SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
Thiruvananthapuram-695 011

PROJECT REPORT

NAME : Dr.GIGY V. KURUTTUKULAM

PROGRAMME : D.M. NEUROLOGY

MONTH & YEAR OF SUBMISSION : NOVEMBER 1996

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TITLE OF THE PROJECT **SPINO CEREBELLAR DEGENERATIONS - A DESCRIPTIVE ANALYSIS OF CASES SEEN IN SCTIMST OVER A 10 YEAR PERIOD**

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CERTIFICATE

I, Dr. **GIGY V. KURUTTUKULAM** hereby declare that I have actually, performed all the procedures listed / carried out the project, under report.

Signature G/4.K.

Place : Trivandrum

Name in capital letters **Dr.GIGY V. KURUTTUKULAM**

Date : 11.11.96

Forwarded. He has carried out the minimum requirement of procedures / etc.

Signature

Head of the Department

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CONTENTS

SPINO CEREBELLAR DEGENERATIONS-A DESCRIPTIVE ANALYSIS OF CASES SEEN IN SCTIMST OVER A 10 YEAR PERIOD

INTRODUCTION

SPINO CEREBELLAR DEGENERATIONS (SCD)

The Spino cerebellar degenerations are a complex group of heterogenous neurologic disorders comprising over 50 distinct syndromes. They have in common disturbances of motor co-ordination resulting from progressive degeneration and atrophy of the cerebellum and its connections.[1]

Many of these disorders are genetically transmitted whereas other occur sporadically, seemingly not related to hereditary factors.

In the last three decades, significant advances have been made in the study of SCD's stemming predominantly from the use of biochemical approahces. Although considerable variation can be encountered even within the same family, of pattern of inheritance, constellation of clinical findings and natural course are still considered the most important criteria for the characterization and classification of SCD's[2]. Classification of SCD's is important in epidemiological studies and for the clinician to predict the prognosis, plan therapeutic strategies, and for genetic

counselling. However, current classifications are built on phenotypic variability which has no molecular correlation and thus could be inappropriate and inaccurate. In the future, neurologists will rewrite their classification in this field based on the molecular genetics and the clinical features will fall into place secondarily. The precision of linkage analysis and genotype determination will bring clarity to this area of clinical debate.[3]

Genotypic classification has brought about some clarity regarding the autosomal dominant cerebellar ataxias.

GENOTYPE CLASSIFICATION OF THE AUTOSOMAL DOMINANT CEREBELLAR ATAXIAS

NAME	LOCUS	PHENOTYPE
1. ADCA type I (SCA1)	6p22-p23 with CAG repeats (refs.16,17,30)	Ataxia with ophthalmoparesis pyramidal and extrapyramidal findings.
2. ADCA type I (SCA2)	12q23-24,1 (refs,18,32)	Ataxia with slow saccades and minimal pyramidal and extra-pyramidal findings.
3. SCA3	14q24.3qtr(ref.25) (may be same locus as MJD)	Ataxia with ophthalmoparesis and variable pyramidal and extrapyramidal findings.
4. SCA4	16q24-ter(ref.26)	Ataxia with normal eye movements, sensory axonal neuropathy and pyramidal sings.
5. Machado-Joseph disease	14q24,3-q32 (refs.19-22) with CAG repeats (ref.34)	Ataxia with ophthalmoparesis and variable and variable pyramidal extrapyramidal and amyotrophic features.
6. Dentato-rubro-pallidoluysian atrophy	12p12-ter with CAG repeats(refs.23,24)	Ataxia, choreoathetosis, dyst-onia, seizures, myoclonus, dementia.
7. SCA5	Centromeric region of Chromosome 11 (ref.36).	Ataxia and dysarthria.
8. ADCA type II	Not mapped (refs.27,31)	Ataxia with retinal degen-eration.

SPECIFIC AIMS:

1. To study the clinical profile of patients with SCD, seen in SCTIMST, during 1983 through 1993.

2. To study the frequency of different types of SCD's in this hospital based cohort.

3. To study the pattern of inheritance and intrafamilial clustering.

4. To identify whether there are any clinical features that are clearly distinct from the well known clinical types described.

5. To delineate the natural history of individual disorders.

MATERIALS AND METHODS

Case ascertainment:

All case records of patients registered in the medical records division of SCTIMST from January 1983 to December 1993 will be searched for patients with SCD's. Those with diagnostic indices of Friedreich's ataxia, Olivo ponto cerebellar atrophy, spino cerebellar degeneration, cerebellar degeneration, Wadia syndrome, multisystem atrophies, congenital and intermittent ataxias will be selected for this study. The criteria laid down by Harding (1981) will be used for ascertaining and classifying SCD's into Friedreich's ataxia, early onset cerebellar ataxia and late onset cerebellar ataxia (Table 1 & 2). Adult onset ataxia with slow saccades, intact pursuits and peripheral neuropathy will be grouped under Wadia syndrome. Those cases with features similar to those described by Roger Duvoisin will be placed under OPCA's (Table 3). Multisystem atrophy will be diagnosed in patients with ataxia, pyramidal signs, extra pyramidal signs and autonomic imbalance.

Data Collection

From the records of patients with above mentioned features, the clinical data will be abstracted using a prepared proforma (appended). The family history, symptoms

and signs will be carefully recorded. The disability status at follow up will be obtained by telephone or postal contact with patients or their relatives. Any atypicalities of the clinical features of the disease will be analysed to define any indigenous syndrome.

Data analysis

Major part of the data will be presented in a discriptive manner. Ascertainment of a sizeable number of patients may necessitate construction of univariate and multivariate models to predict the outcome in the form of disease progression and disability status.

