental stages during infancy can be observed. Severe neurological sequelae such as severe mental retardation and motor retardation can be observed. Diagnosis is established between 4-5 years of age in PMG cases, usually following the first seizure. Microcephaly may develop during infancy in diffuse malformations. Genetic factors predominate in bilateral symmetrical PMG cases. Clinical features are more severe in diffuse than in localized malformations. Depending on the extent of the malformation, generalized or focal epileptic disorders may be present. Heterotopia cases are sometimes unrecognized at early ages since neurological findings are less prominent and there is mild retardation in mental functions. Generally, they are diagnosed after a seizure that occurs at any age. Seizures are usually in the form of partial seizures and develop at any age. There is only mild mental retardation. Schizencephaly cases are diagnosed at an early age, mostly by seizures, and particularly in unilateral cases, hemiparesis. Prenatal problems, preterm birth and postnatal neurological signs and symptoms are common. Mild mental retardation, clinical signs and particularly focal epileptic disorders are seen in unilateral and closed-lip schizencephaly.

This study provides detailed phenotypic information that would be useful for advanced genetic studies, in addition to outlining the profile of cortical dysplasias with diverse clinical data. More studies are required to assess genotype-phenotype relations.

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REFERENCES

1. Whiting S, Duchowny M. Clinical spectrum of cortical dysplasia in childhood: diagnosis and treatment issues. J Child Neurol 1999; 14: 759-771.
2. Koehn MA, Duchowny M. Preoperative clinical evaluation and noninvasive electroencephalogram in cortical dysplasia. Neurosurg Clin N Am 2002; 37: 35-39.
3. Guerrini R, Carrozzo R. Epilepsy and genetic malformations of the cerebral cortex. Am J Med Genet 2001; 106: 160-173.
4. Kuzniecky RI, Barkowich AJ. Malformations of cortical development and epilepsy. Brain Dev 2001; 23: 2-11.
5. Kurul S, Çakmakçı H, Dirik E. Agyria-pachygyria complex: MR findings and correlation with clinical features. Pediatr Neurol 2004; 30: 16-23.
6. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. Classification system for malformations of cortical development. Neurology 2001; 57: 2168-2178.
7. Pılz D, Stoodley N, Golden JA. Neuronal migration, cerebral cortical development, and cerebral cortical anomalies. J Neuropathol Exp Neurol 2002; 61: 1-11.
8. Couillard-Despres S, Winkler J, Uyanik G, Aigner L. Molecular mechanisms of neuronal migration disorders, Quo vadis? Curr Mol Med 2001; 1: 677-688.
9. Blaser SI, Jay V. Disorders of cortical formation. Radiologic-pathologic correlation. Neurosurg Clin N Am 2002; 37: 41-62.
10. Volpe JJ. Neuronal proliferation, migration, organization and myelination. In: Neurology of the Newborn (3rd ed). Philadelphia: W.B. Saunders Company; 1995: 43-92.
11. Golden JA. Cell migration and cerebral cortical development. Neuropathol Appl Neurobiol 2001; 27: 22-28.
12. Barkowich AJ, Gressens P, Evrard P. Formation, maturation and disorders of brain neocortex. AJNR 1992; 3: 423-446.
13. Montenegro MA, Gerreiro MM, Lopes-Cendes I, Guerreiro CA, Cendes F. Interrelationship of genetics and prenatal injury in the genesis of malformations of cortical development. Arch Neurol 2002; 59: 1147-1153.
14. Barkovich AJ, Ferriero DM, Barr RM, Gressen P, Dobyns WB, Truwit CL. Microlissencephaly: a heterogeneous malformation of cortical development. Neuropediatrics 1998; 29: 113-119.
15. Gobel S, Osler GD, Butnik SM. Understanding Psychological Testing in Children - A Guide for Health Professionals. New York and London: Plenum Medical Book Company; 1986.
16. Barkovich AJ, Chuang SH, Norman D. MR of neuronal migration anomalies. AJNR 1987; 8: 1009-1017.
17. Kuzniecky RI. MRI in cerebral developmental malformations and epilepsy. Magn Reson Imaging 1995; 13: 1137-1145.
18. Barth PG. Fetal disruption as a cause of neuronal migration defects. In: Barth PG (ed). Disorders of Neuronal Migration. London: Mac Keith Press; 2003: 182-194.
19. Clarren SK, Alvord EC, Sumi M, Streissguth AP, Smith DW. Brain malformations related to prenatal exposure to ethanol. J Pediatr 1978; 92: 64-67.
20. Dvorak K, Feit J. Migrations of neuroblasts through partial necrosis of the cerebral cortex in newborn rats. Contributions to the problem of morphological development and development period of cerebral microgyria. Acta Neuropathol 1997; 38: 203-212.
21. Richman D, Stewart R. Cerebral microgyria in a 27 week fetus: an architectonic and topographic analysis. J Neuropathol Exp Neurol 1974; 33: 374-384.

