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SPINOCEREBELLAR ATAXIA TYPE 7 (SCA7)

Family princeps' history, genealogy and geographical distribution

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ABSTRACT - We conducted a 320 year retrospective survey of the history and genealogy of a large Brazilian family with SCA7. The ancestral couple was from the State of Ceará, Brazil, and the genealogical tree was composed of 577 individuals, including 217 males (37.6%), 255 females (44.1%) and 105 individuals of unknown sex (18.1%). Based on collected information, the 118 individuals consistently affected were distributed in generations IV (n=2), V (n=28), VI (n=57), VII (n=25) and VIII (n=6) of the genealogical tree. Sixty affected members are alive, 37 of them (61.6%) live in the Northeast region, 12 (20%) in the Southeast, 9 (15%) in the Center-West and 2 (3.3%) in the North. This genealogical survey was based only on 4 of the 10 children of the ancestral couple since the destiny of the remaining 6 is unknown. We propose that other Brazilian families with SCA7 may have the same genetic origin.

KEY WORDS: autosomal dominant cerebellar ataxia (ADCA), spinocerebellar ataxia type 7 (SCA7), neurodegenerative disease, trinucleotide repeat expansion.

Ataxia espinocerebelar do tipo 7 (AEC7): história, genealogia e distribuição geográfica da família princeps

RESUMO - Avaliamos retrospectivamente 320 anos da história e da genealogia de uma família brasileira portadora de ataxia espinocerebelar do tipo 7 (AEC7). O casal ancestral é oriundo do Estado do Ceará e a árvore genealógica foi composta de 577 indivíduos, sendo 217 do sexo masculino (37,6%), 255 do sexo feminino (44,1%) e 105 de sexo ignorado (18,1%). Até o presente momento, 118 indivíduos foram acometidos, distribuídos nas gerações IV (n=2), V (n=28), VI (n=57), VII (n=25) e VIII (n=6) da árvore genealógica. Entre os doentes atualmente vivos (n=60), 37 deles (61,6%) encontram-se na região Nordeste, 12 (20%) na região Sudeste, 9 (15%) na região Centro-Oeste e 2 (3,3%) na região Norte. Uma vez que a reconstituição da árvore genealógica foi baseada em apenas 4 dos 10 filhos do casal ancestral devido ao desconhecimento do destino dos outros 6, levantamos a hipótese de que outras famílias brasileiras com AEC7 possam ter a mesma origem genética.

PALAVRAS-CHAVE: ataxia cerebelar autossômica dominante (ACAD), ataxia espinocerebelar tipo 7 (AEC7), doença neurodegenerativa, expansão de trinucleotídeos CAG.

Spinocerebellar ataxia type 7 (SCA7) is an autosomal dominant neurodegenerative disorder mapped on chromosome 3p12-p13[1-6] whose mutation was identified as being an abnormal CAG expansion in the ataxia 7 gene[7,8], with the contribution of the genetic data of a large Brazilian family, first presented by Professor Wagner Horta in an informal case presentation to the late Professor Anita E. Harding in the 16th Brazilian Congress of Neurology happened in Fortaleza in 1994 (personal communication). The mutated protein results in neuronal loss affecting mainly cells of the cerebellum, regions of the brainstem, inferior olivary complex and retina[9]. Clinically, the most important manifestations are progressive cerebellar ataxia and visual loss[10-13].

In the present study, we reevaluated this family with the objective of establishing its history and genealogy.

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METHOD

The history and the genealogy of this family were investigated through surveys of registries and registrations of churches, interviews with family members belonging to different generations and data present in the files of the Beneficent Association for help to the Carriers of Ataxia type II (ABPAT), maintained by members of the family. The "ancestral couple" was defined as the ancient couple from which all the family branches originated. Although their direct descendents were all normal, several of them originated the first clearly affected cases. We excluded from the present study the characteristics of three branches of the family whose members were persistently normal throughout the generations.