REVIEW OF LITERATURE

Locomotor ataxie was in common usage in the early nineteenth century and was employed as a name for tabes dorsalis by Duchenne (1858). Nicolaus Friedreich was the first author to describe patients with a hereditary form of ataxia and he made quite clear the distinction between his cases and those with 'locotmotor ataxie'.[4] Wilson wrote in 1940 "The group of degenerative conditions strung together by the common feature of ataxia is one for which no very suitable classification has yet been devised"- a statement that is as appropriate today as when it was written 50 years ago.[5] The difficulties in nosolgic classification and clinical anatomic correlation stem from several obvious and some inapparent sources. First, many of the clinical and anatomic studies have been incomplete, especially on the anatomic side. Secondly, the established and 'classic' types of disease seem to be infrequent in comparison to aberrant and transitional types. Third, a large part of the neocerebellum has no assigned functions. Thus, an undeveloped cerebellar hemisphere may be discovered at postmortem examination in an individual who has had no symptoms of cerebellar deficit during life. Finally, it is well known that lesions of the brain stem, spinal cord and parietal lobe may cause a cerebellar type of ataxia with no

visible abnormality being noted in the cerebellum itself. Greenfield has reviewed the many early clinical and pathologic reports of heredo familial spino cerebellar diseases. Becker (1971) has identified over 60 different diseases or syndromes from published reports and it is very difficult to ascertain whether all these are caused by seperate mutant genes or if some are variants of the same genetic entities. Holmes (1907) appreciated the difficulties of classification from the clinical view point and firmly stated that 'classification of disease must be based on morbid anatomy and pathogenesis' Greenfield (1954) stated that it is a common place that no differential diagnosis is possible during life between the different forms of cerebellar and spino cerebellar disease. Thus from the clinical view point, it is no exaggaration to state that there are as many classification as there are authors on the subject. In recent years, the use of enzyme assays, other biochemical advances, and the advent of recombinant DNA technology, have made the investigation of the etiology of genetically determined neurodegenerative diseases a realistic proposition. The clinical classification proposed by Harding (1981) is currently the most popular (Table 1).

Friedreich's ataxia

Friedreich's ataxia is the most common of the

hereditary ataxias. This condition was first described by Nicolaus Friedreich in 1863. Harding (1981) after studying 90 families with Friedreich's ataxia, proposed primary and secondary diagnostic criteria for FA.

DIAGNOSTIC CRITERIA FOR FRIEDEICHS ATAXIA (HARDING 1981)[4]

1. Essential criteria for diagnosis

   i. Within 5 years of onset of symptoms

      - Age of onset of symptoms before 25 years
      - Progressive ataxia of limb and gait.
      - Absent knee and ankle jerks
      - Extensor plantar responses
      - Motor nerve conduction velocity > 40 mts. in upper limbs with small or absent sensory action potentials.

   ii. After 5 years since onset of symptoms

      - As in (1) plus dysarthria.

2. Additional criteria not essential for diagnosis present in more than two-thirds of cases.

      - Scoliosis
      - Pyramidal weakness in lower limbs
      - Absent reflexes in upper limbs
      - Distal loss of joint position and vibration sense in lower limbs.
      - Abnormal electrocardiogram.

3. Other features: Present in 50% of cases or less

      - Nystagmus
      - Optic atrophy

- Deafness
- Distal weakness and wasting.
- Pes cavus
- Diabetes

Early onset cerebellar ataxia with retained tendon reflexes: (EOCA)

Harding (1981) described twenty patients with a distinctive clinical syndrome characterised by progressive cerebellar ataxia developing within the first two decades. This is associated with dysarthria, pyramidal signs in the limbs, normal or increased knee jerks and upper limb reflexes and in some instances sensory loss. Inheritance is probably autosomal recessive in the majority if not all, of the cases. The preservation of tendon reflexes distinguishes this disorder from Friedreich's ataxia. Other important differences from Friedreichs ataxia are absence of optic atrophy, cardiomyopathy, diabetes mellitus and severe skeletal deformity. The prognosis was better in the present series than in cases of Friedrichs ataxia, patients remained ambulant on average for more than 10 years longer.[6]

The Olivoponto cerebellar atrophies

The term OPCA was employed descriptively by Dejerine and Thomas (1900). Greenfield (1954) in his classic

monograph on the spino cerebellar degenerations divided the reported cases of OPCA into two major categories, the dominantly inherited Menzel type and a sporadic type illustrated by the cases of Dejerme and Thomas. Kondo, Hirtoa and Katagin (1981) defined OPCA as a cerebellar syndrome of adult onset accompanied by two or more of the following features: dementia, rigidity or dystonia, involunatry movements or tremer and dysautonomia. Table provides the clinical diagnostic features of OPCA.

DIAGNOSTIC CRITERIA FOR OPCA

Essential Features:

- Cerebellar dysfunction and or atrophy
- Extrapyramidal dysfunction

Features usually or often present

- Cortico spinal tract manifestations
- Peripheral neuropathy.
- Cerebellar eye signs

Features of variable occurence

- Positive family history
- Supra nuclear ophthalmoplegia
- Optic nerve atrophy
- Retinal degeneration
- Orthostatic hypotension

- Incontinence
- Impotence
- Antidrosis
- Palatal myoelomus
- Amyotrophy
- Dementia

The development of extra pyramidal features in sporadic cases presenting initially as a pure cerebellar syndrome, suggests OPCA. The CT and MRI in OPCA patients demonstrate atrophy of the basis pontis, mid brain and cerebellum. Harding concurs with Oppen hemiers' (1984) view that the OPCA's should be included under the broader pathological rubric of the multiple system degeneration (progressive autonomic failure, atypical parkinsonism, or cerebellar ataxia).[7]

Machado-Joseph's disease:

In 1976, Rosenberg described a progressive motor system disease beginning in the second and third decades in a portuguese family, the Joseph family of California, consisting at that time of 329 persons in 9 generations. This disorder is now known as Machado Joseph's disease. Jain and Maheswari (1986) described two families of Machado-Joseph's disease with purely Indian ancestry.

