THESES

CONGENITAL MUSCULAR DYSTROPHY: A STUDY OF PHENOTYPICAL VARIABILITY AND CLINICAL-IMMUNOHISTOCHEMICAL CORRELATION (ABSTRACT)*.**THESIS**. **SÃO PAULO**, **1999**.

*UMBERTINA CONTI REED***

We studied 57 patients with congenital muscular dystrophy (CMD) and among them 40 were assessed for 5-laminin chains (alfpha-1, alpha-2, beta-1, beta-2, and gamma-1) by immunohistochemistry on the muscular biopsy, and 7 only for alpha-2 laminin (merosin). Of the 47 patients assessed for merosin, 22 were merosin-deficient and 25 merosin-positive, including two typical cases of Walker-Warburg syndrome with "cobblestone" lissencephaly, hydrocephalus, severe mental retardation, microphthalmia and other ocular abnormalities. A subgroup of 7 patients with merosin deficiency showed only a partial reduction that was detected by both antibodies for alpha-2 80 kDa and alpha-2 300 kDa in 6 and only by the antibody for alpha-2 300 kDa in one, thus demonstrating that the antibody for alpha-2 300 kDa offers a more precise immunohistochemical detection of the partially deficient type of CMD.

Twenty-one merosin-deficient patients had abnormal T2 sequence signal of white matter on magnetic resonance imaging (MRI) and one had hypodensity of brain white matter on computerized tomography (CT) scanning; no patient in this group achieved independent walking except one with partial deficiency who after a period of independent walking lost it at the end of the first decade of life. Among the remaining patients with partial deficiency of merosin we observed that three patients with complete absence of one merosin fragment and reduction of the other showed a more severe clinical phenotype than other three who had a partial expression of both fragments. The immunohistochemical pattern of the remaining merosin chains in 19 merosin-deficient patients who had complete immunohistochemical analysis of laminin chains on muscle biopsy was characterized by overexpression of alpha-1 chain in 100% and weakly reduced expression of beta-1, beta-2 and gamma-1 chains in 89.5%, 73.7% and 57.9%, respectively.

Excluding the two cases with Walker-Warburg syndrome, in addition to the remaining 23 merosin-positive patients we included 5 familiar cases without biopsy whose phenotype was identical to the respective siblings. Of the last 5 patients without any immunohistochemical analysis, three had abnormal white matter on brain MRI and severe muscle involvement and were included within the merosin-deficient group and two had respectively mild and moderate clinical phenotype, one of them with no abnormalities of brain white matter on CT scanning, while the other did not perform neuroimaging examination. Both patients were included among merosin-positive group. In the total group of 30 merosin-positive patients, 70% achieved independent walking and among 19 who had a complete immunohistochemical analysis of laminin chains, 31.6% showed alpha-1 overexpression, and 26.3%, 21.1% and 21.1% showed a slight reduction of expression of beta-1, beta-2 and gamma-1 laminin chains, respectively.

Considering the total amount of patients with and without immunohistochemical study, we observed homogeneous clinical severity in the merosin-deficient group (25 cases) and strong clinical heterogeneity in the merosin-positive group (30 cases), that included 5 cases with associated central nervous system involvement (brain cortical atrophy in one and mental retardation in 4, two of them also with cataracts), two possible cases of rigid spine syndrome and one possible case of hypotonic-sclerotic type of CMD.

Statistical analysis between the two groups was done and there was a significant difference regarding many different parameters. In relation to clinical phenotype - age of onset, poor sucking and respiratory distress at birth, degree of congenital hypotonia, maximal motor capacity, muscular weakness, facial involvement, facial dysmorphism, creatine kinase level, and type of clinical course - showed statistical significance and pointed to a prognosis much more severe in merosin-deficient patients. In relation to muscle biopsy - lipomatosis, endo-perimysial fibrosis, and variation in fiber size - were significantly higher in the merosin deficien group. Finally, also the results of the immunohistochemical analysis showed that both - the overexpression of alpha-1 chain, and the slight reduction of beta-1, beta-2 and gamma-1 chains expression - were significantly more marked in the merosin-deficient type of CMD.

We conclude that the overexpression of the alpha-1 chain associated with a slight reduction of beta-1 and beta-2 laminin chains is characteristic of the merosin-deficient group that is better defined by the utilization for the alpha-2 300 kDa and even in a few merosin-positive cases who had a greater clinical severity (30%) there are heterogenous manifestations and it is not possible to demonstrate clinical overlap between the two subgroups.

KEY WORDS: **congenital muscular dystrophy**, **phenotypical variability**, **clinical-immunohistochemical correlation**.

