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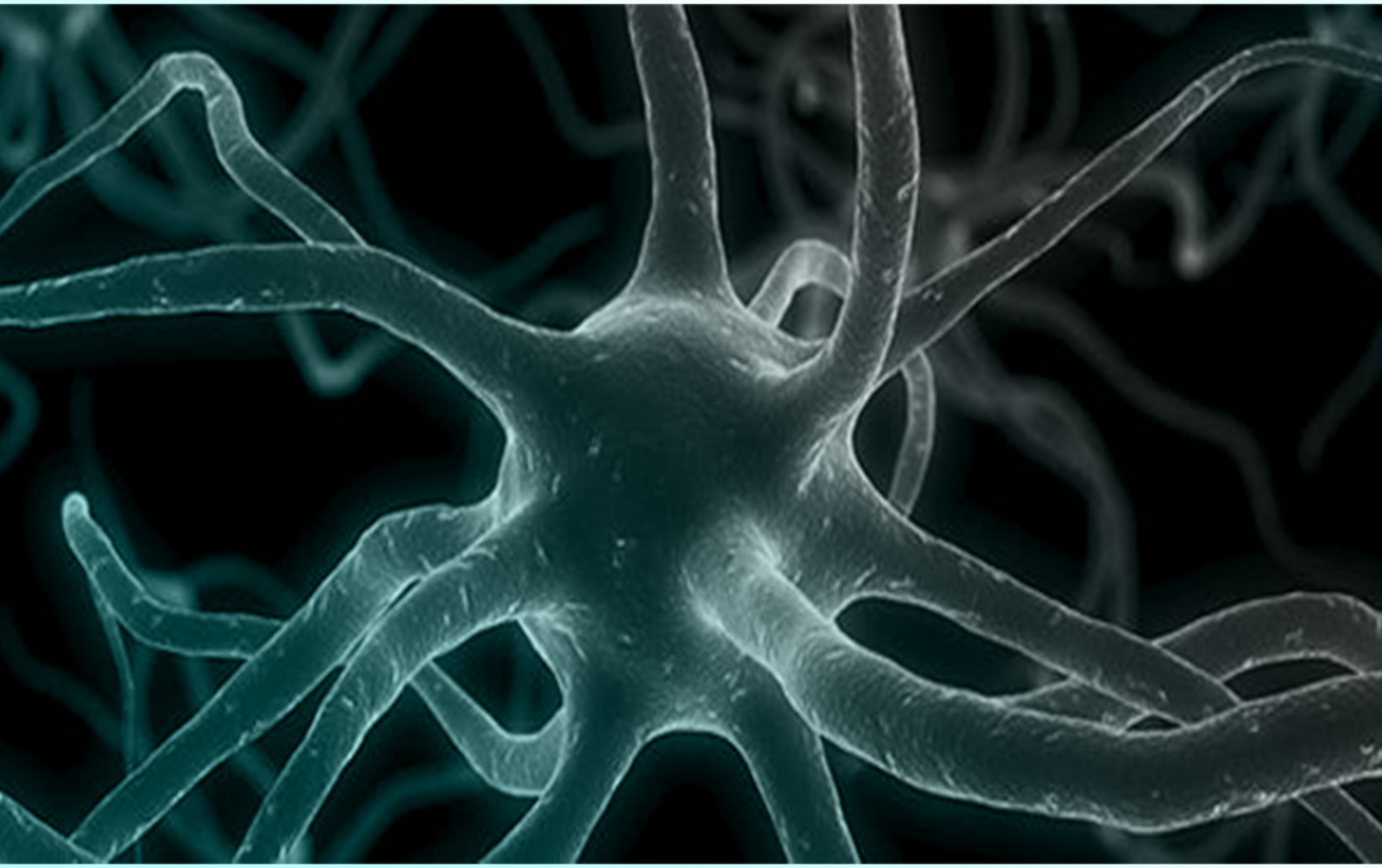

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Editorial

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Endovascular treatment of Stroke: Historical Perspective

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Effective acute ischemic stroke therapy hinges on rapid restoration of blood flow to the ischemic tissue. Since the National Institute of Neurological Diseases and Stroke r-tPA study,[1] intravenous fibrinolytic therapy in appropriately selected patients has been the primary method used to open the vessels and improve neurological outcome from stroke. The intravenous administration allowed for widespread dissemination of the technique, since therapy could be started very rapidly after the diagnosis is made. However, successful treatment with r-tPA requires careful patient selection and adherence to strict inclusion and exclusion criteria. As a result, there is a significant number of patients who could not receive the therapy. Even though significantly better than placebo for most stroke patients, some still suffered a poor outcome in spite of therapy. This raised the question whether there could be a way to directly apply the fibrinolytic agent to the occlusive thrombus with catheter-based techniques in an effort to more effectively treat large vessel occlusions. Intra-arterial thrombolysis was reported helpful in restoring flow in relatively small series of patients, especially situations like basilar thrombosis, with a dire natural history.[2] However, only one study, the PROACT study showed a positive impact on neurological outcome compared to placebo.[3] Results of this study were often used to justify endovascular treatment of patients ineligible or unresponsive to intravenous r-tPA but intra-arterial administration of the fibrinolytic was often unsuccessful restoring flow in the occluded vessel, and not infrequently was associated with hemorrhagic transformation of the stroke. The endovascular armamentarium increased in the early years of the 21st century with the development of the MERCI device (Stryker, Fremont, CA, USA), a cork-screw-like device designed to mechanically retrieve thrombus.[4,5] This resulted in a higher success rate in opening occluded vessels compared to pharmacological methods and could be used in patients in whom r-tPA is contraindicated. In the years that followed, additional mechanical thrombectomy devices were introduced including stent-like retrievers like the Solitaire (ev3-Medtronic, Irvine, CA, USA), and the Trevo (Stryker, Fremont, CA, USA), and the Penumbra aspiration system (Penumbra, San Leandro, CA, USA) which all appeared to be far more effective than Merci in opening occluded vessels. The IMS III study sought to provide evidence of the effectiveness of endovascular techniques plus intravenous r-tPA versus intravenous r-tPA alone, but it enrolled patients when these newer devices were just becoming available. Most endovascular patients were only treated with intra-arterial r-tPA and, not surprisingly, the study showed no benefit in outcome.[6] This prompted some to predict the death of endovascular stroke therapy. A short time later, results of well-designed studies beginning with the MR CLEAN study[7] appeared in rapid succession showing significantly improved outcome with endovascular treatment of large vessel occlusions using the modern stent-like retrievers.[8-11] Within a short period of time, endovascular therapy went from being on the verge of extinction to being an integral part of comprehensive stroke care. The future will no doubt see investigations refining patient selection criteria, evaluating the role of advanced imaging techniques, evolving and improving the devices and techniques and improving infrastructure to allow all appropriate patients have access to these devices and the trained physicians that can use them safely and effectively.

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Research

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Treatment of the Carpal Tunnel Syndrome with Laser

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ABSTRACT

Objecive: To test the effectiveness of low intensity laser therapy in patients with carpal tunnel syndrome (CTS).
Methods: Patients with clinical and ENMG diagnosis of CTS never previously treated were included and submitted to clinical evaluation and conduction studies before and after treatment. Sensory and motor conduction studies were performed by conventional described techniques. Low intensity laser treatment was by 660 nm wave length, average power of 30 nw, continuous operation area of 0.06 cm^2, fluence of irradiation of 10 J/cm^2, exposure of 10 seconds per point, totalling 6 points of irradiation on the carpal tunnel, from the proximal to the distal sense. Laser was positioned at 90° to the skin, 2 sessions per week during 3 months were performed (24 sessions). To this moment 30 hands of 18 patients were studied.
Results: Clinical data and different parameters on the conduction studies of the median nerve showed improvement after the treatment.
Conclusion: In our opinion low intensity laser therapy is a new, not expensive and easy to apply encouraging treatment for CTS.