The clinical phenotype of MJD includes a specific constellation of features, prominent eyes due to lid retraction, limited range of eye movement, slow saccades, facial and lingual fasiculations without atrophy, dystonia, spasticity and parkinsonian features of tremor at rest, brady kinesia and rigidity. Rosenberg has divided MJD into four types (Table 4)

Clinical types of MJD: (Rosenberg)

Type I: Occurs early in individuals with pyramidal and extra pyramidal signs.

Type II: Intermediate age of onset (20-50 yrs) with cerebellar, pyramidal and extrapyramidal manifestations.

Type III: Later onset (after 50 years) and is associated with a progressive pan cerebellar syndrome and peripheral neuropathy.

Type IV: Refers to dominantly inherited parkinsonism, with ataxia, distal atrophy and sensory less.[8]

Wadia Syndrome:

In 1968 Kini and Venugopal were the first to report about this type of hereditary ataxias with slow saccades. Subsequently in 1971, Wadia N.H and Swami R.K. reported

cases of adult onset cerebellar ataxia with slow saccades. This is considered as a seperate clinical entity under OPCA's.[9]

In view of this report, indigenous forms of the disease should be looked into.

Classification of the Hereditary ataxias and Paraplegias

I. Congenital disorders of unknown etioloty

i. Joubert's syndrome (congenital ataxia with episodic hyperpnea, abnormal eye movements and mental retardation.

ii. Congenital ataxia with mental retardation and spasticity (includes pontoneo cerebellar hypoplasia).

iii. Congenital ataxia ± mental retardation (includes granule cell hypoplasia).

iv. Congenital ataxia with mental retardation and partial aniridia (Gillespie syndrome).

v. Dysequilibrium syndrome.

vi. X-linked recessive ataxia with spasticity and mental retardation (Paine syndrome).

II. Ataxic disorders with known metabolic or other cause.

1. Intermittent ataxic syndrome

i. With hyper ammonaemia

ii. Amino acidurias without hyperammonaemia

iii. Disorders of pyruvate and lactate metabolism

2. Progressive unremitting ataxic syndromes.

3. Metabolic disorders in which ataxia may occur as a minor feature.

4. Disorders characterised by defective DNA repair.
   Ataxia telangiectasia
   Xeroderma pigmentosum
   Cockayne's syndrome

III. Ataxic disorders of unknown etiology

A. Early onset cerebellar ataxia (onset usually before 20 years).

i. Friedreich's ataxia

ii. Early onset cerebellar ataxia with retained tendon reflexes.

iii. With hypogonadism ±deafness and/or dementia.

iv. With myoclonus (Ramsay Hunts syndrome Baltic myoclonus)

v. With pigmentary retinal degeneration ± mental retardation and/or deafness.

vi. With optic atrophy ±mental retardation.

vii. With cataract and mental retardation (Marinesco Sjogren

syndrom).

viii. With childhood onset deafness and mental retardation.

ix. With congential deafness.

x. With extra pyramidal features

xi. X-linked recessive spino cerebellar ataxia.

B. Late onset cerebellar ataxia (onset usually after 20 years).

i. Autosomal dominant cebellar ataxia with optic atrophy/ ophthalmoplegia/dementiaextrapyramidal features/amyotrophy (ADCA type I).

ii. ADCA with pigmentary retinal degeneration± Ophthalmoplegia and/or extrapyramidal features.

iii. Pure ADCA of later onset (over 50 years)

iv. ADCA with myoclonus and deafness

v. ADCA with essential tremor.

vi. Periodic ADCA

RESULTS

The various types of hereditary ataxias encountered shown in Table 1. Out of 83 cases, majority belonged to OPCA (n=16) and LOCA (n=28).

Table 1

TYPES OF HEREDITARY ATAXIAS

Type	No.of patients
1. Friedreich's Ataxia	9
2. OPCA	16
3. LOCA	28
4. Wadia syndrome	8
5. Cerebellar degeneration	8
6. EOCA with retained reflexes	8
7. Machado Joseph's disease	2
8. Others	4
Total	83

Table 2

AGE OF PATIENTS AT PRESENTATION

Type	Age	
	Mean	SD
FOR ENTIRE POPULATION	30.06	15.18
1. Friedreich's Ataxia	19.02	4.80
2. OPCA	33.56	11.38
3. LOCA	32.53	13.67
4. Wadia syndrome	37.50	16.18
5. Cerebellar degeneration	43.20	21.60
6. EOCA with retained reflexes	17.50	6.90
7. Machado Joseph's disease	24.50	2.12
8. Others	9.75	4.03

Table 3

AGE AT ONSET

Type	Age	
	Mean	SD
FOR ENTIRE POPULATION	23.77	15.92
1. Friedreich's Ataxia	12.33	6.24
2. OPCA	27.60	11.79
3. LOCA	27.14	14.66
4. Wadia syndrome	26.62	15.47
5. Cerebellar degeneration	38.50	23.36
6. EOCA with retained reflexes	10.87	7.56
7. Machado Joseph's disease	20.50	2.12
8. Others	2.75	3.50

