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Neurodegenerative diseases in Latin American countries: a view from the III International Conference on Hereditary Ataxias.

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Still under the effects of Ike and Gustav, two of the worst hurricanes hitting Cuba in the last 50 years (Cuba: Hurricane Season 2008, 2009), a group of young scientists from the Caribbean island organized the III International Conference on Hereditary Ataxias (1-8 October 2008). The conference hosted researchers from Austria, Canada, Colombia, Germany, Guatemala, India, Italy, Mexico, Portugal, Spain, and UK. The themes discussed covered areas such as Biotechnology, Bioinformatics, Genetics, Epidemiology, Neurology, Metabolism, Neuroimaging, Pharmacology, Neurophysiology, Neuropathology, and Cognition. One striking feature of the meeting was that as the researchers fostered their understanding of Neurodegenerative Diseases and Hereditary Ataxias, patients and carers were trained by the experts in parallel workshops on the management of the clinical outcomes of these disabling disorders.

Why is Cuba interested in Hereditary Ataxias?

In the 1970’s and 80’s, Cuban scientists described a disease known as Spinocerebellar Atrophy, the main clinical outcome of which is ataxia (Orozco et al., 1989; Valles, Estrada, & Basterrechea, 1978). A form of Ataxia commonly
found in Holguín, a province located in North-East Cuba, is characterized clinically by impairment in movement control with emphasis on gait, speech, limb coordination, and eye movements (Orozco et al., 1989; Orozco, Nodarse, Cordovés, & Auburger, 1990). An important characteristic of the disease is its early onset, with some cases presenting as early as age 10. Due to the early onset and loss of movement control, sufferers become unable to perform a wide range of everyday life activities. The prevalence of the disease in Holguín was found to be 41.3 per 100,000 (Valles et al., 1978), suggestive of a familial cluster of Ataxia in this region which is the largest of Spinocerebellar Ataxia Type-II (SCA-II) described to date (Velásquez et al., 2001). Therefore, it is easy to understand why Holguín was chosen as the venue to discuss advances on SCA-II and related disorders.

**What is the picture on Neurodegenerative Diseases in Latin America?**

A suggested mechanism to explain the high prevalence of SCA-II in Holguín is a *founder effect* (Orozco et al., 1989). The founder effect is described as a dramatic decrease in genetic diversity caused by the formation of clusters of individuals who remain isolated (Templeton, 1979). Orozco et al. (1989) suggested that an alternative explanation for the SCA-II of Holguín might be an interaction between a mutant gene and unidentified environmental factors. However, Cuba is not the only Latin American country where genetic clusters of neurodegenerative diseases have been observed. Two further examples are Huntington’s disease (HD) in Venezuela (see Wexler et al., 2004; also see Okun & Thommim, 2004 for a revision of the early studies) and Alzheimer’s disease (AD) in Colombia (Lopera et al., 1997) which are the largest clusters of familial HD and AD reported to date. The III International Conference on Hereditary Ataxias celebrated in Holguín, offered a suitable scenario wherein different aspects of these neurodegenerative diseases may be considered for discussion.
Aware of the impact that the study of these clusters would have on the understanding of the mechanisms underlying the development of neurodegenerative diseases, in 2003 a group of scientists from different countries launched the ALFA Euro-Caribbean Network (Red Eurocaribeña de Neurociencias, 2009). The ALFA Network was aimed at supporting the advanced integral preparation of researchers and academics working on social, clinical, and biological aspects of neurodegenerative diseases. The ALFA Network was a project funded by the European Union, and it gathered efforts from higher education institutions of three European countries (Prof. Sergio Della Sala’s team from the University of Edinburgh, United Kingdom, Dr Francisco Wadosell’s team from the Autonomous University of Madrid, Spain, and Dr Muriel Darnaudéry’s team from the University of Lille 1, France) and three Latin American countries (Dr Francisco Lopera’s Neuroscience Group from the University of Antioquia, Colombia, Dr Mitchell Valdé’s team from the Cuban Neuroscience Centre, and Dr Gladys E. Maestre’s team from the University of Zulia, Venezuela).

