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APERT SYNDROME

Factors involved in the cognitive development

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ABSTRACT - Apert syndrome is characterized by craniosynostosis, symmetric syndactyly and other systemic malformations, with mental retardation usually present. The objective of this study was to correlate brain malformations and timing for surgery with neuropsychological evaluation. We also tried to determine other relevant aspects involved in cognitive development of these patients such as social classification of families and parents' education. Eighteen patients with Apert syndrome were studied, whose ages were between 14 and 322 months. Brain abnormalities were observed in 55.6% of them. The intelligence quotient or developmental quotient values observed were between 45 and 108. Mental development was related to the quality of family environment and parents' education. Mental development was not correlated to brain malformation or age at time of operation. In conclusion, quality of family environment was the most significant factor directly involved in mental development of patients with Apert syndrome.

KEY WORDS: Apert syndrome, mental development, magnetic resonance.

Síndrome de Apert: fatores relacionados ao desenvolvimento cognitivo destes pacientes

RESUMO - A síndrome de Apert é caracterizada por cranioestenose, sindactilia simétrica e outras malformações sistêmicas. O retardo no desenvolvimento neuropsicomotor é freqüentemente observado. Este trabalho tem como objetivo analisar as malformações do sistema nervoso central, o momento da cirurgia e a classe sócio-econômica associada ao nível educacional dos pais como variáveis que possam influenciar no desenvolvimento cognitivo. Foram estudados 18 pacientes com diagnóstico de síndrome de Apert com idade entre 14 e 322 meses e as alterações encefálicas foram observadas em 55,6%. O quociente de inteligência variou de 45 a 108 e estava correlacionado com a classe sócio-econômica e com o nível de instrução dos pais; não se correlacionou com as alterações encefálicas nem com o momento do tratamento neurocirúrgico. Em conclusão, a condição sócio-econômica e o nível de instrução dos pais foram relevantes na determinação do desenvolvimento cognitivo destes pacientes.

PALAVRAS-CHAVE: síndrome de Apert, desenvolvimento mental, ressonância magnética.

The Apert syndrome (AS) corresponds to the acrocephalosyndactyly type I. It was described by Apert[1] and it is characterized by craniosynostosis with fusion of any suture of the cranium and/or of the skull base, associated with midface hypoplasia, symmetric syndactyly of the hands and feet and other systemic malformations. Mental retardation is considered usual for patients with Apert syndrome and may be due to brain malformations, high intracranial pressure or family environment. AS answers for 4.5% of all craniosynostoses[2]. One estimates the incidence of AS from one to 160,000 born alive[3] to one for 55,000 born alive[4].

The malformations of the central nervous system (CNS) usually reported in this syndrome are abnormalities of the corpus callosum (CC), hypoplasia or absence of the septum pellucidum, hippocampal hypoplasia or dysplasia and cerebral cortex dysplasia[5].

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Ventriculomegaly, megaloencephaly and gyral malformation are also reported among them[5,6].

Early surgical treatment of both cranial and facial malformations reduces the deleterious effects of increasing intracranial pressure on nervous structures, therefore leading to a harmonious development of cranioencephalic set, minimizing the cognitive loss[4]. Although the correct surgical timing is still controversial[7], the present tendency is to perform it early, before the first year of life[4,7]. The surgical treatment proposes to remodel the skull in order to improve and redirect the vectorial growth of the restricted cranium, reflecting in better breathing conditions and improving the aesthetic aspects of the patients. The mental development is also related to the quality of the family environment and parents' education.

This study has as objective to correlate the brain malformations and the timing for surgery with the neuropsychological evaluation. We also tried to determine other relevant aspects involved in the cognitive development of these patients such as social classification of the families and parents' education.

METHOD

We studied 18 patients with the diagnosis of AS established by genetics, clinical examination and complementary exams, including magnetic resonance imaging (MRI) from 09/19/1999 to 11/31/2000. The evaluation of the patients was performed by an interdisciplinary team.

