Arq Neuropsiquiatr 2007;65(4-A):965-968

# THE HISTORY OF SPINOCEREBELLAR ATAXIA TYPE 10 IN BRAZIL

## Travels of a gene

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ABSTRACT - The authors report the history of spinocerebellar ataxia 10 (SCA10), since its first report in a large Portuguese-ancestry Family with autosomal dominant pure cerebellar ataxia, till the final identification of further families without Mexican ancestry. These families present a quite different phenotype from those SCA10 families described in Mexico.

KEY WORDS: spinocerebellar ataxia, spinocerebellar ataxia type 10, "pure" cerebellar ataxia.

**A história da ataxia espinocerebelar tipo 10 no Brasil: as viagens de um gene**

RESUMO - Os autores apresentam a história da descoberta da ataxia espinocerebelar tipo 10 (AEC10) no Brasil, desde o primeiro relato em uma família com ancestrais portugueses com ataxia cerebelar pura, autossômica dominante, até a identificação de famílias sem ancestrais mexicanos. Essas famílias apresentam um fenótipo de AEC10, com ataxia cerebelar "pura", distinta daquele descrito nas famílias no México.

PALAVRAS-CHAVE: ataxia espinocerebelar, ataxia espinocerebelar tipo 10, ataxia cerebelar pura.

Spinocerebellar ataxias (SCA) comprise a large group of neurodegenerative disorders involving the cerebellum and its connections[1]. They are characterized by a large genotypic and phenotypic heterogeneity. About 30 types of SCA have been described to date and a genic locus is already known in 11 out of this increasing group of diseases. Machado-Joseph´s disease or SCA type 3 is the most prevalent form of SCA in several series around the world and in Brazil[1-4].

SCA type 10 is an autosomal dominant form of SCA caused by a repeating expansion of the pentanucleotide ATTCT of an intronic region of SCA10 gene. SCA type 10 was originally identified only in Mexican familes and had a phenotype characterized by a combination of cerebellar ataxia and epilepsy[5-9].

In 2004, Teive et al. described 28 patients out of 5 Brazilian families who presented a homogeneous phenotype of pure cerebellar ataxia, but without epilepsy. Those families were identified as having the same repeating expansion of the pentanucleotide ATTCT, described in SCA type 10.[10] Nowadays, SCA type 10 is the second most common form of SCA in Mexico and Brazil, after SCA type 3[11].

In this paper, the authors describe the historic trajetory of the first Brazilian family with SCA type 10, since its first clinical description till the final molecular genetic diagnosis.

*The Study Group for the Hereditary Ataxias* – In 1987, Walter Arruda (WA) and Hélio Teive (HT) created the Study Group for the Hereditary Ataxias at the Neurology Service of Hospital de Clínicas, from the Federal University of Paraná, Curitiba, Brazil. The main objective of this group was to identify and study different forms of hereditary cerebellar ataxias, especially in autosomal dominant (AD) forms. At this time, WA started evaluating a large pedigree with AD SCA, with several members living in Parana and Santa Catarina (city of São Francisco). This family had a clear Azorean Portuguese ancestry. The study of this family culminated in a Master's Degree in Sciences (MSc) dissertation, presented by Arruda at the Federal Univer-

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Received 27 April 2007, received in final form 25 July 2007. Accepted 27 August 2007.

