

## THESES

APERT SYNDROME: SKULL ABNORMALITIES, BRAIN MALFORMATIONS, NEUROPSYCHOLOGICAL EVALUATION AND TIMING FOR SURGERY (ABSTRACT)\*. **THESIS. SÃO PAULO, 2002.**

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The Apert syndrome corresponds to the acrocephalosyndactyly type I, 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. Most frequently the abnormal fusion occurs in the coronal sutures. Mental retardation is considered usual for patients with Apert syndrome and may be due to brain malformations, high intracranial pressure or family environment.

The objectives of this present study are: to summarize the brain malformations observed in magnetic resonance images; and detect the bone abnormalities of the cranium and the skull base observed in the helical tomography images of the patients with Apert syndrome; to analyze the changes in the disposal of the brain structures after surgery; to correlate these findings 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, parents' education and the timing for surgery. The relevance of the mental development of the patient to his/her family's quality of life was also analyzed.

In the present study, 18 patients with Apert syndrome were thoroughly studied based on protocols previously completed. In February of 2001 the age of the patients was between 14 and 322 months. The evaluation of the patients was done by an interdisciplinary team. The image studies included helical tomography with three-dimensional reconstruction of the skull and they showed short anterior cranial fossa in seven patients and deep medial and posterior cranial fossa in all cases. Using the magnetic resonance images of the brain, ventriculomegaly was observed in five cases, hypoplasia of corpus callosum in five cases, hypoplasia of septum pellucidum in five cases, cavum Vergae in two

cases and arachnoid cyst of the posterior fossa in two cases.

Forty-four percent of the patients did not present any brain abnormalities. Morphologic measurements of the corpus callosum were established and showed values between 0.4409 and 1.0237. There were statistical correlation of these data with the results of the surgery ( $p = 0.012$ ;  $t = 2.83$ ). The social analysis of the families showed that 12 of them were of low-income and 6 were of middle-income. The intelligence quotient or developmental quotient was obtained with each neuropsychological evaluation and the values observed were between 45 and 108 (average = 74). The quotients were unsatisfactory (below 70) in 4 patients. A short form of the Questionnaire on Resources and Stress was used to analyze the quality of life of the patients and their families. In this questionnaire factor II - "Pessimism" was the most frequent factor observed. On the other hand, the intelligence quotient of the patients was directly correlated to the factor I - "Parent and Family Problems" ( $p = 0.036$ ,  $r = -0.497$ ) and to the factor III - "Child Characteristics" ( $p = 0.017$ ,  $r = -0.556$ ). The mental development was also 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 ( $p = 0.296$ ;  $r = -0.329$ ).

In conclusion, morphologic measurements of the corpus callosum are evidence of changes in the disposal of the brain structures after surgery. Quality of the family environment was the most significant factor directly involved in the mental development of the patients with Apert syndrome and this is relevant to determine the quality of life of these families.

**KEY WORDS:** Apert syndrome, surgical approach timing.

\*Síndrome de Apert: correlação entre as alterações cranianas e encefálicas, avaliação neuropsicológica e momento cirúrgico (Resumo). Tese (Doutorado), Universidade de São Paulo (Área: Neurologia). Orientador: José Píndaro Pereira Plese.

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PITUITARY MORPHOLOGY IN THE GH DEFICIENCY FOR MUTATION IN THE GROWTH HORMONE-RELEASING HORMONE RECEPTOR GENE. (ABSTRACT)\*. **DISSERTATION. ARACAJU, 2001.**

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The objectives of this study were: to evaluate the pituitary morphologic characteristics by NMR examinations, of the pituitary-hypothalamus region in affected homozygous adults and children individuals and in heterozygous adults individuals, all with a mutation (IVS1 + 1G → A) in the receptor gene of the releasing hormone of the growth hormone (GHRH-R); to compare the values of the pituitary volume and the cranial volume of the affected homozygous adults individuals, with the values of a group of non-affected adults individuals of the same region; to verify the occurrence of pituitary hypoplasia, morphology of the pituitary stalk and neurohypophysis location in the affected adults and children group.

We studied 38 individuals from the community of Carretéis and surroundings – Itabaianinha-SE. They were divided in 4 groups: Group I – 9 adults (5M and 4F), normal homozygous (WT / WT), with age of  $38 \pm 11.7$  years (Control Group); Group II – 13 adults (6M and 7F), heterozygous (MUT / WT), with age of  $42.33 \pm 8.60$  years; Group III – 8 adults (3M and 5F), affected homozygous (MUT / MUT), with age of  $41.37 \pm 15.04$  years; Group IV – 8 children (3M and 5F), affected homozygous, with age of  $11.87 \pm 2.47$  years.