KEYWORDS: Carpal tunnel syndrome; Laser; Treatment.

ABBREVIATIONS: CTS: Carpal Tunnel Syndrome; VAS: Visual Analogic Scale; CFA: Carpal Flexion Amplitude; SAPB: Strength of the Abductor Pollicis Brevis.

INTRODUCTION

The Carpal Tunnel Syndrome (CTS) is the most common entrapment neuropathy. After surgery different types of complication may occur,[1-10] then search for new clinical forms of treatment is necessary. The main clinical treatments are physical therapy, bracing, steroid injections and alternative therapies as yoga and acupuncture.[11-13] In recent years, it has taken on increasing importance treatments with ultrasound and laser.[14]

The effects of laser on the peripheral nervous system are controversial. Laser application on the distal sensory branch of the radial nerve led to increased latency and decrease velocity.[15] Application on the median nerve in 51 normal volunteers, led to a slight increased latency in sensory antidromic conducting study.[16] Such data were not confirmed by others, whose normal volunteers showed no changes in conduction studies after application of Laser.[17] Some authors described effectiveness of Laser in reversing carpal tunnel syndrome,[18] but this was not confirmed by others.[19] In one meta-analysis, only 2 papers with clinical and conduction studies improvement were found.[20] One Brazilian study proposed a randomized controlled trial, which will be useful to assess the effectiveness of the conservative treatment and low-level laser therapy for patients with carpal tunnel syndrome.[21] The aim of this study was to test the effectiveness of low intensity laser therapy in patients with CTS.

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METHODS

After approval by the Ethics Committee on Human Research of our Institution, patients with clinical and ENMG diagnosis of CTS never previously treated were included. Exclusion criteria were diabetes and other endocrine diseases, renal failure, alcoholism or occupational exposure to environmental toxic agents, patients with any other medical conditions that cause polyneuropathy, and antecedents of previous surgery, trauma, burns or fractures in the affected limb. Visual Analogic Scale (VAS), Carpal Flexion Amplitude (CFA) using a goniometer and Strength of the *Abductor Pollicis Brevis* (SAPB) muscle using a dynamometer (Daniels) were determined before and after treatment. Antidromic sensory conduction studies using ring electrodes, and motor conduction studies using standard surface disc electrodes were performed by conventional described techniques[22] – Figure 1. Low intensity laser treatment using gallium-indium-phosphorus-aluminium Laser emitter was by 660 nm wave length, average power of 30 nw, continuous operation area of 0.06 cm^2, fluency of irradiation of 10 J/cm^2, exposure of 10 seconds per point, totalling 6 points of irradiation on the carpal tunnel, from the proximal to the distal sense. Laser was positioned at 90° to the skin, 2 sessions per week during 3 months were performed (24 sessions) – Figure 2. Statistical analysis from the data obtained before and after treatment was done by the paired "t" test. Correlation between clinical and conduction studies was performed by the Spearman correlation test and Pearson correlation test.

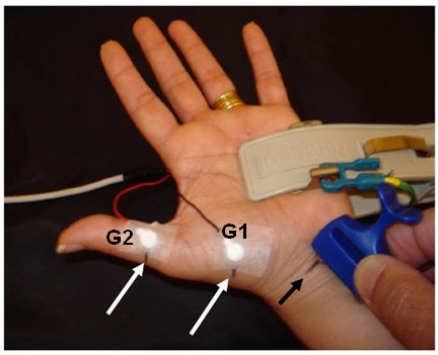

Figure 1: Motor conduction study. The distal motor latency of the median nerve is obtained by stimuli applied with distal cathode (blue, black arrow) and G1 and G2 electrodes positioned according to the belly-tendom technique (white arrows).

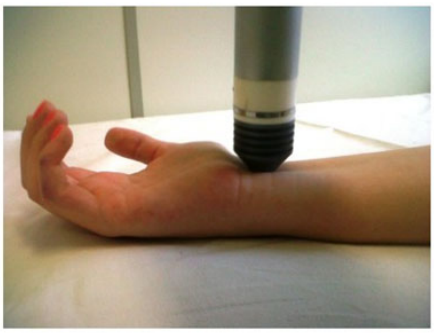

Figure 2: Application of the low-level laser on the median nerve across the carpal tunnel.

RESULTS

To this moment 30 hands from 18 patients were analysed (6 with unilateral CTS; 12 with bilateral CTS). From the clinical study, VAS, CFA and SAPB showed improvement after treatment ($p<0.001$, $p<0.0028$ and $p<0.0001$, respectively). VAS values are showed in the Graphic 1. From the conduction studies, distal motor latency and sensory conduction velocity improved after treatment ($p<0.0003$ and 0.0002, respectively). Distal motor latency values are showed in the Graphic 2. For the amplitude no significance was observed. In the Spearman correlation test, no statistic significance was observed. In the Pearson correlation test negative correlation between distal motor latency and SAPB was found (for larger values of latency minor values of strength). It was also observed positive correlation between distal motor latency and VAS (for larger values of latency larger values on the visual analogic scale of pain).

DISCUSSION

The analysis of the 30 hands from 18 patients was possible in the last 2 years. For these 30 hands, visual analogic scale, carpal flexion amplitude, strength of the APB muscle, distal motor latency and sensory conduction velocity showed improvement. One study found no statistically significant clinical differences between the group of patients treated with laser and the placebo group, but improved sensory conduction in patients who received Laser was observed, similarly to our data.[23] The Spearman correlation test between clinical data and conduction studies parameters showed no statistic significance. As the Spearman correlation test applies predominantly to ordinal scale variables, and, as in our study the only ordinal scale used was the VAS (visual analogue scale of pain, ranging from zero to ten), we opted for conducting also the Pearson correlation test. The results by this test were logical and predictable, for larger values of distal motor latency, minor values of the strength of the APB muscle and larger values of the VAS were found.

In the last years some encouraging results of Laser for the CTS were described, as subjective improvement;[24,25] or improvement of the conduction studies and clinical data.[26,27] In a recent prospective, randomized, placebo-controlled trial Evcik, et al. reported positive effects on hand and pinch grip strengths after low-level laser therapy.[28] Beneficial effects of the combination of laser therapy with other methods as night orthopedic splint[25] or magnetic stimulation[29] were also reported.

CONCLUSION

In our opinion, low intensity laser therapy is emergent as a new, not expensive and easy to apply encouraging treatment for CTS.

