PROJECT REPORT

TITLE

OLIVOPONTOCEREBELLAR DEGENERATION (WADIA TYPE) -A CLINICAL, ELECTROPHYSIOLOGICAL AND RADIOLOGICAL STUDY

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Note:— (i) In the case compilation of procedures done, the contents and the subsequent pages should be made into different sections (a) Procedures done (b) Procedures assisted (c) Procedures participated (d) Procedures attended / participated etc. in Other Centres. Each section should be preceded by a leaf carrying the name of the section that is succeeding.

(ii) The Contents page will carry information as per model given under

PROCEDURES DONE

Closed Mitral valvotomy ---------- 124 (say)

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.....

PROCEDURES ASSISTED

Closed Mitral valvotomy ---------- 100 (say)

.....

(iii) In the subsequent pages details of each procedure done/assisted should be given in the format given below :—

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Date	Name of the patient	Age	Sex	Patient No.

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INTRODUCTION

The term Olivopontocerebellar atrophy (OPCA) was employed descriptively by Dejerine and Thomas (1900). It is a cerebellar syndrome of adult onset accompanied by two or more of the following features: dementia, rigidity or dystonia, involuntary movements or tremor and dysautonomia. (Kondo, Hirota and Katagine 1981).

Several methods of classification of this disease group have been suggested. In 1900, Dejerine and Thomas separated their isolated case from the familial type described by Menzel. Greenfield (1954) divided the OPCA's into a heriditary type (Type A, Menzel), and a sporadic group, exemplified by Dejerine and Thomas' case. Pratt (1967) in his review of heriditary disease of nervous system divided the OPCAs into two groups: those with spinal cord involvement, and those with absence of spinal cord involvement. Konigsmark and Weiner (1970) have classified OPCAs based on heriditary, clinical and pathological data into five main types. These include dominant OPCA I; recessive OPCA II; OPCA with retinal degeneration-III; the Schut-Haymaker type-IV; and OPCA with dementia and extrapyramidal signs -V. Many transitional and mixed forms exist, in which involvement of the extra-pyramidal system and autonomic failure are present in addition to the

cerebellar disorder; these forms have been labelled multisystem atrophy (MSA).

Many cases of heredo-familial spinocerebellar disorders have been reported from India. No epidemiological survey of this group of disorders has been made, but hospital based data from different parts of India is available. (Jolly et al 1966; Sumra and Virmani 1972; Wadia and Amin 1976; Wadia and Desai 1980; Jagannathan 1985; Bansal et al 1988). There is a greater prevalence in India of a variety of OPCA distinguished by autosomal dominant inheritance, slow eye movements and peripheral neuropathy. Wadia and Swami (1971) from India, first drew attention to this variety of OPCA. They had seen 26 families since 1962. These patients came from three dominant communities of India (Hindus, Muslims and Christians). Subsequent to the publication of the paper by Wadia and Swami (1971) reports from various parts of the world usually of single families, often comparing them with those of Wadia and Swami (1971) have appeared. In some of these families, autopsies have been performed and olivoponto-cerebellar degeneration found. Kini and Venugopal (1967) were the first to report similar case of a father and daughter from Calicut, South India. Wadia maintains that this is the most common clinically identifiable heriditary ataxia in India, including Friedriech's ataxia.

The symptoms and signs of these diseases are attributed to the degenerative lesions in the cerebellum and its connections to the brainstem, posterior columns and corticospinal tracts. The clinical diagnostic criteria for OPCA are as follows:

Essential features:

- Cerebral dysfunction and or atrophy
- Extrapyramidal dysfunction

Features usually or often present

- Corticospinal tract manifestations
- Peripheral neuropathy
- Cerebellar eye signs

Features of variable occurrence:

- Postive family history
- Supranuclear ophthalmoplegia
- Optic nerve atrophy
- Retinal degeneration
- Orthostatic hypotension
- Incontinence
- Impotence
- Anhidrosis
- Palatal mycolonus
- Amyotrophy
- Dementia

From pathological studies, OPCAs are characterised by atrophy of the pons, middle cerebellar peduncles and cerebellar hemispheres. Since the clinical features of several cerebellar degenerative and non-degenerative diseases overlap those of OPCA, and since a unifying biochemical marker is lacking, positive neuroimaging findings have become essential in diagnosing OPCA. The diagnosis can be made when there is a combination of the appropriate clinical picture and the appropriate brain-stem and cerebellar atrophy demonstrated by means of computerised tomography or MR imaging. However, studies of the functional state of brain stem, visual pathway and peripheral nerves using evoked potentials (VEP, BAER), blink reflex and nerve conduction studies are not well known and are scanty.

OPCA-Wadia type:

In this specific variety of autosomal dominant cerebellar ataxia with slow sacades and peripheral neuropathy, absence of nystagmus and abnormal ocular movement of slow saccades are unique features.

Peculiar to the Wadia type of OPCA is the additional pontine pathology of loss of neurones in the parapontine reticular formation (PPRF). This explains the saccadic slowing, and the relative sparing of the flocculus of

cerebellum correlates with the intact smooth pursuit eye movements (Plaitakis 1987, Wadia 1984). The former findings, for the first time, indicated the location of an anatomical substrate in humans for the burst and pause neurones.However, electrophysiological correlates of brain stem involvement have not been well studied in this type of OPCA. Abnormalities of brain stem auditory evoked responses (BAER) have been detected in patients with a pure cerebellar syndrome (Chopra 1992) and follow up studies in such patients may help us to reclassify them as OPCA especially when the clinical picture is dominated equally by lesser signs as cerebellar ataxia and slow saccades.

While CT and MRI of all patients with OPCA share common features, some distinction can be made of Wadia's variety. Also, it can differentiate the disease from other acquired and familial cerebellar atrophies. The earliest morphological changes are seen in the anterior lobe of the cerebellum and tegmentum of the pons. As the disease progresses, the fourth ventricle becomes ballooned and the brain stem appears like a 'molar tooth' (Huang and Plaitakis 1984; Plaitakis 1987) because of the associated atrophy of the brachia pontis (middle cerebellar peduncles) and superior cerebellar hemispheres. The atrophy of the cerebellar hemispheres that soon follows affects both the

cortical and subcortical regions (pan cerebellar). But, the flocculus, seen more clearly with MRI, is much better preserved. A further step towards specificity is the demonstration of abnormal signal intensity in structures that are known to degenerate with this disease. Previous reports have not mentioned abnormal signal intensities in patients with OPCA. Also, signal intensity changes in the supratentorial compartment, especially in the basal ganglia, help us to differentiate cases of multisystem atrophy from OPCA..pa

AIMS OF THE STUDY

1. To study the demographic, clinical, radiological and electrophysiological profile of OPCA-Wadia type.

2. To study the pattern of inheritance, and whether there is any intrafamilial or regional clustering.

3. To identify any electrophysiological or radiological features which is distinct from established reports of other types of olivopontocerebellar degenerations, multisystem atrophy and other familial or acquired cerebellar atrophies.

REVIEW OF LITERATURE

It was Wadia and Swami (1971) who for the first time drew attention to a variety of familial, essentially autosomal dominant, cerebellar ataxia. It is differentiated as a specific subtype by its constant association with slow saccadic eyemovements. Later, Wadia alone and with other colleagues reported: (a) Oculographic confirmation of the saccade, progressively decreasing in velocity with advancing disease (Kulkarni and Wadia 1975); (b) evidence of peripheral neuropathy from electromyographic and sural nerve biopsy examination (Wadia 1977; Wadia and Desai 1980); (c) Olivo-pontocerebellar and spinal cord degeneration in autopsies of 4 patients (Wadia 1977, 1984, 1991); and (d) the more specific degeneration of the neurones in the paramedian pontine reticular formation (PPRF) and the relative preservation of the flocculus as opposed to those of the cerebellar hemispheres, to explain the slow saccade and the relatively normal pursuit movement respectively.

Reference to earlier literature shows that Mass and Scherer (1933) in Germany and Sigwald et al in France (1963) had reported similar autopsy proven cases, though no type specificity was demonstrated. No family member was similary affected. They considered their case as rare and compared it to the patients of Menzel. From France, Garcin and Man

(1958), from Italy, Gentili and Zambonelli, (1960) and from South India Kini and Venugopal (1967), have reported similar cases, but were not confirmed by ocluometric recordings or autopsy.

Subsequent to publication from Wadia and Swami (1971), a number of mostly single families have been reported from all over the world; some with autopsy confirmation. (Starkman et al 1972; Singh et al 1973; Wadia et al 1976; Plaitakis et al 1987).

Analysis of clinical material (Wadia 1971-1991):

The clinical features described are of 30 patients from 9 families. The disease affected 19 males or 11 females. Age of onset was 22 years, oldest being 30 yrs and youngest 20 yrs. The disease was strongly familial, affecting several generation in 6 families, while the other 3 were similar sporadic cases. There was no parental consanguinity in any family.

Neurological manifestations:

1. Cerebellar disorder: The disease began in all patients as gait ataxia progressing over many years to affect upper limbs and speech. Trunk ataxia was very severe. Postural titubation and intention tremors were seen in the more severe cases. Nystagmus was not detected.