The following parameters were analyzed: family history, geographic localization, consanguinity and gender. We considered a member to be affected when (1) abnormalities were clinically evident according to an objective neurological evaluation, perfomed always by the same author (SCL), or (2) if there was a clear report of a higly suggestive manifestation such as walking or speaking like a drunk or a history of progressive visual loss. These reports were considered only if the descendents or siblings of the reporting person had a similar condition.

For the available members and after informed consent, DNA was extracted from peripheral blood cells according to routine methods. The analysis of the CAGn expansion in the ataxin 7 gene was perfomed the polymerase chain reaction (PCR) according to David et al. [7]. The segment of interest was amplified with the forward primer labeled with a fluorescent dye. The fluorescent PCR product was analyzed in a 377 ABI automatic Sequencer (Perkin Elmers-ABI) with the GENESCAN (ABI) software.

The present study was approved by the Research Ethics Committee of our hospital.

RESULTS

The historical data gathered revealed that the ancestral couple of this large Brazilian family with SCA7 originated from two clans, one descendant from Portugal and another from the State of Pernambuco, in the northeast of Brazil. Their migration to the State of Ceará happened at different times. The patriarch of the Portuguese clan arrived in Brazil in the 1680s and established himself initially along the bank of San Francisco river, in a region that today is part of the State of Alagoas. His mission was to colonize the lands of the Brazilian northeast. To increase his territorial domains, he moved to Inhamuns, in the State of Ceará. His past history is unknown as is the family history of his wife. The patriarch of the Pernambuco clan arrived in Ceará around 1800, and also settled at Inhamuns. Nothing is known about his wife and their previous life. The ancestral couple of this large Brazilian family with SCA7 married in the 1820s, with the husband the one of Portuguese descent.

Seven females and 3 males were born from this union. We were unable to follow the destiny of 6 of them. From the known data, the third generation was composed of 27 individuals, including 15 males (55.5%) and 12 females (44.4%). In this generation, 8 consanguineous marriages were registered and 89 individuals affected with the disease appeared in subsequent generations. In the fourth generation, 38 individuals were identified, 22 of them males (57.8%) and 16 females (42.1%). Another consanguineous union occurred in this generation, from which 29 additional affected cases were identified, corresponding to 118 known affected persons in the known branches of the family.

The consanguineous marriages among descendents the first cases of the disease registered in the family occurred in the third and fourth generations, being labeled for operational purposes as subfamilies I to V.

Subfamily I, originated from a consanguineous marriage, is composed of 83 individuals, distributed into 4 generations, including 31 males (37%), 22 females (25.9%) and 30 of unknown gender (37%). Twenty six of them are known to be affected, 13 of each gender. In the sixth generation of this subfamily, 12 (66.6%) of the affected members did not form a family, consequently reducing the number of affected in the following generation (n=2). Eleven of the affected patients are still alive and 4 of them participated in the clinical phase of this study (Fig 1).

Subfamily II, that also originated from a consanguineous marriage, is composed of 93 individuals distributed into 5 generations, with 27 being males (30.1%), 47 females (50.5%) and 18 of unknown sex (19.3%). This subfamily originated from subfamilies I and III. In this subfamily there were 29 cases of SCA7, 13 males (44.8%) and 16 females (55.1%). Twenty-one of the affected patients are still alive, and 11 of them participated in this study.

Subfamily III is composed of 162 individuals distributed into 6 generations, including 55 males (33.9%), 67 females (41.3%) and 40 subjects of unknown gender (24.6%). This subfamily also originated from a consanguineous marriage and 34 members are affected, including 18 males (52.9%) and 16 females (47%). In this subfamily, the first case of SCA7 appeared in the fourth generation. There are 19 affected alive and 10 of them agreed to participate in this study (Fig 2).

