



**I International  
Symposium  
on Hereditary  
Ataxias**

**II Caribbean  
Meeting  
on Dementias**

**I Simposio  
Internacional  
Sobre Ataxias  
Hereditarias**

**II Encuentro  
Caribeño  
Sobre Demencias**



"Dedicated to all persons suffering from ataxia and dementia, to those who have died from it and to their relatives, who for more than 20 years have collaborated with scientific investigations"

"Dedicados a todas las personas que sufren de ataxia y demencia, a aquellos que han fallecido a causa de estas enfermedades y a sus familiares que por más de 20 años han colaborado con las investigaciones científicas"

**Holguín - Cuba  
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**W**elcome to Holguín! On behalf of the Organizing Committee, we are most honored to welcome you to the I International Symposium on Hereditary Ataxias and the II Caribbean Meeting on Dementias.

This meeting brings reality to the dream of gathering scientists from the Caribbean, North America, Europe and Asia in the friendly and warm atmosphere of Holguín to discuss advances in the field of hereditary ataxias. The frequency of hereditary ataxias in Cuba constitutes the highest in the world, with more than 11,000 presymptomatic members of affected families. We want to share what we have learned, the infrastructure that we have built, the multidisciplinary experience that we now have, with the hope that we can learn from colleagues while they take the best of our knowledge.

Scientific development is no longer an isolated, self-sufficient activity. When we started thinking about the possibility of celebrating the I International Symposium on Hereditary Ataxias and the II Caribbean Meeting on Dementias simultaneously, in Holguín, very quickly we realized that it would be a great opportunity to exchange advances in each field and to gain insight about the common mechanisms involved in the neurodegenerative processes that underlie these disorders.

We have made a tremendous effort on bringing students from the Caribbean region involved in active research. We ask you to set some time aside to share with them not only your views about science but also your thoughts about the capacities and values required nowadays to become a successful researcher.

We wish you all a successful encounter with new ideas, with old and new colleagues and with a friendly Holguín. Bienvenidos!

Luis Velázquez Pérez, MD, PhD and Gladys E. Maestre, MD, PhD

## ORGANIZERS

**Gladys Maestre**, University of Zulia, Venezuela.

**Luis Velázquez Pérez**, Center for the Investigation and Rehabilitation of Hereditary Ataxias, Holguín, Cuba.

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**A B S T R A C T S**

# **SPECIAL POPULATIONS IN THE CARIBBEAN**

**Francisco Lopera, Chair**

**G.E, Maestre - ATAXIA AND DEMENTIA IN THE CARIBBEAN**

**L. Velázquez-Pérez - CUBAN SCA2: HIGHEST PREVALENCE IN THE WORLD**

**F. Lopera - MRI FINDINGS IN 2 COLOMBIAN LARGE KINDRED WITH CADASIL**

# HEREDITARY ATAXIA AND DEMENTIA IN THE CARIBBEAN

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**G. E. Maestre**

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Hereditary ataxia and dementia are complex and diverse disorders, where genetic substrates are modified by environmental exposures, lifestyles and health habits. Although most of the cases of ataxia and dementia in the world are not mendelian, in the Caribbean there are three focus of very high prevalence of these disorders: spinocerebellar ataxia type 2 in Holguín, Cuba; Familial Alzheimer's disease in Medellín, Colombia; and Huntington's disease in Maracaibo, Venezuela. The presence of these special populations have been determinant in the identification of pathogenic mutations causing this diseases. In addition they provide a challenging situation from the public health perspective. In addition, the not uncommon presence of very large families in the Caribbean has also allowed the study of genes, including apolipoprotein E, involved in the familial clustering of late onset, nonmendelian Alzheimer's disease and related disorders as CADASIL.

Few population based studies exist in the region to clarify the epidemiology of sporadic cases of ataxia and dementia, particularly in light of the demographic transition and the accelerated expansion of the elderly population. However, the existent evidence and the epidemiological characteristics of the population of the region point to the fact that there is a high prevalence of underdiagnosed cases of neurodegenerative disorders of late onset as dementia. Low levels of education, poor health habits, high prevalence of cardiovascular risk factors, poor health access and an inadequate understanding of normal aging are ubiquitous in the region. All these factors known to be associated with a high risk of brain disorders in the elderly. This presentation will consider these issues and draw on the Maracaibo Aging Study to illustrate them.

Family caregivers of people victims of these disorders are known to experience significant psychological morbidity. The importance of integrating them within a multidisciplinary approach to early intervention is emphasized. There are few specialized centers for the care of disabled elderly, being informal care the most common type of caregiving.

The standardization of early detection procedures, the search for accesible therapeutic strategies and the design of family support systems are atrgets of most needed research in the area.

# CUBAN SPINOCEREBELLAR ATAXIA TYPE 2. THE HIGHEST PREVALENCE IN THE WORLD

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**Introduction.** Autosomal Dominant Cerebellar ataxias are a heterogeneous group of neurological disorders characterized by degeneration of the cerebellum, spinal cord and brainstem. Genetic analysis has revealed 17 different molecular forms of dominant cerebellar ataxias. The most frequent molecular form in our country is the Spinocerebellar Ataxia 2 (SCA2). It is characterized by a dominant autosomic pattern of inheritance. The most frequent symptoms in the SCA2 are gait ataxia, cerebellar dysarthria, dysmetria and adiadochokinesia. SCA2 was linked to the human chromosomic region 12q23-24.1 by Gispert et al. The SCA2 Gene was recently identified dependently by three groups using three different approaches, and the mutation responsible for the clinical features of SCA2 disease was defined as the intergenerational expansion of a CAG tract on exon I of the gene. The hereditary ataxias in Cuba make up the highest concentration of these patients in the world. **Objectives.** To determine the prevalence and incidence of hereditary ataxias. **Patients and methods.** We made a descriptive study of 770 patients and 11 600 members of families at risk from this disorder in Cuba. We calculated the prevalence rate and incidence. **Results.** In Cuba, the general prevalence for cerebellar ataxia is 9,12 cases per 100 000 inhabitants. There are already 770 patients and 11 600 of relative at risk to be sick in the next few years. However in the province of Holguín there are 440 sick people and the prevalence reaches up values up to 43 cases per 100 000 inhabitants with remarkable figure of 503 cases per 100 000 inhabitants in Potrerillo, an area of the municipality of Báguano, for that reason the Hereditary Ataxias are a very important health problem in Cuba. The age group that was most affected was that of 30-39 years, with a prevalence of 63.97 cases per 100,000 inhabitants. The rural population showed the highest prevalence (62.04 cases per 100,000 inhabitants). The risk of members of affected families showing the disorder was 159.33 cases per 100,000 inhabitants in this province. The highest incidence was 18.08 cases per 100,000 inhabitants in Cacocum, where the incidence in the province was 4.39. Santos et al reported that the age of disease onset was inversely correlated with the CAG repeat expansion. Sixty seven percent of the patients with (CAG)41 and 99% of the patients with (CAG)42-79 presented clinical symptoms at 30 years old or younger. Two patients presented symptoms at 65 years old, harboring 35 and 37 CAG repeats, respectively. One of the longest alleles causing the SCA2 neurodegeneration was also found. A child carrying 79 trinucleotide units developed clinical manifestations at 2 years old. The normal alleles ranged from 13 to 30 CAG repeats, with one or two CAA interruptions. Two affected twin sisters were found with disease manifestation at 57 and 61 years old, respectively, being homozygotic for (CAG)34 without CAA interruptions. **Conclusions.** On average the disorder passes from one state to the next every year, which suggests that the extent of the disorder worsens with time. The prevalence and incidence are the highest in the world. This together with the dominant pattern of inheritance, the effect of anticipation and inexorably progressive course of the disorder shows the serious health problem that affects the Eastern region of Cuba.

# MRI FINDINGS IN 2 COLOMBIAN LARGE KINDRED WITH CADASIL

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**F. Lopera, D.A. Sepúlveda-Falla, J.E. Gutierrez , J. Arboleda-Velásquez, S. Vargas**

*Grupo de Neurociencias, Universidad de Antioquia. Colciencias grant # 1115-04-11919*

## **Objetives**

Identify MRI anomalies in two Colombian large kindred suffering from CADASIL.

## **Methods**

MR imaging examinations were performed with 1.5 T Philips Magnet, 9 mm Continuous axial plane images were performed in T1w, T2w and FLAIR; 5 mm continuous sagittal plane for T1w y T2w. Images were evaluated with Cabanis – Iba Sizen scale and Scheltens scores.

## **Results**

The sample were 25 individuals, 15 women y 10 men with an age average of 47,32 years old (SD=14,42); 15 patients with the R1031C mutation in Notch3 and 10 with C455R mutation. The Cabanis scale average was 3,88 (SD=1,96) and Schelten's score average was 17, 32 (SD=14,3). A Spearman's rho was performed to evaluate correlation between Schelten's scores and Cabanis scaling (rho= 0.9, p=0.000). Three diagnostic groups were defined for evaluate correlation between diagnosis vs. Cabanis scaling: patients without symptoms, minor symptoms and cardinal symptoms of CADASIL. Non parametric test of Mann -Whitney shows that there is not a significative difference between without symptoms and minor symptoms groups (p=0.177) meanwhile there is a significative difference between minor symptoms and cardinal symptoms groups (p=0.000).

## **Conclusions**

Mean age and mean value for Cabanis scale shows a bilateral early damage of subcortical white matter on MRI. There is a correlation between Schelten's scores and Cabanis scaling, but there is no evident relationship between damage severity visible on MRI and minor clinical symptoms in the two kindred evaluated, this could be related with the localization of damage in some areas that Cabanis scale does not evaluate, and that MRI visible damage of subcortical white matter does not account for neural disfunction or symptoms in CADASIL.

