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Understanding the Pathophysiology of Spinocerebellar Ataxias through genetics, neurophysiology, structural and functional neuroimaging

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SUMMARY

Over the past 10 years a large cohort of 656 index patients with clinically suspected degenerative ataxias were clinically evaluated under various research projects. Of these, 625 index patients underwent genetic tests for the clinically suspected most probable diagnosis. A diagnosis could be achieved in 218 patients (34.9%). Among these 218 index patients, 82 each were SCA1 and SCA2, 32 were SCA3, 4 were SCA12, and 18 were Friedreich's Ataxia. Thus among the Autosomal Dominant Ataxias (SCAs) there was equal prevalence of SCA1 and SCA2 (41% each) followed by SCA3 (16%) and SCA12 (2%). This high prevalence of SCA1 is in contrast to the available National and International literature. The rate of clinical disease progression, especially in SCA2, was dependent on the CAG repeat size, and may commence linearly from birth.

Apart from cerebellar involvement, a comprehensive evaluation of the neuroaxis in various subsets of this genetically proved cohort showed subclinical involvement of the cerebral cortex, central motor and sensory pathways, peripheral nervous system and autonomic nervous system. Important findings include: (a) A mixed sensorimotor and pure sensory neuropathy was seen in all the three subtypes of SCAs, while pure motor neuropathy was uncommon; (b) There was reduced cortical excitability and prolonged central motor conduction time, most evident in SCA1 and least in SCA2; (c) Cardiac autonomic dysfunction, predominantly parasympathetic, was seen in SCA, and the severity correlated with the duration of illness in SCA1; (d) In SCA1 there was a global impairment of balance, with greater instability in anterior–posterior than

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medio–lateral directions; (e) In all the three SCAs there was a significant loss of gray matter in both cerebellar hemispheres and vermis. Vermian atrophy was more pronounced in SCA3, while SCA1 and SCA2 had significant white matter atrophy. Pontine white matter atrophy was more pronounced in SCA2; (f) Cerebellar activity was largely absent with additional activity in contralateral cortices and in thalami in patients with SCA1; increased thalamic function could be one of the causes for disinhibition of the motor cortex contributing to uncoordinated movements.

Studies on larger cohort of each subtype of SCAs to validate the above findings, follow-up studies to determine the rate and nature of progression of neurodegeneration and evaluation of pre-symptomatic genetically confirmed SCAs will help understand the pathophysiology of the SCAs.

Spinocerebellar ataxias (SCA) are genetically mediated autosomal dominant neurodegenerative disorders. The burden of SCAs in India is large and diverse ethnicity of Indian population has led to different types of SCAs in different parts of India. Documentation of the geneotypic-phenotypic correlation and understanding the pathophysiology of SCAs are crucial in management of these patients.

Though in the past 2 decades there has been significant understanding in the genetics of Hereditary Ataxias, in particular SCAs (autosomal dominant ataxias), it is disturbing that there are very few Indian Research Centres which are dedicated to research in the field of Hereditary Ataxias. One of the primary reasons behind this is the lack of understanding of the pathophysiology and lack of any specific treatment for SCAs.

Twenty-five years back, when I joined the National Institute of Mental Health & Neurosciences (NIMHANS), as a student in DM Neurology, I developed interest in Neurodegenerative Disorders, especially the Ataxias. Pursuing my dissertation in Cerebellar Ataxias, I systematically studied the clinical, neuropsychological, electrophysiologic and imaging aspects of patients with Friedreich's Ataxia, Early-onset Cerebellar Ataxia with Retained Tendon Reflexes and Olivopontocerebellar Atrophies, based on the classification prevalent at that time. The results of this study have been published in several National and International journals (1-5). Over the next decade, rapid genetic discoveries in the field of Autosomal Dominant Ataxias, later designated as Spinocerebellar Ataxias (SCAs), mandated a new look at the Hereditary Ataxias in India along with genetic studies.