2. Ocular disorder:

All 16 patients had abnormal ocular movements. Examinaticn revealed initially a slowing of the horizontal sacaades. However, there was a compensatory head-jerk to keep the eyes on the target, and is often an early sign. Eventually, the eyes move more slowly, the vertical movement become affected and a staring look appears. The patient often blinks to initiate the slow saccade. The slowing later becames so marked that the eyes can hardly be moved voluntarily, giving the impression of a peripheral ophthalmoplegia. However, full movements can be produced reflexly by caloric stimulation and the doll's eye manoeuvre. In contrast, smooth pursuit remains intact, until a later stage of the disease. There is no ptosis, diplopia, squint or pupillary abnormality. Optokinetic nystagmus is absent, or a slow oscillation may occur at an early stage.

The cerebellar ataxia and ophthalmoplegia develop and deteriorate simultaneously, but at times the ocular disorder trails behind the ataxia. In 4 families (Sigwald et al 1964; Starkman et al 1972; Ozawa et al 1974; Wadia et al 1976) the 2 were not seen together.

Mechanism of slow saccades:

There are 2 types of eye movements - the slow following movements at a velocity of about 45 degrees/second, and the fast saccadic ones at velocity of 600 ^{o}/sec. The former movements are meant to follow with accuracy slowly moving objects, while the latter are used for quick general scanning of the surroundings.

The lower controlling mechanisms of both these types of movements is through a common pathway which includes the pontine gaze centre, MLF, both the 3rd and 6th nerve nuclei and nerves of the oculomotor muscles. But their higher control representation are separate. Area 8 of Brodmann in the frontal lobes and area 18 (perhaps 17 and 19 also) in the occipital lobes, control these movements. The projection fibres from the frontal (oculogyric) centre and the occipital (psychovisual) centre go through the anterior and posterior limbs of the internal capsule respectively, and by pathways not yet clearly defined, make connections with the lower controlling mechanism. Electrical stimulation of both the frontal and occipital areas produce conjugate movements of the eyes in the opposite direction, but it has been shown that the former has more powerful control and is mainly responsible for the volitional rapid movements, while the latter controls the slower psychovisual reflex activity of the eyes.

Other Neurlogical manifestaions

1) Abnormality of tendon reflexes: Wadia (1991) mentioned only 6 out of 40 patients with normal reflexes. In the other they were more often depressed than exaggerated. On the whole, the ankle jerks are more often and earlier lost than the knee jerks. The tendon reflexes of the upper limbs are normal but sometimes become depressed even before those of the lower limbs. An extensor plantar response and lower limb spasticity are seen in a small number of patients. Impairment of Vibration and postural sense in lower limbs are frequent.

Wadia et al (1976) found distal amyotrophy as a common sign in advanced cases. Mild bilateral facial weakness (Wadia 1984, 1991) and facial dystonia (Rondon et al 1983) have been reported. Chorea (Wadia and Swami 1971), action myoclonus (Cambier et al 1978) and athetosis (Koeppen and Hans 1976) have been seen.

Mild to moderate mental deterioration may occur at an advanced stage, but attention has been drawn by Sears et al (1975) to significant dementia starting with defect of recent memory and going on to a vegetative state.

Macular degeneration (Sharpe 1976), coincidental

narcolepsy and postural hypotension (Ozawa et al 1974) and optic atrophy and bulbar palsy (Wadia 1984, 1991) have been rarely reported. Cataracts, Kyphoscoliosis and pescavus are seen in a few, but no cardiac or electrocardiographic abnormality have been found.

Age at onset:

Can be as young as 6-7 years (Wadia 1984, 1991) and as old as 75 years (Sigwald et al 1963, 1964), but in most patients the disease begins between 15 and 40 years. The average age among Indians was 27 and 28 years (Wadia 1984).

The course of the disease is judged by the progress of cerebellar ataxia. The cerebellar disorder proceedes inexorably, eventually leading to incomprehensible speech, considerable disability and decubitus, on an average in 8 years with death in 13 years (Wadia 1984). However, Murphy and Goldblatt (1977) and Koeppen (1977) have reported patients alive after 30 years.

Genetic Data:

Genetic data have been evaluated recently by Wadia (1991) in 54 families. Autosomal dominant inheritance was noted in 29. In 20 families, only 1 sib was affected and a new mutation seemed most likely. In the remaining 5 families, more than one member of a sibship of non-

consanguinous parent were affected by the disease. History and examination of parents in 4 of the 5 families showed that they were unaffected, while in 1 this information was not available. Further, in 2 of these families, only 25% of the sibs were affected by the disease, suggesting the possibility of recessive inheritance despite absence of parental consanguinity. In addition, there is the autosomal dominant family of Rondot et al (1983) which had escaped review and 2 more families (1 autosomal dominant and 1 sporadic) examined after the reevaluation. (Wadia, personal communication to 14th World Congress of Neurology, New Delhi 1989). The overall impression is that this variety of heriditary ataxia is mostly autosomal dominant, that new mutation frequently occurs and occasional recessivity is not entirely ruled out.

Epidemiology:

Though no epidemiological survey of this heriditary ataxia has been made, it is clear that this variety is more prevalent or recognised in India. In fact, Wadia says that this is the commonest variety of heriditary ataxia seen in India. Unlike some autosomal dominant neurodegenerative disorder such as Huntington's chorea and Joseph's disease, where families living far apart can be traced to a single family (founder effect), this variety of OPCDs cuts across

race, caste and religious boundaries. Affected families have been found proportionately in the 3 biggest religious groups of India, the Hindu, Muslims and Christians. The families reported from else where came from many countries and cases have been found in both the black and white races in USA (Singh et al 1973) and Canada (Sharpe 1976).

Pathology:

The pathology has been well described (Wadia 1984, 1991). All except one showed olivopontocerebellar atrophy Histology revealed that atrophy was due to the degeneration of groups of neurones and resulting nerve fibre loss. In the cerebellum, the Purkinje cells were maximally affected followed by neurones in the granular layer. The molecular layer was relatively spared. Buttner-Enever et al (1985) mentioned that the vermis and cerebellar hemispheres were most affected and the flocculonodular lobe (flocculus) was considerably spared. The nuclei pontis and olivary neurones were also as severely degenerated as those of the cerebellum. The cerebellar white matter, the transverse pontine fibres, the olivary hilum and the middle cerebellar peduncles were severely demyelinated, but there was only little loss of fibres in the floccular region. In many brains, the substantia nigra, and in some the dentate nucleus were also degenerated. Mild loss of frontal lobe neurones has been

reported, but in the Sears family, it was severe. The basal ganglia, red nucleus, thalamus and neurones of the oculmotor nerves (3,4,6) were intact, but the subthalamic nucleus showed degeneration in the patient of the Sears family (1975) and the locus ceruleus in the families of Sigwald et al (1963, 1964) and Oppenheimer (1980).

Recently Buttner -Ennever et al (1985,1986) performed careful morphometric measurements (cell size and counts) and enzymatic staining in 2 patients and normal controls and found marked loss of large and medium sized neurones in a restricted region of the PPRF. Using cytoarchitectural criteria these were found to be cell groups homologous to the pre-motor saccadic burst and ommipause neurones found in the PPRF of cat and monkey.

The posterior columns were severely demyelinated throughout the length of the spinal cord in most autopsies and the anterior horn cell degenerated in half. The lateral columns, including the corticospinal tracts were almost invariably intact. The posterior root ganglia have not been satisfactorily examined, but Mass and Scherer (1933) and Wadia (1984, 1991) have reported loss of posterior root fibres. Wadia et al (1980), and Zee et al (1976) have shown axonal degeneration at sural nerve biopsy, especially of the large and medium-sized myelinated fibres.

The clinico-pathological correlation is similar to the other varieties of OPCD except for the ocular disorder. The morphometric demonstration of the loss of large and medium sized neurones in the PPRF and the preservation of the Purkinje cells in the flocculus would fit well with the clinical observation of abnormally slow saccades and normal pursuit movements respectively. This observation is supported by similar morphological changes depicted in vivo by CT and MRI in the pons and cerebellum as reported by Plaitakis (1987) and Wadia (1991).

MATERIALS AND METHODS

Case ascertainment:

30 patients (12 female and 18 males) with OPCA - Wadia type, attending the Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, from January 1988 to March 1994 were selected for the study. Case records of all patients registered in the Medical Records Department of this institute from January 1988 to March 1992 with diagnostic indices of OPCA, cerebellar ataxia, OPCA with slow eye movements, OPCA Wadia-type, spinocerebellar degeneration, multisystem atrophy and parkinsonism plus syndromes were searched. Besides, prospectively diagnosed cases of OPCA- Wadia type who attended the department of Neurology from January 1992 to March 1994 were also included.

Data Collection:

From the records of the patients, clinical data were abstracted using a prepared proforma. They were then subjected to a detailed clinical examination and electrophysiological investigation. The prospective 19 patients seen from January 1992 till March 1994 were also carefully examined and those satisfying the following clinical criteria were included for the study: (Wadia and Swami 1971).

1) Patients with cerebellar ataxia - familial or sporadic.
2) Abnormal ocular movements in the form of slow saccades, normal pursuit and convergence.
3) No nystagmus/ptosis/squint.
4) Evidence of peripheral neuropathy.

