Spinocerebellar Ataxia-12 (SCA–12): A tremor Dominant Disease, Typically Seen in India

KK Sinha

Neurologist, Ranchi, INDIA.

123

Spinocerebellar ataxias, which are now simply called SCAs are a group of late onset, autosomal dominant hereditary progressive neurodegenerative disorders which are basically characterized by cerebellar ataxia. However they are a heterogenous group with many other neurological features in addition to ataxia, which give rise to variable and overlapping phenotypes and they are therefore not readily distinguished from each other by clinical features alone. Affected individuals manifest cerebellar symptoms which is the core dysfunction, but may have other neurologic signs, indicating abnormalities in other parts of the nervous system including the cerebral cortex, basal ganglia, brainstem, retina, spinal cord and peripheral nerves. Based on clinical features, they were differentiated by late Anita Harding of London, into four basic groups of adult onset dominant cerebellar ataxias or ADCAs.[1]

Recent advances in human molecular genetics have led to a new classification of ADCAs based either on identification of the mutant gene or strong linkage to a specific genetic locus. As mentioned earlier, they are now called spinocerebellar ataxias or SCAs. Their current number is large and includes SCA-1 through SCA-25.[2] Over 30% of dominantly inherited spinocerebellar ataxias however, still remain unlinked to specific genetic markers.

Spinocerebellar ataxia-12 (SCA-12) is one of the recently identified SCAs, first described by Holmes, O'Hearn and colleagues in a single large American pedigree of German ancestory in 1999, at John Hopkins University Medical School, USA.[3] Most members of this family lived in the Mid Atlantic region of the United States, but the family originally immigrated to America from Southern Germany in the early 19th century.

PHENOTYPE IN THE AMERICAN FAMILY

The proband was a 64 year old woman, who at the age of 38 years developed postural and kinetic tremor in her upper limbs.[4] During the next 10 years a tremor of her head appeared and when she was in her 50s she became ataxic and by age 60, developed prominent limb dysmetria and mild dysarthria. Abnormally brisk reflexes were also noted and MRI showed cerebellar atrophy. The other affected members presented in the fourth decade of life with postural tremor of the head or arms. When in her early 60s, marked cognitive impairement including disorientation, memory loss, dyscalculia and perseveration appeared.

Hyperreflexia of deep tendon reflexes, ataxia, dysmetria and dysarthria appeared subsequently, but were not as disabling as they were in other types of spinocerebellar ataxias. Parkinsonian features, dementia and other psychiatric symptoms including depression, anxiety or delusions were noted in some and neuroimaging showed cerebral and cerebellar atrophy.

The age of disease onset in this family ranged from 8 to 55, but most individuals began to show symptoms in middle age.

DISCOVERY OF GENETIC MUTATION

The genetic mutation was an expansion of the trinucleotide CAG (cystosin + adenine + guanosine) within a gene called PPP2R 2B, located on chromosome 5q-31-33.[3,4] CAG triplet encodes amino acid glutamine, so the expanded CAG repeat meant an expanded polyglutamine track. In 394 normal individuals the CAG repeat number in this gene varied from 7 to 29 triplets in length. But the affected members of this family had expanded repeats containing as many as 66-78 trinucleotides. Interestingly enough, the CAG repeat expansion in these patients was not located in the protein coding region of the PPP2R2B gene, but in its promoter region which is not a direct coding segment. It was speculated that the repeat expansion in the promoter region therefore did not change the protein structure but somehow changed the instructions that regulate the expression of the protein. These instructions basically included two things; "how much of the protein should be made?" and "when the protein should be made?". The protein encoded by the PPP2P2B gene regulates an important brain specific enzyme called protein phosphatase 2 A (PP2A) which is involved in protein phosphorylation and is thought to be an important regulator of many cellular activities, including cell division and neuronal cell death. It was hypothesized that the CAG expansion in the PPP2R2B gene somehow changes the instruction to the protein making machinery of the brain, which now begins to make much less of this vital regulatory protein PP2A than what is expected, which then results in injury or death of certain neurons in the brain.

This is the story of the discovery of first pedigree of SCA-12 patients and the mutant gene. No other families of SCA-12 were subsequently reported in U.S.A. At this stage it was believed that SCA-12 is a rare ADCA[5]. The second pedigree was reported by Fujigasaka et al in 2001, and interestingly enough this was a family of Indian ancestory.[6] An expanded CAG repeat ranging from 55 to 61 triplets was detected in 6 affected and 3 asymptomatic but genotypically positive individuals in this Indian family in the same gene, PPP2R2B on chromosome 5

Table 1 : Clinical features of SCA-12 patients in Ranchi study.