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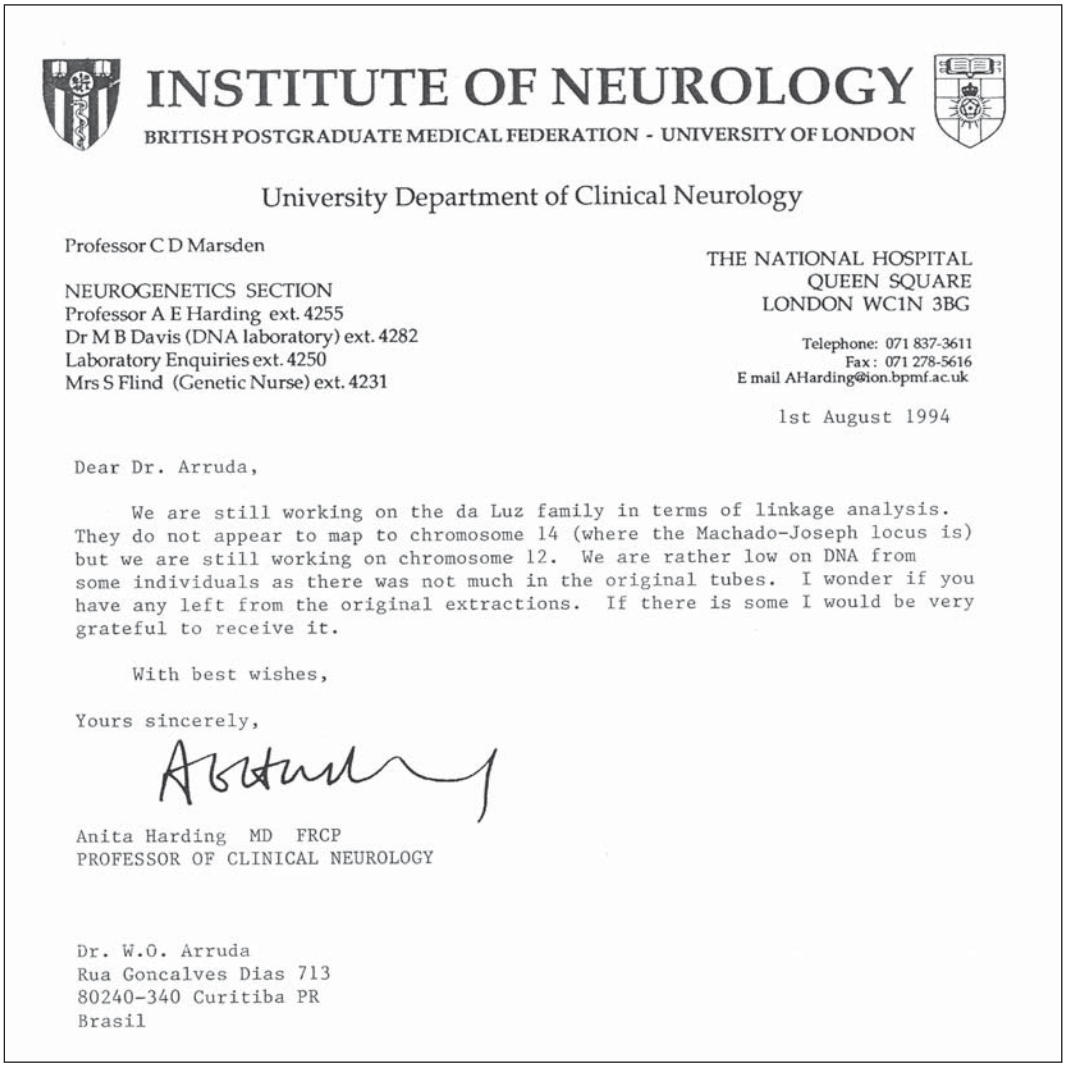
sity of Paraná in 1989 and entitled "Ataxia cerebellar hereditária autossômica dominante – description of a Family with HLA genotype and linkage study". HLA genotyping and linkage studies were possible through the valuable help of Prof. Maria Luiz Petzl-Erler, Department of Genetics, Universidade Federal do Parana, and Prof. Ott, Columbia University, New York[12].

From 1993 on, after the identification of the first genic locus of SCA type 1, shortly after the discovery of SCA 2 and SCA 3 genes, our group started a collaborative study with several neurogenetic groups. Prof. Anita Harding, Institute of Neurology, Queen Square, London, UK was one of our first contacts, and we shared opinions and ideas with her about this family and other families that we had been studying over some years. Other groups included Prof. Paula Coutinho and Jorge Sequeiros (Unigene, IBMC, Universidade do Porto, Portugal) and Prof. Guy A. Rouleau, at the Centre for Research in Neuroscience, McGill Universiy, Montreal, Canada.

*SCA in Brazil* – Since 1996 many Neurogenetics Services identified different forms of SCA in Brazil, based on clinical and molecular genetics studies. SCA type 3, or Machado-Joseph disease, turned out to be the most common form of SCA, regardless the geographical background, followed by much less frequent forms of SCA such as types 1, 2 and 7[2-4].

SCA type 10 was first described by Grewal et al, in 1998, when they evaluated 11 patients of a Mexican family affected by an AD form of cerebellar ataxia complicated by concomitant epilepsy[6].

In 1999, the locus of this new form of SCA was mapped independently by Zu et al.[7] and Matsuura et al.[8] in chromosome 22q13. Interestingly, Zu et al., leaded by Stephan Pulst in Los Angesles, CA, and Matsuu-



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1st August 1994

Dear Dr. Arruda,

We are still working on the da Luz family in terms of linkage analysis. They do not appear to map to chromosome 14 (where the Machado-Joseph locus is) but we are still working on chromosome 12. We are rather low on DNA from some individuals as there was not much in the original tubes. I wonder if you have any left from the original extractions. If there is some I would be very grateful to receive it.

With best wishes,

Yours sincerely,

Anita Harding MD FRCP
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*Figure. Anita Harding's letter reporting the results of genetic studies in the first described family with SCA type 10 in Brazil (W.O. Arruda, 1988).*

ra et al., leaded by Tetsuo Ashisawa, Houston, Texas, defined that the ancesters of two families studied by the two groups were from the same region of Mexico, suggesting a common ancestry[7,8].

In 2000, the Houston group, in collaboration with the Los Angeles group, discovered the genetic mutation causing SCA type 10; a large pentanucleotide (ATTCT) expansion located in intron 9 of the SCA type 10 gene[13]. Their results came out from the study of the two original Mexican families and three additional Mexican families identified by Astrid Rasmussen[13].