Subfamily IV is composed of 133 individuals distributed into 5 generations, 63 of them males (47.3%) and 70 females (52.6%). This subfamily originated

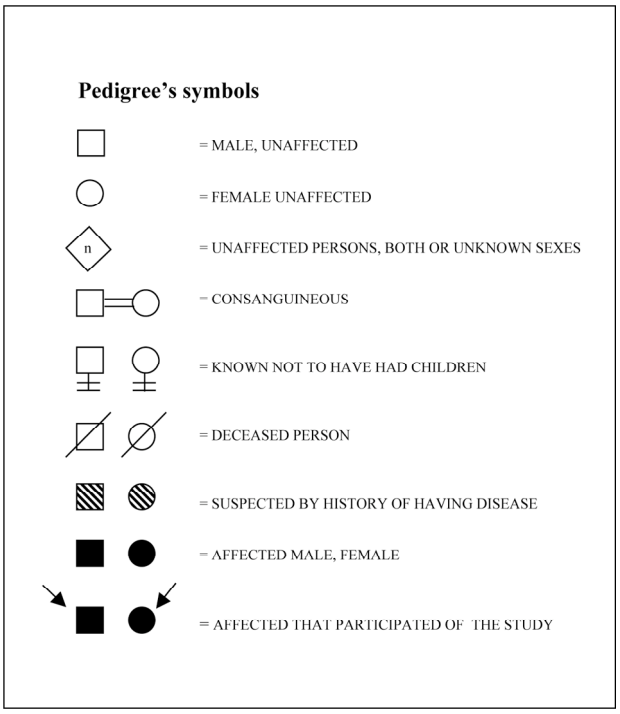
from a consanguineous marriage in the third generation of the family and possesses 11 affected individuals, 8 of them males (72.7%) and 3 females (27.2%). Two of them are alive, but none of them was included in this study.

Subfamily V is composed of 69 individuals distributed into 5 generations, including 26 males (36.2%), 25 females (36.2%) and 19 of unknown sex (27.5%). This subfamily also originated from a consanguineous marriage in the third generation of the family and 18 members were affected, 11 males of them (61.1%) and 7 females (38.8%). Seven are alive and 5 participated in the present study (Fig 3).

Thus, the genealogical tree was composed of 577 individuals, including 217 males (37.6%), 255 females (44.1%) and 105 of unknown sex (18.1%). The first known patient was identified in the 1930's and to date 118 individuals are known to be affected, 63 of them males (53.3%) and 55 females (46.6%).

We personally examined 30 patients. Age of onset was 33.3±14.8 years ranging from 11 to 75 years. Ataxia was the onset manifestation in 18 of them, visual impairment in 11 and spastic paraparesis in remaining one (submitted).

Many descendants of the ancestral couple emigrated from the State of Ceará, resulting in the detection of cases of SCA7 of the same genealogical origin in other areas of the country. Considering only the 60 alive patients that we were able to identify, 37 of them (61.6%) still live in the Northeast region



