CLINICAL FINDINGS IN 16 PATIENTS WITH TOMOGRAPHIC DIAGNOSIS OF SCHIZENCEPHALY*

Maria do Carmo de Souza Rodrigues[1], Alexandra Maria Vieira Monteiro[2], Juan Clinton Llerena Junior[3], Alexandre Ribeiro Fernandes[4]

Abstract **OBJECTIVE: To establish a correlation between clinical features in a group of children with tomographic diagnosis of schizencephaly and clefts extent and localization. MATERIALS AND METHODS: Retrospective study of dossiers from the archives of Neurology and Medical Genetics Services at Instituto Fernandes Figueira/Fiocruz and Hospital Municipal Jesus, Rio de Janeiro, RJ, Brazil, in the period between 2000 and 2003. The study included 16 patients, nine female and seven male, with tomographic diagnosis of schizencephaly investigated for clinical findings, psychomotor development, motor/cognitive deficits and epilepsy. RESULTS: Predominance of bilateral clefts in 10:16 patients, open-lip schizencephaly type in 23:27 patients, and small lips in 11:27 patients. As regards anomalies associated with schizencephaly, pellucid septum absence was the most frequent one (10:16 patients). As regards clinical findings, 15 patients presented with developmental delay and motor deficit, six patients with cognitive deficit and ten with epilepsy. In three patients, we observed discordant clinical findings and cleft sizes, although the clefts were small, the clinical features severity was high because of other cerebral anomalies. CONCLUSION: The clinical features of schizencephaly are related to the size of the clefts, regardless laterality, presenting higher severity when associated with other cerebral anomalies.**
Keywords: Schizencephaly; Computed tomography; Clinical findings.

Resumo *Aspectos clínicos em 16 pacientes com diagnóstico tomográfico de esquizencefalia.*
OBJETIVO: Correlacionar o quadro clínico de um grupo de crianças com diagnóstico tomográfico de esquizencefalia com a extensão e localização das fendas. MATERIAIS E MÉTODOS: Estudo retrospectivo de prontuários do arquivo dos serviços de Neurologia e Genética Médica do Instituto Fernandes Figueira e Hospital Municipal Jesus, Rio de Janeiro, RJ, Brasil, no período de 2000 a 2003. Foram incluídos 16 pacientes, nove do sexo feminino e sete do sexo masculino, com diagnóstico tomográfico de esquizencefalia e analisados quanto a aspectos da tomografia computadorizada, desenvolvimento neuropsicomotor, déficit motor e cognitivo e epilepsia. RESULTADOS: Predominaram as fendas bilaterais em 10:16 pacientes, lábios abertos em 23:27 fendas e pequenas em 11:27 fendas. Das anomalias associadas à esquizencefalia, a ausência de septo pelúcido foi a mais freqüente (10:16 pacientes). Dos aspectos clínicos, 15 pacientes apresentaram atraso do desenvolvimento e déficit motor; seis apresentaram déficit cognitivo e dez apresentaram epilepsia. Em três pacientes observamos discordância entre o quadro clínico e o tamanho das fendas: embora as fendas fossem pequenas, o quadro clínico foi intenso, em virtude de presença de outras anomalias cerebrais. CONCLUSÃO: O quadro clínico guarda relação com o tamanho das fendas, independentemente da lateralidade, sendo mais intenso quando há associação com outras anomalias cerebrais.
Unitermos: Esquizencefalia; Tomografia computadorizada; Aspectos clínicos.

INTRODUCTION

Schizencephaly[1] is an extremely rare congenital disorder characterized by a full-thickness cleft within the cerebral hemispheres, delimited by an abnormal cortex[2–4], extending from the ventricular surface to the arachnoid space[3,4]. Frequently, schizencephaly involves the perisylvian regions[2,5] and large portions of the cerebral hemispheres may be absent and replaced by fluid[2].

Presentations are highly variable, depending on the clefts extent and localization, but patients present from a normal intelligence to convulsions and severe neurological involvement[2,3,5,6]. The differential diagnosis should take into consideration holoprosencephaly[7], porencephaly[7–9], hydranencephaly[7,9,10] and subarachnoid cysts[9,10].