I was fortunate to get a second opportunity to pursue my research interest in Cerebellar Ataxias when I joined NIMHANS as a Faculty in the Department of Neurology in 2000. In

collaboration with Dr. Mitali Mukherjee of the Institute of Genomics and Integrative Biology (IGIB), New Delhi and Prof. Sanjeev Jain at Genetic Laboratory of NIMHANS, we started a prospective study (2003) on "Phenotypic-genotypic correlation of Spinocerebellar Ataxias in Southern India", funded by a research grant from Indian Council of Medical Research (ICMR), New Delhi. This was the beginning of a large ongoing prospective research study on Hereditary Ataxias. In the next 10 years, two more research grants from ICMR and several dissertations of students pursuing DM in Neurology helped us in establishing a large cohort of patients with hereditary ataxias.

The objectives of our study was to (i) establish a clinical and genetic database of hereditary ataxias with emphasis on epidemiology of hereditary ataxias in India, (ii) try to achieve phenotypic-genotypic correlation, (iii) clinical, radiological, electrophysiological characterization of genetically proven patients with hereditary ataxias, (iv) comparison of genetically proven patients from Southern and Northern India.

The results of our research in ataxias have been published in 22 articles in various National and International journals in the past one decade. Clinical data is still being analyzed and several projects are ongoing. A large section of the cohort of our patients still do not have a genetic diagnosis and future genetic studies are required to identify the uncommon and novel genes. Various imaging and electrophysiological investigations have been done only in subsets of patients with genetically proven SCAs. Presented below are the salient findings in genetically proven cohort of SCAs.

Methods :

Cohort :

Over the past 10 years a large cohort of **656 index patients** with clinically suspected degenerative ataxias were clinically evaluated under various research projects supervised by me. Most of the patients were examined by me. The patients were mainly from Southern India (Karnataka, Andhra Pradesh, Tamil Nadu and Kerala) and a considerable number of patients were also present from other parts of India, especially West Bengal, Bihar, Jharkhand, Assam, Orissa, Maharashtra, etc. Some patients were evaluated in their respective States by Neurologists, and we cannot be certain if they were genetically evaluated by their treating physicians.

Blood sample was taken after written informed consent from the 656 index patients and ~367 relatives (total samples~**1023**) and genetic studies of were done initially at IGIB and later at NIMHANS initially for the clinically suspected types of ataxias (viz. SCA1, SCA2, SCA3 , SCA 12, and Friedreich's ataxia). When negative, further genetic tests in some samples were done for other types of ataxias in India (SCA6, SCA7, SCA8 and DRPLA, episodic ataxias, etc.) at IGIB.

In addition, several research studies were performed in small cohorts of genetically positive patients, focused on comprehensive evaluation of the neuro-axis, using:

(A) Electrophysiology:
  a. Nerve conduction studies
  b. Multimodal Evoked Potentials (VEP, BAER, Median and Posterior Tibial SSEP)
  c. Transcranial Magnetic Stimulation
(B) Autonomic Function Tests
(C) Spirometry
(D) Balance Evaluation
(E) Neuroimaging:
  a. Structural: Routine and voxel-based morphometric studies using 3-Tesla MRI
  b. Functional : fMRI for correlating the functional correlates of incoordination?

Results :

Epidemiology:

Of the 625 index patients, a genetic diagnosis could be achieved in 218 patients (34.9%) and in the asymptomatic 330 relatives in whom genetic analysis was done, another 28 patients (8.5%) were positive for one of the genes tested. Among the 218 index patients, 82 each were SCA1 and SCA2, 32 were SCA3, 4 were SCA12, and 18 were Friedreich's Ataxia. Thus among the Autosomal Dominant Ataxias (SCAs) there was equal prevalence of SCA1 and SCA2 (41% each) followed by SCA3 (16%) and SCA12 (2%). Thus in our cohort, mainly from Southern India, the prevalence of SCA1 was equal if not higher than SCA2, which is similar to that reported by a study from (Vellore) Tamil Nadu, but in marked contrast to studies from rest of India, where most have reported highest prevalence of SCA2 (Delhi, Kolkata and Mumbai) and one study reporting highest prevalence of SCA3 (Kolkata). In most studies outside India, the prevalence of SCA3 is reported to be higher than SCA1 and SCA2. However, this difference of prevalence of the SCA1, 2 and 3 in various studies within India, needs to be validated in larger cohorts. Moreover, there is a possibility of the same subjects taking part in genetic studies in more than one centre, due to referral practices.