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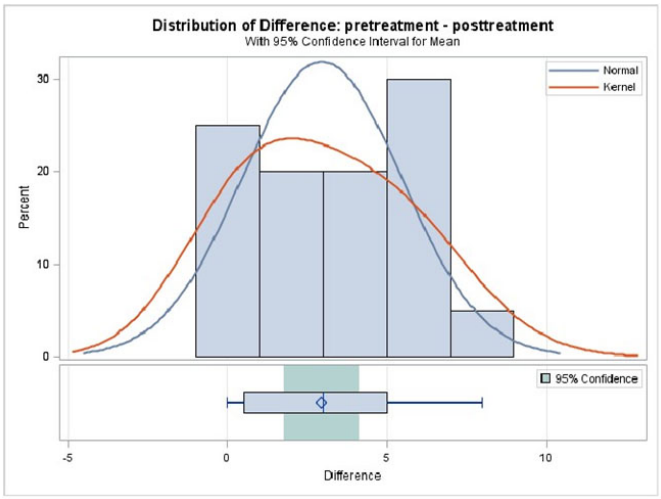
The TTEST Procedure

Difference: pretreatment - posttreatment

N	Mean	Std Dev	Std Err	Minimum	Maximum
20	2.9500	2.5021	0.5595	0	8.0000

Mean	95% CL Mean		Std Dev	95% CL	StdDev
2.9500	1.7790	4.1210	2.5021	1.9028	3.6545

DF	t Value	Pr > |t|
19	5.27	<.0001



Graphic 1: Paired "t" test for the visual analogic scale (before and after treatment).

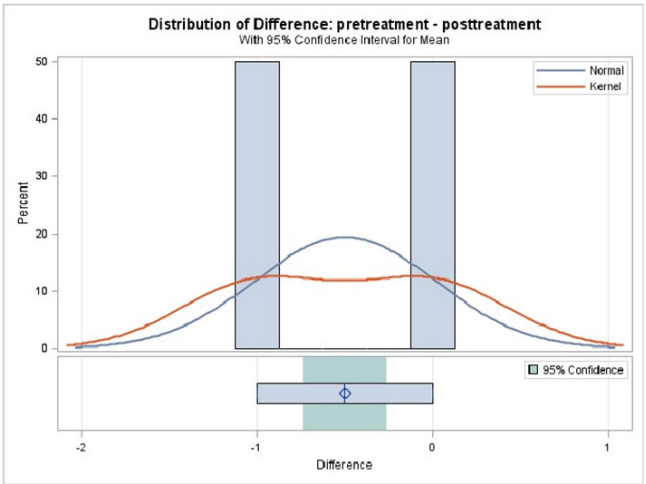
The TTEST Procedure

Difference: pretreatment - posttreatment

N	Mean	Std Dev	Std Err	Minimum	Maximum
20	-0.5000	0.5130	0.1147	-1.0000	0

Mean	95% CL Mean		Std Dev	95% CL	StdDev
-0.5000	-0.7401	-0.2599	0.5130	0.3901	0.7493

DF	t Value	Pr > |t|
19	-4.36	0.0003



Graphic 2: Paired "t" test for the distal motor latency (before and after treatment).

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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CONSENT STATEMENT

The authors have obtained written informed consent from the patient before submission of this manuscript for publication.

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Case Report

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Gaucher's Disease, Myoclonic Seizures after Splenectomy: A Case Report

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SUMMARY

Gaucher's Disease (GD) is the most prevalent lysosomal storage disorder, resulting from the accumulation of glucocerebrosidase in the cells of macrophagemonocyte system due to a deficiency in lysosomal glucocerebrosidase. Here we report a case of GD, a patient that presented with myoclonic seizures after splenectomy, was just diagnosed as myoclonic seizures at first attending a neurologist. GD is so rare that it is easily missed diagnosis or misdiagnosis in the clinic. When neurologists engage a patient presented with myoclonic seizures, it is importance to collect more information about his medical and family history, have him done essential examinations, especially of children with unexplained splenomegaly.

KEYWORDS: Gaucher disease; Splenectomy; Myoclonic seizures.

ABBREVIATIONS: GD: Gaucher's Disease; EEG: Electroencephalographic; INR: International Normalized Ratio; PTT: Partial Thromboplastin Time; HBV: Hepatitis B Virus; CT: Computed Tomography; GC: Glucosylceramide.

INTRODUCTION

GD is an inherited autosomal recessive metabolic defect due to a deficiency in the lysosomal enzyme b-glucocerebrosidase, which leads to deposition of glucocerebroside in cells of the macrophagemonocyte system, predominantly in the spleen, liver, and bone marrow. There are three clinical types, including type 1 (GD1), the non-neuronopathic type; type 2 (GD2), the infantile-onset, an acute neuronopathic type and type 3 (GD3), the juvenile-onset, a chronic neuronopathic type 1.[1] The third type was divided into three subgroups (GD3a, GD3b and GD3c) on various clinical features. In GD3a, patients exhibit as progressive myoclonic epilepsy, with or without horizontal supranuclear gaze palsy, and mild systemic findings. A young man of GD3a we reported as follows, who was treated only as myoclonic seizures at first attending our neurology clinic, while he had been diagnosed as GD years ago.

CASE REPORT

An 18 year-old boy with main complaint of convulsions in the left upper limb came to see a neurology doctor in our hospital. The left upper limb tic occurred several to dozens of times a day, and each time just lasted for seconds. And he was diagnosed as myoclonic seizures, with lamotrigine 25 mg once a day and a Electroencephalographic (EEG) examination. The routine EEG revealed generalized nonrhythmic paroxysmal rapid spikes with occipital predominance increased by photic stimulation and normal background activity. The frequency of spikes increased in harmony with the frequency of flicker (up to 25 Hz) and spikes frequently occurred on eye closure (Figures 1A, 1B and 1C). The EEG neurologist got a medical history that his convulsions developed after the splenectomy about 3 years ago, and he had been diagnosed as GD before. He was first discovered to have an enlarged spleen because

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of a cold and was diagosed with "GD combined hepatosplenomegaly" (without details) in Guangdong Provincial People's Hospital since 6 years old. He was suggested to take enzyme replacement therapy (ERT), but not accepted it for lack of money. In the decades that followed, he took traditional Chinese medicine, and rechecked by B-ultrasonic irregularly still with hepatosplenomegaly. His β glucosidase levels was considerably subnormal (without accurate number recorded), which can be diagnosed with GD, tested in Peking Union Medical College Hospital on December 17th, 2010. He was a Chinese and born with a parents with no consanguineous marriage. He was delivered after full-term normal pregnancy. Development of the child was normal. There was no history of easy bruising or prolonged bleeding on trauma, hematemesis, fever, night sweats, and weight loss or bone pains. His father' brother had splenomegaly with unknown reasons. His other family members, including his parents