MRI was performed on a 0.5 T system (Flexart, Toshiba, Japan) with use of head coil. T1 weighted spin-echo, T1 weighted inversion recovery, T2 weighted fast spin-echo and fluid-attenuated inversion recovery (flair) images were obtained. The planes used were sagittal, coronal and axial.

Ventriculomegaly was defined as the non-progressive enlargement of the ventricular system without signs of hypertensive dilation such as periventricular lucency. The hypoplasia of the CC was defined as the reduction in the extension or in the thickness of the CC that is well seen in the sagital and coronal planes. Abnormalities of the septum pellucidum were classified as hypoplasia when one observed reduction in the thickness of the septum pellucidum, well demonstrated in the coronal T2 and axial flair images. The cavum Vergae was defined as a cavity posterior to the septum pellucidum. These criteria for brain abnormalities were cited before[8].

The social analysis of the families was done by using the Graciano et al.[9] method proposed in 1999 that includes the number of members in the family, educational degree, type of the habitation, employment and salary.

The cognitive evaluation was obtained by using the scale of development of Gesell and Amatruda[10], the scale of Terman and Merril[11], the WISC-III[12], WPPSI[13] and the WAIS[14]. The developmental quotient (DQ) and the intelligence quotient (IQ) were obtained as well[15].

Statistical analysis used the Spearman correlation test and the Fisher test.

RESULTS

In February 2001, the patients' age ranged from 14 to 322 months (average 107 months). Fathers' age at the time of birth ranged from 20 to 44 years (average 32.38 years) and mothers' age from 17 to 36 years (average 27.72 years). In six cases (33.3%) both father and mother were 30 years old or older. As to the gender, six patients were male (33.3%) and twelve were female (66.7%). Twelve patients underwent surgical treatment (66.7%); the age when the surgery was performed ranged from 1 to 108 months (average 30.5 months). Seven were operated before one year old. These data are summarized in the Table 1.

The social analysis of the families given by using the Graciano et al.[9] method showed that three of them were of low-inferior income, nine were of low-superior income, five were of middle-inferior income and one was of middle income. The school level of the parents pointed only three parents with superior complete level of education (Table 1).

MRI demonstrated CNS alterations as ventriculomegaly in five (27.8%) patients (Fig 1A and 1B), CC hypoplasia in five (27.8%) (Fig 1A), septum pellucidum hypoplasia in five (27.8%) (Fig 1E), cavum Vergae in two (11.1%) (Fig 1D) and arachnoid cysts in the posterior fossa in two (11.1%) (Fig 1C and 1F).All patients presented conformational alterations in the temporal lobe mesial structures, being in a more vertical position, secondary to deep middle fossa of the skull. Eight patients (44.4%) had no morphological alterations in CNS, three patients (16.7%) presented one alteration, five patients (27.8%) presented two alterations and two patients (11.1%) presented three alterations in the CNS.

Ventriculomegaly was observed in three patients that underwent surgical treatment and in two non-operated patients. CC hypoplasia was observed in three patients associated with ventriculomegaly and in two patients without ventriculomegaly (primitive CC hypoplasia) and the septum pellucidum hypoplasia was observed in two patients associated with ventriculomegaly and in three patients without ventriculomegaly (Table 1).

The intelligence quotient (IQ) or developmental quotient (DQ) was obtained with each neuropsychological evaluation and the values observed were between 45 and 108 (average 74). The age of the

Table 1. Casuistic. The social analysis of the families based on the number of members in the family, educational degree, type of the habitation, employment and salary, brain malfor mations.