The following is a summary of the Clinical and genetic profile of 126 genetically positive patients of SCA1, 2 and 3. Part of these results have been published earlier (6).

The prevalence of SCA1 (40.5%) and SCA2 (39.7%) were almost equal, while SCA3 constituted the rest (19.8%). We found that patients of the three groups were comparable with regards to the mean age, mean age at onset of symptoms and duration of illness. All the three subtypes of SCAs presented with ataxia, dysarthria and incoordination of limbs. However, the severity of ataxia, as measured by the IARS scores was higher in SCA2 compared to the other groups.

Age at presentation and gender distribution:

The mean age of the patients at the time of presentation was in the fourth decade in all three groups. The mean age of patients of SCA1 was 34.1±10.7 years (range: 13-59 years). The mean age of patients of SCA2 was 32.9±12.8 years (range: 7-70 years). The mean age of patients of SCA3 was 36.8±12.2 years (range: 8-55 years). There was no statistical significant difference between the three groups.

There was a male preponderance in all the three groups. There were 37 males (72.5%) in SCA1, 39 (78%) in SCA2 and 13 (52%) in SCA3. There was no statistical significance in the gender distribution.

Age of onset and duration of illness:

The mean age of onset of illness was 29.8±9.9 years (range: 10-54 years) in SCA1, 27.6±12.2 years (range: 3-65 years) in SCA2 and 32.8±12.4 years (range: 4-53 years) in SCA3, which was not statistically significant.

The mean duration of illness was 4.7 ±4.1 yrs in SCA1 (range: 0.3-20 years), 5.3 ±4.3 years (range: 0.5-15 years) in SCA2 and 4.1 ±2.8 years (range: 0.5-10 years) in SCA3. The statistical analysis for age of onset of illness and duration of illness did not reach statistically significant difference.

Family history:

There was a positive family history present in a total of 101 patients (80.2%). Out of these patients an autosomal dominant pattern of inheritance could be discerned in 43 patients (84.3%) of SCA1, 38 patients (76%) of SCA2 and 20 patients (80%) of SCA3. The rest of the patients with a positive family history had affected siblings but a history of affection of parents was not forthcoming and since the parents were not examined, the pattern of inheritance could not be determined. There were a total of 7 patients with negative family history (i.e. sporadic inheritance): 4 patients of SCA1 (7.8%), one patient of SCA2 (2%) and 2 patients of SCA3 (8%).

CAG Repeat length:

The CAG repeat lengths were available in 118 patients. The mean CAG repeat length was 29.43 ±2.18 (range of 39-72) for SCA1, 22.24 ±1.07 (38-66) for SCA2 and 21.88 ±5.82 (43-79) for SCA3.

Clinical Features:

1. Skeletal abnormalities were most commonly observed in SCA3(40%), followed by SCA2 (30%) and SCA1 (21.6%).
2. All the three groups presented with unsteadiness of gait, dysarthria and incoordination of limbs as the commonest presenting symptoms.

3. The mean International Ataxia Rating Scale (IARS) scores significantly differed among the three groups with SCA2 patients having the greatest severity [SCA1: 32.3±13.7 (range: 8-63), SCA2: 41.1±17.1 (range: 14-94) and SCA3: 31.1±21.2 (range: 10-94)].
4. Cognitive disturbances were commonest in SCA1(15.7%) followed by SCA2 (6%) and SCA3 (4%).
5. Slow saccades were commonest in SCA2 (88%) followed by SCA1 (49%) and SCA3 (40%). Nystagmus was more often observed in SCA3 (80%) than in SCA1 (19.6%) and SCA2 (10%).
6. Spasticity was seen more often in SCA1 (29.4%) compared to SCA2 (16%) and SCA3 (8%). However, hypotonia was more in SCA3 (36%), followed by SCA2 (34%) and SCA1 (23.5%).
7. Vibration sensation loss in the lower limbs was more commonly seen in SCA2 (20%) compared to SCA1 (9.8%) and SCA3 (4%).
8. SCA1 had more hyperreflexia (58.8%) compared to SCA3 (52%) and SCA2 (14%), while SCA2 had more of hyporeflexia (22%) compared to SCA1 (7.8%) and SCA3 (0%).
9. Extensor plantars were more commonly seen in SCA1 (52.9%) than in SCA3 (48%) and SCA2 (32%).
10. Exptrapyramidal signs (EPS) (7, 8):