Electrophysiological evidences of peripheral neuropathy (using NCV and EMG by standard techniques) were used in patients who had all the other above mentioned clinical criteria, but with uncertain clinical evidence of peripheral neuropathy.

Electrophysiological tests:(methodology)

1. Brain stem auditory evoked response (BAER):-

BAER was obtained using the Dantec E-4000 system. The test was performed in a silent room with the subject resting on an easy chair. The scalp is cleaned thoroughly and surface electrodes are used with impedence below 5000 ohms; fixed to the vertex and mastoids with bentonite. A click stimulus of 12Hz frequency, 100 msec duration and 65 db intensity above the hearing threshold was used. Recordings were done from vertex to the ipsilateral mastoid with monoaural stimulation. The responses were recorded with a sweep speed of 1 msec/division and band pass with upper frequency of 5Hz and lower frequency of 100 Hz. 2500-4000

responses were averaged. The averaged response was obtained at a sensitivity of 0.2 uv/div. Two recordintgs were obtained from each ear and the waveforms superimposed to test the waveform consistency before the latencies were recorded. Then the interpeak latencies were measured from waves I through V. BAER abnormalities were defined as (1) absence of 2 or more waves from I-V (2) increase in interpeak latencies III-V or I-III. beyond 3SD. (Table 1-Control data).Table 1. BAER - Control Data (I-III)

Age group	Nos	Right ear Mean	3SD	Left ear Mean	3SD
11-20	5	1.72	0.15	1.58	0.32
21-30	15	2.27	0.54	2.27	0.73
31-40	5	2.08	0.28	1.98	0.44
41-50	5	1.93	0.14	1.86	0.35
Total	30	2.01	0.36	1.93	0.49

BAER (Control data III-V)

Age group	Nos	Right ear Mean	3SD	Left ear Mean	3SD
11-20	5	1.91	0.33	2.03	0.30
21-30	15	2.10	0.13	2.05	0.09
31-40	5	1.63	0.17	1.70	0.15
41-50	5	2.06	0.20	2.01	0.10
Total	30	1.89	0.28	1.91	0.24

2. Visual Evoked Response:

The visual evoked responses were performed on Dantec-E 4000 system by monocular stimulation, using a reversing black and white checker board pattern at a rate of 2Hz. The contrast and luminance of the pattern did not vary. The subject was made to sit at a distance of 1 metre from the television screen. The main recording electrode were placed in the midline at the vertex and 2.5 cm above the inion using standard cleaning, impedance checks and grounding. The responses were recorded with sweep speed of 30 msec/div and band pass width upper frequency of 1 Khz and lower frequency of 2 Hz. Artefact rejection was employed and both the raw and the averaged potentials were constantly monitored. Two separate sets of 200 trials were run for each eye for conformity. Five hundred trials were used occasionally, if the responses were not well formed. The averaged response was measured at a sensitivity of 2uv/div. The peak latency was then measured to the major positive peak (p 100) (Table 2-VEP control data).

The VER and BAER results were compared to values in a control group of 30 adults (18 males, 12 females). All control subject were neurologically normal persons with a age range of 25-40 yrs (mean $\pm$SD 30.5$\pm$9.9) and were not related to the patients. Results were considered abnormal when they exceeded the mean$\pm$ 3SD of the control group.

Table 2(a): VEP - Control Data (Individual eyes)

Age	No.	Right eye mean	Right eye (SD)	Left eye mean	Left eye (SD)
11-20	5	95.5	3.16	96.15	2.47
21-30	15	97.0	4.95	97.45	2.78
31-40	5	97.4	4.02	96.80	2.30
41-50	5	94.73	1.83	95.63	2.00
Total	30	96.14	96.46	3.49	2.26

Table 2(b): VEP control data - inter eye variation

Age	No.	Mean	SD
11-20	5	1.45	0.719
21-30	15	3.15	2.21
31-40	5	2.067	0.70
41-50	5	1.083	0.728
Total	30	96.14	96.46

3. Blink reflex studies:

Blink reflex study was also recorded using the Dantec E-4000 system. Patients were made to lie supine, relaxed with eyes gently closed. The active electrode was placed on the inferior orbicularis muscle below the outer canthus of the eye. The reference electrode was similarly placed on the skin over the nasal bone. The leads were connected to separate channels of the Dantec machine. The ground electrode was kept on the chin. The frequency filters of the amplifiers were kept between 2-1000 Hz sensitikvity, was adjusted so that 200 MV would produce a deflection of 1 cm.The direct response (DR) to stimuation of each facial nerve at the stylomastoid foramen was done first to exclude any peripheral facial nerve lesion. The current duration was 0.1 ms and the strength was increased supramaximally till a constant response was obtained. The latency of this direct response was measured on each side from the stimulus artefact to the first deflection of the evoked motor response and recorded.

Next, the blink reflex was obtained by stimulation of the supraorbital nerve at the supraorbital foramen. The blink reflex consists of 2 temporarlly separated components - an early ipsilateral R1 and a late bilateral R2 response. Current duration was 0.1 ms and the current strength was

increased to get well defined R1 and R2 responses of maximum amplitude and minimal distortion. Then the latencies of R1 and R2 responses were measured from the stimulus artefact to the onset of the responses and the amplitudes were measured from peak to peak.

Normal values: The upper limits of normalcy was 4.3 msec for direct response latency; 10.5±2.5 msec for R1 latency; 31±10 ms for ipsilatetal R2 and 32±10 ms for contralateral R2. Similar values for right to left difference for R1 was 1.2 ms; the difference between ipsilateral and contralateral R2 was 5ms; and the difference between bilateral R2 to right or left sided stimulation was 8 ms. Values above these were considered abnormal (Table 3).

Table 3. Blink reflex control data

Direct response			R1 component		R2 component			
	DR	Left-right difference	R1	Left-right difference	Ipsilateral (I/L)	Contralateral (I/L)	I/L-C/L difference	Left-right difference
Mean latency (m.sec)	3.35	0.08	10.21	0.37	31.99	32.65	0.45	3.34
SD	0.32	0.06	0.64	0.33	3.04	3.55	1.45	3.154
M+3SD	4.3	0.26	12.12	1.36	41.1	43.3	4.80	12.80

Neuroimaging studies:

Computerised tomographic (CT) scan (plain) was done for all patients and MRI brain (plain) was done for patents who could afford the test. CT/MRI evidence of brain stem (especially pontine) and cerebellar atrophy were looked for.

Values of VEP, BAER and Blink reflex were compared with age and sex matched control group of 30 adults (18 males, 12 females). All control subjects were neurologically normal persons with an age range of 25-40 yrs (mean $\pm$SD 30.5$\pm$9.9) and were not related to the patients. Results were considered abnormal when they exceeded the mean $\pm$ SD of the control group.

RESULTS

Thirty patients with features of OPCA-Wadia type constituted the material for this study. Majority of the patient (15) were in the age group 21-30 years (mean age of 27.5 years); 5 were in the second decade and 10 were in the higher age group (Table 1).

Table 1: Age & Sex distribution

Age group	Male	Female	Total(30)
11-20	3	2	5
21-30	10	5	10
31-40	3	2	5
41-50	2	3	5
Total	18	12	30

Majority of the patients were males (18) and females were 12 in number; male: female ratio being 3:2.

I.CLINICAL DATA (Fig. 1)

All thirty patients had evidence of cerebellar involvement - in various combinations - cerebellar dysarthria with intention tremors in 12; cerebellar speech with limb ataxia in 13; gait ataxia alone in 3; truncal ataxia (1); titubation and intention tremor (1).

All 30 patients had slow saccadic eye movements, out of which 5 were mild, 15 were moderately severe and 10 were severe (visual impression). All of them had normal pursuit and none had nystagmus.

21 patients out of the thirty (70%) had clinical evidence of peripheral neuropathy - out of which 14 had diminished reflexes and impaired sensation (impairment of vibration was the commonest) and 7 had distal amyotrophy of the hands and sole of feet associated with distal weakness (moderate weakness of small muscles of hand and hand grip in 5; and moderate weaknes of dorsiflexors of feet in 2). 9 out of the thirty patients (30%) had evidence of peripheral neuropathy only by electrophysiological studies.

Claw hand deformity was seen in 2 patients.

Skeletal deformities in the form of Kyphoscoliosis (mild-moderate) were detected in 10 patients and club feet in 3 pateints.

Extrapyramidal features were detected in 10 patients - 4 had evidence of facial and limb-choreiform movements; and 6 patients had cogwheel rigidity of wrists and elbow joints bilaterally. None had myoclonus, mask-like facies, dystonia, or rest tremors.

Dementia was detected in 6 patients using Folstein's Mini-mental scoring - out of which 4 patients were mildly demonted with a minimental score of 20/30 and 2 of them had moderately severe dementia with a score of 14/30. Severity of mental deterioration correlated with the disease duration.

Evidence of pyramidal tract involvement in the form of brisk reflexes and extensor plantar response was noted in 8 patients out of the total.

Significant bilateral primary optic trophy was detected in 2 out of the 30 patients and weakness of facial musculature in 4 patients.