Table 4

DURATION OF SYMPTOMS

Type	Age	
	Mean	SD
FOR ENTIRE POPULATION	64.02	56.03
1. Friedreich's Ataxia	82.66	81.04
2. OPCA	71.25	69.62
3. LOCA	52.28	45.75
4. Wadia syndrome	55.50	42.99
5. Cerebellar degeneration	56.75	49.84
6. EOCA with retained reflexes	82.50	66.48
7. Machado Joseph's disease	48.00	-
8. Others	78.00	22.97

Table 5

ONSET SYMPTOMS

	Frequency	Percentage
Gait ataxia	83	100
Generalised clumsiness	70	85.5
Delayed milestones	9	12
Tendency to trip	37	44.6
Scoliosis	5	8.4
Tremor	17	20.5
Cardiac symptoms	0	0
Ataxia		
Congenital	6	7.2
Progressive	77	92.8
Palpitation	0	0
Dyspnea on exertion	1	1.2
Angina	0	0
Cardiac failure	0	0
Autonomic Disturbance	2	2.4
Extrapyramidal features		
Tremor	16	19.3
Rigidity	1	1.2
Chorea	1	1.2
Myoclonus	1	1.2

Onset symptoms

The symptoms which indicated the onset of the disease, were analysed. The ataxia was congenital in 6 cases, and in the rest (77), ataxia onset was later in life and progressive.

Gait ataxia was present at onset in all the cases, making it the commonest onset symptom. Generalised clumsiness of motor activities was reported in 70 (85.5%) of the cases. Frequent tendency to trip was another symptom which was present at onset in 37 (44.6%) cases. Scoliosis, reported either by the patient or relatives, was noted at onset only in 5 cases (8.4%).

Delay in attainment of motor milestones was noted in 9 cases, out of which, 6 patients had ataxia from infancy onwards.

Extrapyramidal features as an onset symptom was rare, except for 16 cases (19.3%) who reported tremulousness on action.

None of the patients had significant cardiac symptoms at onset, except for 1 patient who experienced mild dyspnea on exertion and 2 others who had autonomic disturbance in the form of symptomatic orthostatic hypotension.

Table 6

CLINICAL FEATURES

	FA n=9	OPCA n=16	LOCA n=28	WADIA n=8	EOCA n=8
Cataract	-	-	-	-	2
Pes cavus					
Mild	2	4	6	1	4
Moderate	2	1	3	1	-
Total	4	5	9	2	4
Scoliosis	6	5	9	2	4
Icthyosis	-	-	-	-	1
Telangiectasia	-	-	-	-	-
Dementia					
Mild	-	2	1	-	-
Moderate	-	2	1	-	-
Severe	-	2	-	-	-
Dysarthria	7	15	20	8	8
Titubation	-	6	3	2	4
Nystagmus	3	6	11	2	7
Slow eye movements	-	9	4	8	2
Broken pursuit	-	5	3	4	1
Pigmentary retinal degeneration	-	-	1	-	-
Optic atrophy	1	1	2	-	1
Deafness	-	3	7	-	-
Bulbar palsy	-	1	-	-	-
Finger nose ataxia	7	7	20	2	5

	FA n=9	OPCA n=16	LOCA n=28	WADIA n=8	EOCA n=8
Dysdiadochkinesis	7	9	21	3	5
Pyramidal weakness	-	3	5	2	1
Distal wasting					
Upper limb	-	-	1	1	1
Lower limb	1	-	1	1	1
Muscle tone					
Hypertonia	-	10	8	2	2
Hypotomia	6	2	9	4	2
Heel Shin ataxia	9	16	27	8	8
Giat ataxia	9	15	27	8	7
DTR					
Ankle jerk alone absent	2	2	4	1	-
AJ&KJ	1	-	-	-	-
All DTR absent	6	1	3	1	-
All DTR present	-	3	5	4	5
Hyper reflexia	-	10	16	2	3
Plantar					
Flexor	2	10	17	5	5
Extensor	7	6	11	3	3

	FA n=9	OPCA n=16	LOCA n=28	WADIA n=8	EOCA n=8
Vibration sense					
Lost in LL	4	1	10	4	0
Lost in UL & LL	4	2	2	0	1
Normal	1	13	16	4	7
Joint Position Sense					
Lost in LL	5	1	10	3	0
Lost in UL & LL	2	1	2	0	1
Normal	2	14	16	5	7
Light touch					
Lost in LL	0	1	3	1	0
Lost in UL & LL	0	0	0	0	0
Normal	9	15	25	7	8
Pain					
Lost in LL	0	0	0	1	0
Lost in UL & LL	0	1	0	0	0
Normal	9	15	28	7	8

FAMILY HISTORY

	FA n=9	OPCA n=16	LOCA n=28	WADIA n=8	EOCA n=8
SCD	0	2	2	3	3
Pescavus	0	1	0	0	0
Scoliosis	0	1	1	0	0
Family members					
1st Degree	0	1	3	2	3
2nd Degree	0	0	0	1	0
3rd Degree	0	0	0	0	0
Inheritance					
Sporadic	9	12	25	5	5
Aut.recessive	0	1	2	2	3
Aut.dominant	0	2	1	1	0
X-linked recessive	0	0	0	0	0

INVESTIGATIONS

	FA n=9	OPCA n=16	LOCA n=28	WADIA n=8	EOCA n=8
NCV					
Normal	2	12	15	2	3
Demyelination	4	1	2	4	2
Axonopathy	0	0	0	0	0
Both	1	1	2	0	0
EMG					
Normal	3	3	11	2	2
Denervation	1	6	5	2	4
CT					
Normal	3	3	17	1	2
Cerebellar hemi-pherical atrophy	0	0	1	1	3
Vermian atrophy	0	0	1	0	0
Cerebellum +Brain stem atrophy	0	6	1	3	1
Cerebellum +Brain stem atrophy	0	6	1	3	1