    We specifically analyzed the prevalence of EPS in 85 patients of the above cohort who had genetically confirmed SCA (SCA1 = 40, SCA2 = 28, SCA3 = 17). Forty-one SCA patients (48.2%) had one or more types of EPS. The prevalence of EPS was 60.7% in SCA2, 52.9% in SCA3, and 37.5% in SCA1. Among the SCA2 patients, bradykinesia was most frequent (35.3%), followed by reduced facial expression, postural tremor and dystonia (29.4% each), rest tremor, titubation and rigidity (23.5% each), and lip/jaw tremor and chorea (11.8% each). In SCA3 the common EPS were bradykinesia (44.4%), staring look, postural tremor and dystonia (33.3% each), and reduced facial expression and rigidity (22.2% each). In SCA1, staring look was the most common (53.3%), followed by dystonia and bradykinesia (33.3% each), and postural tremor (26.7%). In all the three groups, there was no significant difference in the mean length of repeat of the abnormal allele between those with and without EPS.

    In summary, bradykinesia, staring look, dystonia and postural tremor were the most frequent EPS observed in SCA. In SCA1, these signs were seen more often in younger patients with early onset of symptoms.

Electrophysiology assessment of the peripheral and central motor and sensory pathways and structures:

(a) Nerve conduction studies (9) :

Subclinical neuropathy is an important feature of spinocerebellar ataxias (SCA) but the true prevalence and electrophysiological characteristics in genetically proven patients of SCA 1, 2 and 3 are largely unknown. There are no large comparative studies among SCA1, 2 and 3.

We prospectively compared the electrophysiological characteristics of neuropathy in 61 genetically confirmed cases of SCA (SCA1=28, SCA2=16 and SCA3=17) of the above cohort. Nerve conduction studies were performed in at least one sensory and one motor nerve, in right upper and lower limb using standard methods.

The mean age of patients and duration of illness were comparable among SCA groups; mean age (years): SCA1=34.1±12.7, SCA2=35.2±13.9 and SCA3=38.1±11.3; mean duration (years): SCA1=5.4, SCA2=6.1, and SCA3=4.4). Electrophysiological evidence of neuropathy was highest in SCA1 (96.4%), followed by SCA3 (94.1%) and SCA2 (87.5%). A mixed sensorimotor neuropathy was commonly observed in all the subgroups (SCA1=78.6%, SCA2=50%, and SCA3=41.2%). Pure sensory neuropathy was most common in SCA3 (55.9%), followed by 31.3% in SCA2 and 17.9% in SCA1. Pure motor neuropathy was uncommon (6.3% in SCA2 and none in SCA1 and SCA3).

In summary, electrophysiological evidence of mixed sensorimotor and pure sensory neuropathy was seen in all the three subtypes of SCAs, while pure motor neuropathy is distinctly uncommon. Electrophysiological profile revealed higher abnormalities of motor conductions in both upper and lower limbs in SCA1 compared to the other two groups. However, the sensory conductions were more often abnormal in SCA2 and SCA1 in upper limbs and were almost comparable among the three groups in the lower limbs. The abnormalities of sensory nerves were more often observed in the upper limbs than in the lower limbs in all the three groups of SCAs, which points in favour of a non-length dependent sensory neuropathy in the SCAs.

(b) Evoked potentials (10) :

Multimodal evoked potential studies are useful tools to determine the integrity of the central pathways, viz. visual, auditory and somatosensory. Clinical sensory symptoms are usually uncommon in SCAs, and therefore it is of utmost importance to determine subclinical involvement, especially in the early disease, to devise symptomatic therapeutic strategies, prognostication, and determine the efficacy of therapeutic interventions. In SCAs, BAER was the most common abnormality among the

evoked potentials studied. SCA1 patients had more often abnormalities of VEP abnormality, SCA2 of BAER, and SCA3 of median SSEP.