22. Hayward JC, Titelbaum DS, Claney RR, Zimmerman RA. Lissencephaly-pachygyria associated with congenital cytomegalovirus infection. J Child Neurol 1991; 6: 109-114.

23. Barth PG. Disorders of neuronal migration. Can J Neurol Sci 1987; 14: 1-16.

24. Huttenlocher PR, Taravath S, Mojtahedi S. Periventricular heterotopia and epilepsy. Neurology 1994; 44: 51-55.

25. Dobyns WB, Elias ER, Newlin AC, Pagon RA, Ledbetter DH. Causal heterogeneity in isolated lissencephaly. Neurology 1992; 42: 1375-1388.

26. Barkovich AJ, Koch TK, Carrol CL. The spectrum of lissencephaly: report of ten patients analyzed by magnetic resonance imaging. Ann Neurol 1991; 30: 139-146.

27. Küçüködük Ş. Yenidoğanın ilk değerlendirilmesi ve stabilizasyonu. Yenidoğan ve Hastalıkları. Samsun: Ondokuz Mayıs Üniversitesi Çocuk Sağlığı ve Hastalıkları Yayını; 1994: 129-155.

28. Liang JS, Lee WT, Young C, Peng SS, Shen YZ. Agyria-pachygyria: clinical, neuroimaging, and neurophysiologic correlations. Pediatr Neurol 2002; 27: 171-176.

29. Nabi NU, Mezer E, Blaser SI, Levin AA, Buncic JR. Ocular findings in lissencephaly. J AAPOS 2003; 3: 178-184.

30. Sarnat LF. Hemimegalencephaly: Part 1. Genetic, clinical, and imaging aspects. J Child Neurol 2002; 17: 373-384.

31. al-Qudah AA. Clinical pattern of neuronal migrational disorders and parental consanguinity. J Trop Pediatr 1998; 44: 351-354.

32. Guerrini MD, Dubeau F, Dulac O, et al. Bilateral parasagittal parietooccipital polymicrogyria and epilepsy. Ann Neurol 1997; 41: 65-73.

33. Denis D, Chateil JF, Brun M, et al. Schizencephaly: clinical and imaging features in 30 infantile cases. Brain Dev 2000; 22: 475-483.

34. Guerrini R, Barkovich JA, Sztriha L, Dobyns WB. Bilateral frontal polymicrogyria. A newly recognized brain malformation syndrome. Neurology 2000; 54: 909-913.

35. Gressens P, Barkovich AJ, Evrard P. Polymicrogyria: role of the excitotoxic damage. In: Barth PG (ed). Disorders of Neuronal Migration. London: Mac Keith Press; 2003: 170-181.

36. Guerreiro MM, Hage SR, Guimaraes CA, et al. Developmental language disorder associated with polymicrogyria. Neurology 2002; 59: 245-250.

37. Caraballo R, Cersosimo R, Fejerman N. A particular type of epilepsy in children with congenital hemiparesis associated with unilateral polymicrogyria. Epilepsia 1999; 40: 865-871.

38. Leventer RJ, Dobyns WB. Periventricular gray matter heterotopias: a heterogeneous group of malformations of cortical development. In: Barth PG (ed). Disorders of Neuronal Migration. London: Mac Keith Press; 2003: 72-82.

39. Poussaint TY, Fox JW, Dobyns WB, et al. Periventricular nodular heterotopia in patients with filamin-1 gene mutations: neuroimaging findings. Pediatr Radiol 2003; 30: 748-755.

40. Palmini A, Andermann F, Olivier A, et al. Focal neuronal migration disorders and intractable partial epilepsy: a study of 30 patients. Ann Neurol 1991; 30: 741-749.

41. Dobyns WB, Truwit CL. Lissencephaly and other malformations of cortical development: 1995 update. Neuropediatrics 1995; 26: 132-147.

42. Packard AM, Miller VS, Delgado MR. Schizencephaly: correlations of clinical and radiologic features. Neurology 1997; 48: 1427-1434.