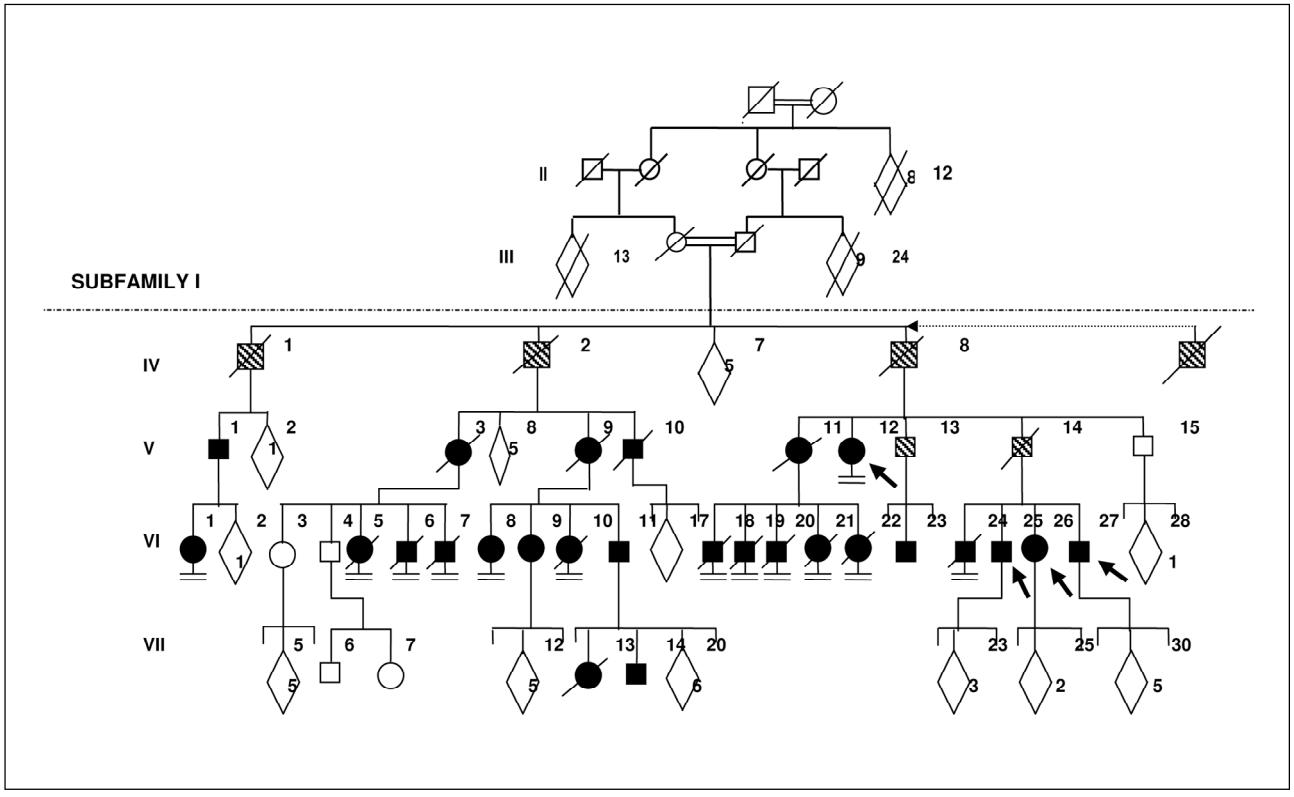


Fig 1. Pedigree of subfamily I with 81 persons in 4 generations and 26 affected.