Family History:

There were 10 patients (6 males and 4 females) with evidence of autosomal dominant trait; with incomplete penetrance where the parent were not affected (in 8 cases); and complete penetrance in 2 cases with affected parent (father). Out of these, 6 families with four other affected member were examined personally. A history of 2-5 other similarly affected members could be obtained from the other 4 patients. There was no parental consanguinity in any family.

II. Electrophysiological data

All the 30 patients were subjected to the following electrophysiological studies (BAER, Blink reflex, VEP and NCV; 9 patients had EMG studies of upper limb-(1st dorsal interosseous, APB & biceps) and lower limb muscles (quadriceps and tibialis anterior).

I. BAER: (Fig.2)

BAER was abnormal in 19 out of the 30 patients (63.3%). Out of which there were 2 patients in whom no waves were elicited (6.6%) bilaterally; one patient had a unilateral abnormality on the left side alone (prolonged I-V latency); 11 patients had abnormally prolonged III-V latencies (36.6%) bilaterally and 5 patients had bilateral prolonged abnormal I-III latencies (16.6%). (Reference table No.4)

BAER - Patient Data (Table 4)

No.of pts		III-V bilateral		I-III bilateral	I-V (bilateral)
1	*	2.68		2.31	N
2.	*	3.01		2.22	N
3.		2.02		1.98	N
4.		1.42	**	3.01	N
5.		1.98		2.14	N
6.		1.14		2.26	N
7.		1.21	**	2.94	N
8.		1.44	**	3.12	N
9.		1.12		2.13	N

BAER - Patient Data (Table 4 contd)

No.of pts		III-V bilateral	I-III bilateral	I-V (bilateral)
10.	*	2.94	2.14	N
11.	*	3.12	2.02	N
12.		2.01	2.24	N
13.		-	-	-
14.		2.15	1.84	N
15.		2.01	1.67	N
16.		-	-	-
17.	*	3.24	2.12	N
18.		2.11	2.24	N
19.		1.74	** 2.89	N
20.		1.02	** 3.14	N
21.		1.41	2.02	N
22.	*	3.55	2.27	N
23.	*	2.97	2.30	N
24.	*	3.14	2.12	N
25.		1.12	2.45	N
26.	*	3.62	2.16	N
27.	*	2.82	1.44	N
28.	*	2.96	1.92	N
29.		1.64	1.64	N
30.		N	N	Abnormal

* - Abnormal (III-V); ** - Abnormal (I-III)

Blink Reflex Study:

Abnormalities were detected in 16 patients out of the total of 30 cases (53.33%). Of these, 7 patients had delayed R1 response (23.33%) bilaterally and 9 (30%) had delayed R1+R2 responses bilaterally (4 patient who had bilateral facial weakness were excluded from this test).

BLINK REFLEX-PATIENT DATA

Table No.5

	LEFT			RIGHT		
	R1	R2		R1	R2	
No.of pts	Ipsil-ateral	Ipsil-ateral	Contra-lateral	Ipsil-ateral	Ipsil-ateral	Contra-lateral
1	N	N	N	N	N	N
2	* 18.0	N	N	17.25	N	N
3	N	N	N	N	N	N
4	** 17.2	N	73.0	15.20	N	66.0
5	** 18.0	N	52.0	18.0	N	55.0
6	N	N	N	N	N	N
7	** 17.2	N	54.0	17.0	N	54.0
8	* 15.5	N	N	18.20	N	N
9	** 16.0	N	60.0	15.2	N	65.0
10	* 16.2	N	15.0	N	N	N
11	N	N	N	N	N	N

BLINK REFLEX-PATIENT DATA
Table No.5 (Contd.)

	LEFT			RIGHT		
	R1	R2		R1	R2	
No.of pts	Ipsil-ateral	Ipsil-ateral	Contra-lateral	Ipsil-ateral	Ipsil-ateral	Contra-lateral
12	** 18.41	N	N	18.1	N	N
13	N	N	N	N	N	N
14	* 16.50	N	N	15.0	N	N
15	N	N	N	N	N	N
16	** 15.5	N	70.0	15.0	N	66.0
17	** 15.0	N	66.0	15.0	N	60.02
18	* 18.0	N	N	15.12	N	N
19	N	N	N	N	N	N
20	* 16.0	N	52.0	18.0	N	56.0
21	** 17.0	N	55.0	17.2	N	60.0
22	N	N	N	N	N	N
23	N	N	N	N	N	N
24	N	N	N	N	N	N
25	N	N	N	N	N	N
26	N	N	N	N	N	N
27	* 17.0	N	N	16.21	N	N
28	**16.0	N	66.0	N	N	N
29	N	N	N	N	N	N
30	N	N	N	N	N	N

* - Abnormal; ** - Abnormal R1 & R2

Comparing BAER and blink reflex studies, it was seen that 12 patients who had normal BAER had abnormal blink reflex.

Visual Evoked Response:

Visual evoked responses were found to be normal in all the patients except the 4 patients who had bilateral significant primary optic atrophy who showed asymmetrical and delayed P100 latencies in both eyes.

Nerve Conduction and EMG Studies:

Nerve conduction velocity study was done for 9 patients who had clinically doubtful peripheral neuropathy, along with EMG studies. Motor conduction velocities were slowed only in 2 patients (both common peroneal nerves in one patient and left posterior tibial nerve in another); SNAP was abnormal in all the 9 patients (absent in 4 - those recorded from both median and ulnar nerves in 2; and sural SNAPS in another 2). SNAPs were decreased in amplitude with reduced conduction velocity in other 5 patients and were recorded from sural nerves in 2 and both median and 1 ulnar nerve (L) in the other 3 patients.

III. Neuroimaging Studies:

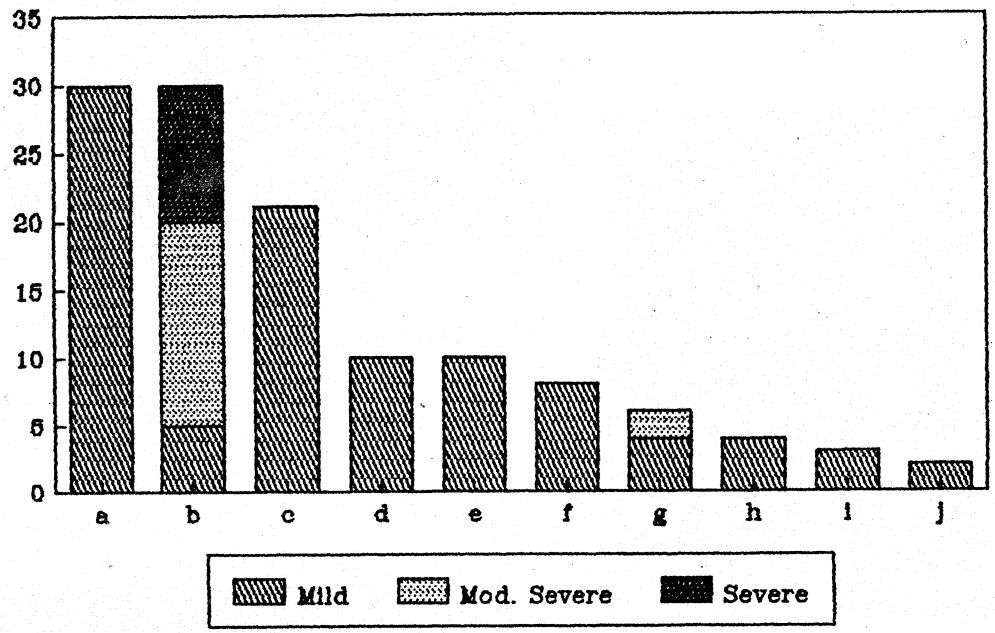
Plain CT scans of brain was obtained in all 30 patients and non contrast MRI brain in 10 patients. (1 had only MRI)

21 patients with CT brain showed evidence of cerebellar and pontine atrophy. 9 out of the 21 patients showed evidence of cortical atrophy too. 9 out of the 30 patients in whom CT brain showed only cerebellar atrophy, additional brain stem atrophy was detected by MRI brain - this was shown by the 'molar tooth' appearance with its root projecting posteriorly because of the excavation of the floor of the 4th ventricle together with atrophy of the brachium pontis (middle cerebellar peduncle) and brachium conjunctivum (superior cerebellar peduncle). The atrophy of the cerebellar hemispheres affected both the cortical and subcortical regions (pan cerebellar) and was seen as widened sulci.

All the 10 patients who had MRI brain showed cerebellar and brain stem atrophy (3 had cortical atrophy also). The flocculus was seen clearly on MRI and was better preserved.