	FA n=9	OPCA n=16	LOCA n=28	WADIA n=8	EOCA n=8
MRI					
Normal	2	0	4	1	2
Cerebellar hemispherical atrophy	0	0	1	0	0
Vermian atrophy	0	0	0	0	0
Cerebellum+Brain stem atrophy	0	3	1	2	1
Chest X-ray cardiomegaly	0	1	1	0	0
ECG Hypertrophy	1	1	1	0	0
ECHO					
Increased LV thickness	2	1	1	0	0
Diabetes	0	1	2	0	0

STATUS AT LAST FOLLOW UP

	FA n=9	OPCA n=16	LOCA n=28	WADIA n=8	EOCA n=8	ATAXIA TELANG n=4
Independant and employed	1	1	2	1	0	-
Independant and not employed	4	5	10	2	2	-
Partially dependant for ADL	2	3	5	1	4	-
Totally dependant for ADL	0	0	3	0	1	-

Friedreich's ataxia

There were 9 cases of Friedreich's ataxia. The mean age at onset was 19.02 years with a standard deviation (19.02±4.8). The mean age at onset was (12.33±6.24 years), and the mean duration of symptoms was 82.66 months.

Analysis of the clinical features revealed, Per cavus in 4 cases (2 mild, 2 moderate), varying degrees of scoliosis was noted in 6 cases. None of the patients showed evidence of cognitive decline. Dysarthria was prominent in 7 cases. Ocular saccadic or pursuit movement abnormalities were not found. One patient had features of optic atrophy with decline in visual acuity.

Cerebellar involvement, as evidenced by gait ataxia and heel shin ataxia was seen in all 9 cases, however finger nose ataxia and dysdiadochokinesis was noted only in 7 cases (77.8%).

Muscle wasting was not seen, except in one case in which mild distal wasting was noted in the lower limbs. Ankle jerk alone was absent in one case whereas all DTR's were absent in 6 cases. 7 patients had pyramidal involvement are evidenced by upgoing plantar response. The sensory impairment was predominantly of vibration and joint position sense, which was impaired in lower limbs alone, in 5

patients, and both upper and lower limbs, in 4 patients.

All the 9 cases were sporadic in occurence.

On investigation, NCV showed demyelination in 4 patients and both axonopathic and demyelinating features in one patient. Radiological evaluation including CT and MRI were done in 3 patients which were normal. ECG and Echocardiography showed evidence of LV hypertrophy in 2 patients.

LOCA

There were 28 patients belonging to this group. The mean age was 32.53 years with a standard deviation of 13.67. The mean age at onset was 27.14 $\pm$ 4.66. The mean duration of symptoms was 52.28 months.

Clinical features

Mild to moderate per cavus and scoliosis were noted in 9 patients. Mild to moderate cognitive impairment was seen in 2 patients Dysarthria was evident in 20 patients, prominent titubation in 3 patients. Nystagmus was seen in 11 patients. Eye movement abnormalities in the form of slow eye movements and pursuit abnormalities were seen in 8 patients. There was evidence of pigmentary retinal degeneration in one patient. Optic atrophy was seen in 2 patients. Significant hearing impairment was present in 7

patients. Upper limb inco-ordination evidenced by finger nose ataxia and dysdiadochokinesia was seen in 21 patients. Lower limb inco-ordination in the form of heel shin and gait ataxia was present in all patients.

Out of 16 patients with hyperreflexia, 11 had extensor plantar response. 8 had hypertonia and only 5 had weakness due to pyramidal involvement.

Distal limb wasting was noted in 2 patients.

Ankle jerk was absent in 4 patients and generalised areflexia in 3 patients. Sensory involvement was predominantly of joint position sense and vibration, which was lost in 16 patients, whereas touch and pain sensation were impaired only in a minority (3 patients).

The inheritance was sporadic in 25 patients and in 2 patients (autosomal recessive) and one patient (autosomal dominant). 1st degree relative was affected in 3 patients, 2 had spinocerebellar degeneration and 1, significant scoliosis.

Nerve conduction studies were normal in majority. Evidence for demyelination and axonopathy were seen in 2 patients each. CT scan was normal in 17 patients and one patient each showed, cerebellar hemispherical, vermian and brain stem atrophy. MRI also was normal in 4 patients wereas

one patient had cerebellar hemispherical atrophy and one patient had in addition, brain stem atrophy also. ECG and Echocardiography wise, LV hypertrophy was seen in one patient.

OPCA

16 patients could be diagnosed as having features of Olivo ponto cerebellar degeneration.

The mean age of the patients was 33.56 yrs with a standard deviation of 11.38 yrs. The mean age at onset was 27.6 yrs $\pm$ 11.79 yrs. The mean duration of symptoms at the time of presentation was 71.25 months with a standard deviation of 69.62 months.

Clinical Features

10 patients had significant per cavus and 5 had scoliosis. Cognitive decline was present in 6 patients. Dysarthria was evident in 15 patints. Only 6 patients had prominent titubation. Nystagmus was seen in 6 patients. Eye movement abnormalities of pursuit and saccades were seen in 14 patients. One patient had features of optic atrophy, and 3 patients had deafness. One patient had evidence of bulbar palsy. Upper limb in co-ordination shown by finger nose ataxia and dysdiadochokinesia was seen in 9 patients. Out of 10 patients with hyperreflexia, 10 had hypertonia and

only 3 had weakness due to pyramidal involvement. Lower limb in co-ordination was evident in all 16 patients. Majority of the patients had hyperreflexia (10 patients). Ankle jerk alone was absent in 2 patients and total areflexia was seen only in one patinet. Eventhough hyperreflexia was seen in 10 patients an upgoing plantar response was seen only in 6 patients. Only 4 patients had impairment of joint position and vibration sense, whereas touch and pain was impaired only in one patient.