Action tremor
Intention tremor
Postural tremor
Rest tremor
Cerebellar signs
Hyperreflexia
Babinski's sign
Dysarthria
Slow saccades
Hypertonia
Cognitive impairment
Dystonia
Cramps
Parkinsonism

q 31-33 providing additional evidence that the mutation is the cause of the disease.

A little later in 2001, five other unrelated smaller pedigrees of SCA-12 were identified by Srivastava et al at the All India Institute of Medical Sciences in New Delhi, while analyzing 77 unrelated Indian families with different autosomal dominant cerebellar ataxia phenotypes.[7] The sizes of the expanded trinucleotides in the affected members of these families ranged from 55 to 69 CAG repeats, whereas the size of the normal alleles ranged from 7 to 31 repeats. These patients also initially presented with action tremor followed by gait ataxia much later. Extensor plantar responses and deep tendon hyperreflexia were also noted. Nystagmus and dystonia were seen in a few. Other subtle extrapyramidal features such as bradykinesia and paucity of spontaneous movements were common. Their study suggested that while SCA-12 may be rare in some populations, it was not as rare in some other geographic populations. Upto this point in time, investigators also concluded that comparison of the clinical features of SCA-12 with other SCAs revealed no specific signs that could consistently identify SCA-12, indicating that genotyping was essential for its accurate diagnosis. However they added that those ADCA patients that presented with hand tremor in a setting of mild ataxia with brisk reflexes, evidence of subclinical peripheral neuropathy, and cerebral and cerebellar atrophy in neuroimaging could be suspected to have SCA-12.

In a phenotype genotype study conducted at Ranchi with our collaborators in the Institute of Neurology, London and Saha Institute of Nuclear Physics in Kolkata, between January 1997 and December 2003 on 54 families with ADCA, our group identified 12 families with SCA-12 mutation.[8] There were a total of twenty one members in these families that tested for the mutant SCA-12 locus. The age of onset ranged between 16 and 62 years (mean age 39 year). Their clinical features are summarized in Table –1. Eleven of these families belonged to a specific ethnic caste, known as the Agrawals, a well known north Indian community which originated in antiquity from a small town called Agroha in Haryana.

Six of the 21 members who tested positive for mutant SCA-12 locus were however asymptomatic, suggesting variability in gene penetrance or expression. It became evident that the most frequent symptom at presentation was action tremor, predominantly seen in the limbs, but also observed in trunk, head, tongue, jaw and lips (71%). Postural tremor was noted in 42% and intention tremor in 19%. Some of these patients carried the diagnosis of "essential tremor" on the initial evaluation. Rest tremor was noted in only three. Cerebellar signs mainly in the form of dysmetria, intention tremor and gait ataxia were observed in 52%, however they usually seemed to appear later in the course of the illness. Interestingly, affected members of a few families exhibited prominent cerebellar signs, whereas, those in others, cerebellar sign were either absent or not very prominent at the time of the first examination. There was also a prominent intrafamilial variation in signs; while some showed a predominant tremor syndrome, others were seen to present mainly with cerebellar signs. Dysarthia and tremulous voice were seen in a number of individuals. Upper motor neuron signs with positive Babinski's reflex were noted in nearly a third of patients. Dystonic posturing of hands was noted infrequently, which were often suppressed by sensory tricks used by patient. While parkinsonism was noted in the majority of members of the original American family, only one of our patients, an elderly female, had it. Infact, parkinson's disease was the initial diagnosis made by the physician who saw her first. Slowing of ocular saccades was seen only occasionally. Some patients complained of painful cramps. Early signs of cognitive impairment in the form of memory loss and poor comprehension was observed in 3 patients, who were old and at a fairly advanced stage of the illness. Signs of cerebellar and cerebral atrophy of variable degree were visible in neuroimaging, but the basal ganglia and brainstem looked normal. Of the ten patients, who underwent electrophysiological testing, four showed abnormalities. Electrical evidence of sensory motor peripheral neuropathy was found in one and that of distal axonal motor neuropathy was detected in others; but none of them had clinical evidence of neuropathy.