In this study, we evaluated 43 genetically proven SCA (SCA1= 19, SCA2=13, SCA3=11) with median somatosensory evoked potential (mSSEP), visual evoked potential (VEP) and brainstem auditory evoked response (BAER) by standard procedures and compared with normative laboratory data. The aims were to determine the pattern and prevalence of abnormalities of EPs in each type of SCA and additionally evaluate if EP can be used to differentiate between them.

The most common abnormality was of BAER (86.1%) followed by VEP (34.9%) and mSSEP (30.2%). The degree of abnormality in VEP, mSSEP, BAER among patients with SCA1 was 42.1%, 41.2 % and 73.3% respectively; among patients with SCA2 was 38.5%, 27.3% and 100% respectively; among patients with SCA 3 was 18.2%, 37.5% and 88.9% respectively. The differences between the subgroups of SCAs were not statistically significant.

In summary, subclinical involvement of the visual, auditory and somatosensory pathways was very common in SCAs. BAER was the most frequent abnormality in SCA types 1, 2 and 3; abnormalities of mSSEP were comparable in the three SCAs whereas abnormality of VEP was less often noted in SCA3.

(c) Transcranial Magnetic Stimulation (11) :

Transcranial Magnetic Stimulation (TMS) is a useful non-invasive tool to state the changes of cortical excitability changes in neuro-psychiatric disorders. The prevalence of changes in the cortical excitability and central motor conduction time (CMCT) in these disorders is largely unknown, and there are few studies which have compared these findings in the subtypes of SCA.

The objectives of this study were to measure the cortical resting motor threshold (RMT) and CMCT using transcranial magnetic stimulation in patients with SCA1, SCA2, and SCA3. Thirty-two genetically confirmed patients with SCA (SCA1=15, SCA2 =11, SCA3 = 6) were studied. TMS was performed using a figure-of-eight coil attached to Magstim 200 stimulator. Motor evoked potentials were recorded from first dorsal interosseous at rest. RMT was determined using standard techniques and the CMCT by 'F' wave method. Comparison was made with data from 32 healthy controls.

We found that compared to controls, the patients with SCA had significantly higher mean RMT as well as CMCT (RMT: 49.9±9.1 vs. 41.5± 6.6, $p < 0.0001$; CMCT: 7.7±2.3 ms vs. 4.8±0.6 ms; $p < 0.0001$). When compared separately with the controls, while all the three subtypes of SCAs had significantly

prolonged CMCT, only SCA1 and SCA3, but not SCA2 had significantly greater RMT. RMT and CMCT between patients with SCA2 and SCA3, and between SCA1 and SCA3 did not differ significantly, while SCA1 had significantly higher RMT and CMCT than SCA2.

In summary, we found that patients with SCA have reduced cortical excitability and prolonged central motor conduction time, which was most evident in SCA1 and least in SCA2.

Autonomic functions (12):

Progressive cerebellar ataxia because of neurodegeneration is seen in autosomal dominant spinocerebellar ataxias (SCA), autosomal recessive ataxias, idiopathic late onset ataxias and multiple system atrophy of cerebellar type (MSA-C). In these disorders, apart from progressive gait and limb ataxia, there are varying degrees of abnormalities of ocular movements, pyramidal signs, propioceptive loss and autonomic dysfunction. Autonomic dysfunction in these progressive ataxias result from degeneration of central autonomic neurons as well as degeneration of rostral fastigial nucleus of cerebellum which actively participates in regulation of orthostatic homeostasis and other autonomic control mechanisms. While autonomic dysfunction is well documented in MSA-C, there is sparse information of its nature and prevalence in idiopathic late onset ataxia not fulfilling the criteria of MSA-C, and in SCAs apart from SCA3 /Machado-Joseph disease (MJD). Among the various manifestations of autonomic dysfunction, cardiac autonomic dysfunction may be an important cause of morbidity and mortality and therefore merits early detection.