Case	Gender	Age (months)	Father's age (years)	Mother's age (years)	Age at surgery (months)	Educational level	Social degree (income)	Ventriculomegaly	Corpus callosum	Septum pellucidum	Arachnoid cysts
1	M	210	27	27	76	primary I complete	low-inferior	–	normal	normal	–
2	F	112	44	27	12	superior complete	middle-inferior	–	normal	normal	–
3	M	139	41	32	96	superior complete	middle-inferior	–	hypoplasia	normal	–
4	F	203	26	30	108	primary II incomplete	low-superior	–	normal	Cavum vergae	present
5	F	322	28	26	No	primary II incomplete	low-superior	–	normal	normal	–
6	F	94	39	32	29	primary I complete	low-superior	present	hypoplasia	normal	–
7	F	65	36	29	11	secondary complete	middle-inferior	–	normal	normal	–
8	F	56	34	35	1	superior incomplete	low-superior	–	normal	normal	–
9	M	102	32	27	2	superior incomplete	middle-inferior	present	hypoplasia	hypoplasia	–
10	M	41	22	17	No	primary II complete	low-superior	–	normal	normal	–
11	F	114	42	36	2	primary I complete	middle-inferior	–	hypoplasia	hypoplasia	–
12	F	70	29	21	24	superior complete	middle	–	normal	normal	–
13	F	148	30	30	4	secondary complete	low-superior	present	normal	hypoplasia	–
14	F	17	30	22	No	primary I incomplete	low-inferior	–	normal	hypoplasia	–
15	M	22	41	25	No	primary I incomplete	low-inferior	present	hypoplasia	normal	present
16	M	14	29	30	No	primary II complete	low-superior	present	normal	Cavum vergae	–
17	F	145	20	23	1	primary II complete	low-superior	–	normal	hypoplasia	–
18	F	60	33	30	No	secondary complete	low-superior	–	normal	normal	–

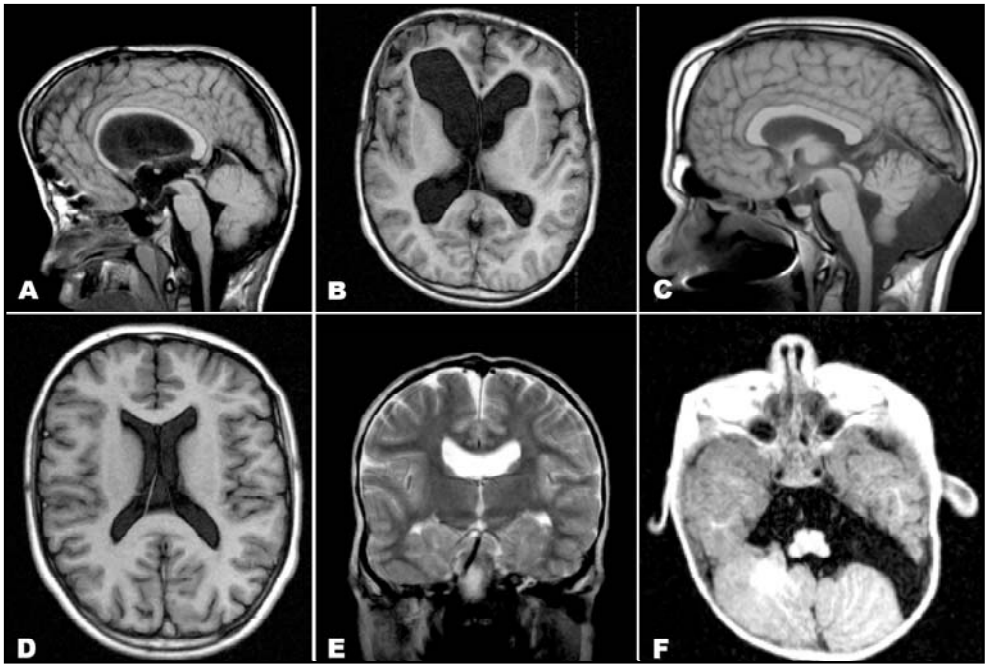

Fig 1. Ventriculomegaly and corpus callosum hypoplasia - MRI in sagital plane and T1 acquisition (A) and axial plane and T1-IR acquisition (B). cavum Vergae and arachnoid cyst in the posterior fossa - MRI in sagital plane and T1 acquisition (C) and axial plane and T1-IR acquisition (D).Septum pellucidum hypoplasia - MRI in coronal plane and T2 acquisition (E). Arachnoid cyst in the posterior fossa - MRI in axial plane and T1-IR acquisition (F).