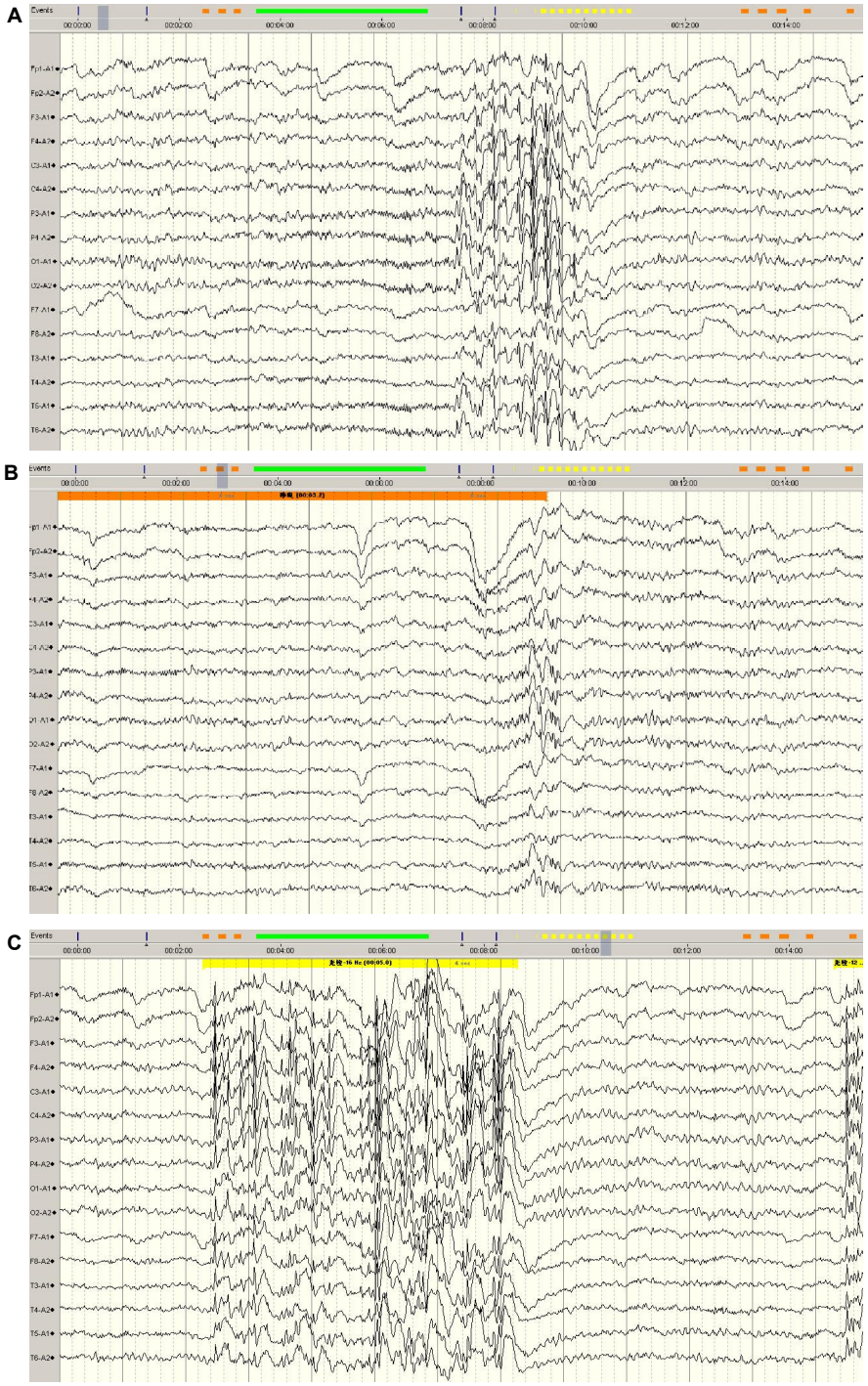

Figure 1: Generalized nonrhythmic paroxysmal rapid spikes and normal background activity are observed in the routine EEG examination of the patient (1A). There is marked eye closure sensitivity (1B). The frequency of the flicker is 9-22Hz (1C).

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and two siblings, were normal. 3 years ago, he was admitted into our hospital, the chief complaint was splenomegaly for 10 years and left abdominal pain for 2 days. On physical examination, he looked malnourished; however there was no icterus or lymphadenopathy. He had firm, non tender massive splenomegaly and no hepatomegaly. There were no signs of ocular motor problems or other neurological abnormalities. The patient and his family denied any apparent intellectual decline noticeable in his daily life. Rest of systemic examination was essentially normal. Lab investigations revealed bicytopenia (hemoglobin=9.9 g/dl, white blood cells=3.17*109/L and platelets=73*109 /L). Liver enzymes were normal (aspartate aminotransferase=34I U/ml, alanine aminotransferase=19 IU/ml), and the same as serum proteins and albumin, kidney function test and urine analysis. PT (Prothrombin Time) was 15.3 s [International Normalized Ratio (INR)=1.29] and Partial Thromboplastin Time (PTT) was 50.5 s. Hepatitis B Virus (HBV), Syphilis and HIV (human immunodeficiency virus) antibody test were negative. Computed Tomography (CT) revealed grossly enlarged spleen (247*140 mm) [Figures 2A, 2B] and splenic and portal veins had large diameter. Bone marrow [Figure 3] aspiration was performed which revealed Gaucher cells in a background of proliferous erythroid, myeloid and megakaryocytic lineage cells. Splenectomy was performed and one section completely capsulated, soft and dark red, partially drab yellow, were sent to pathological biopsy. Lots of Gaucher cells were seen in spleen sections (Figure 4). Final diagnosis was GD3a.

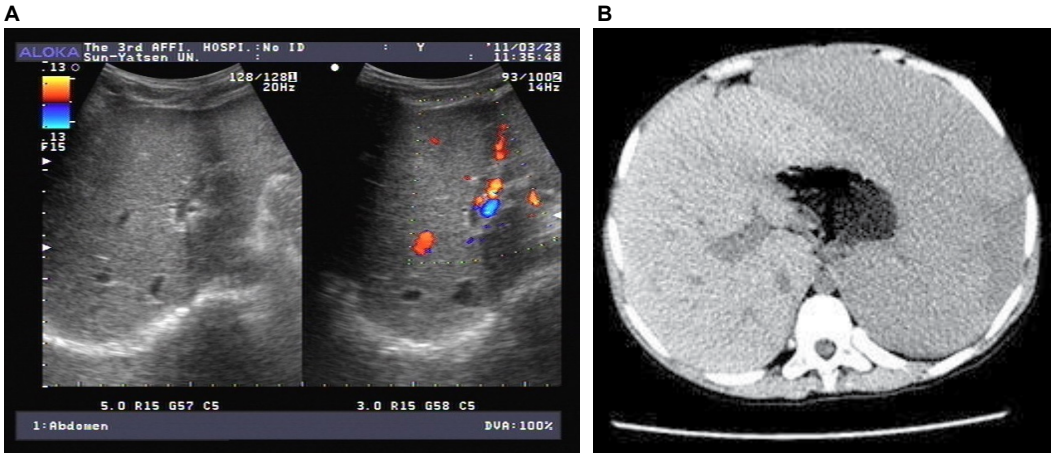

Figure 2: A. US and B. CT show grossly enlarged spleen.

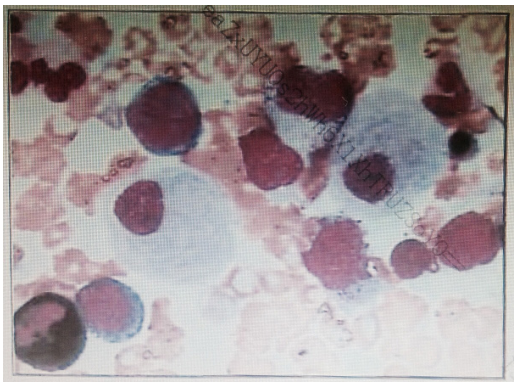

Figure 3: Gaucher cells in marrow smear (Wright Giemsa stain*100).

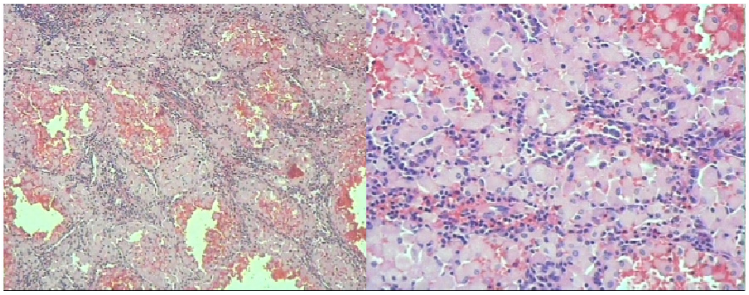

Figure 4: Lots of foamy cells were seen in spleen sections.