# GENETIC EPIDEMIOLOGY OF HEREDITARY ATAXIAS IN CUBA

**Osiel Gámez, Chair**

**J. García-Zacarias** - DOMINANT AUTOSOMIC SPINOCEREBELLAR ATAXIA IN THE SANCTI SPIRITUS. PREVALENCE AND CLINICAL MANIFESTATIONS

**O. Gámez** - TYPE 2 SPINOCEREBELLAR ATAXIA AND OTHERS DOMINANTS ATAXIAS. A PRELIMINARY APPROXIMATION IN SANTIAGO DE CUBA / 2002

**N. Márquez-Ibañez** - COMPORTAMIENTO EPIDEMIOLÓGICO DE LOS DESCENDIENTES DE PACIENTES CON ATAXIA ESPINOCEREBELOSA TIPO 2. URBANO NORIS. 2002

**O. Alemán** - CLINICAL- EPIDEMIOLOGICAL CHARACTERIZATION OF THE HEREDITARY ATAXIA IN THE PINAR DEL RÍO PROVINCE PROVINCIAL PEDIATRIC HOSPITAL PEPE PORTILLA PINAR DEL RÍO

# **TITLE: DOMINANT AUTOSOMIC SPINOCEREBELLAR ATAXIA IN THE SANCTI SPIRITUS. PREVALENCE AND CLINICAL MANIFESTATIONS**

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**J. García -Zacarias, J. González -Montesino, M. S. Denis, L.T. Hernández, J. C. García-Gonzalez, Y. González-Rodriguez, R. L. Castro**

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**Summary.** Introduction The Dominant Autosomic Spinocerebellar Ataxia (SCA) are constituted by a group of neurodegenerative pathologies, produced by abnormal expansion of trinucleotides in different genes. Being very invalidant, there is no curative medical treatment and we only can prevent its trasmission by means of the genetic advisory . **Objetives.** To determine the number of ill persons and descendants with a 50% of possibilities to develop the disease.To describe the clinical manifestations .**Patients and methods .** We carried out a province cencus defining the families with SCA , the ill persons . The main clinical features were identified. **Results.** There are 6 families in our province that present the disease . There are 18 sick persons and 45 individuals with a 50% of possibilities to develop it . The prevalence is 3,88 and 9,7 x 100 000 habitants, respectively .The most frequent clinical picture corresponds to group I according to Harding`s classification. **Conclusions.** The SCA prevalence in the Sancti Spiritus province is similar to the national mean, being Trinidad and Sancti Spiritus the most affected municipalities .Molecular studies will be carried out in the near future .

**Keywords:** Ataxia

Spinocerebellar Ataxia

Inherited Ataxia

Dominant Autosomic Ataxia

Ataxia Prevalence.

# **TYPE 2 SPINOCEREBELLAR ATAXIA AND OTHERS DOMINANTS ATAXIAS. A PRELIMINARY APPROXIMATION IN SANTIAGO DE CUBA / 2002**

**O. Gámez, Y. Lozada, I. Quintana, A. Fiffe, A. Montoya**

*Clinic for Investigation and Rehabilitation of the Hereditary Ataxia.*

## **Summary**

Summary: The hereditary autosomic- dominants ataxias are a group of neurodegenerative affections that are heterogeneous point of view clinical and genetic. The main characteristic is a disorder in the motor coordination because the progressive degeneration of the cerebellum's neuron cerebral trunk's nucleus, thornocerebellar's tract. The enlightening at molecular level of the production's mechanism of this disorders had facilitate a better clinical- genetic delimitation of them. The more frequently form in Cuba is the SCA 2. Objective: To value the prevalence of these hereditary ataxias in Santiago de Cuba. Materials and methods: It has done an exploratory- descriptive study. It detected 39 cases in the period April-June /2002. Results: Prevalence in Stgo de Cuba  $3.74 \times 100\ 000$  hab. Locality with highest number: II Frente  $12.16 \times 100\ 000$ . More frequently clinical form: SCA 2 ( 69.4 %). Initial symptom: march's ataxia ( 71 %), dysathria ( 5.3 %) and both ( 23.7%). Actual clinical stages: light (55.3%), with external support (31.6%) and confined to rolling's chair (13.1%). Evolution time: 6 to 10 years (36.1%), 11 to 15 years (30.6%). Conclusions: The hereditary autosomic- dominants ataxias have an small prevalence in Stgo de Cuba. The SCA 2 is the most frequently clinical- molecular typical of this patiens and the persons who run the risk of to fall ill.

# COMPORTAMIENTO EPIDEMIOLÓGICO DE LOS DESCENDIENTES DE PACIENTES CON ATAXIA ESPINOCEREBELOSA TIPO 2. URBANO NORIS. 2002

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**N. Márquez-Ibañez, R. Pavón**

*Center for the Investigation and Rehabilitation of Hereditary Ataxias, Holguín, Cuba*

## **Summary**

A descriptive study about patients who are direct descendant of persons who have SCA -2 was made “Urbano Noris” municipality, during the period of time between April and may, 2002. The main objective was to determine the epidemiological behavior of that pathology. Twenty five (25) cases (children and brother and sisters) out of total of twenty nine (29) patients were selected. The data obtained by means of different surveys were analyzed, processed, and stored according to the EpiInfo 6 computerized system. Among the principal results was found out that most descendants belonged to the masculine sex. The most relevant group of ages were between 31 -40 and / 51 -60 year - old - people. The predominant heritage I was the maternal one; the schooling level with most cases was the secondary school level and most of the were married. About the number of children of the study patients, we found out they have 0 -2 children and the most affected generation was the fourth one. When this study was finished, an investigation about the total cases of direct descendants carriers of the SCA-2 gen was suggested and also the study of this pathology was recommended to be generalized in all of the provinces of the country.

# CLINICAL - EPIDEMIOLOGICAL CHARACTERIZATION OF THE HEREDITARY ATAXIA IN THE PINAR DEL RÍO PROVINCE PROVINCIAL PEDIATRIC HOSPITAL PEPE PORTILLA PINAR DEL RÍO

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**O. Alemán, I. Martínez, M. González, J. M. Zaldívar, G. B. Alvarez.**

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In the period from July to August –2002, in Pinar del Rio an investigation was made with the objective of detecting patients suffering from Spinocerebellar Degeneration Autosomal Dominant and others recessive ataxia. An survey was applied that contained 8 tools of work concerning epidemiological and clinical aspects, socioeconomical conditions and sheltering, quality of life, work environment, risk factors, Barthell Index, Lawton Index, and a cognoscitive minimal test. 23 patients were detected suffering from hereditary ataxia; 19 of them dominant autosomal and 4 recessive autosomal. It was proved that 5 families suffered from Autosomal Dominant Spinocerebellar Degeneration type 2 (SCA2), while realizing a pedigree to each family and it was determined that exist 40 descendents with a risk up to 50% suffering the condition and 28 persons having a 25% of getting sick. There was no significant difference according to sex and the black race was predominant with a number of 14 patients. The municipality that shows a major number of ill persons is Pinar del Rio, with 10 cases, 9 of them with hereditary Recessive Autosomal (Friederich Ataxia). According to the clinical state of the patients, 16 are in the slight clinical stage and with external support back up. Up to now there are 4 patients in wheelchair and 3 permanent bed rest. The prevailing rate of the SCA2 in the Pinar del Rio province is the  $3.1 \times 100.000$  in habitants.

# NEUROGENETICS OF HEREDITARY ATAXIA

Luis Almaguer Mederos, Chair

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# **ATAXIA, DEMENTIA, EXTRAPYRAMIDAL SIGNS AND EPILEPSY: SCA17 IN SOUTHERN ITALY**

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We recently observed two large families with a complex neurological syndrome with dominant inheritance. The first family included 14 patients in 5 generations. The onset was at a mean age of 32 years (range 22 -53) without anticipation. Onset was with cognitive impairment, psychiatric disturbances (depression, personality disorders and hallucinations) or cerebellar signs. During the disease, extrapyramidal signs (dystonia, facial dyskinesias, rigidity) and generalized seizures appeared. In the advanced stages of the disease, the patients became bedridden, anarthric, and incontinent. Myoclonus was present in some.

The second family included nine patients in four generations. Anticipation was observed with onset in 5<sup>th</sup>-6<sup>th</sup> decade in the first two generations, in 3<sup>rd</sup>-4<sup>th</sup> decade in third generation, and at the age on 3 years in the only fourth -generation patient. The onset was always with ataxia, followed by other cerebellar signs, dementia, psychiatric disturbances, seizures and extrapyramidal signs. In both families, MRI showed cerebellar and cerebral atrophy.

Autopsy of a patient showed extreme generalised atrophy of the brain (600 g), more marked in the frontal lobes, the caudate, the cerebellum and the brain stem.

Direct mutational analysis and linkage study allowed excluding familial dementias and parkinsonisms, prionic diseases and the most frequent SCAs. Because of the presence of anticipation in the second family, we performed immunoblot with 1C2 antibody, which showed an abnormal band, corresponding to the expanded polyglutamine sequence. We also used 3G3 antibody, whose epitope is the N-terminal portion of the TATA binding protein (TBP). This antibody showed that the polyglutamine sequence is located in TBP. The PCR analysis showed the presence of a CAG expansion in the TBP gene (SCA17).

In conclusion, even though the clinical presentation is different in the two families, it is possible to define the SCA17 phenotype as an association of ataxia and dementia with prominent psychiatric features, extrapyramidal signs and generalized seizures. SCA17, already described in Japan and northern Europe, is also present in southern Italy.

# A NOVEL AUTOSOMAL DOMINANT SPINOCEREBELLAR ATAXIA TYPE 2 LINKED TO CHROMOSOME 1q22 -24

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**Bing-wen Soong**

The autosomal dominant cerebellar ataxias (ADCA) are a clinically, pathologically and genetically heterogeneous group of disorders. Ten responsible genes have been identified for spinocerebellar ataxia types (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, and SCA17) and dentatorubral-pallidoluysian atrophy (DRPLA). The mutation is caused by an expansion of a CAG, CTG, or ATTCT repeat sequence of these genes. Six additional loci SCA4, SCA5, SCA11, SCA13, SCA14, and SCA16 have also been mapped. The growing heterogeneity of the autosomal dominant forms of these diseases shows that the genetic etiologies of at least 20% of ADCA have yet to be identified. We ascertained and clinically characterized a four-generation Chinese pedigree segregating an autosomal dominant phenotype for cerebellar ataxia. Direct mutation analysis, linkage analysis for all known SCA loci, and a genome-wide linkage study were performed. Direct mutation analysis excluded SCA1, 2, 3, 6, 7, 8, 10, 12, 17 and DRPLA, and genetic linkage analysis excluded SCA4, 5, 11, 13, 14, and 16. The genome-wide linkage study suggested linkage to a locus on chromosome 1q22-24, with the highest two-point LOD score at D1S1167 ( $Z_{\max} = 3.68$  at  $q = 0.00$ ). Multipoint analysis and haplotype reconstruction traced this novel SCA locus (SCA22) to a 16.8-cM interval flanked by D1S2721 and D1S2878 ( $Z_{\max} = 3.54$ ). The age at onset ranged from 10 to 46 years. All affected members had gait ataxia with variable features of dysarthria and hyporeflexia. Head MRI showed atrophy of the cerebellum without involvement of the brainstem. In six parent-child pairs, median onset occurred 10 years earlier in offspring than in their parents, suggesting anticipation. This family is distinct from other families with SCA and is characterized by a pure cerebellar ataxia.

