Clinical features of 21 patients with lissencephaly type I (agyria – pachygyria)

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SUMMARY: Özmen M, Yılmaz Y, Çalışkan M, Minareci Ö, Aydınlı N. Clinical features of 21 patients with lissencephaly type I (agyria-pachygyria). Turk J Pediatr 2000; 42: 210-214.

Lissencephaly (agyria-pachygyria) is the most severe neuronal migration disorder, characterized by total or partial absence of gyri. In this study, 21 patients with lissencephaly type I (9 girls, 12 boys) with a mean age of 19±21 months (2 weeks-8 years) were evaluated clinically and graded according to neuroradiological findings (19 patients by magnetic resonance imaging MRI and 2 by computed tomography CT). Three patients were classified as lissencephaly grade 2 and 18 patients as grade 3 or 4. Clinically, 12 patients (57%) had microcephaly, and eight (38%) had facial dysmorphism. All the patients had prominent psychomotor retardation, moderate to severe; the most frequent neurological findings were spastic guadriplegia (36.4%) and hypotonia with exaggerated tendon reflexes (27.3%). Seventy-eight percent of the patients had epileptic seizures resistant to conventional treatment. Lissencephaly is a cerebral cortical malformation that should be considered in children with developmental delay with or without microcephaly and facial dysmorphism. In addition, it should be investigated in the etiology of early-onset childhood epilepsy.

Key words: lissencephaly, neuronal migration disorders, childhood epilepsy, psychomotor retardation.

Neuronal migration disorders (NMD) are a rare group of malformations of the brain caused by insults to migrating neuroblasts between the second and sixth months of gestation[1-4]. Several different types of these disorders have been described, of which lissencephaly (agyria-pachygyria) is the most severe form, characterized by total or partial absence of cortical gyration[2,5-8].

Although lissencephaly was first described more than 100 years ago, there had been few reports until the introduction and widespread use of computed tomography (CT) and particularly magnetic resonance imaging (MRI)[5,8-10]. Pathologically the disorder consists of different subtypes, including type I or classical lissencephaly, type II or cobblestone lissencephaly, and other rare or atypical types[1,5,7,11,12]. Type I lissencephaly, the most common form, is characterized by a flattened and thickened cerebral cortex with absent or reduced cortical gyri. This type can occur as an isolated defect, which is referred to as isolated lissencephaly sequence (ILS) or as a part of a recognizable multiple congenital anomaly syndrome known as Miller-Dieker syndrome (MDS)[3,7,13].

Type I lissencephaly may manifest by variable clinical findings. In this paper we report the clinical features of 21 patients with lissencephaly type I.

Material and Methods

Twenty-one patients with lissencephaly (9 girls, 12 boys) admitted to the Pediatric Neurology Division were studied. The children were referred for evaluation of developmental delay and/or microcephaly, and/or seizures.

The diagnosis was made by MRI in 19 patients and CT in two patients. All patients had type I lissencephaly (isolated lissencephaly sequence) according to the criteria of Barkovich and Dobyns[1,3]. None of the patients had clinical findings, or muscular or ocular abnormalities consistent with type II lissencephaly. The severity of gyral malformation was graded according to

the grading system by Dobyns (grade 1: diffuse agyria; grade 2: diffuse agyria with some shallow sulci in the frontal regions; grade 3: mixture of agyria and pachygyria; grade 4: diffuse or widened pachygyria with no areas of agyria; grade 5: mixed pachygyria and subcortical band heterotopia; grade 6: subcortical band heterotopia)[7]. Chromosome analysis was performed in three patients with grade 2 lissencephaly to exclude Miller-Dieker syndrome and no chromosomal abnormality was detected.

Physical and neurological findings and types and frequency of the seizures were evaluated and developmental status tested with Denver II Developmental Screening Test (adapted to Turkish children) and Brunette Lezine test. The relationship between severity of lissencephaly and clinical status was assessed.

Results

Mean age of patients at first visit was 19±21 months, range from one month to eight years (77% under 2 years; 95% under 4 years of age). Mean age during the last follow-up visit was 31±22 months. Three patients (14%) were classified as lissencephaly grade 2 (Fig. 1), five patients (23%) grade 3 (Fig. 2) and 13 patients (61%) grade 4 (Fig. 3). Pachygyric lesions were located mostly in the frontoparietal regions in grade 3 patients.