*Distrofia muscular congênita: estudo da variabilidade fenotípica e análise da correlação clínico - imuno-histoquímica (Resumo) Tese de Livre-Docência, Faculdade de Medicina da Universidade de São Paulo (Disciplina de Neurologia Infantil).
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PHYSIOPATHOGENY OF MOEBIUS SYNDROME AND ARTHROGRIPOSIS DUE TO IN UTERO MISOPROSTROL EXPOSURE (ABSTRACT)*. **THESIS**. **SÃO PAULO**, **1999**.

*MARIA JOAQUINA MARQUES-DIAS***

Misoprostol, a PGE1 marketed as Cytotec, has been misused as the most popular abortifacient in Brazil. The drug may determine congenital malformations mainly of the extremities and central nervous system when it fails to cause the abortion.

Neuroclinic, neurophysiologic, imaging and neuropathologic studies of 42 children exposed to the drug in the 1st trimester of pregnancy, with Moebius syndrome (MS, 31) or arthrogriposis multiplex (AMC, 11) revealed suggestive anomalies that support an embryonic vascular disruption as the main causative mechanism of these abnormalities.

In the MS group, 4 patients presented the syndrome as the sole congenital anomaly; in 19 MS was associated with abnormalities of the extremities; and 8 also had associated congenital hydrocephalus.

All patients with AMC presented other anomalies of the extremities, and 4 associated to congenital hydrocephalus.

Cranial CT revealed brainstem calcifications in 2 patients. Neuropathologic study in 3 patients disclosed bilateral old foci of gliosis, necrosis with calcifications, in the brain stem, bilaterally, situated very close to some cranial nerve nuclei. In 9 patients with AMC electroneuromyographic study revealed a neurogenic pattern and in 8 muscular CT scanning showed marked atrophy and replacement of muscle by adipose tissue. CT in patients with hydrocephalus revealed supratentorial dilatation of ventricles with relative preservation of IV ventricle volume.

The clinical aspects studied allow us to suggest that MS and AMC in these patients would be caused by a transient arterial disturbance related to misoprostol in the territories of the subclavian artery between the 4th and 6th or of the spinal arteries until the 12th weeks, respectively.

KEY-WORDS: **misoprostol**, **Moebius syndrome**, **congenital arthrogriposis multiplex**.

*Fisiopatogenia da síndrome de Moebius e da artrogripose decorrentes da exposição *in utero* ao misoprostol (Resumo). Tese de Livre-Docência, Faculdade de Medicina da Universidade de São Paulo (Disciplina de Neurologia Infantil).
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PRIMARY HEADACHES IN ADOLESCENTS: CLINICAL CHARACTERISTICS (ABSTRACT)*. **DISSERTATION**. **NITERÓI**, **1998**.

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The clinical features of 53 adolescents presenting primary headache have been analyzed, according to the criteria of the International Headache Society (IHS, 1988). The studied group was constituted by 53 patients, 35 females (66%) and 18 males (34%), whose ages ranged from 12 to 18 years-old.

The analysis of the headache characteristics allowed the diagnosis of migraine in 36 subjects (67.9%), tension-type headache (TTH) in 10 (18.9%) and TTH associated migraine in 7 (13.2%).

In the group presenting migraine (n= 36), 69.44% presented migraine without aura (MOA); 16.67%, migrainous disorder not fulfilling the criteria of migraine (MD); and 13.89%, had migraine with aura (MWA).

In the TTH group (n= 10), eight patients presented episodic tension-type headache (ETTH); and two, chronic tension-type headache (CTTH).

In the group having TTH associated migraine (n= 7), four had MOA and ETTH; two had MWA and ETTH; and one, had MD and ETTH.

Among those suffering from migraine, the headache was of a pulsating quality in 91.67%; mild to severe intensity in 100%; unilateral location in 38,89%; duration longer than four hours in 80.55%; and with aggravation by habitual activities in 91.67%.

In the patients presenting TTH, the headache was of a non-pulsating quality, mild to moderate intensity, bilateral location and duration longer than 30 minutes. Aggravation by habitual activities was mentioned by one individual.

Changes in the pattern of the headache in relation to menstruation and menarche were more frequent in migraine than in TTH. From the 35 females evaluated, 13 (37.14%) referred changes in the pattern of the headache after menarche. Among those, 10 presented migraine; two TTH; and one, TTH associated migraine. Only four (11.43%) related their attacks to menstruation, all of them having migraine. Only three migrainous females (8.57%) had previous use of oral contraceptives, and all of them did not refer any change, after their administration.

KEY WORDS: **headache**, **headache in adolescent**, **primary headache**.

*Cefaléia primária em adolescentes: características clínicas (Resumo). Dissertação de Mestrado, Universidade Federal Fluminense (Área: Neurologia). Orientador: Pedro Ferreira Moreira Filho.

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NEUROCONDUCTION EXAMINATION IN PATIENTS WITH HTLV-I ASSOCIATED MYELOPATHY (ABSTRACT)*. **DISSERTATION**. **NITERÓI**, **1999**.