The affected homozygous individuals (MUT / MUT) had a particular clinical phenotype: short stature, sharp voice timbre, cherubim facies, central obesity, thin and wrinkled skin, very reduced IGF-1 concentration and GH response to the clonidina and insulin hypoglycemic tests.

All individuals were evaluated regarding: anthropometric measures (stature, head circumference and cranial volume) and IGF-1 concentration. Pituitary-hypothalamus region was examined by NMR scans. Pituitary height, length and width were measured in order to build its volume by using the cubic ( $V = h \cdot l \cdot w$ ) and elliptical ( $V = h \cdot l \cdot w / 2$ ) shapes. Pituitary volume and the cranial volume were compared through the following variations: Pituitary Volume Fraction (PVF), Cranial Volume Fraction (CVF) and Volume Ratio (VR). The statistical analysis was carried out through the SSPS.8.0 program (Statistical Packet for Social Science) and data expressed in average  $\pm$  SD. It was considered statistical significance when  $p < 0.05$ .

In adults cephalic perimeter showed no difference between Groups I and II ( $54.66 \pm 1.22$  cm and  $54.57 \pm$

$1.63$  cm respectively) and was reduced in Group III ( $50.42 \pm 1.14$  cm).

There was no difference in pituitary height between Groups I and II ( $4.41 \pm 0.62$  mm and  $4.61 \pm 1.55$  mm respectively). In Group III, the pituitary height was  $2.67 \pm 0.87$  mm and the pituitary height SDS,  $-1.95 \pm 0.58$ ; in Group IV, the pituitary height was  $2.87 \pm 0.79$  mm and the pituitary height SDS,  $-2.84 \pm 0.04$ . Pituitary hypoplasia was present in all Group IV individuals and in 5/8 of Group III patients.

The pituitary volume resulted normal in Groups I and II ( $414.56 \pm 71.57$  mm<sup>3</sup> and  $417.12 \pm 140.86$  mm<sup>3</sup> respectively), meanwhile in Groups III and IV ( $124.13 \pm 64.23$  mm<sup>3</sup> and  $155.68 \pm 39.79$  mm<sup>3</sup> respectively) they were reduced, characterizing the pituitary hypoplasia, it seems to be due to a presence decrease of the somatotrophs resulted from the genetic involvement in the GHRH-R gene that blocks GHRH action.

A comparative study was developed between the pituitary and the cranial volumes, through the PVF, the CVF and the VR. There was no difference between Groups I and II, in PVF (1/1) and CVF (1 / 0.99). When the comparison was done between Groups I and III, the PVF (1 / 0.29) has a difference of 71% while the CVF (1 / 0.78) has a difference of 22%.

Groups I and II VR had the same values (0.015  $\pm$  0.040); in Groups III and IV, the values (0.006  $\pm$  0.02) were 3 times lower than Groups I and II. The relation pituitary / cranial volume is 0.015% in Groups I and II and 0.006% in Groups III and IV.

In the affected homozygous treated children (Group IV), it was observed that pituitary hypoplasia was present for the entire group (the pituitary height SDS,  $-2.84 \pm 0.79$ ), when compared before and after treatment, an increase in both stature and a cephalic perimeter was found. The treatment of the affected children with recombinant GH influences more the height bone growth and the cephalic perimeter.

We conclude that there is a pituitary hypoplasia in the homozygous adults and children individuals affected by the IVS1 + 1A → G mutation. The decrease of the pituitary volume is higher than the decrease of the cranial volume in the affected homozygous individuals. The decrease of pituitary volume is not exclusively due to decrease of the cranial volume but on the reduction of the somatotrophs too.

Pituitary volume was similar in heterozygous and normal homozygous individuals.

All analyzed individuals had complete pituitary stalk and neurohypophysis in topical location.

The finding of hypoplasia isolated from the pituitary suggests the DIGH presence, especially by the GHRH-R mutation.

**KEY WORDS:** pituitary hypoplasia, nanism, GHRH-R mutation.

\*Morfologia da hipófise na deficiência de GH por mutação no receptor do hormônio liberador do GH (Resumo). Dissertação de Mestrado. Universidade Federal de Sergipe (Área: Medicina). Orientador: Manuel Hemínio de Aguiar Oliveira.