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DISCUSSION

GD is inherited as autosomal recessive traits with a overall incidence of approximately 1 in 100,000 live births.[1] GD is characterized by accumulation of Glucosylceramide (GC) in the cells of monocyte/macrophage system located in liver, spleen or central nervous system called Gaucher cells, which causes splenomegaly or epilepsy. And the glucocerebrosidase gene located on chromosome 1q21 and consists of 10 introns and 11 exons[2] has been described in the GBA gene region with more than 300 mutations, including point mutations, deletions, insertions, splicing aberrations and various rearrangements.

Gaucher disease can also present as hydrops in the perinatal period which is often lethal. There may be congenital ichthyosis, also known as collodion baby.[3] GD should therefore be considered as a differential diagnosis of any hydrops in pregnancy. Diagnosis of GD is made on the basis of clinical history, physical examination, laboratory test and confirmed by a blood test showing deficient glucocerebrosidase enzyme and genetic mutation studies when the diagnosis is doubtful.

The case we reported onseted with splenomegaly at the age of 6 and continued to enlarge in the last years. Thrombocytopenia, anemia and leucopenia are seen on the blood counts. Liver enzymes were normal and PT and PTT were prolonged a little without an increased tendency to bleeding. His β glucosidase levels was considerably subnormal (without accurate number), that measurement of glucocerebrosidase enzyme activity in leucocytes or skin fibroblasts on a skin biopsy is the gold standard for diagnosing Gaucher disease.[4] The patient's biospies of bone marrow and spleen all supported diagnosis of GD. EEG findings in our case demonstrate a similar pattern, as a case report before,[5] with rapid spike activity, photosensitivity in harmony with the flicker frequency and eye closure sensitivity, which is few reported in GD.

ERT is the standard of care for patients of GD 1 and GD 3.[6] ERT is most effective in reducing the liver and spleen size and the bone symptoms, and improving blood counts. When there is no access to expensive ERT, bone marrow transplants and liver transplants may be an option, albeit inferior to ERT. Splenectomy is rarely indicated for palliation for more than 15 years in Western with a higher risk of cholesterol gall stones, pulmonary complications including pulmonary hypertension, avascular necrosis of bone and iron overload states.[7-10] The patient here didn't have enough money to receive ERT at the beginning and had splenectomy 3 years ago to relieve pain. Then the disease progressed and developed myoclonic epilepsy. It can be expected that, without ERT, the patient's symptoms will be worse and with new symptoms.

CONCLUSION

GD is so rare that it is easily missed diagnosis or misdiagnosis in the clinic. Patients presented with myoclonic seizures should be considered in the differential diagnosis of those with unexplained splenomegaly especially with an extended period of time. It is importance to collect his detailed medical and family history, and have him done some essential laboratory tests and auxiliary examinations.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

The patient has provided written permission for publication of the case details.

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Research

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Adult Attention-Deficit and Hyperactivity Disorder and Fibromyalgia: A Case-Control Study

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ABSTRACT

Introduction: Fibromyalgia syndrome (FMS) is a disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory and mood issues. An association between attention deficit and fibromyalgia was reported. However, to our knowledge, there are few articles reporting an association between adult Attention Deficit Hyperactivity Disorder (ADHD) and FMS.
We hypothesized that ADHD should be frequently associated with FMS. To confirm this hypothesis we conducted this study.
Methods: Patients with Cognitive Complaint (CC) recruited from the membership of the Italian Hospital Medical Care Program in Argentina from 2009 to 2013 were classified as ADHD or without ADHD, and compared with Normal Controls (NC) about the presence of FMS. Adapted DSM-IV criteria for adult ADHD and validated to Spanish Wender Utah Rating Scale were used to identify individuals with adult ADHD. FMS was diagnosed according to Criteria Classification of Fibromyalgia of American College of Rheumatology of 1990. Analysis of categorical variables was carried out using chi-square. Mann-Whitney test was used for continuous variables. Statistical significance was $P<0.05$.
Results: We identified 154 patients with ADHD, 71 NC, and 262 with CC without ADHD. Amongst ADHD cases, 37.7% were men, the median age was 72.5 years, in NC group, 40.8% were men with a mean age of 71.9, and in CC group, and 40% were men with a median age of 71.4 years. No significant differences in these variables between groups or in the years of education were found.
Frequency of FMS was 24.7% in ADHD cases, 4.6% in CC group and 0% in NC. Prevalence of FMS in ADHD patients was significantly higher compared with other control groups ($P<0.00001$, 95% confidence interval extends from 0.0786 to 0.1330).
Conclusion: In our sample, FMS is more prevalent in adult ADHD cases than in NC and CC patients as we expected. It should be done future studies to characterize the association of this disorders.

KEYWORDS: ADHD; Fibromyalgia; Adult attention-deficit and hyperactivity disorder; FMS.

ABBREVIATIONS: FMS: Fibromyalgia syndrome; ADHD: Attention Deficit Hyperactivity Disorder; CC: Cognitive Complaint; NC: Normal Controls; IHMCP: Italian Hospital Medical Care Program; WURS: Wender Utah Rating Scale.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) affects 5-12% of children in the United States[1] being the most prevalent cause of childhood learning disabilities.[2,3] The only epidemiological report of our country (Argentina) shows similar finding, with a prevalence of 9% of this disorder in children.[4]

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This disorder is characterized by symptoms of inattention, hyperactivity, and impulsivity. These characteristics persist into adulthood.[5,6] Unfortunately, there are very few epidemiological studies in adulthood and this disorder is usually underdiagnosed.[7] However, in recent years, there are some reports about this disorder comorbidities.[8]

Fibromyalgia syndrome (FMS) is the second most common disorder, after osteoarthritis, observed by rheumatologists. It's a chronic, and debilitating disorder that impair the quality of life of 2-4% of the population, with 9:1 female-to-male incidence ratio.[9] The defining symptoms of FMS include chronic widespread pain, intense pain in response to tactile pressure (allodynia), prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching, palpitations and diffuse tenderness, along with fatigue, sleep disturbance and cognitive impairments. These impairments affect short and long- term memory, short-term memory consolidation, speed of information processing, and include reduced attention span and limited multi-tasking performance as well.[10-12]

The profile of cognitive symptoms in FMS and ADHD is very similar, and ADHD is commonly mistaken with anxiety, depression and other behavioral disorders[13] which are comorbidities of FMS.[14,15] FMS and ADHD are part of a family of related disorders known as affective spectrum disorders.[16] These disorders share physiologic abnormalities and genetic risk factors that may be central to their etiology.[17] One previous report showed an association between fibromyalgia and a polymorphism of the dopamine D4 receptor and its relationship to novelty seeking personality traits, which symptoms are very similar to ADHD.[18] Furthermore, the polymorphism of the dopamine D4 receptor has been associated to ADHD in children and adulthood.[19] Considering these investigations, in both disorders (FMS and ADHD), an overlap in clinical features and neurobiologic substrate was found. However, to our knowledge, there are few articles reporting an association between adult ADHD and FMS.[20-22] Moreover, there is no case-control study of the association.