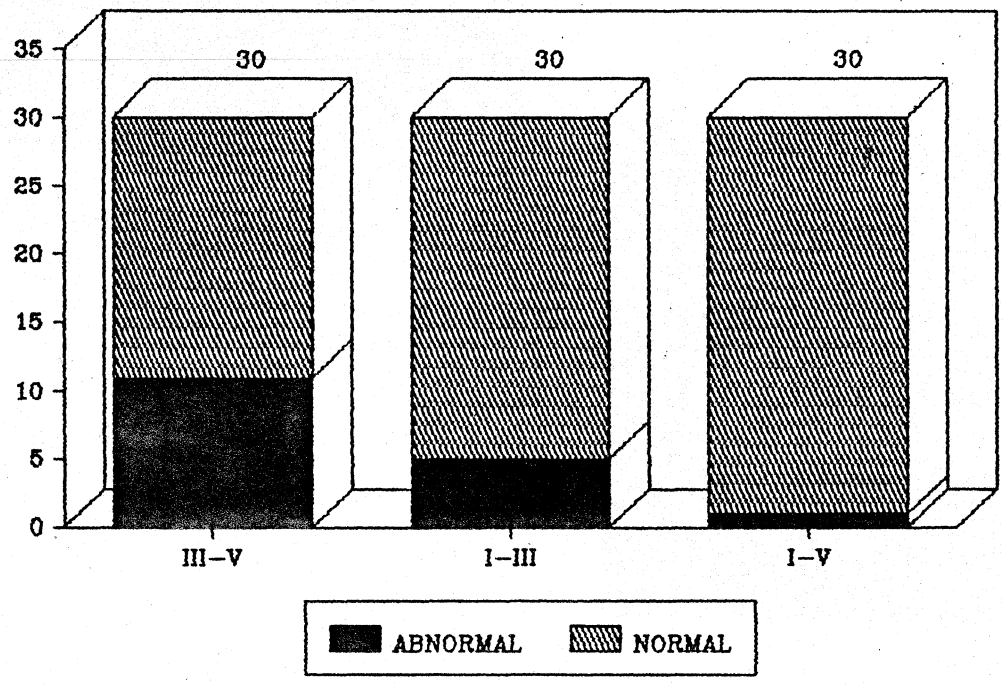
None of them had hypodensities in the basal ganglia, ruling out MSA. Neuroimaging findings of brain stem and cerebellar atrophy correlated well with the duration of the illness.

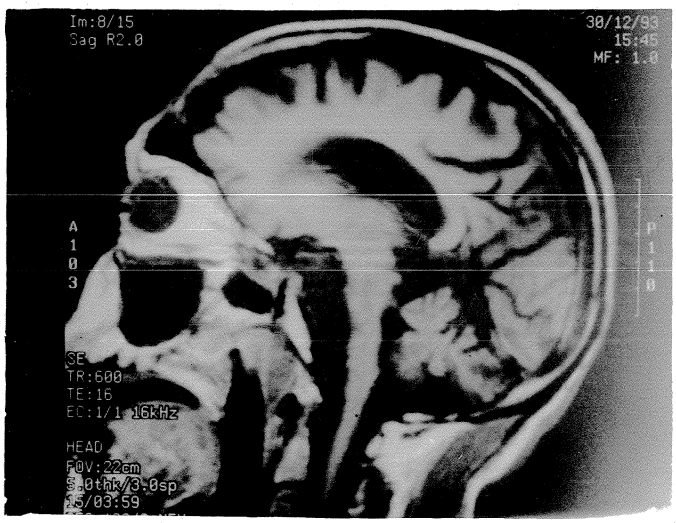
Fig.1: Frequency of Various Signs & Symptoms



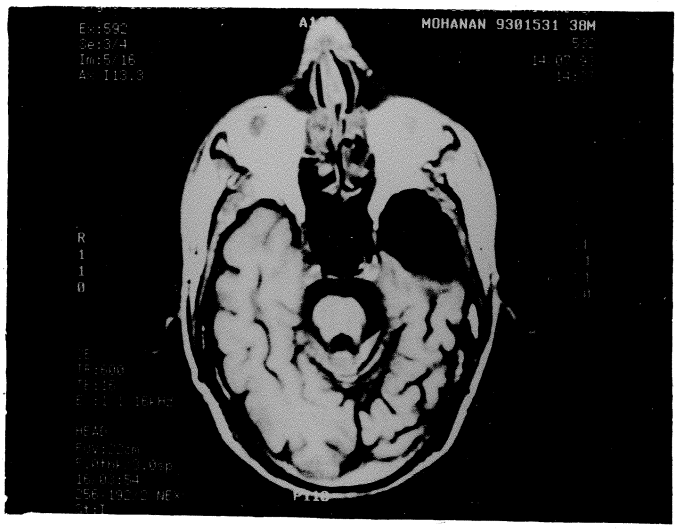
a. Cb. Signs
b. Eye movts
c. Neuropathy
d. EP features
e. Kyphoscoliosis
f. Pyr. tract
g. MR
h. Optic atrophy
i. Club feet
j. Claw hand

Fig.2: BAER -Patient Data

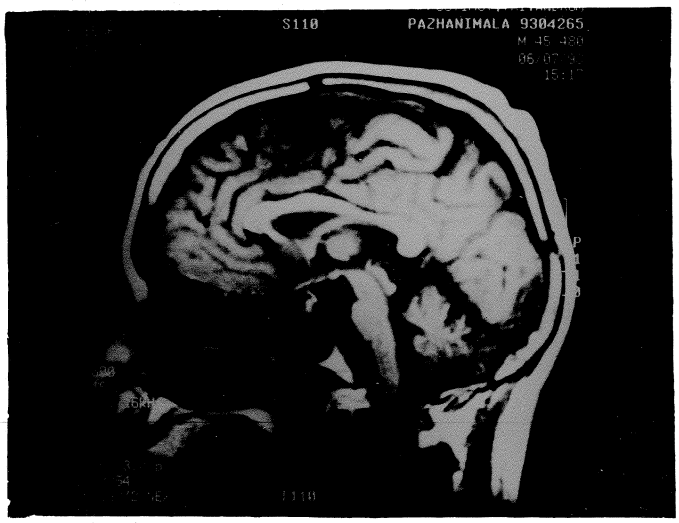




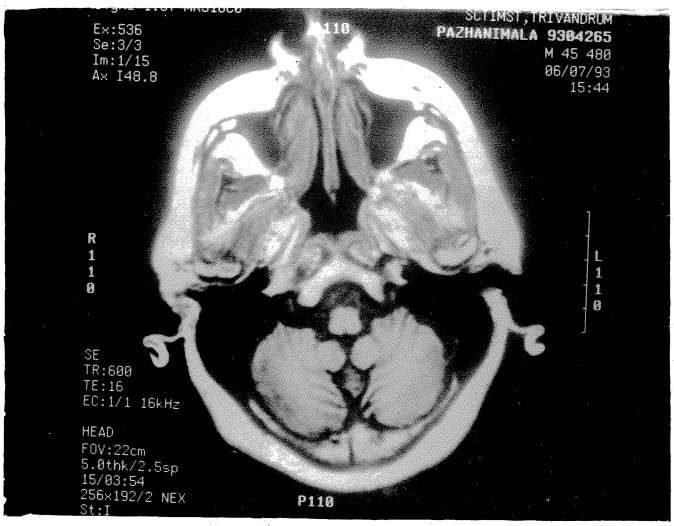
I.a)MRI, T_1 WI - Midsagittal cut.
Severe atrophy of pons & cerebellum.



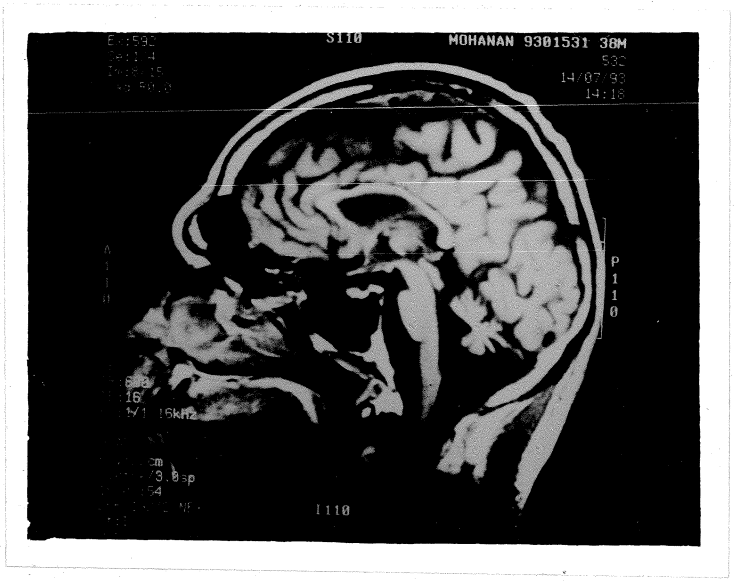
b) MRI, T_1 WI-Axial cut Atrophy of Brach. Conj. +tegmentum -'molar-tooth' appearance.



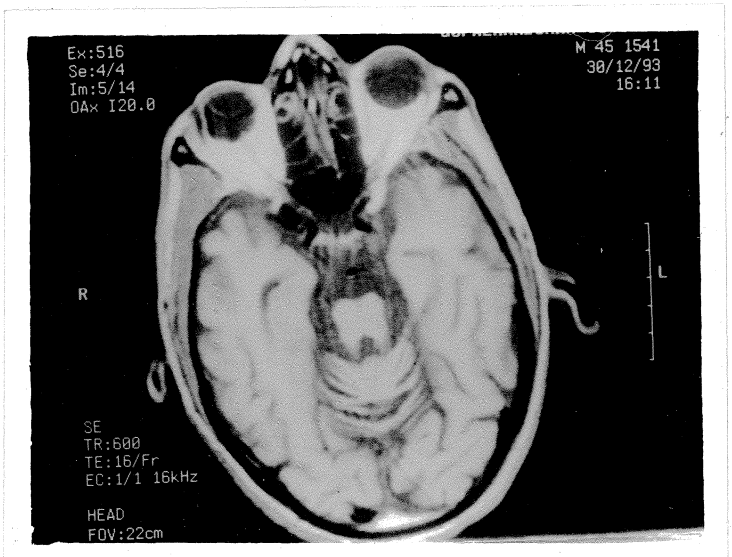
2.a) MRI-T_1 WI -Midsagittal cut.
Mod. atrophy of pons, cb, cortex.



b) MRI-T_1 WI-Axial cut.
Atrophy - brain stem and vermis.