Keeping the above in mind, we did a comparative evaluation of cardiac dysautonomia in SCA and idiopathic sporadic ataxias (IA) not fulfilling the criteria of multiple system atrophy. Cardiac autonomic functions were evaluated in 14 SCA (SCA1 = 6, SCA2 = 5 and SCA3 = 3) and 10 IA patients, comparable for age, age at onset, duration and severity of illness. The results were categorized as early, definitive, or severe autonomic involvement (EI, DI and SI respectively) based on the degree of abnormalities on tests of parasympathetic and sympathetic pathways.

It was found that cardiac autonomic dysfunction was present in all (EI = 25.0%, DI = 41.7% and SI = 33.3%), parasympathetic dysfunction being an early feature. SI was most often present in SCA3 (100%), followed by those with SCA1 (66.7%), and SCA2 (20%) and none in IA (12).

Therefore, cardiac dysautonomia was common in both SCA and IA, although the severity was greater in SCA. Among SCAs, the severity was greatest in SCA3, followed by SCA2 and least in SCA1.

In another study (13) we studied the cardiac autonomic function by using analysis of heart rate variability in 22 genotypically proven SCA patients (SCA1 = 11, SCA2 = 6 and SCA3 = 5) and compared with that of age- and gender-matched controls. Consecutive RR intervals were analyzed for time- and frequency- domain parameters.

There was a reduction in the standard deviation of RR interval (RR_SD) in 72.7% of SCA patients. There was a reduction in both the parasympathetic and sympathetic parameters in SCA without any change in the ratio of low- to high- frequency power. In SCA1, there was a significant negative correlation between RR_SD and duration of illness but not with the CAG repeat lengths of the abnormal allele. Small sample size of SCA2 and SCA3 precluded similar comparison.

This study showed that cardiac autonomic dysfunction, predominantly parasympathetic, was seen in SCA, and the severity correlated with the duration of illness in SCA1.

The above information is of paramount importance for prognostication of SCAs and also cautions when using drugs in SCA which can cause autonomic dysfunction, especially cardiac, even in those patients who do not have clinical autonomic dysfunction. The SCA3 patients are more likely to have the maximum severity of cardiac dysautonomia.

Spirometry:

The presence of cerebellar and brain stem atrophy has been reported in SCA, and imaging and pathological studies suggest degeneration of certain neurons and their pathways in the olivopontocerebellar system. Because of the proximity of the respiratory neurons with these areas, it is logical to expect dysfunction in the respiratory control mechanisms which may manifest as altered pulmonary function tests (PFTs). Similar pulmonary dysfunction has been studied in other degenerative neurological disorders such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, ataxia telangiectasia and multiple system atrophy. However, to the best of our knowledge, there are no large studies which have specifically evaluated pulmonary dysfunction in SCA. Therefore we undertook this study to look for evidence of pulmonary dysfunction in SCA and if present, determine its nature, extent and correlation, if any, with the clinical characteristics such as functional disability, duration of illness and type of genetic abnormality.

Thirty patients (F:M = 7:23;age: 35.0±11.3 years; SCA1=13, SCA2=9 and SCA3= 8) without clinical manifestations of respiratory dysfunction and 30 controls underwent pulmonary function tests (14). It was observed that there was subclinical restrictive type of pulmonary dysfunction in all the SCA subtypes, though SCA1 and SCA2 patients appeared to be more affected than SCA3. In addition, there was a possible presence of upper airway

obstruction. Therefore chest physiotherapy and breathing exercises should be introduced early in management of SCA. Patients with early morning fatigue, reduced cognition should be carefully evaluated for sleep apnea as a result of upper airway obstruction.

Balance assessment:

Evaluation of balance in degenerative ataxias is often clinical and subject to bias. Very few studies have attempted to determine the characteristics of abnormal balance in SCA, quantify the degree of impairment, and compare with balance characteristics of healthy subjects. Such information is essential to plan balance rehabilitation strategies, determine the effectiveness of therapeutic interventions and to prognosticate ataxic disorders.

We undertook this study to determine the prevalence, nature, and degree of balance impairment in patients of genetically proven SCA1, using Biodex balance measurement system (15). The findings were compared with age and gender matched controls. We also attempted to correlate the balance indices with age, body weight, and clinical severity of symptoms, age of onset, duration of symptoms and the size of CAG repeat.