Table 2. IQ and DQ scores.

Case	Test	IQ verbal	IQ execution	IQ	DQ	Final score
1	WAIS	71	74	71		71
2	WISC-III	100	108	104		104
3	WISC-III	65	71	65		65
4	WAIS	78	68	70		70
5	WAIS	71	74	70		70
6	WISC-III	75	73	72		72
7	WPPSI (PRE-WISC)	79	81	78		78
8	Terman-Merril (LM)	–	–	75		75
9	WISC-III	100	106	108		108
10	Terman-Merril (LM)	–	–	84		84
11	WISC-III	74	86	78		78
12	WPPSI (PRE-WISC)	79	78	76		76
13	WISC-III	71	78	72		72
14	WISC-III	48	51	47		47
15	GESELL	–	–	–	45	45
16	GESELL	–	–	–	87	87
17	WISC-III	59	60	56		56
18	Terman-Merril (LM)	–	–	74		74

Gesell, developmental scale of Gesell; Age, age at the neuropsicological evaluation; DQ, developmental quotient; IQ, total intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; Terman-Merril (LM), Terman-Merril Test (LM), review of the Stanford-Bin et test; WISC, Wechsler Intelligence Scale for Children; WISC-III, Wechsler Intelligence Scale for Children, third edition; WPPSI (PRE-WISC), Wechsler preschool and primary scale of intelligence.

Table 3. Statistical analisys (factors correlated to the IQ).

Correlation	Test		
Brain abnormalities	Fisher exact test	p = 0.069	
Occurrence of surgery	Fisher exact test	p = 0.407	
Age at surgery	Spearman correlation	p = 0.296	r = -0.329
School level	Spearman correlation	p = 0.035	r = 0.499
Social degree	Spearman correlation	p = 0.009	r = 0.595

patients during the cognitive evaluation was 9 to 311 months (average 107 months), and the IQ was obtained in 16 cases and the DQ in two patients. These scores (IQ and DQ) were analyzed together and four cases (22%) presented scores below 70 as the normal inferior limit), as seen in Table 2.

Statistical analysis (Table 3) shows that the mental development was related to the quality of the family environment ($p = 0.009$; $r = 0.595$) and parents' education ($p = 0.035$; $r = 0.499$). The mental development was not correlated to brain malformation (Fisher; $p = 0.068$) or age at the time of operation ($p = 0.296$; $r = -0.329$).

DISCUSSION

Considering the analysis of the epidemiological data of this study, we observe accordance with the literature concerning the high frequency of both parents being older than 30 years[16]. Average ages of 28.9 years for mothers and 34.1 years for fathers were reported by Tolarova et al.[16], who also described that in 20% of cases both father and mother were older than 35 years by the time of the patients' birth. The high frequency of parents older than 35 years old by the time of the patients' birth has also been underlined by other studies[17]. Older paternal age should influence new mutations[17].

The majority of AS cases occurs sporadically, with dominant genetic inheritance and complete penetrance. The most accepted current concept is that AS is originated from two mutations in the gene which codifies the fibroblast growth factor receptor 2 (FGFR2)[17-19]. A discrepancy regarding the prevalence of female patients was observed in the present study, which showed a two-for-one proportion whereas the literature demonstrates a one-for-one proportion[4,16].

The most frequently reported cranial malformation is bilateral craniosynostosis of the coronary and lambdoid sutures allied with reduction of the anterior cranial fossa and deep middle and posterior cranial fossa[20], what is able to justify some abnormalities in the placement of brain structures in these patients. Cranial shape alterations due to multiple craniosynostosis can put a limit on cerebral growth and development. Intracranial hypertension (ICH) can occur in up to 45% of the cases[4,21], and can be in agreement with a higher morbidity in Apert syndrome[22].