# “ATAXIA -TELANGIECTASIA ASSOCIATED WITH ANAPLASTIC LARGE B -CELL LYMPHOMA: POSSIBLE ASSOCIATION BASED ON CHROMOSOMAL INSTABILITY AND MOLECULAR GENETICS”

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Ataxia-Telangiectasia (A-T) is an autosomal recessive disorder characterized by progressive cerebellar ataxia, oculocutaneous telangiectasias, immunodeficiency, chromosomal instability, hypersensitivity to ionizing radiation and cancer susceptibility. It has been suggested that the very high frequency of lymphocyte-associated rearrangements in peripheral blood chromosome preparations is a diagnostic criterion of the disease. During their lifetimes, 30-40% of A-T homozygotes develop a malignancy. Roughly 85% of these malignancies are either leukemia or lymphoma. In younger patients, an acute lymphocytic leukemia is most often of T-cell origin. Lymphomas, in contrast, are usually B-cell type. Anaplastic large B-cell lymphoma (ALBCL), is a diffuse large B-cell proliferation. Its cause remains unknown. Previous immunodeficiency is an important risk factor, being Epstein-Barr Virus (EBV) positive. The objective of this Case-report is to explain the possible association between both two entities. We describe the case of an eleven year old girl with A-T, who presented at age 6 with gait problems, and was found to have the neurological, dermatological and immunological features characteristic of A-T, along with a history of frequent sinopulmonary infections and oral ulcers. Suspecting a lymphoid malignancy, an excisional lymph node biopsy was practiced, and the histopathology report showed loss of architecture by large lymphoid cells with vacuolated eosinophilic cytoplasm, ovoid nuclei with prominent nucleolus, atypical cells and mitosis. Immunocytochemistry: CD30(+), EMA(+), ALK(focally +), CD15(-), TdT(-), and EBV(+). The diagnosis was ALBCL. The A-T gene (ATM) was mapped on chromosome 11q22-23 in 1988. ATM is a key regulator of multiple signaling cascades, which respond to DNA strand breaks induced by damaging agents or by normal processes, such as meiotic or V(D)J recombination. Lymphoid cells normally experience DNA strand breaks during gene rearrangements, and probably the G1-S checkpoint is important in the avoidance of errors in that process. Thus increased recombination is a component of genetic instability in A-T and may contribute to the cancer risk. The vast majority of both leukemia and lymphoma in A-T occurs during childhood. It can be explained for the high rate of gene rearrangements in lymphoid cells during childhood, secondary to the exposition of bigger amounts of antigens compared with adulthood. It produces a greater chromosomal instability. There is certainly a clear predominance of T-cell tumors, although the proportions of T- to B-cell tumors in A-T patients remain uncertain. B-cell tumors may arise in individuals with either inherited or induced primary immunodeficiencies, and EBV infection may be an important cofactor in the development of lymphoma in A-T patients. Loss of the paired ATM allele have been demonstrated in Diffuse large B-cell lymphoma (including anaplastic variety), and the majority of these mutations were associated with a second mutation or deletion of the normal allele, consistent with biallelic inactivation of ATM, as in A-T. Whether the order of occurrence of additional genetic changes in A-T is important or it is the total accumulation of changes that is sufficient to allow tumorigenesis is still unknown. Chromosomal instability, increased recombination, immunodeficiency, EBV infection, and ATM biallelic defect, could explain the development of this lymphoma in the patient.

# DISTRIBUTION TO THE NUCLEUS OF AN N - TERMINAL ATAXIN -2 EPITOPE IN BRAINSTEM NEURONS

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Spinocerebellar ataxia type 2 (SCA2) stands out by the observation that nuclear localization or aggregation of the disease protein ataxin-2 are not necessary for pathogenesis in cerebellar Purkinje neurons. We have investigated SCA2 tissues including cerebellum, brainstem, midbrain, basal ganglia, hippocampus, cortex, spinal cord with a novel polyclonal antibody SCA2-14 which is directed against an N-terminal peptide and other available antibodies against ataxin-2, polyglutamine (1C2), and ubiquitin. We could confirm the occurrence of classical spherical nuclear inclusion bodies in brainstem neurons. Furthermore the SCA2-14 antibody detects a distribution of ataxin-2 to the nucleus outlining the inner nuclear membrane or filling diffusely the nucleoplasm. This pattern was observed in practically all neurons in the inferior olive and a majority of neurons in the pons nuclei, but it was not observed in substantia nigra and cerebellar Purkinje neurons. Since SCA2 is characterized by early olivo-ponto-cerebellar atrophy, this difference between equally vulnerable neurons supports the notion that the pathogenetic pathways in polyglutamine diseases are tissue-specific and that Purkinje neurons may be affected by trans-neuronal mechanisms.

# A LATE ONSET LIKELY AUTOSOMAL RECESSIVE FAMILIAL FORM OF SPINOCEREBELLAR ATAXIA WITH CLINICAL AND NEUROPATHOLOGICAL FEATURES OF SCA2

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We have ascertained a family of five siblings, two of whom developed a late onset form of spinocerebellar ataxia. The parents were unaffected and lived well into the 80's. Their maternal grandmother and paternal grandfather were distantly related. The kindred settled on Magdellan Island off the east coast of Canada late in the 19<sup>th</sup> century. The proband died at the age of 71 after a 15 year course characterized by ataxia of gait, dysarthria and progressive deterioration.

The proband's sister, now 65, developed ataxic gait at the age of 59 with progressive loss of balance. Neurological examination demonstrated down-beat nystagmus, dysarthria without ataxia on finger-nose testing and signs of distal neuropathy. An MRI exam was unremarkable. An SCA panel including CAG repeat alleles for Ataxin 1, Ataxin 2, MJD1, CACNL1A4, Ataxin 7 and Ataxin 8 were normal.

**NEUROPATHOLOGY – PROBAND:** The brain weighed 1370 grams before fixation. On examination there was no evidence of cortical atrophy but the spinal cord showed somewhat atrophic anterior and posterior spinal roots. Coronal sectioning of the cerebrum demonstrated diffuse atrophy of the cerebellar cortex with normal input nuclei. There was no definite atrophy of cortical spinal tracks in the pons, medulla or spinal roots.

**MICROSCOPIC EXAMINATION:** In the medulla the nucleus solitarius showed moderate neuronal loss and the tractus of the nucleus was moderately to severely depleted of axons.

The cerebellar cortex showed moderate to severe Purkinje cell depletion with marked attenuation of the molecular layer.

Rarely there was marked attenuation of the underlying granular layer. Bergmann gliosis denoted focal Purkinje cell depletion. Cortical cerebellar degeneration was particularly severe in the vermis.

The spinal cord showed marked degeneration of posterior columns, especially the fasciculus gracilis. The lower motor neurons were normal in number and morphology. There was subtle neuronal loss in Clark's column as well as the dorsal horns of the thoracic and lumbar spinal cord. There was no evidence of myelin thinning or active demyelination of the peripheral nerve fascicles. There was a variable degree of axonal depletion, particularly in the sural nerve.

The neuropathological diagnosis was spinocerebellar ataxia with:

- Moderate to severe cerebellar cortical degeneration, especially vermis
- Degeneration of tractus and nucleus solitarius
- Degeneration of dorsal columns, especially nucleus gracilis
- Mixed motor and sensory peripheral neuropathy
- Neurogenic atrophy of skeletal muscle, especially lower limbs

This family is presented as a possible example of an autosomal recessive form of spinocerebellar ataxia. Neuropathological features are presented for discussion as to the likely genetic counselling implications for the next generation in this large family.

## INTERGENERATIONAL INSTABILITY AT THE SCA2 LOCUS

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Trinucleotide repeats sequences constitute an important cause of hereditary neurodegenerative diseases. Expanded sequences beyond certain limits are unstable during intergenerational transmission, showing a general tendency to increase in size. The general purpose of this work was to characterize meiotic instability at the SCA2 locus in 192 parent to child pairs, belonging to 52 Cuban families with spinocerebellar ataxia type 2. We also evaluated the possible influence of several physiological and molecular factors on meiotic instability. We found that SCA2 gene total instability was of 76,6 %, occurring 1 contraction per 6 expansions. Paternally transmitted alleles were more unstable than those maternally transmitted. Progenitor conceptive age showed a significant correlation with meiotic instability only during paternal transmission. On the other hand, a significant association was not observed between meiotic instability and child gender or CAG repeat number at normal allele. Intergenerational instability showed a marked tendency to increase with longer CAG repeat tracts. This study suggests that there is an obvious 'parental effect' working on meiotic instability at the SCA2 locus, probably due to a negative selection of oocytes with long repeats. It also suggests that CAG repeat size and paternal conceptive age are important determinants of intergenerational instability at the SCA2 locus.

# **BIOLOGY OF NEURODEGENERATION**

**José Ortíz**

**K. B. Kegel -**

**M.A, Robinson-Agramonte - INFLAMMATION AND OXIDATIVE STRESS IN  
ALZHEIMER'S DISEASE AN INTEGRAL SURVEY FROM CYTOKINES STUDY AND  
ANTIOXIDANT ACTIVITY**

**J.C. García - GLUTATHIONE S TRANSFERASES AND THEIR SIGNIFICANCE IN ATAXIA  
SCA-2**

**J. Ortíz - GLUTAMATE AND NEURODEGENERATION**

# BIOLOGICAL ACTIVITY OF HUNTINGTIN: FUNCTION AND DYSFUNCTION

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Huntingtin is a large protein, approximately 350 kD, that is essential for embryonic development and neurogenesis, and can affect other developmental processes such as hematopoiesis. Expansion of a polyglutamine tract near the N terminus of huntingtin causes Huntington's Disease (HD), a neurodegenerative disorder. Huntingtin is present in both the nucleus and the cytoplasm and undergoes proteolytic processing, but its molecular function is still unclear.

Huntingtin contains the amino acid sequence PLDLS, a candidate-binding site for the transcriptional corepressor C-terminal binding protein (CtBP), another protein essential for development. We found that full-length huntingtin interacts with CtBP using co-immunoprecipitation assays, and that mutant huntingtin interacts less efficiently compared to wild-type huntingtin. In addition, Gal4-huntingtin fusion proteins can repress transcription of the herpes virus thymidine kinase promoter when tethered to DNA via proximal Gal4 binding sites. Eliminating the central and C-terminal regions of huntingtin (including the PLDLS site) abrogates transcriptional repression by wild-type huntingtin in the same assay. However, similar N-terminal mutant huntingtin fragments retain the ability to repress transcription, suggesting that polyglutamine expansion in huntingtin disrupts normal transcriptional regulation. Huntingtin interacts with other proteins involved in transcription, and contains candidate-binding sites for additional proteins important for differentiation, cell cycle regulation, and apoptosis. Together, these data suggest that huntingtin may affect development and regulate the cell cycle in part through transcriptional regulation. Proteolysis of mutant huntingtin may result in deregulation of transcription at certain promoters due to reduced interactions with CtBP, and inappropriate transcriptional repression mediated by N-terminal mutant huntingtin. The interaction with CtBP may also be necessary for a vesicle trafficking-related cytoplasmic function of huntingtin. Our results suggest that HD pathology result from mechanisms involving both a loss of function and gain of function.