Clinical findings of the patients are listed in Table I. Twelve patients (57%) had microcephaly and eight (38.1%) had facial dysmorphism consisting of bitemporal narrowing (n: 6), small jaw (n: 4), narrow forehead (n: 4), large ear lap (n: 2), and malformed low-set ears (n: 1). At the

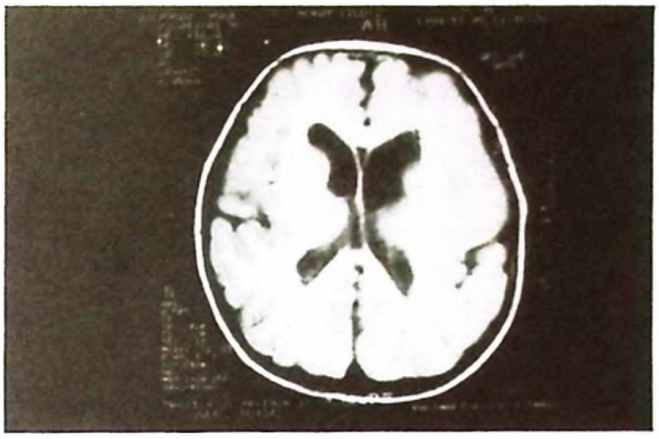

Fig. 2. Cranial MRI of Case 5 (grade 3 lissencephaly, axial view).

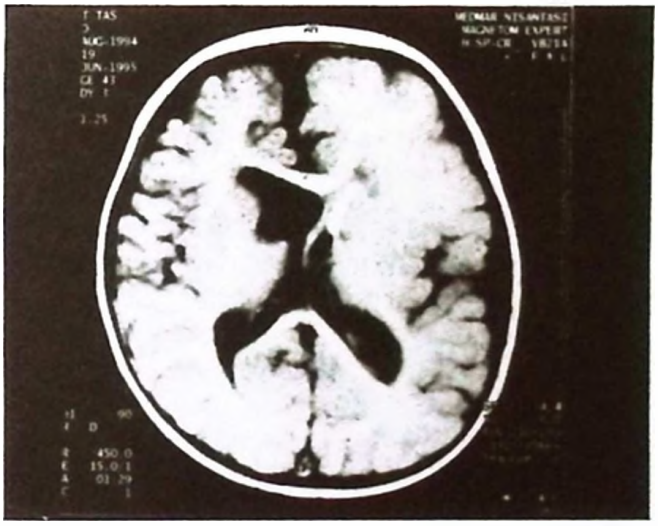

Fig. 3. Cranial MRI of Case 16 (grade 4 lissencephaly, axial view).

(a) (b)

Fig. 1. Cranial MRI of Case 1 (grade 2 lissencephaly) (A: axial view; B: sagittal view).

last examination, 11 patients were older than two years of age. Seven cases (64%) only had head control, one patient (9%) could sit without support, two patients (18%) were able to walk, and one patient (9%) had no motor development including no head control. The most common neurological findings were spastic quadriparesis (47%) and hypotonia with exaggerated tendon reflexes (28%).

lissencephaly. Similarly, seizures were observed in grades 2, 3 and 4 lissencephaly in 100, 80 and 69 percent of cases, respectively.

Discussion

Lissencephaly, meaning literally "smooth brain", refers to a genetically, clinically, neuroradiologically, and histologically heterogeneous group of conditions that are characterized by total or partial

Table I. Clinical Findings and Grades of Lissencephaly of the Patients

Patient	Age* (yrs; mths)	Age** (yrs; mths)	Sex	Grade of lissencephaly	Dysmorphism	Microcephaly	Neurological findings	Seizure/ epilepsy	Psycho/ motor retardation
1	3;7	6;3	F	2	–	+	Hypotonia	LGS	Severe
2	2;2	3;8	F	4	+	+	Hypotonia	LGS	Severe
3	0;5	1;3	F	3	–	+		IS	Severe
4	1;1	1;10	M	4	+	+	SQ	NS	Severe
5	3;2	4	M	3	–	–		LGS	Moderate
6	0;8	2;2	M	4	–	–	SQ	NS	Moderate
7	0;7	1;7	M	4	+	–	SQ	generalized	Moderate
8	1;7	1;8	M	4	–	+		NS	Mild
9	0;11	4;10	F	4	+	+	SQ	LGS	Severe
10	1;7	1;10	F	2	–	+		IS	Severe
11	0;6	2	M	3	–	–	Hypotonia SQ	IS	Severe
12	2;10	3;4	M	4	+	+		LGS	Severe
13	0;6	3;4	F	3	–	–	SQ	NS	Severe
14	8;0	8;0	M	4	+	–	Hypotonia	NS	Severe
15	0;3	2	M	4	–	–	SQ	Focal clonic, generalized tonic	Moderate
16	0;10	1;5	M	4	–	–	Spastic left hemiparesis	generalized clonic, tonic, atonic	Moderate
17	0;5	0;6	F	2	–	–	Hypotonia	IS	Severe
18	1;5	1;6	F	4	+	+	SQ	generalized tonic	Severe
19	1;8	1;8	F	4	–	+	Hypotonia	generalized tonic	Moderate
20	0;3	0;3	M	3	–	+	SQ	IS	Severe
21	0;11	2;5	M	4	+	+	SQ	IS	Severe

* At the first examination.
** At the last examination.
F: Female. M: Male. SQ: Spastic quadriparesis. IS: Infantile spasm. LGS: Lennox-Gastaut syndrome. NS: No seizure.