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The main neurological manifestation of the Human T-Cell Lymphotropic Virus Type I (HTLV-I) is spastic paraparesis, of progressive nature, also known as HTLV-I associated myelopathy (HAM) or tropical spastic paraparesis. Since the discovery of the virus, other neurological manifestations, like polymyositis and peripheral neuropathy, have been associated to it.

A group of 54 individuals positive to HTLV-I associated myelopathy were surveyed from the electrophysiological point of view (neuroconduction). The evaluated nerves were: the radial, the ulnar and the median from the upper limbs; and the fibular, the tibial and the sural, from the lower limbs. From the neuroconduction examination, we observed that the peripheral nerve is compromised in 68.5% of the patients. In this group, 37.8% presented a mononeuropathy, the median nerve was the most compromised, 24.4% manifested multiple mononeuropathy, and 37.8% presented polyneuropathy (84.6% presented sensorymotor polyneuropathy and 15.4% presented exclusively a motor polyneuropathy; 61.5% manifested a mixed polyneuropathy, with 30.8% indicating that myelin is compromised and 7.7% presenting axonal polyneuropathy).

The most frequent detected electrophysiological alterations were increased latency on the sural nerve (30.2%) followed by the decrease median motor amplitude (25.6%).

Statistical analyses were performed comparing two samples using the Student t test: Sample 1 (patients with myelopathy presenting alterations in the neuroconduction exam) and Sample 2 (patients with myelopathy not presenting alterations in the neuroconduction examination). Statistical results showed that the association of myelopathy to neuroconduction alterations was not casual. All the evaluated parameters showed significant statistical values, with the only exception being the fibular nerve latency.

We conclude that electrophysiological compromising of the peripheral nerve is frequent in patients with HTLV-I associated myelopathy. Furthermore, electrophysiological compromising can arise even

when the patient does not present clinical manifestations denoting this kind of problem. Hence, the study of the neuroconduction has to become a routine for patients with HTLV-I.

KEY WORDS: **nerve conduction**, **HTLV-I**, **peripheral neuropathy**.

* Estudo da neurocondução em pacientes com mielopatia pelo HTLV-I (Resumo). Dissertação de Mestrado, Universidade Federal Fluminense (Área: Neurologia). Orientador: Osvaldo José Moreira do Nascimento.

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CRITICAL EVALUATION OF CEREBROSPINAL FLUID ALTERATIONS IN NEUROSCHISTOSOMIASIS (ABSTRACT)*. **DISSERTATION**. **SÃOPAULO**, **2000**.

*ALEXANDRE REMENCIUS***

Objective: The aim of this study was a bibliographical revision about cerebrospinal (CSF) from patients with schistosomiasis (sch) and neuroschistosomiasis (nsch) published in the literature from 1930 to 1998.

Method: 383 samples of CSF from patients with sch and nsch were studied in respect to: aspect and color, opening pressure, manometry, number and type of cells, protein content, protein electrophoresis, glucose content, and immunological tests for sch.

Results: The lowest number of samples was reported in the 1930 and 1940 decades and the major in the 1980 and 1990 decades. Age-bracket more compromised was between 20 and 39 years-old. Masculine gender predominated over the feminin. Mansonic sch was the more frequent, followed by japonic sch and hematobic sch. In 199 cases the indication for puncture was myelopathy without granulomatous pseudotumor. This form represented 41 cases (12.9%). Convulsion corresponded to 24 cases (7.6%) and headache to 22 cases (6,9%) of total cases for which puncture was indicated. In 157 (69.2%) samples the puncture was at lumbar level. CSF was clear and colorless in 100 (80%). CSF cytology was normal in 116 (36.5%). Hypercytosis occurred in 140; it was discrete in 83 (26.1%) and moderate in 57 (17.9%). Protein content is referred in 327; it was normal in 101 (30.9%) and increased in the remaining. Moderate protein increase was more frequent, occurring in 153 (46.8%). Eosinophil cells were cited in 91 samples, corresponding to 44.4% of the total 205 samples with cell description. Gamma globulins were normal in 39 (42.4%) and increased in 53 (57.6%). Glucosis was normal in 177 (76.0%) of the 233 samples in which it was referred; it was decreased in 56 (24.1%).

Conclusion: Cytology, with special attention to eosinophil cells, protein content and protein electrophoresis, and glucose content should always be investigated in CSF samples from patients with suspicion of nsch. Immunologic tests to sch in CSF should always be done to help diagnosis confirmation.

KEY WORDS: **schistosomiasis**, **central nervous system**, **cerebrospinal fluid**.

*Avaliação crítica das alterações do líquido cefalorraqueano na neuroesquistossomose (Resumo). Dissertação de Mestrado, Universidade de São Paulo (Área: Neurologia). Orientador: José Antonio Livramento.

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