# NEURODEGENERATIVE PROCESSES EVALUATED IN A MODEL OF EXPERIMENTAL ISCHEMIA IN RATS

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The relationship between cerebrovascular disease and the possibility to develop dementia or depression is widely accepted by several authors. For instance, patients that had survive a cerebrovascular attack increase ten times their risk to develop dementia as compared with patients that had not. The role of the cerebrovascular system in multi-infarct dementia, Alzheimer's disease and other dementias emphasizes the need to evaluate the impact of cerebrovascular injury on neurodegenerative processes using experimental models. Function of the nervous system depends upon complex electrochemical interactions among different types of local and projection neurons. So it is inappropriate to evaluate only local effects after injury. Axons coming from projection neurons belonging to the injury zone degenerate leaving vacant synapses in exofocal areas. At the same time spared neurons from exofocal areas that project to those zones impacted directly by the ischemic attack (core and penumbra), can not probably reach their targets, if so, they will connect physiological altered neurons. The effect of these aberrant connections has not been extensively evaluated at structural, neurochemical or functional level. In the present work we showed several neurochemical changes in exofocal areas after different survival times using an intraluminal middle cerebral artery occlusion model with reperfusion in adult rats. We found immunohistochemical changes in MAP2, GFAP, tiroxine hidroxilase, Gaba receptors and bcl2 in the contralateral cortex, ipsilateral striatum and substantia nigra, structures that are not irrigated by the occluded artery. In future studies it will be important to correlate this changes with the appearance of new neurological symptoms involving cognitive and emotional alterations after a longer period of survival times, since this changes may imply subcellular and synaptic reorganizations in different circuits such as the cortico-striato-nigro-thalamic-cortical loop that are implicated not only in motor function but also in cognitive and emotional control.. (Proyecto Financiado por Colciencias y la CSCI)

# INFLAMMATION AND OXIDATIVE STRESS IN ALZHEIMER'S DISEASE AN INTEGRAL SURVEY FROM CYTOKINES STUDY AND ANTIOXIDANT ACTIVITY

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## Summary

**Background:** Inflammation and oxidative stress have been referred to neuronal degeneration process in Alzheimer's disease (AD). Biological markers in AD have been studied from different fluids, as a way to look for evidences helping to an earlier diagnosis in this entity. CSF analysis is considered a tool in the diagnosis exclusion of dementia. Nevertheless, others no less important markers from the peripheral fluids may add information on the pathological mechanism of the disease. This paper shows an integral result of the immune - inflammatory response and oxidative stress in AD patients, Vascular dementia and Dementia secondary to Neurosyphilis. **Material and method.** The analysis involved the evaluation of humoral intrathecal immune response (CSF -blood barrier function, intrathecal synthesis to immunoglobulin classes using Reibergram diagram), the quantitative determination of cytokines (IL 1 $\beta$ , TNF  $\alpha$ ) by ELISA, as well as the seric quantitative estimation of antioxidant activity (antioxidant enzyme and lipoperoxide). Also was considered their probable interaction with the evaluated inflammatory parameters. **Results:** The CSF immunoglobulin analysis showed a differential pattern of Reiber diagram to the different class of immunoglobulins to each type of dementia. The quantitative determination of cytokines showed a significant difference to TNF  $\alpha$  in AD patients compared to age control subject ( $p < 0.05$ ) as well as a significant interaction level to this variable with CAT antioxidant activity in AD patient's ( $p < 0.05$ ). A significant increased activity was observed to each one of the antioxidant enzyme evaluated in AD patients, too ( $p < 0.05$ ). **Conclusions** The results tag the reactive oxygen species as cellular messenger instead a simple pathogenic agents to the disease, in addition to the potential value of this markers to evaluate the progression of the disease considering the significant interaction into each other.

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## GLUTATHIONE S TRANSFERASES AND THE IR SIGNIFICANCE IN ATAXIA SCA - 2

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The glutathione S-transferases (GSTs; E.C.2.5.1.18) are a multi-gene family of enzymes involved in the detoxification, and in a few instances, activation of a wide variety of chemicals. GSTs catalyze the nucleophilic attack of glutathione (GSH) on electrophilic substrates, thereby decreasing their reactivity with cellular macromolecules. Although no definitive physiological role for GSTs has yet been identified, several reactive endogenous molecules, including  $\alpha$ -unsaturated keto prostaglandin's (PGA<sub>2</sub>, PGJ<sub>2</sub>), and endogenous fatty acid oxidation products, such as 4-hydroxy-2-nonenal, serve as substrates for certain GSTs. One human GST (hGSTM<sub>2-2</sub>) has recently been found to exhibit unique and high catalytic activity toward reactive quinones of endogenous catecholamines (dopaminochrome, formed by oxidation of dopamine), and thus may play some protective role against endogenous oxidative tissue damage in the brain. Ataxia, another neurodegenerative disease with genetic origin, we detected an increased generation of reactive oxygen species. Ataxia SCA - 2, the most common inherited ataxia in Cuba, due to CAG expansion in a gene. In these work was investigated the enzyme specific activity GST. We also studied the glutathione levels in order to evaluate its possible influence on enzyme activity and with the disease. **METHODS:** Blood samples were obtained from 24 unrelated patients with ataxia SCA -2 and 21 age matched healthy subjects. GST specific activities were determined spectrophotometrically assayed using GSH and CDNB as specific substrates. **RESULTS AND DISCUSSION:** There was both a significant reductions of the GST specific activity and GSH concentrations ( $p < 0.05$ ) in serum of patients with ataxia SCA -2 than in the controls. These results on GST specific activity are opposite to recently report from Tozzi et al (Arch Dis Child 2002 May;86(5):376-9) who reported in blood of patients with Friedreich's ataxia a significant elevation of GST specific activity in blood of patients with Friedreich's ataxia than in the controls. **CONCLUSIONS:** Data show for first time to Cuban's ataxia patients an impairment in vivo of GST/GSH enzymes/substrate in serum from patients with ataxia SCA -2 and provide evidence of an increased sensitivity to cytotoxicity stress, supporting a consistent role of cytotoxicity in the pathophysiology of the disease. These results also suggest a possible physiologic role for GSTs in Ataxia diseases. Molecular epidemiology studies examining the potential importance of GST in ataxia type SCA-2 will be discussed.

## GLUTAMATE AND NEURODEGENERATION

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Glutamate (**Glu**), the predominant excitatory transmitter in the mammalian Central Nervous System (**CNS**) plays a crucial role in processes such as memory and learning. Excessive activation of glutamate receptors (**GluR**), termed excitotoxicity, leads to increase  $[Ca^{++}]_i$ , generation of reactive oxygen species (ROS) and eventually neural death. Many GluR and Excitatory Amino Acid Transporters (EAAT) are subject to complex regulation. Excitotoxicity appears as a common feature in many neurodegenerative disorders. Ischemic insult results in massive accumulation of extracellular Glu ( $[Glu]_o$ ). However, in other neurodegenerative conditions, massive  $[Glu]_o$  accumulation is not observed. It is abundantly clear from the reviewed literature that in many neurodegenerative disorders, there is chronic dysregulation of glutamatergic homeostasis. For example, in amyotrophic lateral sclerosis, dysfunctional SOD (superoxide dismutase) results in oxidative stress which in turn, interferes with glutamate uptake. Pharmacological manipulations of Glu homeostasis have, to a large extent, failed because of the narrow time-window or because the effects are marginal. However, manipulation of  $[Glu]_o$  or of GluR remain as under-explored area.

# GENETIC NEUROPATHOLOGY

**Dalia Duarte, Chair**

**N. J. Sanz-Pupo** - QUANTITATIVE PATHOLOGY. NEUROSCIENCIE'S APPLICATION

**G. Loudianos** - MOLECULAR PATHOLOGY AND DIAGNOSIS OF WILSON DISEASE

**S. Mejía** - NON GENETIC FACTORS AS MODIFIERS OF THE AGE OF ONSET OF FAMILIAL ALZHEIMER DISEASE

**D. Forero** - GENETIC FINDINGS IN LATE-ONSET ALZHEIMER'S DISEASE IN COLOMBIA ANDEVALUATION OF THE ROLE OF SYNAPTIC PLASTICITY IN THE PATHOGENESIS OF DEMENTIA

**D. Duarte** - APO E AND ALZHEIMER DISEASE IN THE CARIBBEAN POPULATION

# QUANTITATIVE PATHOLOGY AND NEUROSCIENCE'S APPLICATION

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## Summary:

Science's development has been related with Humanity's development and with the need to measure necessity. Several quantitative techniques have been employed to characterize and to interpret the complex pathologic phenomena of Medical Science. The stereological and morphometric methods have been employed in Neuroscience too. Histological preparations of nervous tissue permit examination of nervous system development and the interaction between neurons and with their environment. By means of unbiased stereological principles and systematic sampling techniques, the number, the mean volume and many architectural alterations of the neurons and other cells and structures of nervous system have been estimated. In order to evaluate the statistical significance of morphological changes, it is necessary to quantify tissue populations and parameters. Recent advances in Stereology facilitate the gathering of morphometric data, while eliminating sources of error associated with traditional methods. Unfortunately, Stereology has been accepted slowly within neuroscience investigation, but it represents an important extension of qualitative studies of nervous tissue.

