NEUROLOGICAL MANIFESTATIONS OF DENGUE INFECTION: CLINICAL CHARACTERISTICS AND CEREBROSPINAL FLUID ANALYSIS (ABSTRACT)*. **DISSERTATION. NITEROI, 2005.**

*CRISTIANE NASCIMENTO SOARES***

Introduction. Neurological manifestation is considered a rare complication of dengue infection. Encephalitis, myelitis, Guillain Barré syndrome (GBS), cranial nerve palsies have been recognized as clinical consequences of dengue infection.

Objective. To determine and correlate the neurological and cerebrospinal fluid (CSF) characteristics of patients with dengue infection and to evaluate the use of two dengue enzyme-linked immunosorbent assays (ELISA) kits in the CSF.

Method. We report 17 IgM seropositive patients for dengue who presented different neurological manifestations in the course of the acute infection. With these manifestations, patients were divided in four groups: headache, encephalitis, myelitis and GBS. Total and differential cytology count, protein and glucose levels and ELISA for IgM and IgG dengue antibodies were examined in the CSF samples from all 17 patients. In six of them (myelitis and GBS patients), the albumin and IgG concentrations were determined in serum and CSF. CSF and serum from Brazilian and German patients with other neurological diseases were used as controls for IgG and IgM dengue tests.

Result. We had seven patients with encephalitis, two with myelitis, four with GBS and four with headache associated with acute dengue infection. The CSF was normal in the cases of headache and in 42.8 % of the encephalitis cases. GBS showed a CSF-blood barrier dysfunction and the typical protein-cytology dissociation. Patients with myelitis showed specific antibodies intrathecal synthesis. IgM dengue antibodies in CSF were obtained in 47% of the 17 cases but with a high specificity of 97 % for Brazilian controls and 100% for German controls. Otherwise, IgG dengue tests revealed a low specificity when Brazilians controls were used, detecting previous contact with the virus in our population.

Conclusion: In endemic regions, dengue infection should be always investigated as the etiological agent in cases of encephalitis, GBS and myelitis. A normal CSF analysis does not exclude the diagnosis of encephalitis and headache caused by dengue infection. On the other hand, intrathecal synthesis of antibodies may suggest the virus presence in the central nervous system (CNS). Our findings, based on the detection of IgM dengue in CSF were an important tool to confirm dengue infection in the CNS but its absence does not exclude the diagnosis. Further, the high positivity to IgG dengue ELISA in the CSF of our Brazilin controls reflects previous contact with the virus in our population.

KEY WORDS: dengue infection, cerebrospinal fluid, neurological manifestations, viral encephalitis, myelitis, Guillain Barré syndrome.

*Manifestações neurológicas da dengue: aspectos clínicos e análise do líquido cefalorraqueano. Dissertação de Mestrado, Universidade Federal Fluminense, (Área: Neurologia). Orientadores: Marzia Puccioni e Marcos R G de Freitas.

***Address: Rua Aureliano Coutinho 81/605, 25625-000 Petrópolis RJ, Brasil. E–mail: crist_nsoares@yahoo.com.br*

IMMUNOHISTOCHEMICAL STUDY OF THE MOLECULAR ALTERATIONS IN THE ASTROCYTIC TUMORS: TUMORIGENIC PATHWAYS AND RESISTANCE MARKERS (ABSTRACT)*. **DISSERTATION. FORTALEZA, 2005.**

*MÁRIO HENRIQUE GIRÃO FARIA***

The present study aimed to evaluate the expression of genes involved in the tumorigenic process and in the chemoresistance mechanisms of the astrocytic tumors.

A clinical and epidemiological analysis, histopathological evaluation and immunohistochemical study of the proteins Ki-67, c-Myc, GFAP, p53, $p21^{WAF1/CIP1}$, $p27^{KIP1}$, Bcl-2, Bax, EGFR, erbB-2, $p21^{Ras}$, MGMT, GSTπ, TS and TopoIIα using streptoavidin-biotin-peroxidase method were performed in 55 different graduations of astrocytomas (WHO) (13 grade I, 14 grade II, 7 grade III, 21 grade IV) and 05 samples of non-tumoral tissue (control group).

The distribution by age, sex and tumoral localization of astrocytomas patients in Fortaleza reproduced, in a general way, the worldwide trends.

The histopathological findings evaluated with semiquantitative criteria confirmed the classification parameters for astrocytomas established by WHO.

The stain for Ki-67 antigen increased as according to astrocytic tumors progression; its detection in more than 8.0% of the tumoral cells distinguished Astrocytomas Grade IV, labeled index between 1.5 and 8.0% differentiated Astrocytomas Grade III and values below 1.5% discriminated low-grade tumors (I and II).