We hypothesized that both syndromes are associated. Since the cognitive deficit has been described in both entities, to confirm the hypothesis, we conducted this study, comparing a more elderly group with ADHD with another group of cognitive impairment from other causes, assuming that there may be even more cases of FMS than usual, in this kind of control group.

METHODS

Participants

This study was conducted at the Italian Hospital Medical Care Program (IHMCP) in Buenos Aires, Argentina with approval from the institutional Review a Board of the IHMCP research committee. Patients and controls were analyzed after informed consent was signed (a general approval for the release for medical records and data for use in this study). Patients with ADHD and controls were recruited from the membership of the IHMCP, a large prepaid health maintenance organization model. IHMCP provides comprehensive medical and health services through two medical center hospitals and 24 medical office buildings to over 140,000 members primarily located in the urban areas around the Autonomous City of Buenos Aires, Argentina. Approximately, 5-7% of the population in this geographic area is affiliated to the IHMCP. The IHMCP population characteristics are closely representative of the metropolitan population of the Autonomous City of Buenos Aires, as demonstrated by 2001 census data in a series of socioeconomic categories (Table 1).

	City of Buenos Aires (%)	IHMCP (%)
Socioeconomic level		
Upper	10	5
Upper middle	16	19.4
Middle	30	37.5
Lower middle	21	25.6
Lower	17	12.5
Total	100	100
Ethnic origin		
Caucasian	92	95.5
Asian	4	2
African American	1	0.5
Mestizos(²)	3	2
Total	100	100

(*)IHMCP: Italian Hospital Medical Care Program
(²)Mestizos: Spanish term used to designate people of mixed European and Amerindian ancestry living in the region of Latin America.

Table 1: Socioeconomic level and ethnic origin of inhabitants of the Autonomous City of Buenos Aires and IHMCP* affiliates, based on the 2001 Argentinean census.

The period of the study was conducted from 2009 through 2013. The sample included two groups of subjects: Each participant was classified as adult ADHD on the basis of the DSM-IV criteria adapted for the identification of adult patients with ADHD and the validated to Spanish Wender Utah Rating Scale (WURS) were used as an instrument for retrospective diagnosis of childhood ADHD[23,24] to identify patients and controls with preceding ADHD during their adult life.

DSM-IV criteria and the Wender Utah Rating Scale have been successfully adapted for the identification of adult patients with ADHD and have been used in numerous studies in the past.[24,25] To obtain a full diagnosis of adult ADHD, subjects were required to have the following criteria: (i) fully met the DSM-IV criteria for diagnosis of ADHD within the past years; (ii) described a chronic course of ADHD symptoms from adolescence to adulthood; and (iii) endorsed a mild to severe level of impairment attributed to those symptoms.

Participants were also provided with the validated to Spanish Wender Utah Rating Scale for retrospective diagnosis

of ADHD in childhood.[26]

The validated to Spanish version scale comprises 25 items which are rated on a 5-point scale (0-4).[26] The total score ranges from 0 to 100. For the retrospective diagnosis of ADHD in childhood, the authors recommended a cutoff score of 32 or higher to obtain a sensibility of 91.5% and specificity of 90.8%, with a positive and negative predictive value of 81% and 96%, respectively, and a Cronbach co-efficient of 0.94. This cut-off score was used because it demonstrated the best behavior (ROC curve) of the validated scale.[23] Whenever possible, diagnosis was obtained from the patient and a direct informant who had known the patient for at least 10 years and had information obtained from a close relative who knew the patient in childhood.

To avoid other overlapped disorders, we considered as adult ADHD symptoms only those patients who presented symptoms that fully met the DSM-IV criteria for diagnosis of ADHD and who fulfilled the cutoff score of the Spanish Wender Utah Rating Scale of 32 points or higher during their infancy. For example, if a patient had ADHD symptoms in adult life but he/she did not remember if those symptoms were present during childhood, the patient was not considered as a positive case of ADHD symptoms.

Fibromyalgia was diagnosed according to the American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia.[27] As these criteria don´t consider cognitive symptoms to diagnose FMS, they are suitable to search an association with ADHD.

Patients with ADHD and controls were matched as groups on a range of demographic variables to ensure comparability. All patients were evaluated and diagnosed by a trained neurologist. Routine clinical investigations were conducted to exclude other causes of cognitive impairment.

Patients were excluded if formal examination showed evidence of any other brain disorder or physical and/or mental illness sufficient to contribute considerably to the clinical picture. In all cases, we exclude those in which the consumption of psychotropic drugs or alcohol could be a potential confounder. Patient selection was strictly consecutive and included all the prevalent cases in the center who met previous criteria.

Controls

We included 2 groups of controls, one of them composed from those subjects volunteers of our database, living in the geographic area of residence of patients, with the same age and years of education range, subjects with cognitive complaints or impairment were excluded from this group. The same exclusion criteria that we applied in subjects were considered in controls as well. In another group, we included patients with cognitive complaints that didn't meet criteria for ADHD after underwent procedures to ascertainment of this disorder, previously described.

Controls were never duplicated. Records of potential controls were reviewed by a neurologist to exclude those controls in which the presence of any type of neurological disease was suspected before the year of inclusion in database. The list of the entire population from which potential controls were randomly drawn was provided by the record database system of the epidemiological center of the IHMCP, and control subjects were selected for cases using a statistical program.

Procedure and Data Analysis

The evaluation of cases and controls regarding the identification of ADHD using the DSM-IV criteria and the Wender Utah Rating Scale was performed by a trained neurologist unaware of the objective of the study. Only cases and controls fulfilling ADHD criteria by this kind of evaluation, were considered as positive exposure.

Raters who collected the information about ADHD symptom status were blind to the presence of FMS and control status. When the evaluation was completed, data were analyzed by an unblended neurologist aware of the objective of the study.

The presence of FMS was retrieved by a neurologist from the medical records. In all cases the diagnosis was made by a rheumatologist or an expert clinician in this field. Analysis was performed using Stata 8.0 version.

Analysis of differences in the frequency of categorical variables was carried out using the chi-square test. The Mann-Whitney test for independent samples was used for continuous variables. Statistical significance was set up at $P<0.05$.

RESULTS

We identified 154 patients fulfilling criteria for adult ADHD, 71 normal controls (NC), and 262 with cognitive complaint (CC) but without ADHD criteria. All patients authorized the use of their medical records for research. Age, sex and years of education of all groups were in Table 2.

	ADHD	Cognitive complaint (CC)	Normal controls (NC)
N (patients)	154	262	71
Gender, men (%)	58(37.7)	105(40)	29(40.8)
Age, mean (years)	72.5 (range 60-83)	71.4 (range 60-86)	71.9 (range 60-83 years)
Education, mean (years)	10.7 (range 3-18)	11.2 (range 3-18)	11.8 (range 3-18)

Table 2: Demographic and clinical data ADHD *vs.* cognitive complaint and normal controls.

There were no significant differences in these variables evaluated between the three groups.

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The frequency of FMS was 24.7% in ADHD cases (n=38), 4.6% (n=12) in the CC group and 0% (n=0) in the NC group. The prevalence of FMS in ADHD cases was significantly higher when compared with the other control groups. The chi-square statistic is 52.0227 and P-Value is <0.00001. The 95% confidence interval extends from 0.0786 to 0.1330 (Table 3). As expected, all the patients with FMS were females, except only one subject belonged to ADHD group.