# MOLECULAR PATHOLOGY AND DIAGNOSIS OF WILSON DISEASE

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Wilson disease (WD) is an autosomal recessive disorder of copper metabolism that is characterized by impaired copper biliary excretion and reduced copper incorporation into ceruloplasmin. This leads to copper accumulation into the liver and, consequently, to progressive liver damage. Subsequent overflow of copper determines accumulation in other organs mainly in the brain, kidneys, and cornea resulting to neuronal degeneration and kidney malfunction(1). In most populations, WD has a prevalence of approximately 1:30000 with a carrier frequency of 1 in 90 (2). The characterization of genomic structure of ATP7B gene has permitted the definition of molecular basis of WD by mutation analysis. More than 200 mutations have been found in WD patients including single base insertions and deletions, frame -shifts and missense, nonsense and splice site mutations. In the past few years we have carried out systematic mutation screening of the ATP7B gene in 463 unrelated families of Southern European origin (96 Sardinians, 183 Italians, 53 Turks, 50 Greeks, 48 Serbians, 22 Portuguese, 7 Albanians, 2 Spaniards 1 Saudi Arabian, 1 Slovenian). Analysis of genomic DNA was carried out by SSCP both on the coding and promoter regions of the gene followed by direct sequencing of the shifted exons. Using this approach we have characterized the molecular defect in 87.5 % of WD chromosomes and identified 142 mutations of which 25 frameshift, 14 nonsense, 16 splice site, and 95 missense that suggests a high allelic heterogeneity. In the populations analyzed, most of mutations detected are rare and population specific and only a limited number are relatively frequent. Consequently most patients are compound heterozygotes, carrying alleles with two different mutations. The most frequent mutation detected in Italian, Greek and Serbian patients was His1069Gln which accounts for 16, 29, and 46 % of molecular defects respectively. This mutation and five others account for 70 % of Wilson disease chromosomes in patients of Greek descent, while the same mutation with three more mutations account for 70.8% of WD chromosomes of Serbian descent. In the Sardinian population the molecular analysis of WD patients permitted the characterization of the 93.8% of the analyzed chromosomes and the identification of 23 different mutations. The six most common mutations in this population account for approximately 82 % of the total while one of them, -441/-427del, singularly accounts for the 60% of the analyzed chromosomes that suggests the presence of a founder effect. This 15 nucleotide deletion is the only promoter mutation detected to date. Functional assays have showed that -441/-427del results to a 75% decrease of promoter activity. By searching for the presence of the 15nt deletion in 1032 random sardinian DNA samples we detected 32 heterozygotes indicating a carrier rate of 1:29. These data suggest that the search of mutation in the Sardinian population can be used not only for single diagnostic tests but probably also for a systematic mass screening. We have also observed that approximately 70% of the detected defects reside in 10 exons that code for the transmembrane regions and the large ATP loop. These data confirm the critical role of the transmembrane regions as well as of the ATP loop in the protein structure organization and function. On the basis of these data we have designed two strategies for mutation analysis of WD in the analyzed populations. In nonsardinian populations we use SSCP method to analyze the 10 exons where most of defects reside in our experience. Patients not characterized are subsequently analyzed for the remaining gene regions. In the Sardinian population we have developed a multiplex PCR method that permits the simultaneous amplification of the regions containing the six most common mutations in this population coupled with reverse dot blot analysis with ASO probes. Samples not characterized by this first step are subsequently analyzed with the SSCP method used for the nonsardinian populations. The large number of mutations and high prevalence of compound heterozygotes reported to date render genotype -phenotype correlation analysis difficult.

Preliminary observation in Sardinian WD patients carriers of the -441/-427del mutation show no definitive genotype -phenotype association in age at onset, clinical features and biochemical markers. Elucidation of the molecular genetic basis of WD by mutation analysis has permitted new insights into the mechanisms of cellular copper homeostasis and improved our capability of early diagnosis and treatment of toxic effects of tissue copper accumulation.

# NON GENETIC FACTORS AS MODIFIERS OF THE AGE OF ONSET OF FAMILIAL ALZHEIMER DISEASE

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## Summary

The purpose of this investigation was to identify the environmental and personal factors that are present in subject's life before the age of onset of Familial Alzheimer's disease and that could be related with the variability in the age of onset of the disease (36 -62 years). A sample of 49 subjects with Alzheimer Disease belonging to the pedigree carrying the mutation E280A PS -1 gene on chromosome 14 from Antioquia, Colombia, was divided in two groups: 27 participants with age of onset between the 36 and 46 years (early age of onset) and 22 patients with age of onset between the 47 and 62 years (late age of onset). The information regarding environmental and personal factors was picked up through a questionnaire that was responded by each patient's relatives or by the patient if the clinical conditions allowed it. The information was organized in a categorical way. The two groups were compared through the chi squared test. The variables that showed statistical differences were included as independent variables in a logistic regression to predict their association with the early onset. It was found that of the 140 studied variables, only five were different among the groups: surgical history, type of stressful event, education, depression and affective losses. The last three variables entered to the logistic regression model where: high education has almost 15 times more probabilities of association with early age of onset and the presence of affective losses and depressive symptoms, have both 4 times more probabilities of association with early age of onset. The relationship between high education and early age of onset could be in connection with an earlier detection of the symptoms that in turn would be determined by more intellectual and environmental demands. The presence of depression and affective losses some years before the beginning of the disease has been considered a prodromic manifestation or risk factor.

# GENETIC FINDINGS IN LATE -ONSET ALZHEIMER'S DISEASE IN COLOMBIA AND EVALUATION OF THE ROLE OF SYNAPTIC PLASTICITY IN THE PATHOGENESIS OF DEMENTIA

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Alzheimer's disease [AD] is the first cause of dementia in the world. In our sample of our population with late -onset AD there is no association with Alpha -2 Macroglobulin and Angiotensinogen Converting Enzyme polymorphisms. There is an significant association with promoter polymorphisms of Apolipoprotein E and preliminary studies with intronic repeat polymorphism in tau show the possible existence of new alleles. In the context of the approaches to the etiology of AD and with the consideration that classical amyloid theory is not complete and satisfactory, I analyze the possible pathophysiological events that lead to cognitive deficits in AD patients, considering the role of AD - associated proteins in neural and synaptic plasticity, such as the relation of Amyloid in long-term potentiation changes, ApoE to Reelin signaling, presenilin in Wnt and Notch pathways, APP in membrane-to-nucleus communication, and Tau in axonal dynamics. The role of synaptic plasticity related-proteins in AD brains and models are discussed. The proposals of new forms for the study of AD from a functional perspective are in consideration.

# APO E AND ALZHEIMER DISEASE IN THE CARIBBEAN POPULATION

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An association between the E 4 allele of the ApoE gene and Alzheimer's disease (AD) has been confirmed in many studies worldwides especially in late -onset disease. OBJETIVE: In this work has been intended to review specifically the behaviour of this apolipoprotein E in some Caribbean population, and to expose the results obtained from a study based in Cuban families with AD..METHOD: ApoE genotyping was performed using the polimerase chain reaction (PCR) and international criteria. The diagnosis of AD was based on criteria from the NINCDS -ADRDA. RESULTS: It was found in a total of 83 unrelated Colombian patients predominantly late -onset including familial and sporadic AD case a high association ( OR=5.1 95% CI 1.9- 13.6) between ApoE and AD. An ongoin g longitudinal study in Maracaibo, Venezuela, examined the interaction between ApoE genotype and AD. It was found, those carriers of at least one E4 allele were at higher risk for AD. The results support the notions that ApoE epsilon 4 is relevant for late -onset. Other study examined the association between the ApoE4 and familial AD in Caribbean Hispanic population in the greater New York City area, they were from Dominican Republic(81.3), and Puerto Rico.The presence of ApoE4 was strongly associated with AD. In contrast to sporadic AD, late -onset familial AD among Caribbean Hispanic is strongly associated with ApoE4. In Cuba were genotyped 28 cases with FAD and 106 controls. It was found that the ApoE4 allele(0.482) and genotype frequencies(78.6)were higher in the cases than control group. It was observed that the ApoE epsilon 4 is strongly associated with AD and could be an important risk factor for the AD susceptibility. CONCLUSIONS: It is evident that the ApoE epsilon 4 is strongly associated with AD.

# **METABOLISM AND CLINICAL PHYSIOLOGY OF NEURODEGENERATIVE DISORDERS**

**Edilberto Martínez Góngora**

**R. Zambrano** - NUTRITIONAL ASPECTS OF DEMENTIA

**D.A. Duran** - REFERENCE VALUES FOR PLASMA HOMOCYSTEINE IN A MARACAIBO  
ELDERLY POPULATION

**L. Ocando** - MTHFR 677 C<sup>à</sup> T POLIMORPHISM AND HOMOCISTEYNE PLASMATIC LEVELS  
AMONG COMMUNITY DWELLING ELDERLY: FINFINGS OF THE MARACAIBO AGING STUDY

**G. Sánchez-Cruz** - STUDIES OF INTERVALOMETRÍA RR FOR THE FUNCTIONAL  
EVALUATION OF THE AUTONOMOUS NERVOUS SYSTEM IN PATIENT OF  
SPINOCEREBELLAR ATAXIA TYPE 2

**L. Velázquez- Pérez** - NEUROPHYSIOLOGICAL ALTERATIONS IN PRESYMPTOMATIC  
RELATIVES AND PATIENTS SUFFERING FROM SPINOCEREBELLAR ATAXIA TYPE 2

**E. Martínez-Góngora** - CENTRAL MOTOR CONDUCTION TO UPPER LIMB AFTER  
TRANSCRANIAL MAGNETIC STIMULATION IN SPINOCEREBELLAR ATAXIA TYPE 2 (SCA2)

# REFERENCE VALUES FOR PLASMA HOMOCYSTEINE IN A MARACAIBO ELDERLY POPULATION

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Introduction: Homocysteine is an intermediary amino acid. High concentrations of homocysteine in plasma have been associated with higher morbimortality rates for vascular diseases and neurodegenerative disorders. The management of hyperhomocysteinemia requires the use of reference values estimated for each population of interest. The main objective of this study was to estimate, in a population reference sample, reference values for individuals older than 55 years old living in the community in a neighborhood of Maracaibo. Material and Methods: From a population-based registry of 2108 subjects, a reference sample of 905 healthy subjects (66.9% women) with folate and vitamin B12 levels over its specific 33rd percentile was selected. Homocysteine, vitamin B12 and folate levels were estimated by the IMx analyzer from Abbott Laboratories. The partitioning of the reference sample was made according to age and gender. The reference values were estimated by parametric and nonparametric methods according to IFCC recommendations. Results: Homocysteine concentrations were significantly higher in men than women and were associated with age and plasmatic levels of folate and B12 vitamin. The reference values obtained by parametric methods were substantially lower than those obtained by nonparametric methods. Parametric reference values were 9.77 – 15.02  $\mu\text{mol/L}$  and 11.65 – 16.86  $\mu\text{mol/L}$  for age groups of 55 – 69 and 70 years and over respectively in men and 7.96 – 13.13  $\mu\text{mol/L}$  and 9.31 – 14.60  $\mu\text{mol/L}$  for age groups of 55-69 and 70 years and over respectively in women. Conclusion: The reference values adjusted to age and gender were estimated and its range values were close to those reported to act as risk factor for vascular diseases, conferring this values an elevated clinical significance.

# POLYMORPHISM 677 C ? T OF THE METHYLENETETRA HYDROFOLATE REDUCTASE GENE AND HOMOCYSTEINE PLASMATIC LEVELS AMONG COMMUNITY DWELLING ELDERLY: FINDINGS OF THE MARACAIBO AGING STUDY .