Genetic studies showed that the normal CAG repeat length varied between 7 and 16 repeats and the expanded CAG repeats ranged from 53 to 69. The expansion with 53 CAG repeats is usually considered a relatively smaller one and was found in the single non-Agrawal family with SCA-12 in our study. This is the second smallest CAG repeat expansion seen in an affected member of a SCA-12 family, the smallest reported so far has 51 CAG repeats (Srivastava et al 2004).[9]

SPECIAL PHENOTYPIC AND GENOTYPIC FEATURES NOTED IN PATIENTS IN THE PRESENT STUDY

Amongst the affected members of the families that were studied at Ranchi, a few special features were observed. The basic phenotypes noted were a) tremor dominant and b) ataxia dominant syndromes; the former being almost 3 times more frequent. Except for a single family, all belonged to the Agrawal caste. One of the Agrawal patients, a 25 years old young man was homozygous for the mutant allele which is very unusual for a disease with autosomal dominant inheritance. He had a CAG expansion of 62/65 but interestingly he was asymptomatic at the time of evaluation. This happened because Agrawals like other Hindu castes in India, marry within their own caste. His both parents carried expanded CAG alleles; while his father had a

florid tremor with a CAG repeat expansion of 8/66; his mother had a repeat expansion of 8/62 but was asymptomatic at the time of evaluation. These unusual findings suggest two things; (a) that the disease severity is neither related to homozygosity, nor to a dose effect and; (b) that there is a strong probability of reduced penetrance and variable expressivity in this disease. It was also noted that anticipation was not a feature .

SCA-12 was also the second most frequent ADCA after SCA-12 in this study.

Srivastava et al the AIIMS, New Delhi have studied 10 more unrelated families of SCA-12 taking the total to 15 now, and they believe that it is the third common cause of ADCA in India.[8]

As far as is known, no case of SCA-12 except the first one described by O'Hearn et al, has been reported from countries other than India. Personal communication with Srivastava confirmed that all their patients were also from the Agrawal community.[10]

Our current experience indicates that this disease is essentially a disorder of a particular Indian community and it is very much a private mutation within this endogamous ethnic group. Occurrence of a familial tremor in a member of this community should alert the attending physician to the possibility that the patient under evaluation may be showing early signs of SCA-12 ataxia. This diagnostic criteria was applied by our group to arrive at a clinical diagnosis in many cases before confirmation of the diagnosis by DNA test was done. This means that although genotyping is essential for the final diagnosis, those patient of ADCA presenting with action tremor of hands in a setting of milder or florid ataxia, brisk reflexes, evidence of subclinical peripheral neuropathy, cerebellar and cerebral atrophy in neuroimaging, may be suspected to have where SCA-12, particularly if they belong to the Agrawal community.

The search to discover a founder mutation in the population based on determination of strong linkage disequilibirium between the disease gene and a particular haplotype of alleles at different polymorphic loci, surrounding the mutant gene, is what is needed. Since no haplotype data are available, one does not know at what time in the history of human evolution, this mutation was introduced into the Agrawal community.

REFERENCES

1. Harding AE. The clinical features and classification of the late onset autosomal dominant cerebellar ataxias. A study of 11 families, including descendants of the Drew family of Walworth. *Brain* 1982;105:1-28.
2. Stevanin G, Baslam N, Thabois S, et al. Spinocerebellar ataxia with sensory neuropathy (SCA-25) maps to chromosome 2p. *Ann Neurol* 2004; 55(1):94-104.
3. Holmes SE, O'Hearn EE, Mclnnes MG et al. Expansion of a noval CAG trinucleotide repeat in the 5 region of PPP2R 2B is associated with SCA-12. *Nat Genet* 1999;23:391-392.
4. O'Hearn EE, Holmes SE, Calvert PC et al. SCA-12: Tremor with cerebellar and cortical atrophy is associated with a CAG repeat expansion. *Neurology* 2001;56:299-303.
5. Worth PF, Wood NW, Spinocerebellar ataxia type 12 is rare in the United Kingdom. *Neurology* 2001;56:49.
6. Fujigasaki H, Verma IC, Camuzat A et al. SCA-12 is a rare locus for autosomal dominant cerebellar ataxias. A study of an Indian family. *Ann Neurol* 2001;49:117-21.
7. Srivastava AK, Choudhary S, Gopinath MS et al. Molecular and clinical correlation in five Indian families with spinocerebellar ataxia 12. *Ann Neurol* 2001;50:796-800.
8. Sinha KK, Ranjan Sudhir, Jha DK et al. Spinocerebellar ataxia type 12 is not an uncommon form of ADCA in India. *Annals of Indian Academy of Neurology* 2003;6:193.
9. Srivastava AD, Mukerji M, Singh S et al. Molecular and clinical correlation in 20 patients of spinocerebellar ataxia 12 from India. *Neuroplogy* 2004;62 (Suppl 5): A 271.
10. Srivastava AK, Personal communication.