What can the study of familial forms of neurodegenerative diseases offer to neuroscience?

The neurodegenerative diseases mentioned above are familial variants of diseases which are also known to have sporadic forms. Two important differences between sporadic and familial forms of these diseases are (a) the pattern of inheritance and (b) their prevalence.

The familial forms of neurodegenerative diseases found in Cuba, Colombia and Venezuela, follow specific patterns of familial transmission (Mendelian inheritance), whereas, the sporadic forms of these diseases do not follow such patterns. For example, for the familial AD found in Colombia, the pattern is autosomic dominant, that is at least 50% of offspring will inherit the
genetic defect (i.e. will be carriers). It is worth noticing that 100% of the carriers will develop AD. Figure 1 illustrates how the genetic defect responsible for the development of familial AD found in Colombia spreads across 8 generations.

Figure 1. Genealogical tree of 13 families (C1 – C13) with E280A associated AD. Filled items refer to carriers of the mutation. The diagonal line crossing the items means death. Roman numbers are generations and the Arabic numbers are years (see Lopera et al., 1997 for other family trees and a more thorough description of this disorder).

As to the second difference, the sporadic forms of neurodegenerative diseases show a much higher prevalence than familial variants. For example, in the case of AD, familial forms show a prevalence of around 0.1% whereas in people aged 85 years or older living in the western world the prevalence of sporadic AD is between 24% and 33% (Blennow, de Leon, & Zetterberg, 2006). Why would it be worth investigating familial variants? I would like to answer this question by briefly introducing the work I presented at the III International Conference on Hereditary Ataxias held in Holguín, Cuba.
My presentation was entitled “Memory binding deficits as an early neurocognitive marker of Alzheimer’s disease: evidence from an early onset variant due to the mutation E280A of the Presenilin-1 gene”. It is known that memory is the earliest function affected by AD. However, it is still unknown whether all memory systems are evenly impacted by the disease in its early stages. We have recently found that this does not seem to be the case and that short-term memory (STM) for objects defined by bound features (e.g., common objects with colours) seems to be impacted in AD to a greater extent than other forms of non-associative memory (Parra et al., 2009). However, it remains unexplored whether this memory impairment can predict familial AD. To this aim, we devised a novel task which assesses STM for single and bound information (i.e., shapes, colours, or coloured shapes) and assessed with it individuals recruited from the Colombian kindred. We assessed asymptomatic carriers of the genetic defect E280A, patients in the very early stages of AD, and healthy (non-carrier) relatives, who did not have gene defects. We compared performance on the novel task with performance in a large neuropsychological battery. We found that whereas carriers performed the traditional neuropsychological tasks without difficulties, they performed significantly more poorly than healthy relatives, but not than AD patients, only in the novel STM task (Parra et al., submitted). This suggests that STM binding functions could signal the beginning of E280A associated familial AD more effectively than other tasks currently used in the assessment of AD. Hence, STM binding may help to detect AD earlier than other cognitive functions.

This represents a step forward in the early detection of AD which is one of the cardinal strategies for the management and treatment of the disease. However, one question that arises from this study is: Could this type of finding in familial variants of neurodegenerative diseases be used to make decisions in sporadic forms? We do not yet have a clear understanding of the extent to which findings in familial variants of neurodegenerative disorders could be used to
interpret sporadic forms (Godbolt et al., 2005; Ray, A shall, & Goate, 1998).
However, they are valuable insights which prompt actions to investigate similar
issues in sporadic variants.

Conclusions

My experience in the III International Conference on Hereditary Ataxias, could
be summarized by three points. First, I learned that interdisciplinary exchanges
via international collaborations are valuable strategies to create fruitful avenues
through which biological and social issues underpinning problems affecting
large populations could be investigated. Second, familial variants of
neurodegenerative diseases offer promising models to plan sound research
aimed at devising new methods for detecting these diseases early and acting
effectively upon their consequences. Third, neuroscience has much to gain from
developing countries.

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References