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The polymorphism 677 C?T of the methylenetetrahydrofolate reductase (MTHFR) gene has been largely associated to high plasmatic levels of homocysteine (Hcy) in Caucasian populations. However this association has been studied scantily in Latin American and Caribbean populations. In this study, the allelic frequency of the polymorphism 677 C?T has been estimated in a population of 1007 individuals older than 55 years old residents of Maracaibo (Venezuela). In addition, the association between this polymorphism and the plasmatic levels of HCY were analyzed. The most frequent allele was the form 677C of the MTHFR (0.67), and distributed homogeneously by gender and age of the subjects. The frequency of the genotype of the MTHFR exhibited the Hardy –Weinberg equilibrium. The plasmatic levels of Hcy, were significantly increased in subjects with the genotype TT compared with the carriers with genotypes CC and CT (Kruskal –Wallis  $\chi^2=9.67$ ;  $p< 0.008$ ). Consistently, the carriers of the genotype TT exhibited a significantly increased risk of hyperhomocysteinemia when compared to CC and CT carriers (Odds Ratio = 2.04 (IC 95% 1.31 -3.26). This association remained significant when adjusted by folate and vitamin B12 levels. In conclusion homozygous subjects for the thermolabile form 677T of the MTHFR are at higher risk of having hyperhomocysteinemia, in this Venezuelan population.

# STUDIES OF INTERVALOMETRÍA RR FOR THE FUNCTIONAL EVALUATION OF THE AUTONOMOUS NERVOUS SYSTEM IN PATIENT OF SPINOCEREBELLAR ATAXIA TYPE 2

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## SUMMARY

Introduction. The analysis of the changes in the variability of the heart rhythm constitutes the main measure to evaluate the functional state of the Autonomous Nervous System. Objectives. To evaluate the functional state of the Autonomous Nervous System in sick of Spinocerebellar Ataxia type 2. Patient and Methods. We were carried out a battery of studies standardized for the evaluation of the Autonomous Nervous System (Maneuvers of Tilt Table Test and of Valsalva, Tests of Spontaneous and Deep Breathings) in 103 sick persons and 50 healthy fellows. RESULTS AND DISCUSSION: Maneuver of Passive Ortostatic. The comparison of stockings of the Half variables and Standard Deviation in the intervalometría R-R among the group of sick and healthy fellows, during the position of Supine Total demonstrated significant differences between both groups with inferior values in the group of the sick fellows for both analyzed variables (he/she Mediates in the sick persons of 772,1 msec and in the healthy of 900,7 msec with  $p=0,001$ . Standard Deviation in the sick persons of 58,5 msec and of 61,3 msec). For the supine end a similar behavior existed. This same behavior was evidenced in the analysis of variance of the variables that were explored in the different moments of the ortostatic (after vascular), where all the variables, except the Stocking of the Final Ortostatic, showed a significant reduction of its value in the sick persons of SCA2. These results demonstrate the presence of a hyperfunction of the Nervous System under conditions of rest, what is the cause of the extrasistols overventriculars detected in 8% of those investigated under basal conditions and in 25% before the different carried out tests. Test of Spontaneous Breathings. So much in the Standard Deviation (DS) like in the Standard Deviation of the Successive Differences (DSDS) the existence of differences was verified statistically significant he/she enters in both groups of investigated fellows, with very inferior measures in the group of the sick persons. Similar results have been in the cases of neuropathy autonomous vagal what reaffirms us that the decrease of the variability of the heart rhythm detected in the test of passive ortostatic is owed partly to this alteration heart vagal. Test of Deep Breathings. In the group of the sick persons very inferior values of the stocking of the Quotient exist Espiratory/Inspiratory (Coc E/I), with differences statistically significant when comparing it with the group of the healthy fellows. The Coc E/I is much smaller in the sick persons of SCA2 of different incapacity degrees that in the healthy fellows, like it happens in other pathological states that damage the answer vagal, what reaffirms the result of the previous test where the existence of a neuropathy hyperfunction vagal is demonstrated. Maneuver of Valsalva. The Quotient of Valsalva showed bigger figures in the sick fellows (1.80) that in the healthy ones (1.53), although without significant statistical differences, what is given by the increase of the nice tone in the phase II of Valsalva. Conclusions. A hyperfunction of the Nervous System was demonstrated with slight hypofunction of the Parasimpatetic in the sick persons of Spinocerebellar Ataxia Type 2 investigated.

# NEUROPHYSIOLOGICAL ALTERATIONS IN PRESYMPTOMATIC RELATIVES AND PATIENTS SUFFERING FROM SPINOCEREBELLAR ATAXIA TYPE 2

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The Spinocerebellar Ataxia Type 2 (SCA2) has a prevalence of 43 per 100 000 inhabitants in Holguín province, which is the highest one reported worldwide. **Methods** A group of 59 asymptomatic relatives of patients with SCA2 were studied during ten years. The studies included Motor and Sensitive Nerve Conductions Studies, Somatosensory Evoked Potentials of Median and Tibial Posterior Nerves, Brain Stem Auditory Evoked Potentials and Conventional Electromiogram. **Results.** A total of 17 subjects fell ill (31 % of the sample) to whom - before falling ill - four evolution phases were defined: the first was characterized by normal neurophysiological studies in the absence of clinical manifestations; the second one showed decreased amplitude of the sensitive potentials (Median, Sural and Erb Point) as well as mild prolongation in the latency of the P40 component of the Somatosensory Evoked Potentials of Tibial Posterior Nerve even without phenotypical expression of the SCA2; in the third phase the alterations described above are increased and an Electromiogram with a neurogenic pattern without denervation appears whereas in the fourth phase there are blocks in the central and peripheral conduction (absence of response in the studies of conduction of sensitive nerves, somatosensory evoked potentials). The electromiogram showed neurogenic pattern resembling that of the motor neuron disease. These findings suggested that the predominant lesion is that of the axonal degeneration of sensitive peripheral nerves in presymptomatic stages and, subsequently, some alterations at intraxial level suggestive of axonemelinic lesion in posterior cords and brain stem appeared. A second group of 70 sick persons were also studied. The electromiogram study showed the existence of an isolated contraction pattern in sick persons with an evolution time under 5 years while in those of a longer time a very isolated pattern with motor unit potentials of amplitudes

# CENTRAL MOTOR CONDUCTION TO UPPER LIMB AFTER TRANSCRANIAL MAGNETIC STIMULATION IN SPINOCEREBELLAR ATAXIA TYPE 2 (SCA2)

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**OBJECTIVES:** To evaluate central motor conduction to upper limbs in spinocerebellar ataxia type 2 (SCA2). **METHODS:** Motor evoked potentials (MEPs) triggered by transcranial magnetic stimulation (TMS) was used to investigate the functions of corticospinal tracts of 35 patients with SCA2. **RESULTS:** Central motor conduction time (CMCT) to upper limbs were abnormal in 13 patients (37,14 %) and the MEP threshold increased in 11 patients (31.41 %). **CONCLUSIONS:** Corticospinal tract involvement is frequent in patients with SCA2.

# **FAMILY AND SOCIAL IMPLICATIONS OF ATAXIA AND DEMENTIAS**

**Carmen Delia Sánchez**

**C. D. Sánchez** - ALZHEIMER WITHIN THE PUERTO RICAN CONTEXT

**D. Edelmire** - FAMILY PERSPECTIVE ON DEMENTIAS IN JAMAICA

**A. M.Espín** - TRANSDISCIPLINARY APPROACH TO DEMENTIA AT THE CENTRO  
IBEROAMERICANO PARA LA TERCERA EDAD IN CUBA.

**A. Estupiñán-Rodríguez** -REALITIES AND PERSPECTIVES OF THE SOCIAL WORK IN THE  
ATAXIA ESPINOCEREBELOSA TYPE 2 AT HOLGUÍN PROVINCE

**O. Rojas-Ruiz** - EDUCATIONAL PROGRAM "WITH THE LOOK IN THE BRAIN"

# ALZHEIMER WITHIN THE PUERTO RICAN CONTEXT

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**C. D. Sánchez**

*University of Puerto Rico, Puerto Rico*

This presentation offers an overview of the context in which Alzheimer takes place in Puerto Rico. It presents demographic data concerning the elderly population which is the population sector most affected by this illness. Socioeconomic data as well as information on the informal support system of the Puerto Rican elderly is provided relating it to the situation of the Alzheimer elderly patient and his/her family including values and cultural issues affecting or favoring elderly care. A final section is dedicated to the role of the Alzheimer Association of Puerto Rico as it concerns services to patient and families.

# FAMILY PERSPECTIVE ON DEMENTIAS

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## D. EDELMIRE

Dementia is an illness which affects all aspects of a person's life as the ability to function independently is reduced and help is needed. In the Caribbean setting assistance is usually provided by a carer in most cases a family member and not by institutional care. The carer, often a female, is faced with many challenges in providing this care without substantial support systems. The family remains the main support, mental, physical and economical and can be pressured by the effort. The paper examines the reactions both positive and negative of providing care to a demented person and the need for adequate support systems.

# TRANSDISCIPLINARY MANAGEMENT OF DEMENTIA AT THE CENTRO IBEROAMERICANO PARA LA TERCERA EDAD CITED

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**A. M. Espín, D. García Agustín, J. C. García, T. Méndez, D. Duarte**

Dementia is a syndrome of intellectual progressive deterioration in adults, that interfere with personal, familiar and social life and work. Even though memory deficit is the most frequent symptom and the one that makes the patient find professional attention, it should not be considered alone when configuring the clinical syndrome, for the diagnosis and therapeutics should be approach by different specialists in an integrated mode.

Transdisciplinary Methodological Program: When a patient with mnesic problems visits CITED, is referred to the Memory Disorders Clinic where is evaluated by different professionals: geriatrician, Neuropsychologist, neurophysiologist, geneticist, defectologist, and social worker. This program is composed of several phases:

**I. Clasificación ( Initial clinical -cognitive screening):** 1 - Anamnesis and Epidemiology: Through an structured interview to the patient and a family member, current symptoms are interrogated, emphasizing the age of onset of symptoms, length and evolution, age of onset, early neurological signs, history or clinical evidence of systemic diseases (malnutrition, hepatic, renal toxic) or previous psychiatric history, at the same time personal history, lifestyle and nutritional factors are collected. 2 -Physical Examination: A profound and structured physical examination is performed emphasizing the Nervous System. 3 -Cognitive Assessment: Mini Mental State Examination, Psychoaffective Scale (a validaded scale built and validated in Cuba to identify mood disorders in the elderly.

At this time, complementary examination (Biochemichal Profile) is indicated.