The inheritance was sporadic in 12 patients autosomal recessive in one and dominant in 2 patients. 2 patients had 1st degree relatives with features of spino cerebellar degeneration and one had pescavus and scoliosis.

NCV showed evidence of demyelination in only one patient. CT showed evidence of cerebellar hemisperical and brain stem atrophy in 6 patients. MRI was done in 9 patients and 3 showed features of cerebellar hemispherical and brainstem atrophy. ECG and echocardiography showed LV hypertrophy in one patient.

Wadia Syndrome

These were 8 patients who had features of Wadia syndrome. The mean age was 37.50 years 2ith a standard deviation of 16.18 years. The age at onset was mean (26.62

yrs) with a standard deviation of 15.47 yrs and the mean duration of symptoms was 55.5 months.

Clinical features

Pes cavus was present in 2 patients and 2 patients had scoliosis also. Dysarthria was present in all 8 patients Titubation was present in 2 patients, and 2 patients had mystagmus. Eye movement abnormalities in the form of slow saccades were seen in all 8 patients, whereas a broken pursuit movement was seen in only 4 patients. Pigmentary-retinal degeneration, optic atrophy and deafness were conspicous by their absence.

Upper limb finger nose-ataxia and dysdiadochokinesia was seen in 3 patients. Hyperreflexia hypertonia and mild pyramidal weakness were seen in 2 patients and plantar response was upgoing in 3 patients.

Sensory impairment was predominantly of vibration and joint position sense, which was noted in 4 patients.

The inheritance was autosomal recessive in 2 patients and one autosomal dominant. 5 patients, were sporadic in occurence. 3 patients had family members affected with spino cerebellar degeneration and in 2 patients, 1st degree relative was affected and in one patient 2nd degree relative was affected.

NCV showed features of demyelination in 4 patients. CT was normal in one patient, one showed cerebellar hemispherical atrophy and 3 showed cerebellar plus brain stem atrophy. MRI was normal in one patient, showed cerebellar and brain stem atrophy in 2 patients. None of the patients had evidence of cardiac involvement.

EOCA - Early onset cerebellar ataxia with retained reflexes.

There were 8 cases with onset in the first and second decade but had retained reflexes. The mean age was 17.5 yrs with a standard deviation of 6.9 years. The mean age at onset was 10.8 years with a standard deviation of 7.6 years. The duration of symptoms at the time of presentation was 82.5 months (mean) standard deviation (66.5).

Cataract was detected in 2 patients. 4 patients had features of pescavus and significant scoliosis. One patient had prominent icthyosis. None of the patients had cognitive decline. All the 8 patients had dysarthia and titubation was noted in 4 patients. 7 patients had mystagmus. Eye movement abnormalities were not observed. One patient had features of optic atrophy. Upper limb cerebellar signs, evidenced by finger nose ataxia and dysdiadochokinesis was noted in 5 patients. Heel shin and gait ataxia were noted

in all 8 patients. Mild degree of distal wasting was noted in one patient.

Hypertonia due to pyramidal involvement was noted in 2 patients. All patients had retained deep dendon reflexes and 3 had hyperreflexia, and the plantar response was extensor in these 3 patients. All the patients had normal sensations, except one patient who had impairment of vibration and joint position sense in both upper and lower limbs.

Inheritance was autosomal successive in 3 patients, and all 3 had a first degree relative affected with similar disease. Rest 5 patients were sporadic. NCV showed evidence of demyelination in 2 patients.

CT showed cerebellar hemispherical atrophy in 3 patients, and 1 had features of both cerebellum and brain stem atrophy. MRI was done in 3 patients, out of which 2 were normal and one showed evidence of cerebellum and brain stem atrophy.

Ataxia telangiectasia

There were 4 cases of ataxia telangiectasia. (Patient No.29) had symptoms from 1st year of age and had prominent conjunctival telangiectasias. Her 8 years old sister had similar problems and died at the age of 8 years due to pulmonary infection.

Patient No.30 also had symptoms from 1st year of age. Her younger sister who is 4 years has mild ataxia of gait and prominent ocular telangiectasias.

Machado-Joseph Disease

Two patients with clinical features suggestive of Machado Joseph disease were noted. Both had in addition to cerebellar and extrapyramidal features, prominent eyes, facial and lingual fasiculation. Pedigree analysis showed autosomal dominant inheritance, and these was no evidence to suggest a Portugese descent.

Patient No.45: his father and two brothers has similar illness, all of them were examined by the author.

(Patient No.:85) his father has similar symptoms of 10 years duration, and one paternal aunt also has symptoms, both needs assistance.

Marinesco-Sjogren syndrome

Two brothers, born of consanguinous parentage, had cerebellar signs, eye movement abnormalities and cataracts. Other family members were normal.

DISCUSSION

This study being a descriptive retrospective study, done in a referral institute, no conclusions regarding prevalence can be made. The present study which includes 83 patients seen in SCTIMST over a 10 year period, shows a variety of spino cerebellar degenerations.

Of particular interest are:

Majority of cases in different sub-groups appears to be sporadic in origin.

Out of the 9 cases of Friederich's ataxia, all 9 were sporadic. These were no family members affected with a similar illness or having markers of the disease. In comparison with literature, Friederichs ataxia is usually an-autosomal recessive disease.

Harding (1981a) found 90 families with FA among 200 families with spinocerebellar degenerations.

