Autosomal dominant cerebellar ataxia type 1 in a Sudanese family

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ABSTRACT

Objective: To study a large Sudanese family with a progressive autosomal dominant cerebellar ataxia and describe the clinical features and identify the genotype of the disorder.

Methods: This study was conducted during the year 1999 in the University Neurology Department of Shaab Teaching Hospital in Khartoum, Sudan. Affected individuals were identified by clinical examination or by reliable narrative data obtained from relatives of diseased or inaccessible family members. Routine laboratory blood and urine tests, cerebrospinal fluid analysis, cranial computerized tomography and nerve conduction studies were performed on the index patient and, if possible, family members. The genotype was identified by deoxyribonucleic acid analysis.

Results: Ten males and 12 females spanning 4 generations were affected by autosomal dominant spinocerebellar ataxia. Genetic studies identified the mutation to be at the spinocerebellar ataxia 1 locus on chromosome p6.

Conclusion: This is a report of a Sudanese family suffering from Type 1 autosomal dominant spinocerebellar ataxia.

Keywords: Spinocerebellar ataxia type 1.

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Autosomal dominant cerebellar ataxia (ADCA) is a group of genetically heterogeneous disorders characterized by progressive neuronal loss and degeneration in the cerebellum and its connecting pathways in the brainstem and the spinal cord.[1] There is a wide variability and overlap in the clinical picture of hereditary ataxias, which rendered classification of these disorders on a clinicopathological basis less than optimal. However, recent identification of specific genetic mutation at certain chromosomal loci in patients with ADCA enabled a more reliable classification at a molecular level based on genotype.[2] Moreover, genotype identification by deoxyribonucleic acid (DNA) testing has eliminated continuous "shopping" for diagnosis and allowed precise genetic counseling.[2] In this paper we identify and present a large 4-generation Sudanese family with an autosomal dominant progressive ataxia and a positive expression of the mutation at the spinocerebellar ataxia type 1 (SCA1) locus.

Methods. The kindred investigated originated, as far as we could ascertain, from Sudanese ancestry in a central Sudan tribe that is located along the western bank of the White Nile. Information was collected from 71 family members spanning 4 generations. Full neurological and general physical examinations, routine blood and urine laboratory tests, cerebrospinal fluid (CSF) analysis, nerve conduction studies and cranial computerized tomography (CT)

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were performed on the index patient. As far as possible other family members were called for clinical and laboratory assessments. Diseased individuals and those who were not accessible for examination were considered affected when a reliable narrative evidence of a similar progressive ataxia was obtained from their relatives. Molecular genetic studies were performed in collaboration with the DNA Laboratory at the Institute of Neurology, University of London. Screening for DNA neucleotide base cytosine, adenine and guanine (CAG) repeat at SCA loci was carried out.

Results. Twenty-two patients, 10 males and 12 females were affected (**Figure 1**). Seven patients were alive at the time of reporting. Accessible family members in different generations whom we were able to examine manifested essentially similar clinical phenotype. An index patient is presented as follows.

Index patient (Figure 1: III.12). A 45-year-old retired army officer began to notice, from the age of 35 years, a slowly increasing difficulty with balance when walking and clumsiness his of hands. He then started to develop dysarthria. Eventually, the ataxia of gait worsened causing frequent falls and his manual skills deteriorated. For the 2 years prior to his presentation he used a walking stick to support his gait balance. His speech had also progressively deteriorated. He was married and had 3 healthy looking children (**Figure 1: IV: 11, 12, 13**). On examination the patient was thin, weighing 54 kg, and carrying a walking stick. He was not pale or jaundiced. Pulse rate was 74 beats per minute and was regular. Blood pressure was 120/83 mmHg. He appeared to be intelligent oriented and had normal language function. His speech had scanning quality and was markedly dysarthric. Ocular movements revealed impaired pursuit gaze that was replaced by slow saccades and exhibited ocular dysmetria. The optic fundi were normal. Marked cerebellar ataxia was evident as demonstrated by impaired finger-nose and heel-shin tests (intention tremor and dysmetria), rapidly alternating active limb movements (dysdiadokokinesia) and stance and gait (trunkal ataxia). Muscle tone was increased and the deep tendon reflexes were exaggerated. The plantar responses were equivocal. Sensory examination revealed normal perception for light touch, pinprick, vibration and position senses. Blood counts, blood glucose, blood urea, serum sodium, potassium, calcium and phosphate levels and CSF analysis were within the normal limits. Computerized tomography of the brain showed moderate atrophy involving the brainstem cerebellar hemispheres and vermis. Motor and sensory nerve conduction studies and electromyography were normal. Genetic DNA studies for CAG repeats revealed abnormality at the SCA 1 locus at chromosome p6, thus confirming the diagnosis of type 1 ADCA.