	ADHD N=154	CC N=262	NC N=71
FMS (%)	38(25)	12(4,5)	0
No FMS (%)	116(75)	250(95,5)	71(100%)

The chi-square statistic is 52.0227. The P-value is <0.00001. The result is significant at p<0.05.
ADHD: Adult Attention-Deficit and Hyperactivity Disorder, CC: cognitive complaint, NC: Normal Controls, FMS: Fibromyalgia Syndrome

Table 3: Statistical findings in each group.

DISCUSSION

In this case-control study, we identified a higher prevalence of FMS, amongst patients with ADHD than in the normal control group and CC groups. To our knowledge, this is the first study that examined the frequency of FMS in adult ADHD in a case-control study. Furthermore, this study has considered only older adults with ADHD, allowing to determine a true association between FMS and ADHD without confusion with the cognitive disorders of FMS.

There are many previous reports about the features of cognitive disorders in FMS.[28-34] Most of these studies suggested that people with FMS have cognitive dysfunction and are mainly affected more than one domain as attention, working memory and episodic memory.

Despite these findings, it seems that deficits in working memory and attentional tasks are more frequent than in other domains. The fact that these domains are affected in ADHD, showed the need to determine the true source of cognitive symptoms in FMS. The question is whether patients with FMS have cognitive disorders related to FMS itself, or this is secondary to ADHD, which seems to be a common comorbidity of FMS. Our study seemed to answer this question, because our results would show an association between both entities, and we didn't find this association with the CC group. Another interesting fact that supports an overlap between ADHD and FMS, is dysfunction in neurotransmitters in the central nervous system. It has found in FMS, a deficit in serotonin, noradrenaline and especially dopamine.[35-37] Thus, an attenuation of dopamine synthesis and release might contribute to the cognitive dysfunction that is increasingly recognized as a critical aspect of the disorder.[37] This latter dysfunction, coincidentally, have been linked to attention deficit in ADHD and it was reported previously that comorbidity between ADHD and FMS could be explained by both entities sharing a dopamine disorder, proposed as underlying pathophysiology.[18,19] However, there are still few reports describing the characteristics of these dysfunctions, and future studies focused on different subtypes of pre- and postsynaptic receptors, in brain areas associated with cognition, are required. It has been proposed that these alterations in the neurotransmitters may be related to an impaired stress response due to dysfunction of the hypothalamic pituitary axis[38] and may be triggered, according to emerging evidence, by adverse reactions to foods or food components.[39] An understanding of the interactive responses involved in the neuroendocrine-immunological network seems essential for a comprehension of the pathophysiology of ADHD and FM, and has been suggested to study in the future, the role of allergies as an important triggering event in each of the disorders.[39]

The strength of this study was that we examined thoroughly a large group of patients and controls, including only older people. A weakness of our study was that we didn´t control these variables with other potential comorbidities such as depression, anxiety or personality disorders, that could be confounding factors.

Unfortunately, reliable biological tests to examine this hypothesis are lacking. Future studies should focus on the search for biomarkers that allow dopaminergic dysfunction be compared in these populations. Our findings should be confirmed by similar studies. If this confirmation will be achieved, treatments that have already been effective in ADHD could be used in clinical trials for FMS symptoms.

CONFLICTS OF INTEREST

Authors has nothing to disclose.

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Review

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Current Utilization of Mast Cell Stabilizers for Preemptive Treatment of NF1 Neurofibromas

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ABSTRACT

The morbidity and mortality of Neurofibromatosis type I (NF1) are both largely related to the person's neurofibroma burden. That burden can presently be minimized by mast cell stabilizers, with ketotifen as the one most frequently considered for NF1 patients in the published literature. Here, I review pertinent clinical and research publications to 1) document the *rationale* for using mast cell blockers in NF1, 2) consider the NF1 clinical *impact* of mast cell blockers, 3) document the relative *safety* and very modest *expense* of (at least some) mast cell blockers, and 4) suggest that the data are sufficiently robust to *support* the regular, if not *routine use of mast cell blockers to treat NF1*, particularly in children, while the NF1 neurofibroma burden is the least it will be. The rationale for these salutary results have been established by histopathology, *Nf1*+/- mouse models, a series of open-label and double-blind protocols, , compelling case reports and a series of patients who have afforded their own self-determined mast cell stabilizer treatment (most often ketotifen). In addition, in the intervening 20-plus years since the first formal protocol publications, the positive treatment results have never been refuted or contradicted. The results of the mast-cell-stabilizing treatment are designed to keep the NF1 neurofibroma burden and its consequences at their minimums, in effect preempting NF1 neurofibroma initiation and progression as much as possible.

KEYWORDS: Neurofibromatosis 1; NF1; Neurofibroma; Mast cells; Pain; Itching; Pruritus; Ketotifen.

ABBREVIATIONS: DPN: Diffuse Plexiform Neurofibromas; NF1: Neurofibromatosis type I; FDA: Food and Drug Administration.

INTRODUCTION

The morbidity and mortality of NF1 are directly and indirectly related to the person's neurofibroma burden. The person with more and/or larger neurofibromas is at higher risk. Most persons with NF1 are born absent neurofibromas of any type. However, I estimate that between 5% and 15% of NF1 persons have one or more congenital neurofibromas. These are properly referred to as Diffuse Plexiform Neurofibromas (DPN)[1,2] and more technically as epineurial neurofibromas.[1] In addition, almost all NF1 persons are also at risk for the later development of cutaneous neurofibromas (endoneurial neurofibromas)[1] and some NF1 persons are at risk for subcutaneous and nodular plexiform neurofibromas (both of which are perineurial neurofibromas).[1] The latter are likely associated with higher mortality[3,4] and they are especially common in persons with NF1 on the basis of a "whole gene deletion."[5,6]

For the most part, the routine approach to NF1 has been to wait for progression of the NF1 neurofibroma burdens to have major, serious clinical consequences and then use very expensive medications that often have serious side-effects and uncertain abilities to stop or reverse the neurofibroma's progression. In this presentation, I suggest greater reliance on pre-

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emption – minimize the initiation and progression of these mass lesions.

The NF1 neurofibromas can have direct and indirect adverse consequences, precisely as neurofibromas, depending on absolute size, adjacent structures and infiltration into surrounding tissue. Endoneurial (cutaneous) neurofibromas usually first appear in the teenage years, ultimately often accounting for hundreds, even thousands of individual lesions, varying in size from a few grams[7] to several kilograms.[7] At any size they are almost always cosmetically compromising and are the sites of localized itching, pain and tenderness. Perineurial (subcutaneous and nodular plexiform) neurofibromas may occur at any age and are often a source of substantial pain and focal neurological deficits. Nodular plexiform neurofibromas are often paraspinal at multiple sites.[1,8,9] In addition, a minimum 10% of NF1 patients will experience malignant transformation of one or more plexiform neurofibromas, perineurial or epineurial (DPN), the malignant tumor usually a sarcoma, most often a neurofibrosarcoma.[10-12] While it has not been proven that a mast cell blocker preemption approach decreases the malignant transformation risk, it seems likely – even compelling – that an arrested neurofibroma is less likely to realize this transformation. Can there be a better reason for attempting to arrest the growth of NF1 neurofibromas?