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**LEPROSY NEUROPATHY: ADMINISTRATION OF INTRAVENOUS METHYLPREDNISOLONE PULSOTHERAPY (ABSTRACT)\*. DISSERTATION. RIO DE JANEIRO, 2001.**

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Twelve patients diagnosed as leprosy neuropathy were studied, regardless of their leprosy classification. All patients were submitted to a clinical (neurological) evaluation, to an electroneuromyographic exam and, six of them, to a nerve biopsy. They had different clinical symptoms. Some of them were on use of oral corticosteroid. They all received one gram of intravenous methylprednisolone during 90 minutes, for three days and had this same dosage repeated during the two following weeks.

They were then seen at the ambulatory and their symptoms were analyzed according to the Visual Analogic Scale (VAS). After three months of pulsotherapy, another electroneuromyography was performed. Those patients who did not show clinical improvement were submitted to another course of pulsotherapy, according to the histopathological exam. Those who had

major neurological deficits received a monthly treatment (a single dose of one gram of intravenous methylprednisolone).

There was a six to seven points improvement in the VAS. There was no similar improvement concerning the electroneuromyographic exam. Those patients taking oral corticosteroid had a better response to the intravenous medication, considering the period of time they were on oral medication and their complains before the initial treatment with intravenous methylprednisolone.

The intravenous treatment with methylprednisolone in pulsotherapy must be considered in leprosy neuropathy due to its good results and decreased risks in long term therapy.

**KEY WORDS:** leprosy, peripheral neuropathy, methylprednisolone intravenous pulsotherapy.

\*Neuro-hanseníase: emprego da metilprednisolona em pulsoterapia intravenosa (Resumo). Dissertação de Mestrado, Universidade Federal do Rio de Janeiro (Área: Clínica Médica). Orientador: Sérgio Augusto Pereira Novis.

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**COMPARATIVE STUDY OF *CYSTICERCUS LONGICOLLIS* AND *CYSTICERCUS CELLULOSAE* ANTIGENS IN NEUROCYSTICERCOSIS IMMUNODIAGNOSIS OF HUMAN (ABSTRACT)\*. DISSERTATION. CURITIBA, 2000.**

*RUBENS LUIZ FERREIRA GUSSO \*\**

Two immunodiagnosis tests were standardised: indirect fluorescent antibody test (IFAT) and enzyme-linked immunosorbent assay (ELISA), for the detection of anti-*Cysticercus cellulosae* antibodies, in cerebrospinal fluid (CSF), in carriers of neurocysticercosis (with alive or degenerating cysticerci).

Two antigens were studied: a homologous (*Cysticercus cellulosae*) and a heterologous (*Cysticercus longicollis*) antigen. For the production of *Cysticercus longicollis* antigen only the vesicular fluid was used on the ELISA test, which was much superior than *Cysticercus cellulosae*. For *Cysticercus cellulosae*, the parasitic mem-

branes of the scolex and total saline extract were used due to the small yield of the vesicular liquid. For IFAT the number of particles was established in 20 to 30 (for field, increase of 400x). The conjugate concentration used was 1:250. The ELISA test was standardised: antigen concentration: 1 mg/well; dilution of the CSF: 1/1; dilution of the conjugate: 1: 3000; cut-off to *C. cellulosa* was 0.210 and cut-off to *C. longicollis* was 0.306. When compared to the gold standard and the serologic techniques with homologous antigen, characterizing the definitive diagnosis, the IFAT sensitivity was of 90.6%, considering the total number of analyzed samples (39), being 90.5% for patients' samples with cysticerci in activity and 90.9% for patients' samples with calcifications in the encephalon. As for the ELISA

test the sensitivity for the same group of samples was of 90.9%, being from 95.2% and 83.3%, for patients' samples with cysticerci in activity and for patients' samples with calcifications respectively, equally with definitive certainty diagnosis for neurocysticercosis.

The heterologous antigen can be used as alternative to the homologous antigen. The revenue and the control of the environmental variables in the maintenance of the stump and the indicators of the tests allow the use of this biological component for production of extracts destined antigens for the research of anti-*Cysticercus cellulosa* antibodies in CSF.

**KEY WORDS:** *Cysticercus longicollis*; *Cysticercus cellulosa*; neurocysticercosis

\*Estudo comparativo dos antígenos de *Cysticercus longicollis* e *Cysticercus cellulosa* no imunodiagnóstico da neurocisticercose humana (Resumo). Dissertação de Mestrado, Universidade Federal do Paraná (Área: Ciências Veterinárias, Setor de Ciências Agrárias). Orientadora: Vanete Thomaz Soccol; co-orientador: Sérgio Monteiro de Almeida.

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