In the present study only 9 cases could be identified from 83 cases and none showed an autosomal recessive inheritence pattern.

EOCA with retained reflexes, with onset in the first two decades comprised of 8 cases, forms a distinct subset. Harding (1981b) described 20 patients with progressive cerebellar ataxia developing within the first two decades associated with dysarthria, pyramidal

signs in the limbs, normal or increased tendon reflexes and autosomal recessive inheritance, in the majority. In the present study, out of 8 patients 5 were sporadic in occurence and 3 showed autosomal recessive inheritance. All the 3 patients had a 1st degree relative affected with a similar spino cerebellar degeneration. However, special mention should be made to reports of Friedreich's ataxia with retained tendon reflexes (Neurology 1996 46 118-121), where genetic linkage analysis in the family, showed tight linkage to the FRDA locus on chromosome 9.

EOCA with x-linked inheritance, although described (Spira et al, 1979) was not encounterd in the present study.

(Harding, 1982) described patients with autosomal dominant LOCA and pigmentary retinal degeneration as a clinically and genetically distinct entity, pigmentary retinopathy present in all affected members in a given family. In the present study, these were 28 cases of LOCA, out of which 2 showed autosomal recessive inheritance, 1 showed autosomal dominant, and the rest 25 were sporadic in occurence. One patient with LOCA and pigmentary retinal degeneration was encountered, however, there was no evidence of pigmentary

retinopathy in the family members.

A new form of Heredo-familiar spinocerebellar degeneration with slow eye movements were described in 9 families by Wadia and Swami. In this study 8 cases with similar clinical features were found. All had typical eye movement abnormalities. However, unlike the cases described by Wadia, where are autosomal dominant inheritance was noted, in this study, out of the 8 cases, 3 had features of autosomal recessive inheritance, all 3 had a first degree relative with similar clinical features. The rest 5 cases appeared to be sporadic in occurence. CT was norm,al in 1 patient, in 3 features of cerebellum and brain stem atrophy was found. MRI was normal in 1 patient, and 2 had features of cerebellum and brain stem atropy.

4 cases of ataxia telangiectasia were found, inheritance was autosomal recessive and one child expired at the age of 8 years due to pulmonary infection.

Of ineresting, were two cases with clinical features suggestive of Machado Joseph disease. Both the patients, in addition to prominent cerebellar and extrapyramidal features, had prominent eyes, facial as well as lingual fasciculations. The family members were examined personally by the author.

Both the patient's ancestors were from Kerala, and no evidence to suggest a portugese descent could be obtained. Both has family members affected, suggesting autosomal dominant inheritance.

Two brothers with features of Marinesco Sjogren syndrome were also noted.

Apart from these vasiations from the reported cases in literature, no definite phenotypically distinct entity which may be considered indigenous, was encountered in this study.

Only 4 cases of autosomal dominant ataxia were noted, out of which two were grouped under OPCA's. 1 as LOCA and 1 under Wadia syndrome.

CONCLUSION

1. This study revealed a heterogenous group of clinical entities. Being a referral hospital based, retrospective study no conclusion regarding prevalence can be made. Majority of the patients belonged the group of LOCA and OPCA's.

2. No clinically distinct entity which may be considered indigenous was encountered.

3. As noted by other reports, we also encountered cases with features of Machado Joseph disease without a portugese descent.

4. Autosomal dominant ataxias were a minority. Most of the cases were sporadic in occurence.

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APPENDIX-1

Card No. 1

Spino Cerebellar Degenerations: A descriptive analysis of cases seen in STIMST over a 10 year period (1984-1994).

Investigators : Dr.Gigy, Dr.C.Sarada
Dr.K.Radhakrishnan

Name :

Address :

HISTORICAL DETAILS

Column	Code	Item
1-7	- - - - - - -	SCTIMST Number
8-13	- - - - - -	Date of SCTIMST registration (DD/MM/YY)
14-15	- -	Age at registration
16	-	Gender 1=Male; 2= Female
17	-	Income group 1= A; 2=B1 3 = B; 4=C 5 = D
18-19	- -	Age at onset of symptoms in years
20-25	- - - - - -	Delay between onset and Diagnosis (YY/MM/DD)
26	-	Initial Diagnosis (as entered in the records). 1 = Friedreich's Ataxia 2 = OPCA

3 = Spino Cerebellar Degeneration

4 = Wadia Syndrome

5 = Multi System degeneration

6 = Cerebellar Degeneration

7 = EOCA

8 = Others

Onset symptoms

27 - Gaint ataxia

28 - Generalised clumsiness

29 - Delayed milestones

30 - Tendency to trip

31 - Scoliosis

32 - Tremor

33 - Cardiac symptoms

34 - Ataxia

1 = Congenital

2 = Static

3 = Intermittent

4 = Progressive

Cardiac Symptoms

35 - Palpitation

36 - Dyspnea on exertion

37 - Angina

38 - Cardiac failure

39 - Autonomic Disturbance

Symptomatic hypotension

1 = Yes 2 = No

Extrapyramidal features

40 - Tremor

41 - Rigidity 1 = Yes

42 - Chorea 2 = No

43 - Myoclonus 9 = Uncertain

Course: Time interval between the onset symptom and individual major symptoms

1 = 0 - 5 years 4 = 15 - 20 years 7 = 30 - 35 years

2 = 5 -10 years 5 = 20 - 25 years 8 = 35 - 40 years

3 =10 -15 years 6 = 25 - 30 years 9 = details not available

GENERAL EXAMINATION

44 - Cataract 1 = Yes 2 = No

45 - Course (See above)

46 - Pes Cavus 1 = Mild 2 = Moderate

3 = Severe 4 = No

47 - Course (See above)

