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CLINICAL, NEUROIMAGING AND CYTOGENETIC FINDINGS IN 20 PATIENTS WITH CORPUS CALLOSUM DYSGENESIS

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ABSTRACT - Twenty children with corpus callosum agenesis or hypoplasia were evaluated under a standardized investigation protocol. Psychomotor retardation, seizures, and craniofacial anomalies were the most prominent findings. There were three cases of chromosomal anomalies, all of them representing trisomy of chromosome 8.

KEY WORDS: corpus callosum agenesis, chromosomal anomaly, trisomy 8.

Achados clínicos, citogenéticos e de neuroimagem em 20 pacientes com disgenesia do corpo caloso

RESUMO - Vinte pacientes com disgenesia do corpo caloso foram avaliados através de um protocolo padronizado. Retardo neuropsicomotor, convulsões e dismorfias faciais foram os achados mais proeminentes. Três casos de anomalia cromossômica foram observados, todos representados por trissomia do cromossomo 8.

PALAVRAS-CHAVE: disgenesia do corpo caloso, anomalia cromossômica, trissomia 8.

Agenesis of the corpus callosum represents a disorganization of the brain architecture which results from partial or total failure of the "callosal" comisural fibers to cross the midline and form connections in the neocortex between the two cerebral hemispheres. In the absence of other recognized malformations of the central nervous system (CNS) the agenesis of corpus callosum may be asymptomatic, or associated with seizures or other symptoms that caracterize a syndrome of interhemispheric disconnection[1-4]. The associated malformations usually determine the clinical syndromes[5]. Other commonly associated findings are: mental retardation, learning disability, non-CNS congenital malformations and infantile spasms. Both corpus callosum agenesis or corpous callosum hypoplasia may be readily detected on magnetic resonance imaging (MRI), computerized tomography (CT) or ultrasonography (US)[6-8].

The main purpose of this study is to characterize the most common clinical and cytogenetic associated findings in a cohort of 20 children with dysgenesis of the corpus callosum.

METHOD

Twenty children were recruited from two different genetics outpatient clinics (Centro de Genética Médica, Instituto Fernandes Figueira, FIOCRUZ, and Hospital Universitário Gafrée-Guinle, UNIRIO) located in Rio de Janeiro, Brazil. Each patient was submitted to a standardized evaluation protocol that included: neurologic evaluation, neuroimaging study, cytogenetic analysis and other specialized evaluations according to each case. Both the design of the present study and the evaluation protocol had been previously approved by the local institutional ethics committee.

RESULTS

The clinical, radiological and cytogenetic findings are summarized in Table 1. Complete agenesis of the corpus callosum (CCA) was present in 18 patients, whereas 2 patients presented with hypoplasia of the corpus callosum (CCH). One of the patients (Case 18) represents a familial instance of isolated CCA, with CCH present in the clinically unaffected father.

Seven patients presented with other associated CNS malformations, namely, porencephalic cyst (Case

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Table 1. Associated findings.

Case	Sex	Age	Clinical findings	Karyotype	
1	f	8 mo	CCA,PC,PDA,EF,OH,HYD	46,XX	
2	m	1 yr	CCA,SB,PMR,MYC,HYP,ST	46,XY	
3	f	9 yr	CCA,PMR,EF,MYC,CR	46,XX	Congenital toxoplasmosis
4	m	13mo	CA,PMR,MYC,EF,OH,S,VD,HD,micropenis	46,XY	
5	m	9 yr	CCA,PMR,deep creases,eversion lower lip	46,XY/47,XY,+8	Mosaic trisomy 8
6	m	8 yr	CCA,PMR,EF,OH,HD,dilatation renal pelvis	46,XY/47,XY,+8	Mosaic trisomy 8
7	m	1 mo	CCA,hypospadia, dilatation renal pelvis, strabism	46,XY/47,XY,+8	Mosaic trisomy 8
8	m	1 yr	CCH,periventr leukomalacia, VD,MYC,S,hypotonia	46,XY	
9	m	1 yr	CCA,semilobar HPE,syndactyly toes,MYC,PMR,S	46,XY	Smith-Lemli-Opitz syndrome
10	m	1 yr	CCA,PMR,MYC,S,EF,neuronal migration defect	46,XY	Non-ketotic hyperglicinemia ?
11	f	10yr	CCH,PMR,S,EF,OH,hypotonia,dysarthria, dyslexia	46,XX	
12	m	3 yr	CCA,MYC,talipes,ASD,preauricular tags	46,XY	
13	f	2 mo	CCA,PMR,MYC,ACV,DWM	46,XX	Joubert syndrome ?
14	m	1 yr	CCA,PMR,CLP,OH,aphasia,schizencephaly	46,XY	Frontonasal dysplasia
15	m	1 yr	CCA,MAC,PS,CP,impeforate anus, hypospadia	46,XY	FG syndrome
16	f	4 yr	CCA,PMR,S,PC,retinal degeneration,hemivertebra	46,XX	Aicardi syndrome ?
17	f	16mo	CCA,PMR,S,occult SB,hydronephrosis,acromicria	46,XX	
18	m	1 yr	CCA,PMR,MYC , neuronal migration defect	46,XY	
19	f	2 yr	CCA,PMR,S,MAC,advanced bone age	46,XX	Sotos syndrome ?
20	f	7 yr	CCA,S,midface hypoplasia,hypoplasia right pectoral	46,XX	