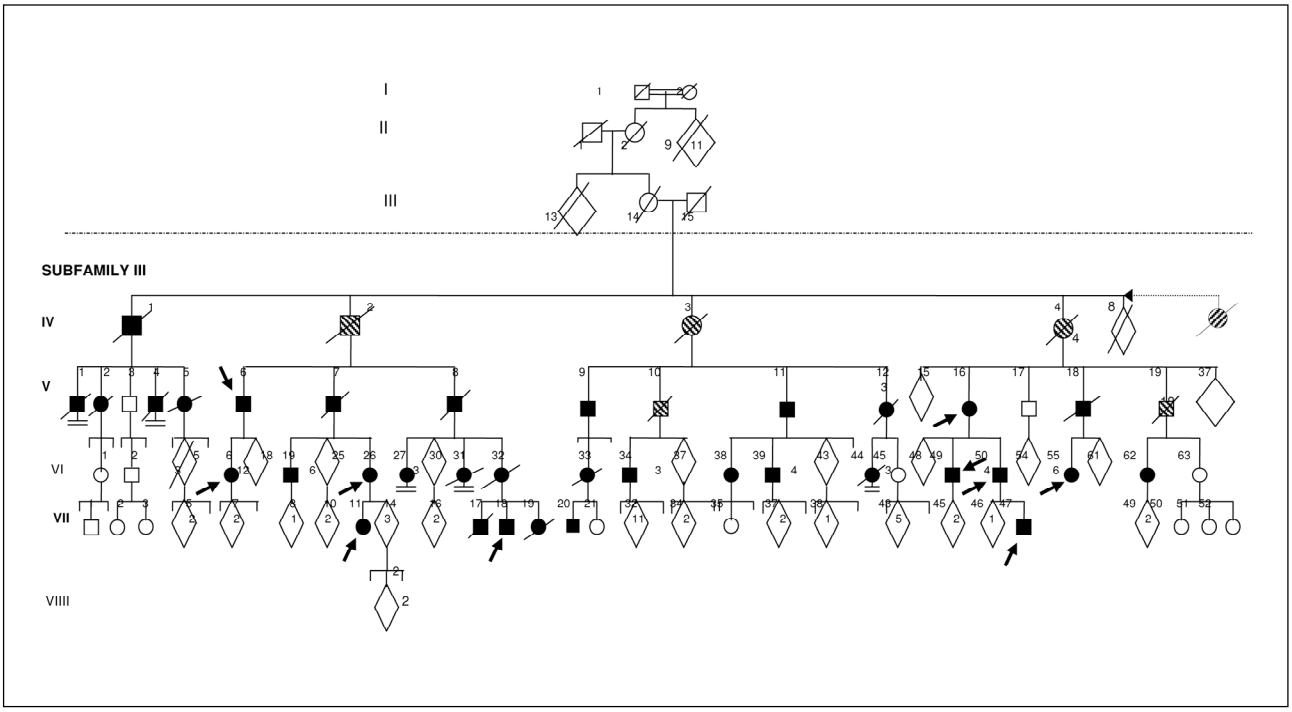


Fig 2. Pedigree of subfamily III with 162 persons in 5 generations and 34 affected.

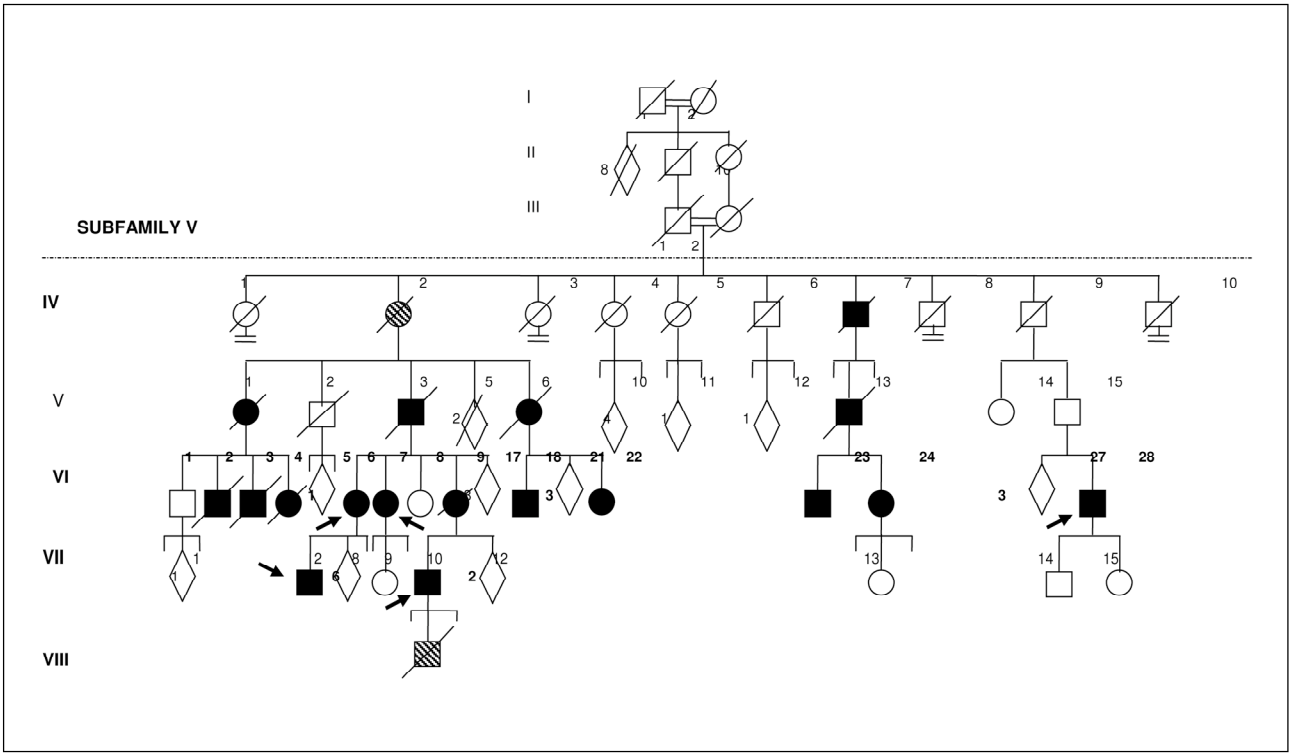


Fig 3. Pedigree of subfamily V with 69 persons in 5 generations and 18 affected.