Dubey *et al*.[7] have reported the cardinal characteristics of schizencephaly: a hemispheric cleft delimited by an usually bilateral ependymal-pial sheath in the perisylvian region; a cleft lined by gray-matter linking the subarachnoid space with the ependyma of the lateral ventricle, and the association with multiple intracranial anomalies such as polymicrogyria, heterotopias, absence of pellucid septum, optic nerve hyperplasia and corpus callosum agenesia.

* Study developed at Centro de Genética Médica Dr. José Carlos Cabral de Almeida/Instituto Fernandes Figueira/Fundação Oswaldo Cruz/RJ and with Program of Post-Graduation in Medical Sciences of Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil. Funding Source: Faperj (E-26/171.077/2002-APQ1).

1. Master in Medicine – Program of Post-Graduation in Medical Sciences at Universidade do Estado do Rio de Janeiro, MD, Geneticist at Hospital Universitário Cassiano Antonio Moraes – Universidade Federal do Espírito Santo.

2. Doctor in Medicine, Adjunct Professor of Radiology for Courses of Post-Graduation at Faculdade de Ciências Médicas da Universidade do Estado do Rio de Janeiro.

3. Doctor in Biological Sciences, MD, Clinical Geneticist, Chief for Centro de Genética Médica Dr. José Carlos Cabral de Almeida, Instituto Fernandes Figueira/Fundação Oswaldo Cruz.

4. Master in Child and Women's Health, Professor of Pediatrics at Universidade Gama Filho, MD, at Department of Neuropediatrics – Hospital Municipal Jesus.

Mailing address: Dra. Maria do Carmo de Souza Rodrigues. Rua Itaporanga, 26, Itaparica. Vila Velha, ES, Brazil 29102-270. E-mail: rodriguesmcs@yahoo.com.br

Received November 1, 2005. Accepted after revision November 16, 2005.

The majority of cases described are of a sporadic nature, although there are reports on familial cases[3,6,11]. Some authors[2,3,6] have described homeotic gene EMX2 (Empty Spiracles, Drosophila, 2, Homolog of) mutations in patients with schizencephaly.

Many features of schizencephaly still remain obscure, such as etiology, developmental mechanisms and stages involved in the disorder pathogenesis. Data reported in specialized scientific publications indicate towards a heterogeneously anomalous pathogenesis and etiology, describing genetic and environmental causes, abnormal cerebral morphogenesis resulting from disruptive factors, and cell proliferation and/or neuronal migration defects, neuronal migration and/or cortical organization defects and cortical areas specification defects.

Amongst the diagnostic imaging methods, computed tomography (CT) may detect the characteristic findings, although magnetic resonance imaging (MRI) is the gold standard method for a more detailed anatomical evaluation[9]. However, MRI disadvantages are its high cost and inaccessibility for the general population[12].

The objective of the present study was to establish a correlation between clinical features in a group of children with tomographic diagnosis of schizencephaly and clefts extent and localization.

MATERIALS AND METHODS

Retrospective study of dossiers of patients with tomographic diagnosis of schizencephaly from the archives of Neurology and Medical Genetics Services at Instituto Fernandes Figueira/Fiocruz (IFF-Fiocruz) and Hospital Municipal Jesus (SUS/RJ), Rio de Janeiro, RJ, Brazil, in the period between 2000 and 2003. Of an initial group of 28 patients, 12 were excluded due impossibility of contact or refusal from the part of the patients´ family to include them in the study. Of the remaining 16 patients, nine were female and seven were male. Terms of Free and Informed Consent were signed by all the persons responsible for the patients and the research was approved by IFF/Fiocruz National Committee of Ethics in Research (process no. 208/2002) and Comissão Nacional de Ética em Pesquisa (Conep) (process no. 4912/2002).

The following clinical parameters were analyzed: neuropsychomotor development, motor deficit, cognitive deficit (in school-aged children) and the presence of epilepsy (type of convulsive crisis, refractoriness to antiepileptic drugs).

Cranial CT studies of each patient were independently analyzed by two examiners and only those presenting diagnostic agreement were included in the present study. The Barkovich & Kjos[5] criterion was adopted for classification of schizencephalic clefts, considering the cleft type (open-lip or closed-lip) and size (small, medium or large).