CCA, corpus callosum agenesis; CCH, corpus callosum hypoplasia; ACV, agenesis of cerebellar vermis; ASD, atrial septal defect; CLP, cleft lip and palate; CP, cleft palate; DWM, Dandy-Walker malformation; EF, epicanthal folds; HD, hearing deficit; HPE, holoprosencephaly; MAC, macrocephaly; MYC, mycrocephaly; OH, ocular hypertelorism; PC, porencephalic cyst; PMR, psychomotor retardation; S, seizures; SB, spina bifida; VD, visual deficit.

1), periventricular leukomalacia (Case 8), holoprosencephaly (Case 9), neuronal migration defect (Cases 10 and 18), Dandy-Walker malformation (Case 13), and schizencephaly (Case 14).

Psychomotor retardation and seizures were the most commonly associated symptoms, being present in 13/20 and 10/20 cases, respectively. The age of onset of the seizures varied between 5 days and 11 months. There was a tendency for the association of psychomotor retardation with an early age onset of seizures. Also, patients with CNS malformations tended to have earlier age of onset of seizures. There was no recurrent EEG pattern in the sample.

Among the craniofacial anomalies the most frequently observed were microcephaly (8 cases), epicanthal folds (6 cases), ocular hypertelorism (4 cases), and macrocephaly (2 cases).

Other malformations found in the present sample included visual deficit (3 cases), hearing impairment (2 cases), congenital heart defect (3 cases), and genitourinary anomalies (3 cases).

Three patients (Cases 5,6, and 7) presented with a chromosomal anomaly, namely, trisomy of chromosome 8 (Fig 1). The aneuploid lineage was detected in peripheral lymphocytes in Cases 6 and 7, and only in fibroblasts in Case 5.

DISCUSSION

Corpus callosum dysgenesis (CCD) is a causally heterogeneous malformation that may present isolated or associated with a number of other anomalies. The failure in development of the corpus callosum may be related to different causes such as environmental (congenital toxoplasmosis and fetal alcohol syndrome, for example), genetic or vascular anomalies[9,10].