The subjects were 20 patients (males: 14, females: 6) with genetically positive SCA1 and 20 age and gender matched healthy subjects. Ataxia was rated using the International Cooperative Ataxia Rating Scale (ICARS). Balance was assessed by dynamic posturography (Biodex, USA) which included: (a) ability to control balance in all directions (overall balance index, OBI), front to back (anterior–posterior index, API) and side-to-side (medio–lateral index, MLI); and (b) the limits of stability (LOS) in all directions. Balance index was considered abnormal if the actual value exceeded the predictive value.

Impaired balance was found in 80% of patients (all indices in 35%, OBI + API in 25%, only OBI in 15%, and OBI + MLI in 5%). Compared to controls, SCA1 patients had significantly higher balance indices and lower LOS scores. Unlike in controls, the mean value of API was significantly higher than MLI in SCA1. LOS was found to the best predictor of balance abnormality. In patients, all balance indices had significant positive correlations with ICARS, static score of ICARS, body weight, severity and duration of illness, but not with the CAG repeat length.

In summary, patients with SCA1 had global impairment of balance, with greater instability in anterior–posterior than medio–lateral directions. Apart from severity and duration of illness, body weight was detriment to maintenance of balance in SCA1. This information may be useful in planning balance rehabilitation in SCA.

Neuroimaging:

Routine imaging:

On MRI study, SCA2 patients had more severe cerebellar atrophy, hot-cross bun sign and inferior pontine atrophy compared to other two groups. SCA3 patients had milder cerebellar atrophy compared to the other two groups.

Voxel-based Morphometry :

There are no unique distinguishing features on routine neuroimaging to distinguish between SCA1, 2 and 3. Therefore we undertook a recently introduced advanced neuroimaging technique-Voxel-based morphometry (VBM), to study the pattern and degree of brain atrophy in patients with genetically proved SCA. VBM provides an automated unbiased analysis of structural MRI scans and gives a comprehensive assessment of anatomical differences throughout the brain. Our aims were to characterize the patterns of atrophy in SCA1, SCA2 and SCA3, determine if any unique pattern of atrophy can differentiate these three most commonly prevalent SCAs and finally to ascertain if a relationship exists between the morphometric measures and the CAG repeat lengths and other attributes of the disease.

We studied 31 genetically confirmed patients suffering from SCA (SCA1=12, SCA2= 9, and SCA3=10) (16). High resolution T1-weighted 3-Dimensional MRI Images were analyzed using the optimized VBM procedure. We found a significant loss of gray matter in both cerebellar hemispheres and vermis in all the three SCAs. SCA3 patients had more pronounced vermin atrophy, whereas SCA1 and SCA2 patients had significant white matter atrophy. Pontine white matter atrophy was more pronounced in SCA2.

Interestingly, only in SCA1 we could find a strong positive correlation with the severity of ataxia (as measured by International Cooperative Ataxia Rating Scale) and the degree of gray matter atrophy in cerebellar hemispheres. However, in all the 3 subtypes of SCAs, the duration of symptoms and lengths of CAG repeats had no correlation with the degree of atrophy.

In summary, this unique study showed that different subtypes of SCAs may have morphometric differences in the cerebellum, brainstem and the supratentorial structures. It is required to serially follow up these patients with VBM to see if the rate of progression of disease correlate with rate of brain atrophy.

Functional imaging :

Functional magnetic resonance imaging (fMRI) of the entire brain was used to study the neural (blood oxygenation level dependent) correlates of motor coordination of both hands in adult right-handed volunteers and 7

patients with SCA1 (17). The subjects performed 5 sets of alternate pronation and supination tasks using either hand in a prescribed sequence as the active phase followed by a period of rest. The motor network consisting of sensorimotor cortex, supplementary motor area, cingulate motor area, putamina and cerebellum, was identified during the task in healthy volunteers. However, in SCA1 group the cerebellar activity was largely absent. In addition there were activities in contralateral cortices and in thalami. This apparent decoupling of sensorimotor cortical and cerebellar areas during coordinated movement in patients with SCA1, suggests malfunctioning of the corticocerebellar loops. Therefore the basis of incoordination in SCA1 was the dysfunctional activity of the striatal and the cerebellar structures resulting in abnormal motor network coordination. (Jayakumar *et al*, 2008).