RESULTS

The data on the clinical-tomographic correlation are summarized in Table 1. Twenty-seven clefts were observed in the 16 patients. As regards the sizes of the clefts, 14:27 were small (Figure 1), 11:27 were large (Figure 1) and 2:27 were medium (Figure 2). As regards localization, parietal clefts predominated (16:27), followed by frontoparietotemporal clefts (5:27). As regards laterality, bilateral clefts predominated (Figures 1, 2 and 3) in 10:16 patients, 5:10 patients presenting open-lip clefts and 5:10 with open and closed (or fused)-lip clefts (Figure 3). Of six patients with unilateral clefts (Figure 4), five presented open-lip clefts.

Periventricular calcifications (Figure 4) were observed in 3:16 patients, all of them presenting negative serology for congenital TORCH infection.

Thirteen of 16 patients presented other central nervous system anomalies associated with schizencephaly, the pellucid septum absence (Figure 1) and cortical dysplasias (Figure 5) being the most frequent findings respectively in 10:13 patients and in 4:13 patients.

Neuropsychomotor development delay was present in 15 patients and six school-aged patients also presented cognitive defi-

Table 1 Clinical-tomographic correlation.

Case	Cleft characteristics	Clinical findings
1	Open-lip, medium, unilateral	NPMD delay, spastic tetraparesia, axial hypotonia, Babinski's reflex, epilepsy
2	Open-lip, large, unilateral	NPMD, right hemibody spasticity
3	Open-lip, large and smal, bilateral	NPMD delay, cognitive deficit, spastic tetraparesia, Babinski's reflex, difficult-to-control epilepsy
4	Open-lip, small and closed-lip, bilateral	NPMD delay, generalized hypertonia
5	Open-lip, large, unilateral	NPMD delay, cognitive deficit, spastic tetraparesia, difficult-to-control epilepsy
6	Open-lip, one large and two small, bilateral	NPMD delay, cognitive deficit, spastic tetraparesia, difficult-to-control epilepsy
7	Open-lip, large and closed-lip, bilateral	NPMD delay, spastic tetraparesia, difficult-to-control epilepsy
8	Open-lip, large, unilateral	NPMD delay, spastic tetraparesia, epilepsy
9	Open-lip, large and medium, bilateral	NPMD delay, central hypotonia
10	Open-lip, small, unilateral	NPMD delay, cognitive deficit, epilepsy
11	Open-lip, large and smal, bilateral	NPMD delay, spastic tetraparesia
12	Open-lip, large and closed-lip, bilateral	NPMD delay, spastic tetraparesia
13	Closed-lip, unilateral	Normal, epilepsy
14	Open-lip, small and closed-lip, bilateral	NPMD delay, cognitive deficit, spastic tetraparesia, difficult-to-control epilepsy
15	Open-lip, large, bilateral	NPMD delay, spastic tetraparesia, difficult-to-control epilepsy
16	Open-lip and closed-lip, small, bilateral	NPMD delay, spastic tetraparesia

NPDM, neuropsychomotor development.

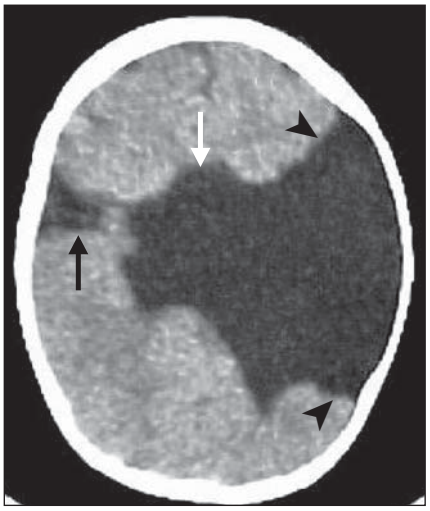

Figure 1. Bilateral schizencephaly. Large parietal open-lip cleft at left (arrowheads), small parietal open-lip cleft at right (black arrow), pellucid septum absence (white arrow)(case 11).