of the country (26 in Ceará, 4 in Piauí, 3 in Maranhão, 2 in Bahia and 2 in Pernambuco), 12 (20%) in the Southeast region (6 in Rio de Janeiro, 5 in Minas Gerais and 1 in São Paulo), 9 (15%) in the Center-West area (8 in Brasília and 1 in Tocantins) and 2 (3.3%) in the North (Belém).

DISCUSSION

The cerebellar ataxias are neurodegenerative disorders characterized by degeneration of the cerebellum and/or the cerebellar connections, either isolated, or associated with involvement of other structures such as the visual and auditory systems, the cortico-spinal pathways, the lower motor neurons, the basal ganglia and the peripheral nerves[7]. The inheritance may be dominant, recessive or X-linked. At least 26 different types of autosomal dominant cerebellar ataxias (ADCA) have been described thus far and at least 11 of them may be diagnosed based on molecular testing: SCAs 1, 2, 3, 6, 7, 8, 10 ,12, 14, 17 and DRPLA.

The association of spinocerebellar manifestations with retinal degeneration in a family with autosomal dominant inheritance and evidence of anticipation is highly suggestive of SCA7[9,14]. The clinical features of the established cases of this Brazilian family with SCA7 included ataxic gait, visual loss, dysartria, nystagmus, ophthalmoplegia, dysphagia, dystonia, pyramidal and extrapyramidal signs, being similar to those already described in the literature[5]. Contrasting with this similarity, the Brazilian patients with SCA10 described by Teive et al.[15] did not have epilepsy, that was present in the Mexican patients[16] and was supposed to be an essential clinical characteristic of the disease. Different phenotypes of the same disease in different populations have important clinical implications, and its origin still have to be determined.

Although generally considered rare, the presence of SCA7 has already been confirmed in several regions of the world. It seems to be prevalent in United States and France[17], and is the most frequent identified form of ADCA in Sweden and Finland[18]. In Spain, the frequency of SCA7 among 72 patients with ADCA was 3%, being lower than the frequency of SCA3/MJD (15%), SCA2 (15%) and SCA1 (6%)[19]. SCA7 also seems to be uncommon in Brazil, with reported frequencies ranging from 2%[20] to 4.4%[15], much less frequent than SCA3 or Machado-Joseph disease that represents about 40% of the ADCAs[21].

Although SCA7 is a dominant condition, several consanguineous marriages have been detected in the first generations of this family, apparently preceding the existence of the disease. In spite of the high consanguinity rate and of the autosomal dominant character of the disease, it was impossible to detect any patient with expansion of the two alleles, a rare occurrence that, according to Palau and Sevilla[22] could have a dosage effect, resulting in a more severe disease.

In this Brazilian family, the first cases of the disease appeared in the fourth generation, but this observation does not exclude the possibility that members of the previous generations carried abnormal alleles. If this was the case, these individuals may not have been identified because they did not survive long enough to manifest symptoms of the disease, since of death was very early at that time, or because the disease was very mild and late due to the small numbers of CAG repetitions. It is virtually impossible to test these hypotheses and, in addition, a new explanation that has become available is the occurrence of *de novo* mutation, that has been shown to be the case in some SCA7 families[23,24].

Most of those affected in the sixth generation of subfamily I did not constitute family. We are unable to state if this fact was a deliberate decision or a biological limitation. Due to the phenomena of anticipation, the disease may move towards extinction, but the presence of intermediary alleles may result in the beginning of a new cycle of the disease[23,24].

The ancestral couple we described had 10 descendents, but only 4 of them constituted the basis of this genealogical tree that we were able to construct. Once the destiny of the other 6 sibs and their descendants is currently unknown, it is highly probable that they have emigrated from the State of Ceará, with the possibility that other cases of SCA7 in other regions of Brazil might have the same family origin.

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