48 - Scoliosis 1 = Mild

2 = Moderate 3 = Severe 4 = No

49 - Course (See above)

50 - Finger contractures

1 = Yes 2 = No

51 - Course

52 - Knee contractures

1 = Yes 2 = No

53 - Course

54 - lothyosis 1 = Yes 2 = No

55 - Course

Cardiac

56 - Edema 1 = Yes 2 = No

57 - Course

58 - Murmur 1 = Yes 2 = No

59 - Cardiac Failure

1 = Yes 2 = No

60 - Course (See above)

61 - Telangiectasia

1 = Yes 2 = No

62 - Dementia 1 = Mild 2 = Moderate

3 = Severe 4 = No

63 - Course (See above)

64 - Dysarthria 1 = Mild

2 = Moderate 3 = Severe 4 = No

65 - Course (See above)

66 - Titubatory tremor of head

1 = Yes 2 = No

67 - Course (See above)

68 - Nystagmus 1= Yes 2 = No

69 - Slow eye movement

1 = Yes 2 = No

70 - Broken-up pursuit

1 = Yes 2 = No

71 - Pigmentary retinal degeneration

1 = Yes 2 = No

72 - Optic atrophy 1= Disc pallor alone

2 = mild decrease in visual acuity

3 = Severe decrease in visual acuity

4 = Normal

73 - Course (See above)

74 - Ophthalmoplegia 1 = Yes 2 = No

75 - Course (see above)

76 - Facial palsy 1 = Yes 2 = No

77 - Course (See above)

78 - Deafness 1=mild 2 = moerate

3 = Severe 4 = Norma;

79. - Course (See above)

80 - Bulbar palsy 1 = Yes 2 = No

81 - Course (See above)

82 - Finger nose ataxia 1 = mil

2 = severe 3 = Normal

84 - Dysdiadochokinesia 1 = Mild

2 = Severe 3 = Normal

85 - Course (See above)

86 - Pyramidal weakness

1 = Upper limb alone

2 = Lower limb alone

3 = Both upper and lower limb

4 = No weakness

87 - Course (see above)

88 - Distal wasting

1 - Upper limb alone

2 - Lower limb alone

3 - Both upper and lower limb

4 - No wasting

89 - Course (see above)

90 - Muscle tone 1 = Increased

2 = Decreased 3 = Normal

91 - Heel Shin ataxia 1 = Mild

2 = Severe 3 = Normal

92 - Giat ataxia 1 = Mild

2 = Severe 3 = Not testable

4 = No ataxia

93 - Course (see above)

Card No.2

Hospital No.....

1. - DTR

1 = Ankle jerk alone absent

2 = Ankle and knee jerks absent

3 = All reflexed absent

4 = All DTR present

5 = Hyper reflexia

2 - Course (See above)

3 - Plantar response 1 = Flexor

2 = Extensor 3 = No response

4 - Course (See above)

5 - Vibration sense

1 = Lost in lower limbs alone

2 = Lost in both upper and lower limbs

3 = Normal

6 - Course (see above)

7 - Joint position sense

1 = Lost in lower limbs alone

2 = Lost in both upper and lower limbs

3 = Normal

8 - Course (See above)

9 - Light touch

1 - Lost in lower limbs alone

2 - Lost in both upper and lower limbs

3 - Normal

10 - Course (See above)

11 - pain

1 = Lost in lower limbs alone

2 = Lost in both upper and lower limbs

3 = Normal

12 - Course (See above)

13 - Age at which chair bound

14 - Course (Age chair bound-Age at onset)

FAMILY HISTORY
Involvement in the Family Member

15 - Spino cerebellar degeneration

16 - Pes Cavus

17 - Scoliosis

18 - Diabetes

19 - Optic atrophy

20 - Cardiac signs & Symptoms

21 - Icthyosis

22 - Others

1 = Yes

2 = No

9 = Uncertain

Family Member Affected

23 - 1 = 1st Degree 2 = 2nd Degree

3 = 3rd Degree

Type of Inheritance

24 - 1 = Sporadic

2 = Autosomal recessive

3 = Autosomal dominant

4 = Sex linked recessive

5 = Uncertain

Investigations

25 - NCV

1 = Normal 2 - Demyelination

3 = Axonopathay 4=Both 2 and 3

26 - EMG

1 = Normal 2 = Denervation

3 = Myopathic

27 - CT Scan 1 = Normal

2 = Cerebellar hemispherical atrophy

3 = Cerebellar Vermian atrophy

4 = Cerebellum + Brain stem atrophy

5 = Diffuse atrophy

6 = Others

28 - MRI Scan (see above No. 27)

29 - Chest X-ray - Cardiomegaqly

1 = Yes 2 = No

30 ECG 1 = Normal

2 = Chamber hypertrophy

3 = Conduction defects

31 - Echo 1 = Normal

2 = Increased LV dimensions

3 = Increased LV thickness

32 - Diabetes 1 = Yes 2 = No

33 - Drugs used 1 = Oral 2 = Insulin

34-39 - - - - - - Date of last contact (DD/MM/YY)

40-43 - - - - Duration of follow up (YY/MM)

- Status at last follow up

1 = Independant and emplyed

2 = Independant and not employed

3 = Partially dependant for ADL

4 = Totally dependant for ADL

5 = Dead 6 = Details not known

45 - Final diagnosis

1 = Friedreich's Ataxia

2 = OPCA

3 = Spino Syndrome (LOCA)

4 = Wadia Syndrome

5 = Multi System degeneration

6 = Cerebellar degeneration

7 = Early onset cerebellar ataxia with retained reflexes

8 = Machado Joseph's disease

9 = Others