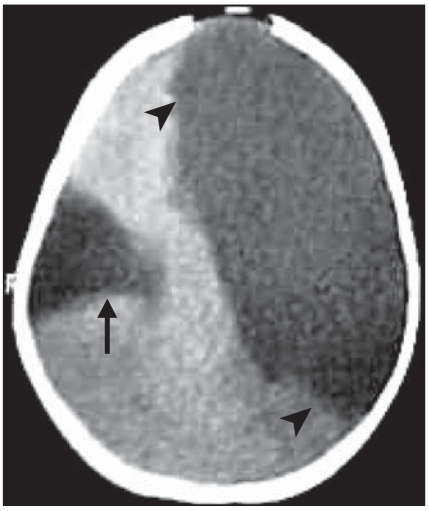

Figure 2. Bilateral schizencephaly. Large frontotemporoparietal open-lip cleft at left (arrowheads), medium parietal open-lip cleft at right (arrow)(case 9).

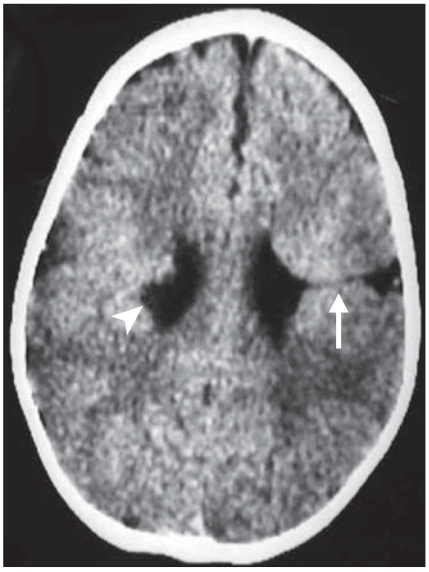

Figure 3. Bilateral schizencephaly. Parietal closed-lip cleft at right (arrowhead), small parietal open-lip cleft at left (arrow)(case 16).

cit. Neurological examination detected anomalies in 15:16 patients, the most frequent finding being pyramidal release signs (spastic tetraparesia) in 11:15 patients. Amongst the 16 patients, ten presented epilepsy, with the first crisis onset in the first year of life of 4:10 patients. The most frequent type of seizure was the generalized tonic-clonic one, reported in 5:10 patients. Epilepsy was difficult to control in 6:10 patients.

DISCUSSION

The clinical feature severity was related to the affected cortical area, both in patients with bilateral and unilateral clefts, according data reported in the specialized scientific literature[2,3,5,6]. Although clefts in three of our patients were small, the clinical feature was severe as a result of the presence of other cerebral anomalies associated with schizencephaly. Therefore, our data suggest that the clinical feature is also related to the presence of other central nervous system anomalies, corroborating the findings of Granata *et al*.[13].

The clinical feature was in agreement with data reported by other authors[6,9,14,15], with the majority of patients presenting motor deficit and neuropsychomotor development delay[8,9].

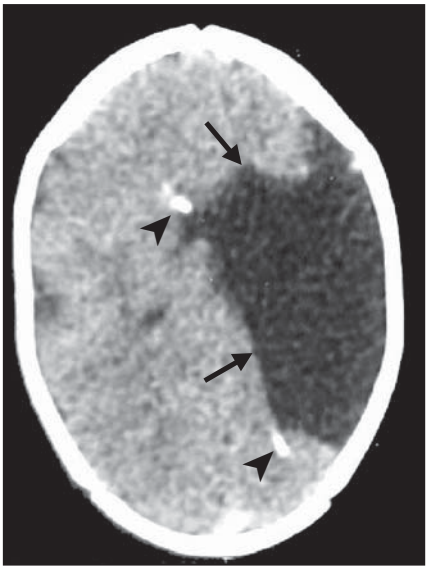

Figure 4. Unilateral schizencephaly – large parietal open-lip cleft at left (arrowheads), bilateral periventricular calcifications (arrows)(case 2).