Seventy-six percent (n: 16) of the patients had epileptic seizures including infantile spasms (IS) (n: 6), Lennox-Gastaut syndrome (LGS) (n: 5), and secondary generalized and mixed type seizures (n: 5) resistant to conventional antiepileptic drugs. The age at onset of seizures ranged from two weeks to 22 months (mean 6±6 months). In 12 patients (57%) seizures occurred before six months of age, and in 14 (66%) before 12 months.

Table II presents the relationship between the clinical findings and grades of lissencephaly. All patients with grade 2 lissencephaly presented severe developmental delay and had seizures (one with IS, two with LGS), whereas severe retardation was found in 80 percent of cases with grade 3 and in 53 percent with grade 4

absence of gyration[1-3,5,6,14]. Several types of lissencephaly have been identified according to the clinical, morphologic, and genetic criteria. The most common types are type I (classic lissencephaly) and type II (Cobblestone lissencephaly)[7,11,12,15,16]. Type I lissencephaly occurs most commonly as an isolated defect (isolated lissencephaly sequence), but is may also be associated with MDS, in which case, it presents in a more severe form[3,7,13,17].

All our patients were diagnosed to have type I lissencephaly, since muscular and ocular anomalies as well as neuroradiological findings characteristic of type II lissencephaly were absent. Chromosomal analyses could be performed in three patients with severe lissencephaly to exclude MDS, and no deletion was found in chromosome 17. In addition, none

of the cases with severe lissencephaly had any facial dysmorphism that occurs in patients with MDS. Therefore, alll cases were classified as type I lissencephaly-ILS.

1990, de Rijk van Andel[17] postulated that grades 3 and 4 have been under-represented in the literature. Based on our findings, we also consider that lissencephaly grades 3 and 4 were more frequently seen than grades 1 and 2. In the near future, with the wide use of MRI, cases with mild and moderate lissencephaly may outnumber more severe forms.

Table II. Distribution of Clinical Findings According to the Grades of Lissencephaly Type I

	Grade 2 (n: 3)		Grade 3 (n: 5)		Grade 4 (n: 13)		Total	
Clinical Findings	n	%	n	%	n	%	n	%
Microcephaly	2	66	2	40	8	61.5	12	57
Facial dysmorphism	0	0	0	0	8	61.5	8	38
Psychomotor retardation							21	100
Severe	3	100	4	80	7	54		
Moderate	0	0	1	20	5	38		
Mild	0	0	0	0	1	8		
Seizures	3	100	4	80	9	69	16	76
Spastic quadriparesis	0	0	2	40	8	61.5	10	47
Hypotonia	2	66	1	20	3	23	6	28
Spastic hemiparesis	0	0	0	0	1	7.6	1	4.7

Patients with lissencephaly type I may present with variable findings including microcephaly, facial dysmorphism, motor deficits, seizures, and developmental delay[12,14,15,18,19]. Most of these patients have poor neurological prognosis. All our patients had psychomotor retardation, and 57 percent exhibited microcephaly. Of 11 patients older than two years, two were able to walk and seven only had head control. Spasticity and hypotonia resulting in severe motor retardation were the most common neurological findings in our series. In the literature, all of the 124 reported patients had developmental delay, and 71 percent were microcephalic[13,14,16-21].

Seizures were present in 76 percent of our cases and half of them had infantile spasms or LGS preceded by IS. Intractable seizures is one of the most common clinical manifestations of patients with lissencephaly. In other series, the seizures have been reported in 75-90 patients of the patients (IS 35-50%)[13-15,18,19]. According to these results, lissencephaly should be considered in children with psychomotor retardation with or without microcephaly and facial dysmorphism. In addition, it should be investigated in the etiology of some early-onset childhood epilepsies, particularly IS.

In our series the most common forms of type I lissencephaly were diffuse pachygyria (grade 4) (62%) and agyria-pachygyria (grade 3) (24%). As far back as 1956, Crome[22] suspected that pachygyria would be much more frequent than agyria, but this has never received much attention in clinical studies[13,17,21]. In

Is there any relationship between the severity of the clinical findings and the severity of cortical malformation? The number of patients in our series was not sufficient for statistical evaluation. However, we noticed that of our three cases with grade 2 lissencephaly all had profound psychomotor retardation and seizures, whereas 54 percent of the patients with grade 4 lissencephaly were severely retarded and 69 percent of these cases had seizure. In the series of de Rijk van Andel[17], all patients with grades 1 and 2 were bedridden and had little contact with their environment, whereas cases with grades 3 and 4 had some social development. Dobyns[13] reported that the developmental level did not correspond with the severity of the brain malformations in these cases. Similarly, Barkovich[14] postulated that there was no relationship between clinical manifestations and MRI findings. Larger series may be helpful to elucidate the relationship between the grade of lissencephaly and the clinical outcome.

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