## **II. Phase of Evaluation**

1-Neuropsychological Assessment: cualitative and psychometric that includes the Dementia Rating Scale of Mattis, the Alzheimer's Disease Assessment Score and Evaluation of Memory. 2-Neurophysiological: Brain mapping EEG 3-Caregiver evaluation: an structure interview, psicosocial scale and the burden test of Zarit

III Diagnostic Phase. Af ter a diagnostic conference one of possible diagnosis is made: Mild cognitive impairment or Dementia, in this case the Hachinski Scale, CDR and Blessed are applied

IV Therapeutic Phase. 1 - Cognitive Intervention and stimulation 2 - Drug treatment 3 - Caregiver care and family support (eduactional porgrams, family guidance, support groups and individualized caregiver assistance to diminish stress and improve quality of life.

# REALITIES AND PERSPECTIVES OF THE SOCIAL WORK IN THE SPINOCEREBELLAR ATAXIA A TYPE 2 IN THE PROVINCE OF HOLGUÍN

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Epidemiological investigations constitute the main source of information about the problems that affect specific groups, generating the actions guided to find solutions. In Holguín, but coming from different municipalities a total of 440 patients and 1633 at risk relatives exists. Due to the lack of a specific treatment for the illness, its high morbidity, and to the biological, physical and psychological deterioration that causes in the patients and their relatives, it becomes necessary to take actions guided to provide a possible solutions to the problems generated and to improve the quality of the patients' life and descendents at risk. The prevalence rate in our country was of 7.3 per 100 000 inhabitants. In Holguín it was of 43 per 100 000 inhabitants. The higher incidence rate was of 18.1 per 100 000 in Cacocum, followed by Baguanos with 10.9 per 100 000, while for the county this it was of 4.4 per 100 000. The affected age group went the one from 30 to 39 years belonging to the rural population. The results obtained in the physical, language and psychological rehabilitation shows us the importance of their continuation, constituting an encouragement for the patients and their relatives. On the other hand, 180 (40.9%) of sick persons receive continuous monetary benefits. The prevalence and incidence rates are the highest worldwide and they have not shown variations in comparison to the first studies, representing a serious problem of health that affects to the oriental region of the country. In spite of the results obtained in the rehabilitation spheres and social attendance, it becomes necessary the sensitization of those sectors that in a way or another can collaborate in the solution of the different problems, which will allow to improve and to elevate the conditions and quality of life of these patients and their relatives.

# EDUCATIONAL PROGRAM "WITH THE EYE IN THE BRAIN"

**O. Rojas Ruiz, G. E. Maestre**

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The Educational Program "With the Eye in the Brain", is based in the notion that scientific knowledge is of use to everyone and scientists have a key role to play trying to bridge the science-society gap. We envision as a social duty of our research team, to communicate science, in particular to translate the knowledge that we acquire and develop to those that surround us, and particularly those that are subjects of our investigations.

The Program began with outreach activities as "Brain Awareness Week" and Simposia directed to health professionals in 1997, in Maracaibo. Nowadays the Program is structured in two types of activities: 1) General Transference, including symposia for health professionals and general public, meetings with the media, and publications for the general public and press releases. 2) Targeted Transference, including Workshops for educators, caregivers, elderly, demented subjects and young people including preschoolers, training of pre and postdoctoral students and students and discussion groups.

A most recent goal of the Program is intended to provide a social platform for improving the quality of life and care of the elderly living in the community of Santa Lucia, in the city of Maracaibo, where the "Maracaibo Aging Study" is carried out. The idea is to promote healthy aging from the preschoolers to the elderly, and kind and efficient care for the demented patients.

Science and scientific applications exert a profound influence on society and the role of science promises to be even greater in the future because of accelerating scientific advances. We intent to accelerate the transference of neuroscience and aging related knowledge in our community and hopefully our experience could be translated to other areas in the Caribbean that share a cultural and social background.

# **COGNITION AND ETHICS**

**Nieves Santos Falcón, Chair**

**G. Pino-Ramírez** - APLICATION OF THE REFERENCE VALUES METHODOLOGY TO NEUROPSYCHOLOGICAL TESTING IN THE DIAGNOSIS OF DEMENTIA

**D.C. Aguirre-Acevedo** - CERAD-COL NEUROPSYCHOLOGICAL BATTERY: CONSTRUCT VALIDITY AND INTERNAL CONSISTENCY IN ALZHEIMER'S TYPE DEMENTIA PATIENTS

**R. R. Armiñan** - MENTAL DISORDERS DETECTED IN PATIENTS WITH SPINOCEREBELLAR ATAXIA TYPE 2 IN CUBA

**N. S. Falcón** - PROGRAMA DEL TEST DE PREDICCIÓN Y ASESORAMIENTO GENÉTICO EN LA ATAXIA ESPINOCEREBELOSA TIPO 2 (SCA2) Y OTRAS ATAXIAS DOMINANTES.

**V. B. Penchaszadeh** - PREDICTIVE GENETIC TESTING FOR DISEASES OF LATE ONSET: MEDICAL, SOCIAL AND ETHICAL ISSUES.

# APPLICATION OF THE REFERENCE VALUES METHODOLOGY TO NEUROPSYCHOLOGICAL TEST USED FOR DIAGNOSIS OF DEMENTIA

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The present study had as objective the application of the Referential Values methodology to establish the cutoff of neuropsychological tests used for the diagnosis of dementia. Additionally we calculated the diagnostic utility in terms of Sensitivity, Specificity, and Positive, Negative and Predictive Values of these cutoff values when they were compared with the clinical diagnosis of dementia. We selected an intentional sample of 1625 subjects from the Maracaibo Aging Study database, who did not suffer or had suffered of pathologies like Dementia, Cerebral Vascular Disease, Psychiatric Disorders, Epilepsy, Nonepileptics seizures, Traumatic Brain Injury, Hypotirodysm, Mental Retardation and severe Visual or Auditory handicap. We used the standardized procedures for the diagnosis of dementia and a brief and core Neuropsychological Battery conformed by Stern and col. (1992). We first established the characteristics of the distributions of each test dividing the sample arbitrarily in six age groups and five groups by educational attainment. The nonGaussian distributions were standardized by logarithmic transformations and/or by the elimination of outliers whose transformed scores were beyond  $\pm 3$  standard deviations. The sample partitioning was made by conforming homogenous groups according to age and education; after that samples were randomly selected to establish the References Values and the Confidence Intervals (CI) for 95, 90, 85, 80 and 75%, using the parametric method,. Finally the Sensitivity, Specificity and Positive, Negative and Total Predictive Values were settled down for each case. The results allowed to make a combination of CI according to the psychometric performance of each test, and to conform a battery with 0.85 of Sensitivity and 0,82 of Specificity. The utility of Reference Values methodology in the field of the psychometrics, as well as the strength and limitations of the design are discussed.

# CERAD - COL NEUROPSYCHOLOGICAL BATTERY: CONSTRUCT VALIDITY AND INTERNAL CONSISTENCY IN ALZHEIMER'S TYPE DEMENTIA PATIENTS

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**INTRODUCTION:** Alzheimer's disease is a public health increasing importance due to its disabling character and its high individual, familial and social cost. Neuropsychological assessment significantly contributes to the early identification of cognitive deficits associated with dementia. The CERAD neuropsychological battery is widely used for evaluation and diagnosis of cognitive deficits associated with Alzheimer's type dementia. It includes eight tests namely: Mini-Mental State Examination (MMSE), Verbal Fluency (VF), Naming Test (NT), Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (LR), Constructional Praxis (CP) and Constructional Praxis (Recall) (CPR). The instrument has been adapted by Grupo de Neurociencias de la Universidad de Antioquia (Colombia) with the name of Cerad-col. **OBJECTIVE:** To determine the usefulness of Cerad-col as an instrument for the detection of Alzheimer's type dementia based on the assessment of the construct validity and the internal consistency, in individuals aged 50 years or more, affected by this disorder. **METHODS:** A retrospective validation study was carried out that included 90 patients with Alzheimer's type dementia diagnosis. Construct validity was determined in two ways: 1. Exploratory Factor Analysis (EFA), and 2. The correlation between CERAD's tests and functional scales FAST and EDG (Convergent Validity). Cronbach's alpha coefficient was used to determine internal consistency. **RESULTS.** EFA extracted 3 factors which explained 79,4% of the variance. The first such factor included the following tests (EMM, CP, TD, MLP, FV) and explained 49.0%. The second factor included ELP and EP and explained 14.8%; the third factor included RLP test explaining 12,8%. Significant correlations were observed between CERAD's test and FAST and EDG ( $p < 0,01$ ), except between WLR and Fast; WLR and EDG; LR and EDG; CPR and EDG. The Cronbach's alpha coefficient for CERAD-COL was 0,81 ( $p = 0.000$ ; CI 95% 0,74 to 0.86). **CONCLUSION:** The first factor can be related to general cognition, the second to short-term memory and the third with recognition. Internal consistency demonstrated that the instrument is homogenous in measurement of cognitive deficits associated with dementia. This results can confirm the construct validity and the internal consistency of Cerad-Col.

# MENTAL DISORDERS DETECTED IN PATIENTS WITH SPI NOCEREBELLAR ATAXIA TYPE 2 IN CUBA

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**Summary. Introduction .** Of the different hereditary ataxias present in Cuba, spinocerebellar ataxia type 2 (SCA2) is the most prevalent molecular type. Over the last years a great amount of progress has been made in clinical, epidemiological, molecular and neurophysiological research. Yet, the main psychiatric disorders that appear in these patients remain unknown. Their proper diagnosis will help to draw up a program of individualized therapeutic interventions for each disorder and will allow the patient to cope better with his or her illness and to take part in an effective physical and psychological rehabilitation program. **Aims.**

To identify the mental disorders that appear in patients suffering from SCA2. **Patients and methods .** We conducted a descriptive study of series of cases in 150 patients with SCA2. Data was obtained by means of a semi-structured interview with patients and their relatives, as well as a thorough psychiatric exploration, which enabled us to sort the symptoms according to spheres. A battery of psychometric tests and the diagnostic and research criteria for the international classification of mental illnesses were also used. **Results.** Findings showed that 88% of those studied present at least one clinical manifestation related with mental disorders. These included, essentially, disorders involving adaptation, sleep, mood and sexual disorders. Mental retardation and dementia were other alterations that were diagnosed. **Conclusions.** Disorders in the psychic sphere are a part of the SCA2 phenotype.

# CENTRAL MOTOR CONDUCTION TO UPPER LIMB AFTER TRANSCRANIAL MAGNETIC STIMULATION IN SPINOCEREBELLAR ATAXIA TYPE 2 (SCA2)

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**OBJECTIVES:** To evaluate central motor conduction to upper limbs in spinocerebellar ataxia type 2 (SCA2). **METHODS:** Motor evoked potentials (MEPs) triggered by transcranial magnetic stimulation (TMS) was used to investigate the functions of corticospinal tracts of 35 patients with SCA2. **RESULTS:** Central motor conduction time (CMCT) to upper limbs were abnormal in 13 patients (37,14 %) and the MEP threshold increased in 11 patients (31.41 %). **CONCLUSIONS:** Corticospinal tract involvement is frequent in patients with SCA2.