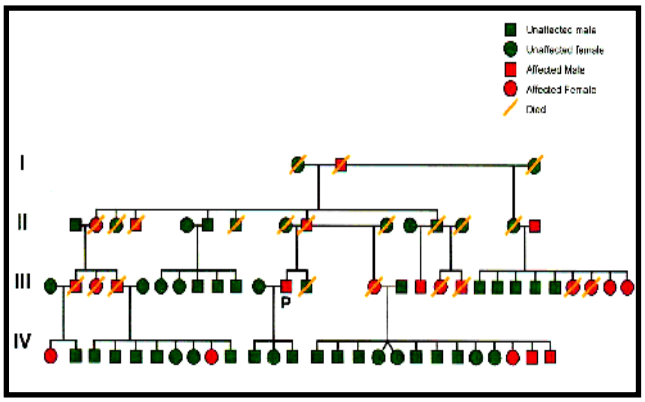

Figure 1 - The pedigree of the family with autosomal dominant spinocerebellar ataxia. The index patient is indicated by the letter P.

Discussion. The kindred we studied were typical of the large consanguineous Sudanese families encountered all over the country. The pattern of inheritance of the disorder was autosomal dominance. The index patient presented had a progressive familial neurological disorder mainly affecting the cerebellar and pyramidal systems, that had fulfilled the diagnostic criteria of ADCA provided by Harding.[1] Genetic studies had identified the specific mutation at SCA1 locus, which established the diagnosis. From our research, we believe that this disorder has not previously been reported from Sudan. The ADCAs are a group of similar neurologic disorders that are sometimes difficult to distinguish on clinical grounds from each other particularly in sporadic cases. Recognition of specific mutations in different gene loci leads to identification of a growing number of subtypes of the disorder. To date 16 loci have been identified, namely, SCA1 to 8, SCA 10 to 16 and the dentato-rubral-pallido-luysian atrophy (DRPLA).[2,7]

Spinocerebellar ataxia type I accounts for 10-15% of all dominantly inherited ataxias and has an age of onset commonly in the 3rd or 4th decade. The earliest presenting symptom is usually a slowly progressive ataxia, which is shortly followed by dysarthria. Early on, the neurological examination reveals a pure bilateral cerebellar syndrome and later on signs of pyramidal tracts affection supervene. The deep tendon reflexes are brisk at the beginning but may eventually diminish as the disease progresses. Abnormal ocular movements such as absent pursuit and slow saccades, as seen in our patient, are common.[3] Optic atrophy, supranuclear and internuclear ophthalmoplegia may occur. Extrapyramidal features, bulbar dysfunction and minor cognitive impairment occur in the late stages. In a course of 10 to 15 years, the ataxia and the

bulbar symptoms usually disable the patient.[1,4]

Molecular genetic studies have identified the mutation responsible for SCA1 as an unstable expansion of the trinucleotide CAG repeat on chromosome 6p from the normal range of 6-44 to 39-82. The number of CAG repeat varies among different families but is stable within each family. The repeat correlates with the age of onset and rate of progression of the disease.[6] A few reports from the Arab world on SCA are available. Tadmouri and Bissar-Tadmouri in their interesting review on genetic disorders in Arabs,[8] listed among other genetic disorder available reports on SCA. We very much agree with, as suggested by those authors, the establishment of a regularly updated database for genetic disorders in Arab communities, particularly if we appreciate the ethnic variability of phenotype in SCA. Admittedly, no specific treatment for SCA is known at present, but the rapidly growing knowledge from gene discovery in this human genome era is throwing much hope in the coming future.

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