3.a) MRI-T_1 WI - Midsagittal cut.
Mod. atrophy-brain stem, cb, cortex



b) MRI-T_1 WI-Axial cut.
Atrophy of PMjn.+ Vermis.

DISCUSSION

Thirty patients with features of olivopontocerebellar degeneration attending the neurology department of SCTIMST from January 1988 to June 1994 constituted the material for this study. Though many cases of heredo-familial spino-cerebellar degeneration have been reported from many parts of India (Jolly et al 1966; Sumra and Virmani 1972; Wadia and Amin 1976; Wadia and Desai 1980; Jagannathan 1985; Bansal et al 1988), there is a greater prevalence of a variety of olivopontocerebellar degeneration described by Wadia and Swami (2,3,4,5) from Central India distinguished by slow saccadic eye movements and peripheral neuropathy. No epidemiological survey of this group of disorders has been made, but hospital based data from different parts of India is available. The first report of its kind came from South India, Calicut, by Kini and Venugopal (1). The incidence of this variety of OPCA seems to be rare. It was detected in patients from the three dominant communities of India (the Hindus, Muslims and Christians). In Kerala, from the present study, a predominance was noted in the Hindu and Muslim communities especially from Malappuram, Manjeri, Calicut and Palghat. Most of them were sporadic cases, and a few were familial (33.33%) with an autosomal dominant

inheritance pattern. None of them had any history of consanguinity in their family (2).

All these thirty patients had the following clinical criteria (2) of (1) Cerebellar ataxia (familial or Sporadic) (2) Abnormal ocular movements in the form of slow saccades, normal pursuit (3) No nystagmus, ptosis or squint and (4) evidence of peripheral neuropathy. Some of the cases of heredo-familial spinocerebellar disorders reported from India also had the above features, but slow eye movements were peculiar to this variety of OPCA described by Wadia (2,3,6,7).

The symptoms and signs of these diseases are attributed to the degenerative lesions in the cerebellum and its connections to the brain stem, posterior columns and corticospinal tracts. An additional pathology in the PPRF, sparing the flocculus, is responsible for the slow eye movements in this specific group of OPCA. However, the functional state of brain stem and visual pathways has not been studied well (8,9,10) which can provide insight to the extent of pathological involvement (Klockgether et al 1990). Most of these studies limit themselves to a single evoked potential modality and frequently to a single syndrome involving a small number of cases. The present study describes brain stem auditory evoked response (BAER), Visual

evoked response (VER), blink reflex, nerve conduction and electromyographic abnormalities in patients with OPCA-Wadia type specifically. BAER was abnormal in 63.3% of cases showing involvement of central auditory pathway in pons, and blink reflex abnormalities were detected in 53.33% of cases. It was also seen that 12 patients (40%) with normal BAER had abnormal blink reflex studies. Thus evoked potential and blink reflex bring out significant abnormalities of pontine pathways, which may not be apparent clinically (11). They may serve as a useful diagnostic tool, and follow up in many other patients may help reclassify these disorders as OPCA if they have only subtle clinical signs early in the course of the disease.

Though CT and MRI of patients with OPCA share common features, there is some distinction in this variety of disorder (8,12). The earliest morphological changes are seen in the anterior lobe of cerebellum and tegmentum of the pons As the disease advances brain stem appears like a 'molar tooth' because of the excavation of the floor of the fourth ventricle together with atrophy of the middle cerebellar peduncles. Pan cerebellar atrophy occurs later, but here, the flocculus is distinctly spared and seen clearly in MRI. On intermediate and T2-weighted MRI, abnormal signal intensity was always seen in the structures

known to degenerate in OPCA (like transverse pontine fibres, middle cerebellar peduncles and cerebellum). Pyramidal tract and superior cerebellar peduncles stand out because of their normal signal intensity. Thus MRI can differentiate this disease from other acquired and familial cerebellar atrophiestoo. (8,13,14,15).

CONCLUSION

OPCA with slow eye movements and peripheral neuropathy, first described by Wadia and Swami, is a rare disorder, with greater prevalence in India. It has a strong familial predisposition, though sporadic cases were more in the present. study. It is prevalent in all communities in India and no specific ethnic predisposition groups or regional variation occurred. Electrophysiologically, abnormaltiies of blink reflex and BAER can occur early in the disease and can serve as a diagnostic tool to distinguish from other, especially when there are only soft cerebellar signs and mild slowing of saccades or routine clinical examination. Neuroimaging using MRI, can also provide clues to differentiate this type of disorder from other acquired and familial cerebellar atrophies. Thus it is evident that this type of OPCA is totally distinct from other types of olivopontocerebellar degenerations.

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PROJECT REPORT

TITLE

NEUROLOGICAL COMPLICATIONS OF INFECTIVE ENDOCARDITIS

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PROGRAMME DM. NEUROLOGY

MONTH & YEAR OF SUBMISSION NOVEMBER 1994

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INTRODUCTION

The term endocarditis encompasses a heterogenous group of diseases which are characterized by inflammation or infection of the atrial or ventricular endocardium or the valvular apparatus. Libman, in 1938, (1) provided a comprehensive classification of endocarditis, differentiating rheumatic, syphilitic, acute bacterial, subacute bacterial and endocarditis of uncertain etiology. The distinction between subacute and acute bacterial endocarditis is no longer entertained because they pose nearly identical problems.

The association between infective endocarditis (IE) and neurological complications has been recognized for more than a century. Sir William Osler, in 1885, (2) in his series of Gulstonian lectures, underscored the clinical triad of fever, heart murmur and hemiplegia. He was the first to suggest that neurological symptoms can be the initial mainfestation of IE. Neurological complications fof IE may occur secondary to embolizatien from endocardial vegetations resulting in occlusion of cerebral arteries, expansion or leakage of mycotic aneurysms, or hematogenous spread of infection resulting in meningitis or brain abscess (3-5).

Recent reports from the West have focussed on the

change in the specturm of IE during the last two to three decades (4-7). These include a change in the patient population with an increased occurrence among elderly, and narcotic and drug abusers, change in the underlying heart disease with a decrease in incidence of rheumatic heart disease, improvememnts in the diagnosis, and a more aggressive management with newer antibiotics and early surgical intervention. However, rheumatic heart disease continues to be a major health problem in third world countries, and facilities for surgical correction of rheumatic and congenital heart diseases are quite limited. A recent report of patients with IE from North-West India concluded that the specturm of IE is different from that seen in Europe and North America (8).

Through this review the major neurological manifestations of IE and their diagnosis and treatment are described. The Indian experience of IE, and the essential differences in the spectrum of IE in the reports from India and Western countries will be highlighted.

AIM OF STUDY

1. To study the clinical profile of patients with infective endocarditis, seen in SCTIMST, from 1977 to July 1994.

2. Define the frequency and pattern of neurological complications in this hospital based cohort.

3. The profile of the neurological manifestations of infective endocarditis among Indian patients described from two national medical institutions are compared.

REVIEW OF LITERATURE

The population incidence of IE has shown a decline in developed countries. Griffin et al (9) observed an annual incidence of 4.3/100,000 during the 1970s in Olmsted County, Minnesota. Decrease in the incidence of rheumatic heart disease, early detection and surgical correction of congenital and acquired valvular lesions, and prophylatic antibiotic therapy in those with pre-existing valvular diseases are the major factors which contributed to the decrease in the incidence of IE (4-7,9). However, new categories of patients have emerged such as drug abusers, the aged, and young children with congenital heart diseases. Today, endocarditis on tricuspid valves, prosthetic valves and normal hearts are also being increasingly recognized (3-7).

Frequency of neurological complications:

In a comprehensive review of the records of 218 patients with IE at Massacheusetts General Hospital, during 1964-1973, 84 cases (39%) manifested clinically apparent neurological complications (10). In another retrospective study of 166 patients with IE, 58 (35%) had neurological sequelae (6). In an autopsy series of 69 patients cerebral emboli were found in over 50% of cases (11).

The frequency of neurological complications during IE ranges from 20-40% in most series, with an average of 30% (2-5). Because of the availability of noninvasive neuroimaging studies and as a result of more intensive search, recent studies have reported a higher frequency of neurological complications.