In 2001, Rasmussen et al published a seminal study about the clinical and genetic findings in 4 Mexican families with SCA type 10[5], including the three families used in the study to identify the mutation[13]. The clinical findings included, in addition to cerebellar ataxia and epilepsy (present in 72.2% of the affected members), peripheral polyneuropathy (66%), mild pyramidal signs and cognitive dysfunction in a few patients. Epilepsy, as a key feature of the SCA 10 phenotype, was confirmed by a further study of Grewal at el in 2002[9].

Therefore, SCA type 10 described in Mexican families showed homogenous phenotype characterized by: 1) Mexican ancestry; 2) pure cerebellar ataxia, frequently complicated by epilepsy; and 3) antecipation phenomena of the age of onset in consecutive generations[10].

Matsuura et al. looked for the presence of SCA type 10 mutation in non-Mexican populations, including North-american Caucasians, French-Canadians, Italians, Spanish and Japanese, in which they found no additional families with this disease[14].

Teive et al., described, in 2004, the first non-Mexican families with SCA type 10 in Brazil, which presented a distinct phenotype of late onset pure cerebellar ataxia without epilepsy as a major component[10].

*The puzzling gene* – From historical standpoint of view, the first Brazilian family with SCA type 10, genetically confirmed in 2004, was clinically evaluated for the first time in 1987 and described by Arruda in 1989, presented as MSc dissertation at the Federal University of Paraná at that time[12]. This report was published by Arruda et al. in 1991, where eight affected members of a large family coming from the coastal region of Santa Catarina (São Francisco county) were affected by an autosomal dominant form of late onset pure cerebellar ataxia[15]. Later, the Study Group for the Hereditary Ataxias diagnosed in another families a quite similar clinical presentation of late onset pure cerebellar ataxia.

In 1992, a collaborative work with the Genetic Unit (Prof. Anita Harding), at the Institute of Neurology, Queen Square, London, was started and the first family[15] with SCA type 10 was genetically evaluated for types 3, and later 1 and 2, which loci were already known by that time, and the results were negative. Figure shows the letter of Prof. Anita Harding reporting the negative results of those molecular genetic studies. Subsequently, from 1993 to 1997, molecular genetic studies of several families with AD cerebellar ataxias were conducted in Montreal, Canada, by Prof. Guy Rouleaux. At that time, Dr. Isabel Silveira, from the UnIGENe, IBMC, University of Porto, Porto, Portugal, and Dr. Iscia Lopes-Cendes, from State University of Campinas (UNICAMP), São Paulo, Brazil, were working at Prof. Rouleuax Service and were the key persons with whom our group kept contact.

Among the large number of samples coming from several families affected by different forms of AD SCA, other families with pure cerebellar AD late onset SCA were later identified as having SCA type 10. At that time, other forms of SCA (eg, types 1, 2 and 3, and DRPLA) were screened and the results were negative.

From 1998 on, the molecular genetic studies were performed at the Medical Genetics Service of UNICAMP, Campinas, Brazil, under the supervision of Prof. Iscia Lopes-Cendes. At that time, the panel of SCA included SCA types 1,2,3,6,7, and Dentatorubral-Pallidoluysian Atrophy (DRPLA).

The tests for detection of SCA type 6 mutation created great expectation. Nevertheless the results were negative in several families with "pure" cerebellar ataxia.

In 1999, Professor Salmo Raskin from the Genetika Laboratory, started genetic studies of SCA patients, followed with the foundation of the Laboratory of Molecular Biology at the Hospital de Clínicas, Federal University of Paraná by Prof. Lineu C. Werneck. At tis time, genetic testing for SCA types 1,2,3,6,7,8,12 and 14, and DRPLA became available, although the particular group of SCA with "pure" cerebellar ataxia still was a genetic puzzle.

In 2004, Raskin introduced in his Laboratory a so called panel of cerebellar ataxias, including all known SCA genes, in particular a recently new described form of SCA in Mexican patients, SCA type 10. He re-studied a patient coming from a family with late-onset "pure" cerebellar ataxia without epilepsy and surprisingly it turned out that this patient and family had the SCA type 10 mutation. With this unexpected finding, other four families with late onset "pure" SCA were investigated for SCA type 10 with positive results.

Subsequently, three other families were diagnosed as SCA type 10, all of them with "pure" cerebellar ataxia without epilepsy.

In 2005, the first case of SCA type 10 with epilepsy was diagnosed in a female patient with early onset SCA associated with cognitive dysfunction and with a negative family history. This case of SCA type 10 showed that a reduced gene penetrance may occur in SCA type 10, with a clinical expression of early onset SCA associated with dementia, when the repeat expansion size is relatively small compared to other patients with SCA type 10[16].

In conclusion, after 20 years of clinical investigation and with the introduction of molecular genetics techniques allowing the identification of an ever increasing number of SCA causing genes, we could define that SCA type 10 is the second most common form of SCA in México and Brazil. Furthermore, we could clearly identify two distinct phenotypic presentation of SCA type 10, one Mexican (with epilepsy) and other Brazilian (without epilepsy)[10,16].

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