MRI is the most accurate test to identify CNS alterations[23], which were previously described by necropsy[3,24]. The present study protocol evidenced CNS morphologic alterations in ten patients (55.6%) by using an organized and uniform analysis. The most frequent findings were ventriculomegaly, alterations in the CC and in the septum pellucidum, which were in accordance with the literature[4,5].

Renier et al.[4] described absence of CNS alterations in 28% of the cases and one malformation in 25% of them, while in this study 44.4% of the patients presented no alterations in the CNS and 16.7% presented only one CNS alteration.

Ventriculomegaly, which was reported in 27.8% of the patients in this study, was observed in 43% of cases according to Renier et al.[4] and in 45% according to Cohen and Kreiborg[5]. In the majority of cases ventriculomegaly has no hypertensive characteristic. The genesis of the ventricular dilation is thought to be multifactorial. In some of the cases it can be hypertensive, presenting the characteristic symptoms and signals. In the present study, it was not observed hypertensive hydrocephalus in any of the cases.

Septum pellucidum alterations characterized by cavum Vergae, hypoplasia or agenesis were reported in 55% of the cases studied by Renier et al.[4] and in 38.9% of the patients in this study. Renier et al.[4] identified the absence of CC abnormalities in 70% of the cases, which is in accordance with the frequency of 72.2% cases with normal CC observed in this study. The occurrence of CC hypoplasia in patients without ventriculomegaly (two cases in this study) suggests primitive hypoplasia of the CC. Otherwise, when it is associated with ventriculomegaly (three cases in this study), the hypoplasia of the CC may be secondary to the enlargement of the lateral ventricles.

As to the occurrence of structural abnormalities, CNS alterations did not correlate to surgical treatment. The conformational alterations of the CNS structures were evident when operated patients were compared to non-operated ones[8]. The classically described rising of the encephalic structures was reduced in operated patients.

The cognitive evaluation was obtained by using indistinguishably the same IQ and DQ because the number of demanded it, as already used in other studies in the literature[25,26]. The average score reported (74) lies within the superior limit observed in the literature.

Considering the score 70 as the inferior limit of normality, 77.8% of the patients presented satisfactory score. Patton et al.[27] related 48% of patient with

AS with IQ scores superior to 70. Renier et al.[26] related 32% in this situation. The average score (74), is in agreement with the data from Lefebvre et al.[28] (73.6) and Murovik et al.[29] (72.5) that did not correlate the IQ with the occurrence of surgery or with ventriculomegaly in 44 patients with AS.

There are plenty of studies trying to correlate brain abnormalities and low scores in cognitive tests since the earliest publications about AS[5,27,28,30,31].

Abnormalities of the septum pellucidum and CC were not correlated with the IQ contrarily to other data that correlate the septum pellucidum abnormalities with low IQ scores[26]. Every case in the present study without brain abnormalities (n=8) had IQ scores higher than 70 and all patients with IQ score below 70 (n=4) had at least one brain abnormality. These numbers have not statistical significance.

The timing of the surgery was not correlated with better IQ scores as in other studies[27,32], differently from Renier et al.[26] that related 50% of satisfactory IQ scores in operated patients with less then one year of age and only 7.1% of satisfactory IQ scores in patients operated later (n=38).

The social and economic aspects are relevant in the mental prognosis of these patients. When the patients live in institutions, they present worse IQ scores[26,27,33]. Some studies show that these children are abandoned at the date of birth[26], then the low IQ score may be the consequence of the institutionalization and not the reason for it.

In the present study the social aspects and the educational degree were correlated to the cognitive development as was observed by other authors[4,26]. All patients in this study live with their families what can explain the better average of the IQs comparing to the literature that present higher percentage of patients living in institutions[4,26].

In conclusion, the quality of family environment and the parents' educational level were the most significant factors directly involved in the mental development of the patients with Apert syndrome.

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