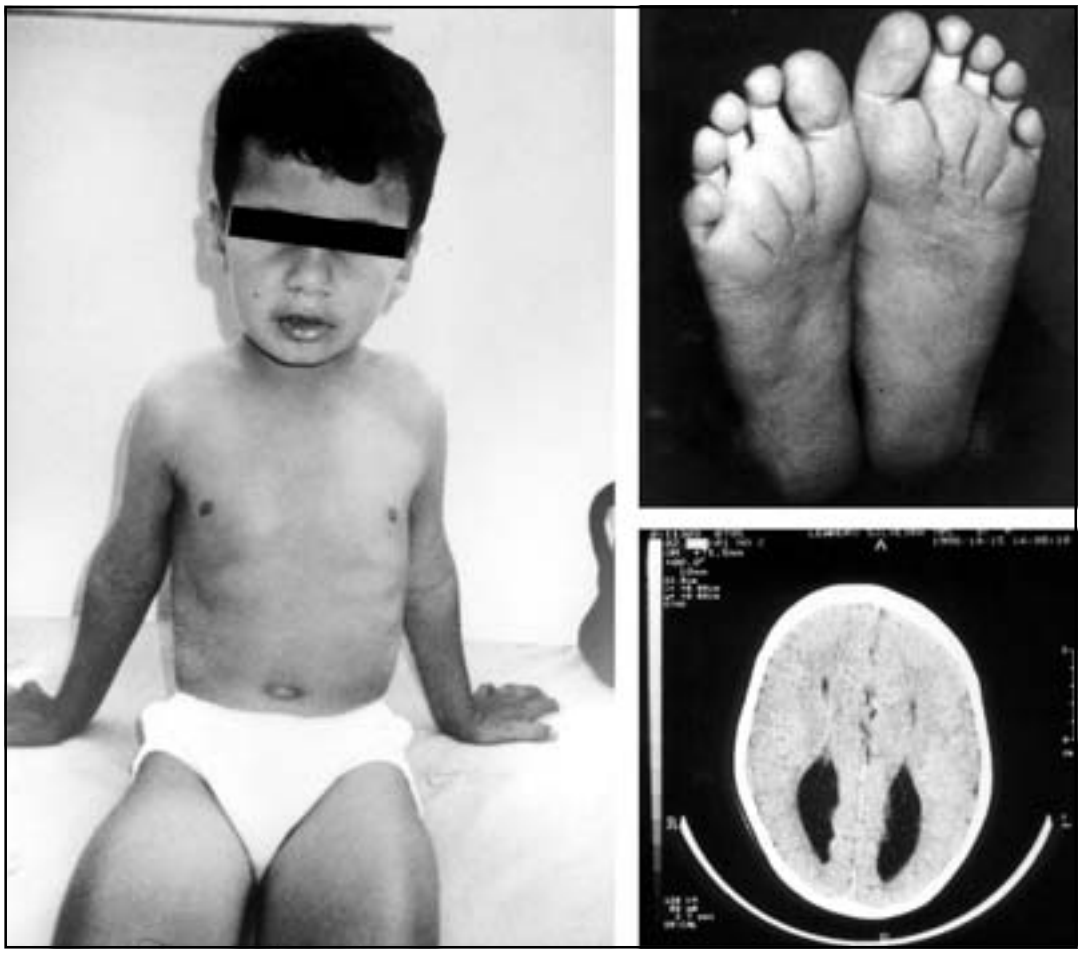

Fig 1. Mosaic trisomy 8. Note eversion of lower lip, deep furrows on soles, and CT scan showing absence of corpus callosum.

In our study group microcephaly (8/20) was more common than macrocephaly (2/20), although a similar study observed a higher frequency of macrocephaly among children with CCD[11]. The most commonly associated clinical findings in our group were seizures and psychomotor retardation. This, however, may reflect a bias towards the ascertainment of only the more severely affected cases, whereas the asymptomatic or mildly affected cases would be missed. The most commonly associated dysmorphies in our group were ocular hypertelorism and epicanthal folds.

Genetic causes of CCD include chromosomal as well as mendelian disorders[9,12,13]. Among the cytogenetic anomalies in our study group, mosaic trisomy 8 was observed in three cases (Cases 5,6,7). Trisomy 8 is a relatively common aneuploidy, with an incidence of one in 25000 births. There is a predominance of affected males, with a male to female ratio of five to one[12]. The majority of cases are mosaics, frequently observed only in fibroblasts. Also, there is a selection against aneuploid lymphocytes, so that trisomic cells are less frequent in peripheral blood cultures as the age increases. For this reason fibroblast cultures should be performed if there is clinical suspicion of trisomy 8.

Patients with CCD associated with psychomotor retardation and/or seizures should be classified syndromically, due to the etiologic heterogeneity of these conditions. The clinical evaluation of these patients should include neurological examination and a thourough search for associated dysmorphies, especially on the face and extremities. Due to a number of inborn errors of metabolism that may present with CCD, a metabolic work up should also be performed. The neuroimaging methods usually available (MRI, CT in any age, and US in babies and infants with open anterior fontanelle) may identify cases of CCD even antenatally, allowing for the prenatal diagnosis of this condition[14,15]. Due to the high frequency of mosaic trisomy 8 in children with CCD, a significant number of metaphases should ideally

be counted in order to exclude a mosaic trisomic lineage. In cases where a clinical suspicion of trisomy 8 is present, a fibroblast culture should be performed in order to establish the diagnosis.

The establishment of a nosologic diagnosis clarifies the etiology of the disease, providing more efficient genetic counseling and treatment options.

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