# PREDICTIVE GENETIC TESTING FOR DISEASES OF LATE ONSET: MEDICAL, SOCIAL AND ETHICAL ISSUES

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Predictive genetic testing can be applied to single -gene conditions (presymptomatic testing) and to diseases with genetic susceptibility (susceptibility testing). In presymptomatic diagnosis, testing positive for the gene mutation gives an almost certainty that disease will eventually develop, although age of onset and severity may remain uncertain. In susceptibility genetic testing, however, genes tested do not determine disease but only a predisposition that may lead to disease only when interacting with other genes and unhealthy environments. The tests results, then, are only probabilistic, as most susceptibility genes for late onset disorders (cancer, coronary disease, diabetes, etc) have low penetrance and their expression is largely modulated by interactions with the environment. The following medical issues must be considered in policy-making regarding implementation of predictive genetic testing: severity and frequency of the disease, biological plausibility of tests, strength of the association between a particular gene mutation and a disease (penetrance), attributable risk of the gene mutation for the disease prevalence, analytical validity, clinical validity and utility of the test, efficacy and risks of medical interventions (prevention, treatment), and psychological and social impact of the disease, including variations by ethnicity. Assessment of clinical validity of a test includes its clinical sensitivity and specificity and its positive and negative predictive value. Clinical utility is assessed by demonstrating a positive balance of benefits and risks and it has subjective components. Social factors to consider include the economic impact of the disease in the community, its impact on psychological well being and quality of life of affected and at -risk individuals, the relative costs of testing, prevention and treatment, how the target population is defined, and professional and public education requirements for a successful program. Ethical issues to consider in predictive testing include the respect for the voluntary and non -coercive nature of genetic testing, the need for objective education as basis for informed decision -making. In order to avoid the ethical pitfalls of eugenics, no genetic testing program should ever pressure individuals, explicitly or implicitly, directly or indirectly, to undergo genetic testing. A cautious approach to testing and a robust process of informed consent must be followed particularly when the disease is severe and stigmatizing and when there are no efficient preventive and therapeutic alternatives. Similar caution must be exercised when the disease affects ethnic groups differentially. Ethical risks associated with predictive genetic testing to consider and prevent include the possibility of family and social stigma associated with genetic traits and genetic discrimination of at -risk and affected individuals and their relatives in health care and employment. Prenatal application of predictive testing deserves close ethical scrutiny to avoid eugenic pitfalls and commodification of children. Similarly, presymptomatic or susceptibility testing of children should be considered only when the medical and psychological benefits are proven and effective. Susceptibility testing for complex disorders is usually associated with misconceptions about the power of genes to actually determine disease independently of the environment (genetic determinism). The tendency to overemphasize the role of genes in the development of cancer, coronary disease, asthma, diabetes, obesity, alcoholism or mental illness should be countered by putting genes in the context of the environment in which they express, and stressing the probabilistic nature of genetic testing for these conditions. Susceptibility genetic testing should not be a substitute for addressing the environmental determinants of most common chronic diseases such as poverty, emotional stress, exposure to toxics and pollutants, cigarette smoking, physical inactivity and unhealthy diets.

# PSYCHOSOCIAL ASPECTS OF NEUROGENETIC DISEASES WORKSHOP

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The actual development of human genetics constitutes a major challenge to psychology and the social sciences. As we know more about genetics and genetic diseases, being able to predict the health status of individual in the future, we face new ethical dilemmas and new demands on psychological intervention.

Based on our experience with Machado-Joseph, Huntington, Spinocerebellar Ataxia type 2 and Familial Amyloid Neuropathy we discuss psychosocial aspects of predictive tests of non-symptomatic individuals, namely the psychological evaluation previous to the test and the follow up of at risk individuals and patients and present a proposal of psychosocial evaluation protocol to implement in neurogenetic centres of diagnostic and follow-up.

At a community level, the study of the ecological settings where the disease has high incidence is an essential part of any affective intervention. We must understand the stereotypes associated with each disease and the social mechanisms to deal with it, to establish a health and social program to support affected families.

At an individual level, we must decide which are the psychological aspects we need to know, in order to prevent mental breakdown during the test process and following the delivery of positive or negative results: What to measure (i.e. depression, anxiety, coping mechanisms) and the predictive power of our evaluation in what concern the future mental health and well being of individuals.

# NEUROTHERAPEUTIC INTERVENTIONS

**Ilbedys Pérez Avila, chair**

**M.dela C.Galardy** - SEXUAL ACTIVITY IN MALE PATIENTS WITH MEDULLAR LESION

**A. Garcés-Leyva** - LOGOPEDIC INTERVENTION: AN EXPERIENCE WITH SPINOCEREBELLAR ATAXIA TYPE 2 PATIENTS

**A. Sentmanat, C. Martínez** - INFLUENCE OF THE INTENSIVE MULTIFACTORIAL NEUROREHABILITATION TO IMPROVE THE PRECISION AND RHYTHM ON PATIENTS BEARERS OF ATAXIA CAUSED BY STROKE OR MULTIPLE SCLEROSIS

**I. Pérez-Avila** - EXERCISE PROGRAM FOR PHYSICAL REHABILITATION OF PATIENT WITH SPINOCEREBELLAR ATAXIA TYPE2.

# SEXUAL ACTIVITY IN MALE PATIENTS WITH MEDULLAR LESION

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We carried out a transversal and exploratory study to 62 medullar traumatized patients of the masculine sex, entered in the Hospital "Julio Díaz" of Havana City, during the period understood among March from the 2000 to March of the 2001, with the objective of exploring the behavior of the sexual activity. The erection was frequently conserved in the group of patients with lesion of the superior motor neuron, while the ejaculation and the orgasm were mainly conserved in the group with lesion of the inferior motor neuron. None of the patients with complete lesion above the lumbar level showed psychic erection. The erection was less damaged than the ejaculation, and this less than the orgasm. We don't find significant differences in the divorce frequency for the marriages before and after the trauma; the sexual dysfunction was not considered the main divorce cause. The sexual desire was not affected in these patients. The types of sexual activity increased with the time of evolution and they are in connection with the objective limitations and the received sexual orientation, which is considered necessary for most of those interviewed.

# LOGOPEDIC INTERVENTION: AN EXPERIENCE WITH SPINOCE REBELLAR ATAXIA TYPE 2 PATIENTS

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**A. Garcés-Leyva**

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The logopedy constitutes a very young science in whose history is mixed the chores of doctors, teachers and other specialists whose professional activity is linked to the quality of the human being life. Today no doubts exist about the fact that communicative competence constitutes a condition for the good social acting of people. In our county a Program of Integral Attention is developed for those that are sufferers of Hereditary Ataxia. One of the aspects of the Program is the rehabilitation of language, since cerebellar dysarthria is one of the most notorious symptoms of Hereditary Ataxia. With our work we seek to offer a methodological alternative addressing the logopedic process that allows to improve the dysfunction of the speech or to slow their appearance to propitiate their social integration. We designed a quasi-experimental study, taking a sample of 52 patients that were participating in the neuro-rehabilitation program at the Clinic for the Investigation and Rehabilitation of the Hereditary Ataxias "Carlos J. Finlay". We could verify that it is an important alternative for logopedic help, and satisfactory results were obtained within the evaluated parameters. Oral expression and the vocabulary were enhanced, by improving communication levels, articulation motricity, pronunciation, breathing, qualities of the voice, cognitive processes, interpersonal relationships, and social abilities. Also, we promote personal growth through group work, and to impact favorably in the auto-valuation of each one, aspiration levels, favoring the adjustment and the adaptation in front of illness and thus, we their quality of life was improved by logopedic intervention.

# **INFLUENCE OF THE INTENSIVE MULTIFACTORIAL NEUROREHABILITATION TO IMPROVE THE PRECISION AND RHYTHM ON PATIENTS BEARERS OF ATAXIA CAUSED BY STROKE OR MULTIPLE SCLEROSIS**

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When a person acquires a certain neurological pathology which directly influences organs and systems that control the coordinating mechanisms, these movements diminish or lose the physical capacity and the general activity is thus affected. The objective of this work is to demonstrate how the intensive multifactorial neurorehabilitation system applied at CIREN, contributes to the recovery of coordinating capacities related to precision and rhythm, and losses caused as sequelae produced by stroke or by multiple sclerosis. We proposed as specific objectives, the appraisal of the patients' physical status before and after treatment, emphasizing on such parameters related to the coordinating capacities of precision and rhythm and the application of an intensive multifactorial rehabilitation program aimed to the improvement of such factors that have to do with coordinated movements. The sample was composed of 41 patients, grouped under 28 bearers of Cerebellar Ataxia caused by sequelae of stroke and 13 bearers of Cerebellar Ataxia as sequel of Multiple Sclerosis. We assessed all the patients before beginning treatment and when finishing it. All the patients were treated for 28 days with the Intensive Multifactorial Neurorehabilitation Program. The result of this appraisal was statistically processed, comparing each patient with himself/herself, according to different groups at the Psychomotor Integral Assessment Laboratory, where tests were conducted. The obtained results show that precision and rhythm had a certain level of improvement on those patients' under study. This allowed us to conclude in a preliminary way, that the applied activity program is effective and it presupposes that on a longer term, it can increase the recovery of such physical capacities related to the coordination, and thus, to contribute to the patients quality of life.

# EXERCISE PROGRAM FOR PHYSICAL REHABILITATION OF PATIENT WITH SPINOCEREBELAR ATAXIA TYPE2

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## Background:

Spinocerebellar Ataxia type 2 is a degenerative neurological disorder with high prevalence and incidence in the province of Holguín, Cuba. At present, there is no drug to attenuate the loss of coordinative motor capacities of these patients. Physical exercise rehabilitation seems the only choice for decreasing the course of disease.

## Objective

To evaluate the effectiveness of a physical exercise training, taking into account quantitative neurological indicators, muscular strength and body composition in SCA2 patients.

## Patients and methods:

By means of a quasiexperimental design (pretest – post-test) a sample of 117 SCA2 patients were undergone to a 6 month exercise training program based on exercise of coordination, balance, and resistance training, neurological quantitative test, both with close and open eyes, were applied, before and after the application of the program. Body composition handgrip and back force were evaluated in the same way.

## Results

All neurological indicators performed with open eyes significantly enhanced in the second measure but with closed eyes effectiveness was the only significant indicator. Maximal period and standard deviation significantly enhanced. Static balance by Romberg test significantly increased, as well as handgrip and back strength. Body composition parameters did not significantly change except body weight, fat mass and muscle mass.

## Conclusion:

Exercise training program provided promising results in SCA2 patients.