Therapeutics:

The treatment options for improving the balance in degenerative cerebellar ataxias are very few. The primary management for SCAs is gait and balance therapy. However Ayurvedic texts have described diverse treatment regimens for this disease. Therefore we undertook an open labeled pilot study using Ayurvedic therapy to determine if this therapy can improve balance indices measured by dynamic posturography (Biodex Balance System, USA).

Ten patients with progressive degenerative cerebellar ataxia (3 women, 7 men; SCA1=2, SCA2=2, SCA3=1; rest of the patients were negative for SCA1,2 and 3) participated in this study (18). The patients were treated over a period of one month. Treatment consisted of Shirobasti (therapeutic retention of medicament over the scalp) in male patients and Shirodhara (pouring of a steady stream of medicament on the forehead) in female patients with Dhanvantaram tailam (medicated oil) for 45 minutes daily, followed by Abhyanga (methodical massage) with Dhanvantaram tailam and Bhashpa sweda (steam bath), for 14 days. In addition, the treatment also consisted Abhyantara aushadha (oral medicines) of Maharasnadi kashayam 15 ml thrice daily, Dhanvantaram capsules 101 two capsules thrice daily, and Ashwagandha tablet 500 mg one tablet thrice daily, for one month. The patients were assessed on the Biodex balance system before and after the treatment.

All patients tolerated the treatment well without any adverse events and reported subjective improvement in walking. There was a statistically significant improvement in the overall and anteroposterior balance indices of dynamic stability. Thus, over the short period of the present study, Ayurvedic therapy was found to be safe and, showed improvement in the balance in patients with progressive degenerative cerebellar ataxia. However, further randomized placebo-control double blind studies are needed to validate the results.

Disease Progression:

Neurodegenerative disorders show a variable rate of disease progression depending on the nature of underlying genetic defect, sites of nervous system involvement, and age of onset. In addition, for the same disease there may be difference in the phenotypic expression, severity and progression of illness among different individuals, even belonging to the same family. It is important to know the rate of disease progression to prognosticate the illness, and to monitor the efficacy of therapeutic measures for symptomatic treatment or disease modification.

We attempted to determine whether there is any correlation between the clinical rate of disease progression at presentation and the CAG repeat size in 71 patients with SCA (SCA1=31, SCA2=25, and SCA3=15) (19). The severity of ataxia was measured using the International Cooperative Ataxia Rating Scale (IARS) in all the patients and the rate of disease progression at presentation was measured by the age adjusted IARS (IARS/Age). For each SCA, correlations of age at onset of symptoms, raw scores of IARS, age adjusted IARS and duration adjusted IARS (IARS/Duration) with the CAG repeat size were determined.

In this cohort, the number of CAG repeats of the abnormal allele ranged from 42 to 67 in SCA1, 38 to 66 in SCA2, and 69 to 79 in SCA3. In all the three types of SCAs, there were significant inverse correlations of AAO with CAG repeat size (SCA1: $r = -0.9$, $p<0.0001$; SCA2: $r = -0.7$, $p<0.0001$; SCA3:-0.8, $p=0.0003$) and significant positive correlations of IARS/Age with CAG repeat size (SCA1: $r = 0.6$, $p=0.0015$; SCA2: $r = 0.9$, $p<0.0001$; SCA3: $r = 0.7$, $p=0.0057$). However, the raw IARS scores and the duration adjusted IARS scores did not correlate significantly with the CAG repeat sizes.

Therefore, our data suggested that the rate of clinical disease progression at presentation, especially in SCA2, is dependent on the CAG repeat size, and may commence linearly from birth.

Advanced genetics in Ataxias: Comparison between North and South Indian populations:

Ancestral origin of the hereditary ataxias and comparison between cohorts from North and South India has been done in collaboration with IGIB, New Delhi. Details of the findings in SCA (20) and Friedreich's ataxia (21) have been published.

We are currently following up this cohort of ataxias at NIMHANS and also studying other changes of sleep pattern in ataxias. A patient with sleep benefit in episodic ataxia has been reported by us (22).

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