The TopoIIα and c-Myc (nuclear) expression demon-

strated association with cellular proliferation in astrocytomas, however not in an exclusive way.

The cytoplasmic c-Myc protein positive index was bigger among high-grade tumors (71.43%), with maximum expression scores in Astrocytomas Grade IV (LI mean=15.57; H mean=24.42).

In general, 76.9% of the Astrocytomas Grade IV tumoral cells revealed moderate positive index for GFAP.

The positive index and expression scores for p53 and $p27^{KIP1}$ (nuclear and cytoplasmic) proteins showed a tendency to increase with the astrocytic tumors progression, while the $p21^{WAF1/CIP1}$ tumor suppressor detection demonstrated opposite orientation (except in grade IV).

The percentage of Bcl-2 and Bax positive tumors increased in accordance with histological grade of astrocytomas, with general positive index of 43.26% and 24.67%, respectively. Bcl-2 staining scores demonstrated propensity to addition according to tumoral evolution, while the scores for Bax was similar in all graduations.

The erbB2 protein expression was evidenced only between Astrocytomas Grade IV (positive index=14.28%), while the overexpression of EGFR protein was distinguished in grade I and IV astrocytic tumors, with respectively 46.15% and 61.90% of positive cases.

$p21^{Ras}$ protein detection was preponderant in Astrocytomas Grade II (positive index=37.71%), being absent in high-grade tumors (III and IV).

The EGFR overexpression and p53 mutation configured mutually exclusive events in astrocytomas tumorigenesis, as well as $p21^{Ras}$ protein and ErbB receptors family overexpression.

High positive index for enzymes MGMT, GSTπ and TS was evidenced in astrocytic tumors. MGMT expression scores were high and constant among different histological categories, including non-tumoral specimens (LI mean = 69.43).

GSTπ scores demonstrated tendency to reduction in accordance with malignant evolution of astrocytomas, while the values for TS reached higher levels on Astrocytomas Grade IV (H mean=63.33).

TopoIIα positive index demonstrated inclination to augment in agreement with the progression of astrocytic tumors, whereas the staining scores had been similar in grade II, III and IV astrocytomas (LI mean=27.71).

The results obtained by current investigation indicated Ki-67 antigen as the best cell proliferation marker. The p53 mutation configured an initial and relevant event in astrocytomas, as well as potential indicative of tumor progression. $p21^{WAF1/CIP1}$ tumor suppressor detection represented important resource for deduction of functional situation of p53 gene, while the $p27^{KIP1}$ functional activation was not compromised by astrocytomas tumorigenic process. Astrocitomas Bcl-2/Bax ratio denoted increasing of cellular survival orientation in accordance with malignant evolution of these tumors.

$p21^{Ras}$ protein overexpression was distinguished as a grade II typical molecular event and a virtual marker of tumor not-progression.

Cytoplasmic accumulation of c-Myc protein configured initial and significant phenomenon in astrocytomas tumorigenesis, being a direct reflex of the nuclear expression of c-myc gene and the tumoral malignance.

The combined analysis of the investigated molecular markers confirmed p53 gene mutation as the main tumorigenic pathway of astrocytomas, even though EGFR overexpression has been the predominant alteration in grade IV tumors and the c-myc gene expression has represented a distinct and alternative molecular pathway to different tumor graduations.

The remarkable presence of MGMT, GSTπ and TS enzymes configured virtual indication of chemoresistance for many antineoplastic agents, while the high expression of TopoII? revealed this enzyme as a potential therapeutic target in the astrocytic tumors

KEY WORDS: astrocytoma, immunohistochemistry, molecular markers, tumorigenesis, tumoral resistance.

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***Address: Laboratório de Genética Molecular – LABGEM (Departamento de Patologia e Medicina Legal), Universidade Federal do Ceará, Rua Alexandre Baraúna s/n, 60430-270 Fortaleza CE, Brasil. E-mail: mariofaria@doctor.com.*

STOMATOLOGIC CONDITIONS EVALUATION IN PATIENTS WITH CONGENITAL HYDROCEPHALUS (ABSTRACT) * **DISSERTATION . ARACAJU, 2005.**

MARIA AUXILIADORA SILVA PEREIRA **

The aim of this study was to evaluate the stomatologic conditions of patients with congenital hydrocephalus.

Thrity children with congenital hydrocephalus were examined with ages between 2 and 6.5 years, from both genders, admitted at Governador João Alves Filho