REVIEW

Pathologists have known for decades that mast cells are an intrinsic element of neurofibromas, whether or not NF1 is present.[13-21] In some instances, NF1 neurofibroma mast cells have been quantified and there is consistently an excess compared to normal tissue.[22,23] However, no attempts seem to have been made to identify the tissue source or detailed nature of the NF1 neurofibroma's mature mast cells, for example, tryptase or chymase predominance.[24,25] Likewise, no efforts have been made to distinguish the immature mast cell[26,27] newly arrived to the incipient neurofibroma in contrast to the "mature," more or less neurofibroma-specific mast cell. Targeting the immature mast cell may be a key to arresting the incipient or very early stage neurofibroma.[28] In any event, numerous pathologists established a role for mast cells in neurofibroma pathogenesis.

Respecting both the pathology data just noted and consistent with NF1 patient reports that likely sites of neurofibroma development were heralded by focal intense itching,[12,29-31] a symptom well-known to indicate mast cell infiltration, Riccardi began emphasizing a key role for mast cells and cell-cell interactions in NF1 neurofibroma pathogenesis.[30,32] A key part of the proffered schema was consideration that the early stages of the neurofibroma are more like wound-healing dysplasia than neoplasia *sensu strictu*.[7,33,34]

Most early (and even many present-day) neurofibroma investigators presumed automatically that a neurofibroma is a tumor from the outset, with a somatic mutation in the normal *NF1* allele (second hit) in a Schwann cell being the literal "cause" of the NF1 neurofibroma.[35-38] This myopic approach ignores the cogent possibility that the initial dynamics of NF1 neurofibroma formation were more related to wound-healing, the wound providing a cellular and extra-cellular milieu affording an increased likelihood of the second hit (incubator effect).[8] Trauma (mechanical, biochemical, hypoxic) and wound-healing became a focus of NF1 neurofibroma pathogenesis in the very early 1980's.[39-46]

Along the way, in 1988, Giorno, et al.,[47] documented that human NF1 neurofibroma fibroblasts (a major portion of the lesion) incorporate mast cell granules into their cytoplasm, consistent with the work of others.[48] These results were also consistent with the massive data generated by the Wade Clapp University of Indiana group using *Nf1* mutant mice.[49-60] They professed and nurtured the notion that "mast cells are necessary, but not sufficient" to generate *Nf1*+/- neurofibromas. One published commentary on that work noted the compatibility of this mouse model with the Riccardi approach.[51] And a 2009 publication[61] showed that the mast cell blocker, tranilast, impaired the ability of *Nf1*+/- mice neurofibroma to progress.

Further indication that mechanical trauma initiated mouse *Nf1*+/- neurofibromas was established by A.C. Lloyd's group.[62] Wound-healing was also emphasized by others.[41,45,63-65] The Lloyd group's article just cited also established that normal (*Nf1*+/+) mast cells were as efficient as *Nf1*+/- mast cells in generating and sustaining mouse *Nf1*+/- neurofibromas. In other words, it is likely that the mast cell *per se* and its ordinary functions contribute to human NF1 neurofibroma initiation and progression. The NF1 mast cell as a therapeutic target of drugs aimed at normal mast cells, as, for example, in asthma and other mast-cell- associated disorders, was and is thereby even more compelling.

All of these developments were in the context of Riccardi's publications documenting that ketotifen (Zaditen®), in both open-label and double-blind protocols, had obvious benefits in treating NF1 neurofibromas. As early as 1987, such benefits were published in the *Archives of Dermatology*.[66] Additional data were published in 1990 and 1993.[33,67] In the 20-plus years since their publication, these data and the conclusions derived therefrom have been casually challenged once,[68,69] but never refuted or contradicted. The published benefits of NF1 ketotifen treatment included 1) a *decrease in the itching, pain and tenderness* associated with neurofibromas of all three types, especially for the endoneurial (cutaneous) neurofibromas and subcutaneous perineurial neurofibromas; 2) a *decrease in the rate of appearance* of cutaneous neurofibromas; 3) a *decrease in the rate of enlargement* ("growth") of all types of neurofibromas; 4) a major *decrease in intra-operative small-vessel hemorrhage* in plexiform neurofibromas; and 5) a consistent declaration of *improvement in the NF1 person's overall sense of well-being*. Parenthetically, this latter phenomenon has been noted in patients treated with ketotifen to minimize surgical scars.[70] In 1998, for

three German NF1 patients were reported[71] to have the same salutary results from ketotifen treatment as reported by Riccardi.

In 2015, I reported the results of 30 years of ketotifen treatment of an NF1 patient from age three months.[72] At age 30, his skin was universally free of any mature neurofibromas. Instead, there was only the monotonous presence of "early," small and flat cutaneous neurofibromas. It was as though these neurofibromas had been arrested and maintained in this very early phase of neurofibroma development. In addition, the patient's right ankle DPN was much smaller than would have been expected without treatment. At about the same time, I established *NFormation*, an online venue to report on advances in NF1 research (www.medconsumer.com). Included were a series of American, European and South American NF1 persons who were undergoing or had undergone self-determined treatment with ketotifen or an alternative mast cell blocker. The consistency of the self-reported results was impressive, both within the self-determined treatment group and when compared with the three protocol-based reports noted above. Finally, the combined data are sufficiently robust to have instigated the already-begun preemptive treatment of a one year old child with NF1 for whom there is expectation of a high cutaneous neurofibroma burden.

Although ketotifen has not been approved by the American Food and Drug Administration (FDA) other than for eyedrops (Zaditor®), there are multiple active investigational ketotifen protocols in the USA and elsewhere to study this drug's influence on minimizing fibrosing conditions[73-75] and excessive scarring in surgical and other wounds.[76-80] Ketotifen is also used extensively world-wide for asthma, atopic dermatitis, helminthic infections, and various eating disorders, among others.[81,82] With such extensive clinical usage, its relative safety is well established. It is relatively inexpensive, with costs per tablet in the range of 15 cents or so. It is now available in generic form and it remains to be established that all of the available brands are equivalent to Zaditen®, the only preparation with which I have extensive personal experience. It also should be noted that the FDA's failure to approve ketotifen was based on that agency's presumption of poor efficacy for treating asthma. Specifically, ketotifen did not have toxicity or adverse effects that contributed to denial of FDA approval.

One of the conditions sometimes very effectively treated with ketotifen is systemic mastocytosis.[25,83-85] This pronouncement brings up the probability that NF1 may be a form of mastocytosis, a consideration raised earlier by myself[86] and others.[87] Ultimately, these and many other considerations will be relevant to the long-term role of ketotifen and other mast cell blockers, for example, the identification of effective biomarkers[88] and the influence of vitamin D congeners.[89] However, our concerns presently are on if and how soon mast cell blockers – especially ketotifen – are made available to *all* persons with NF1. This issue is especially critical for Americans, given the lack of FDA approval of ketotifen, the literal and figurative fuel for elaborating the arguments propounded here.

CONCLUSION

Ketotifen and likely similar mast cell blockers have the potential to reduce drastically the NF1 neurofibroma burden on a world-wide basis. Given the data provided herein, it is not clear why this potential has been overlooked, ignored or dismissed. I can only hope that these few words will make this treatment strategy immediately available to at least some of the earth's estimated two million or more persons alive with NF1 today.

CONFLICTS OF INTEREST

I, the sole author of this manuscript, have no conflicts of interest to declare. Specifically, I have no financial interests of any sort, direct or indirect, with any for-profit organization or semblance thereto. I will realize no financial or other compensation consequent to or otherwise associated with this manuscript.

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