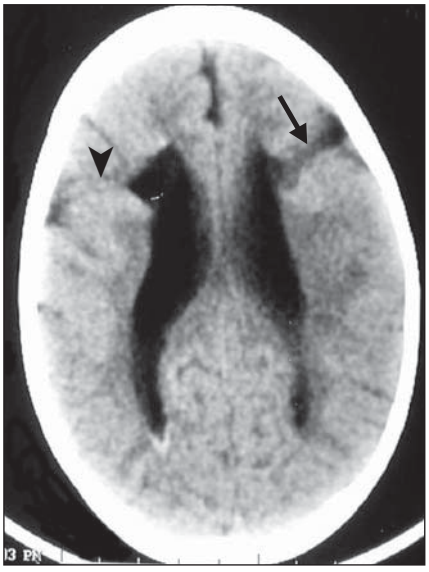

Figure 5. Bilateral schizencephaly. Small parietal open-lip cleft at left (arrow), parietal closed-lip cleft at right (arrowhead). Observe bilateral heterotopia on the corona radiata and bilateral frontotemporoparietal cortical dysplasia (case 4).

Also, we have observed that epilepsy was more frequent and severe in patients with a more significant loss of cortical area, an aspect that has not been described in the studies of Barkovich & Kjos[5], Granata *et al*.[14] and Denis *et al*.[15].

In a comparative analysis of the tomographic data, there was an agreement with data reported by other authors as regards laterality[9], cleft type[5,9] and localization and size[5,14,15]. Amongst associated anomalies, pellucid septum absence was our most frequent finding, similarly to the findings reported by other authors[9,10,13].

Although the presence of cleft(s) is significant for determination of the neurological picture, in some cases there was disagreement between the cleft extent and

clinical findings, as result of the presence of other cerebral anomalies associated with schizencephaly.

REFERENCES

1. OMIM. On-line Mendelian Inheritance in Man. Johns Hopkins University [cited 2002 April 15]. Available from: http://www.ncbi.nlm.nih.gov
2. Brunelli S, Faiela A, Capra V, *et al*. Germline mutation in the homeobox gene EMX2 in patients with severe schizencephaly. Nature Genet 1996;12:94–96.
3. Faiella A, Brunelli S, Granata T, *et al*. A number of schizencephaly patientes including 2 brothers are heterozygous for germline mutations in the homeobox gene EMX2. Eur J Hum Gen 1997;-5:186–190.
4. Guerrini R, Carrozzo R. Epilepsy and genetic malformations of the cerebral cortex. Am J Med Genet 2001;106:160–173.
5. Barkovich AJ, Kjos BO. Schizencephaly: correlation of clinical findings with MR characteristics. AJNR Am J Neuroradiol 1992;13:85–94.
6. Granata T, Farina L, Faiella A, *et al*. Familial schizencephaly associated with EMX2 mutation. Neurology 1997;48:1403–1406.
7. Dubey AK, Gupta RK, Sharma P, Sharma RK. Schizencephaly type-I. Indian Pediatr 2001;38:-1049–1052.
8. Packard AM, Miller VS, Delgado MR. Schizencephaly: correlations of clinical and radiologic features. Neurology 1997;480:1427–1434.
9. Amaral JG, Yanaga RH, Geissler HJ, Carvalho Neto A, Bruck I, Antoniuk SA. Schizencephaly: report of eleven cases. Arq Neuro-Psiquiat 2001; 59:244–249.
10. al-Alawi AM, al-Tawil KI, al-Hathal MM, Amir I. Sporadic neonatal schizencephaly associated with brain calcification. Ann Trop Paediatr 2001; 21:34–37.
11. Robinson RO. Familial schizencephaly. Dev Med Child Neurol 1991;33:1010–1012.
12. Montandon C, Ribeiro FAS, Lobo LVB, Montandon Júnior ME, Teixeira KISS. Disgenesia do corpo caloso e más-formações associadas: achados de tomografia computadorizada e ressonância magnética. Radiol Bras 2003;36:311–316.
13. Granata T, Freri E, Caccia C, Setola V, Taroni F, Battaglia G. Schizencephaly: clinical spectrum, epilepsy, and pathogenesis. J Child Neurol 2005;20:313–318.
14. Granata T, Battaglia G, D'Incerti L, *et al*. Schizencephaly: neuroradiologic and epileptologic findings. Epilepsia 1996;37:1185–1193.
15. Denis D, Chateil JF, Brun M, *et al*. Schizencephaly: clinical and imaging features in 30 infantile cases. Brain Dev 2000;22:475–483.