ETIOPATHOGENESIS OF NEUROLOGICAL COMPLICATIONS

Native Valve endocarditis:

Neurologic complications are more frequently observed in left sided IE; it is much lower in patients with right sided IE (3-5). Vegetations visible on echocardiography increase the risk of embolic stroke by a factor of 5 (12). The frequency of cerebral embolism is greater when aortic and mitral valves are affected simultaneously (13). In one study, 28% of patients with aortic valve disease presented with neurological complications compared to 52% with mitral valve disease (10). By contrast, in a comparison of 64 patients of IE with neurological complications with 111 patients without, similar frequency of valvular localizations were observed, 59% for aortic valve and 32% for mitral valve (13). Cerebral embolism can rarely occur in patients with right sided IE through a patent foramen ovale or pulmonary arteriovenous fistula, or due to septic thrombi in the pulmonary veins.

Prosthetic valve endocarditis

A review of neurological complications in 113 patients with native valve IE and 62 patients with prosthetic valve IE, disclosed a frequency of neurological complications of 35.3% and 38.7% (13). Therefore, patients with prosthetic valve IE do not appear to be at increased risk for neurological complications. However, neurololgical sequelae in the context of prosthetic valve IE raises special concern because of the risk of intracranial hemorrhage due to anticoagulation. The time of occurrence of IE in relation to prosthetic valve placement appears to be relevant; late prosthetic valve IE (>2 months after placement) have been associated with a significantly higher frequency of cerebral embolic episodes when compared to early prosthetic valve IE (14,15).

Intravenous drug abuse:

Intravenous drug abusers with left sided IE have a higher frequency of neurological complications than the nonaddict population, with a range of 45-58% (16). Staphylococcus aureus and gram negative bacilli IE occur with increased frequency among these patients. Mixed infections and fungal infection, most commonly candida, are diagnosed in over 15% IE complicating parenteral drug abuse (16). Candida IE is particularly prone to cause major cerebral

embolic episodes because of large, friable vegetations. In some medical centres, diagnosis of candida IE is considered sufficient indicaticn for an immediate surgical intervention with valve replacement (4,5,16).

Microbiology

The frequency and severity of neurological complications are higher in patients with IE caused by virulent organisms. In a study of 178 episodes of community acquired native valve endocarditis, neurological complications occured in 54% of cases with staphylococcal IE, but only in 19% of Streptococcus viridans IE (17). Prosthetic valve IE caused by Staphylococcus epidermidis was associated with a high frequency of meningitis (4). Large vegetations with enhanced embolic episodes complicate IE caused by hemophilus species, group B beta-hemolytic streptococci and fungi (4,19).

Pathogenesis

The neurological complications of IE may result from occlusion of cerebral arteries due to embolism from the endocardial vegetations; septic emboli or bacteremia causing infection of brain parenchyma, meninges or wall of cerebral arteries; and toxic or immune-mediated injury (3-6).

Intracranial hemorrhage complicating IE has three

pathological mechanisms. Hemorrhagic transformation of an ischemic infarct due to septic emboli is the most frequent mechanism leading to intracerebral hemorrhage. Rupture of pyogenic arteritis and mycotic aneurysms result in subarachnoid and/or intracerebral hemorrhage.

Two theories have been postulated to explain the pathogenesis of intracranial mycotic aneurysms: septic emboli producing destruction of arterial wall and an outward spread of inflammatory process; septic embolic involvement of the vasa vasorum primarily resulting in inflammatory destruction of adventitia and muscularis (20). However, in addition to the site where the embolus lodges, other factors such as virulence of the microorganism, and timing of antibiotic therapy are important in the pathogenesis of mycotic aneurysms.

NEUROLOGICAL MANIFESTATIONS

Table 1 provides a list of neurological manifestations of IE. These may be the presenting symptom in 16-23% of patients with IE (3-6). Although majority of the neurological complications occur either before or within the first two weeks of institution of antimicrobial therapy, cerebral embolism can occur from several months for upto 2 years after the successful completion of therapy for IE, and rupture of a mycotic aneurysm can occur years later (4).

TABLE 1

NEUROLOGICAL COMPLICATIONS IN PATIENTS WITH INFECTIVE ENDOCARDITIS

Embolic stroke
Intracerebral hematoma
Subarachnoid hemorrhage
Mycotic aneurysm
Acute encephalopathy
Meningitis
Brain abscess
Seizures
Head ache
Lumbar diskitis
Spinal epidural abscess
Embolic mononeuropathy
Myalgia

Cerebral embolism:

Cerebral embolism is the most common, (nearly 15%), neurological complication in patients with IE. Transient ischemic (TIA) attacks preceded a stroke in 27% of IE cases reported by Jones et al (21). More than 90% of the emboli lodge in the middle cerebral territory. Multiple microembolism may result in a diverse clinical syndrome

characterized by altered sensorium, seizures and fluctuating focal neurolocal signs.

Intracranial hemorrhage

The frequency of intracranial hemorrhage varies from 3-18%. It is seen more often in IE due to Staphylococcus aureus, ranging from 17-32%. Mycotic aneurysms are recognized clinically in about 2% of cases of IE and are discovered in 5-10% of autopsied cases (306). Cerebral embolism may precede the diagnosis of mycotic aneurysm, denoting its etiopathogenesis. These aneurysms involve most frequently the middle cerebral artery territory, usually in relation to its peripheral branches. In a series reported by Salgado et al (13), no single neurological symptom was significantly more frequent in those with mycotic aneurysm. The delay between the first neurological symptom was significantly more frequent in those mycotic aneurysms. The delay between the first neurological manifestations and final rupture ranged from 2 days to 18 months, with a median of 17 days (13). Mycotic aneurysms may be multiple in about 18% of cases. Following antibiotic treatment mycotic aneurysms can heal and disappear. In a serial study of 21 mycotic aneurysms, Bingham (22) noted total disappearance of these lesions in 11 cases and decrease in size in 6.

Acute encephalopathy:

Acute encephalopathy varies in frequency from 8 to 15% in different series (4,5). It may occur in association with multiple embolism, disseminated hemorrhagic infarcts, or toxic and metabolic factors. Cerebral fluid (CSF) is normal, and acute encephalopathy usually resolves following appropriate antibiotic treatment.

Meningitis and brain abscess:

Meningitis occurs in about 7% of cases of IE with neurological complications (4-6). The frequency of meningitis is higher in patients in whom Staphylococcus aureus and pneumococci are isolated (17). Although multiple microabscesses (less than 1 cm) occurs in 2-4% of patients with neurological sequlae, a large isolated abscess is very rare in IE (4,5).

Seizures:

Seizures have been reported in upto 10% of patients with neurological complications due to IE (4-6). Ischemic infarcts, hemorrhage, microabscesses, metabolic derangements and penicillin toxicity either alone or in combination contribute to the genesis of seizures.

Headache:

Mild intermittent, diffuse headache is found in 25-50%

of cases with IE and may indicate the presence of a number of different neurological or systemic complications (5). The presence of severe migraine - like headaches should raise suspicion of a mycotic aneurysms.

Peripheral manifestations:

In a retrospective analysis, 84 of 192 (44%) patients with IE had musculo-skeletal manifestations (23). Low back ache, presumably related to spondylodiskitis, occurred in 24 patients, and 16 had diffuse myalgia. Acute mono-neuropathies involving median, ulnar, peroneal, sciatic and facial nerves, complicating IE have been reported (24).

Miscellaneous:

Acute and subacute major psychiatric syndromes, involuntary movements, and spinal epidural abscess have figured in anecdotal reports of neurologic complications of IE (4,5).

MATERIALS AND METHODS

Case ascertainment:

All case records of patients registered in the medical records division of SCTIMST from 1977 to July 1994 were searched for patients with infective endocarditis in order to define the frequency and pattern of neurological complications in these patients.

Data Collection:

From the records of patients with infective endocarditis, the clinical data were abstracted using a prepared proforma. Their primary cardiac illness, features of endocarditis as evidenced by clinical signs and symptoms, echocardiographic findings of vegetations, blood culture results, the type of neurological complications and the overall outcome of these patients with neurological complications were carefully recorded.

Data Analysis:

Major part of the data is presented in a descriptive manner. The Indian experience, as depicted by this study, as well as the study published from another national medical institute (PGI, Chandigarh) will be compared with studies from Western countries to find out whether the frequency and pattern of neurological complications among Indian patients are similar or different from patients in the west.

RESULTS

We conducted a retrospective study of patients with IE seen at SCTIMST, during the period 1977 to July 1994, in order to define the frequency and pattern of neruological complications. One hundred and eleven patients, 62 males and 49 females, with a mean age (±S.D) of 23.8±12.2 years (range 0.6 to 52 years) were encountered. Neurological complications occurred in 46 patients (41.4%). Twenty patients had embolic stroke and 3 had subarachnoid hemorrhage. Meningitis occurred in 3 patients. Six patients had headache; 3 of them cn angiography had mycotic aneurysms. Rheumatic heart disease (RHD) was the predisposing lesion in the majority (57.7%); prosthetic valve endocarditis occurred in 9%. Blood culture yielded positively in only 55 out of 111 patients (49.5%). Thirty-five patients (32%) died. The mortality was significantly more in the group with neurological complications. It is concluded that the frequency and pattern of neurological complications in IE is similar to that observed in the West. However, RHD still remains the underlying cardiac lesion in the majority, and the frequency of culture negative IE is disturbingly high in our setup.

DISCUSSION

The profile of the neurological manifestations of IE among Indian patients described from two national medical institutions is depicted in Table 2.

Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, Kerala.

During the period 1977-1994, 111 patients (62 males and 49 females) with IE were encountered. Their age ranged from 7 months to 52 years. Rheumatic valvular disease was the underlying heart disease in the majority (57.7%), followed by congenital heart disease. Prosthetic valve IE occurred in 10 cases. The most frequent site of vegetations at echocardiography was at the mitral valve.

Neurological complications occurred in 46 patients (41.4%). Cerebral embolic episodes were the presenting feature in 20 cases, subarachnoid hemorrhage was encountered in 3. Three patients had mycotic aneurysms (2.7%). Blood culture was positive in 55 patients (49.5%). Staphylococcus aureus (16 cases) and Streptococcus viridans (13 cases) predominated. Candid IE occurred in 3 patients. Thirty-five patients (32%) died.

TABLE 2

COMPARISON OF THE CLINICAL AND INVESTIGATIVE DATA OF TWO INDIAN SERIES CF PATIENTS WITH INFECTIVE ENDOCARDITIS

No.of patients	186		111	
No.of episodes of IE	190		111	
Age(yrs) Mean ±S.D.	25.0±12.0		23.8±12.2	
Range (yrs)	2-75		0.6 - 52	
Sex ratio (M:F)	2.5:1		1.3:1	
Duration of symptoms prior to diagnosis(days)				
Mean	69.0±65.0		22.8±76.1	
Range	3-364		1-730	
Underlying heart disease	N	%	N	%
RHD	79	42	64	57.7
CHD	62	33	33	29.7
Normal	17	9	4	3.6
Prosthetic	2	1	10	9.0
Site of vegetations at ECHO				
Mitral	54	28.4	46	41.4
Aortic	48	25.3	36	32.4
Tricuspid	22	11.6	5	4.5
Pulmonary	6	3.2	1	0.9
Neurological complications	40	28.4	46	41.4
Stroke	31	16.0	20	18.0
SAH	4	2.0	3	2.7

Meningitis	3	2.0	2	2.7
Cranial nerve palsy	2	1.0	-	-
Headache	-	-	6	5.4
Seizures	-	-	7	6.3
Microbiology				
Culture negative	103	54.2	56	50.4
Staphy aureus	32	16.8	15	13.5
Strept. viridans	15	7.9	13	11.7
Gram negative	17	8.9	7	6.3
Candida	2	1.1	3	2.7
Mortality	47	25.3	35	31.5

Postgraduate Insitute of Medical Education and Research (PGIMER), Chandigarh:

Between 1981-1991, 186 patients with 190 episodes of IE were ascertained (8). The age ranged from 2 to 75 years, mean 25±12 years. Rheumatic heart disease was the most frequent underlying heart lesion (42%), followed by congenital heart lesion (33%). Prosthetic valve IE was encountered only twice. Blood cultures were positive in only 47% cases. Overall mortality was 25%. Neurologic complications were observed in 40 episodes of IE (21%).

Interstudy comparisons

The data from both these Indian studies are remarkably

similar and differs from Western experience in the following respects: (1) The mean age of patients are much lower. In a recent large series of 544 cases of IE from United Kingdom, the mean age was 51.6 years, and nearly 30% of the patients were aged >65 years (25); (2) Rheumatic heart disease still remains the major underlying heart lesion among Indian patients. In a recent report from Brazil, 69 of 287 patients (24%) had no known heart disease (26); (3) A low rate of blood culture positivity among Indian patients is a source of real concern. In PGIMER series, a significantly greater number of culture - negative patients has received antibiotics prior to admission. The frequency and pattern of neurological complications among Indian patients are not different from the patients from the West.

Diagnosis

A high index of suspicion is required for the diagnosis of IE. Any patient presenting with stroke, fever and heart murmur should be considered to have IE unless proved otherwise. An elevated ESR makes the suspicion of IE stronger. Prompt blood cluture should be done to establish a bacteriological diagnosis.

Echocardiography (ECHO)

Valvular vegetations can be detected by transthoracic

ECHO in upto 70-80% of patients; transesophageal ECHO has a higher yield, upto 96% of patients with proven IE (4). The role of ECHO in predicting the risk of cerebral embolism in patients with IE is uncertain. Although ECHO evidence of vegetations of >10 mm was associated with a high risk of embolism in one study (27), others could not substantiate this (3). In patients with neurological complications at presentation, ECHO may be negative because the vegetations have already embolized.

Noninvasive neruoimaging:

The most useful investigation in a patient with suspected cerebral embolism associated with IE is CT scan. CT is also useful in the diagnosis of brain abscess and meningitis. It also helps to select patients for cerebral angiography to rule out mycotic aneurysms. Mycotic aneurysm is unlikely to be present when CT scan is normal.

MRI is more sensitive than the CT scan. Ross et al (28) investigated 21 patients with mycotic aneurysm with magnetic resonance angiography (MRA); 3 of them remained undetected by MRA. Therefore, a normal MRA does not exclude a mycotic aneurysm.

Angiography:

The role of angiography, currently digital substraction

angiography (DSA), is to diagnose mycotic aneurysm. A high index of suspicion is required for the diagnosis of mycotic aneurysm. In an acutely ill patient, angiography carries a definite risk. Consequently, angiography is usually reserved for the following IE patients: (1) Those presenting with focal neurological deficits; (2) Those presenting with vascular headaches; (3) Those demonstrating hemorrhagic CSF; (4) Those without focal deficits, if they are under consideraticn for anticoagulation (4,5,13)

CSF examination:

CSF abnormalities were detected in 48 of 69 IE patients of one study (10). Several patterns, including purulent, hemorrhagic, aseptic and normal, can occur. Every patient of IE with a suspicion of meningitis or subarachnoid hemorrhage (without CT scan evidence) should undergo CSF examination. The availability of CT and MRI has obviated the need of CSF examination in the majority.

MANAGEMENT

Medical

Antimicrobial thearpy

Appropriate antibiotic therapy for a period of 6 weeks is the key to a successful management of IE. The initiation of antibiotics is associated with a substantial reduction in the number of cerebral embolic events. According to

Davenport and Hart (18), the daily frequency of embolism in prosthetic valve IE falls from 9% to 0% after antibiotic therapy.

A large proportion of unruptured mycotic aneurysms resolve under appropriate antibiotic administraticn. Since the natural course of mycotic aneurysm under medical therapy is unpredictable, careful follow-up and repeat angiography after 2-3 weeks of thearpy would be required (4,5).

Antiplatelet drugs:

Taha et al (29) compared the CT incidence of stroke and change in vegetations as seen in ECHO, prospectively in a small group of patients with IE randomized to either low-dose aspirin (75 mg/day) or no aspirin. The mean area of vegetation and the frequency of stroke was significantly less in the aspirin group. No aspirin related complications occurred. The role of low dose aspirin therapy in IE warrants further study.

Anticoagulation:

Because of the high risk of intracranial hemorrhagic complications, the use of anticoagulants in patients with native-valve IE is contraindicated. Patients with prosthetic valve IE are at increased risk of thrombo-embolism, and should receive carefully supervised

anticoagulant treatment. In a group of patients with prosthetic valve IE, Wilson et al (30) observed embolic episodes in 58% of nonanticoagulated patients compared to 8% of anticoagulated patients.

Surgical

Neurosurgery

The optimal therapeutic strategy of mycotic aneurysm is uncertain. Majority of the centers practice a case-by-case approach as follows: (1) Superficial unruptured aneurysms are easily accessible surgically; (2) A single unruptured aneurysm proximal to the bifurcation is usually followed under antibiotic therapy with serial angiograms; enlargement or leaking would necessitate surgical intervention; (3) Presence of mass effect or intracerebral hematoma related to mycotic aneurysm needs surgery; (4) Patients with multiple aneurysms are initially treated conservatively, enlargement or leaking in one or more of them requires surgery (4-6).

In most of the patients with multiple abscess, antibiotic therapy results in complete resolution. Patients with isolated abscesses measuring more than 2 cm may need CT guided aspiration.

Cardiac Surgery

Following an acute cerebral embolic episode, there is a risk of hemorrhage into the infarcted region when the

patient is anticOagulated for cardiopulmonary bypass. Many centers advocate a delay of 3-4 days or until CT resolution of cerebral edema before cardiac surgery is undertaken. There have been no instances of rupture of mycotic aneurysm during the perioperative period of cardiac surgery. Hence, valve replacement in patients with mycotic aneurysm can be carried out prior tc neurosurgical intervention unless there is a mass effect or hematoma. In patients with mycotic aneurysm, replacement with bioprosthetic valve is preferred, thereby obviating the need for postoperative anticoagulation.

Prognosis

In thd Massacheusetts General Hospiral series, the mortality rate of 84 patients with neurological complications was 58% in comparison to 20% mortality in 134 patients without neurological deficit (10). In the series of Jones et al (21), the presence of neurological complications increased the mortality by a factor of 1.6. In PGIMER series, there was a significantly higher number of neurological complications in patients who died than those who recovered (8). In patients older than 60, the outcome of Ie is pcorer than in those who are younger (31). In patients with detected mycotic aneurysm, the overall mortality rate was 46% in one study, 30% if the aneurysm remained intact, and 80% if it ruptured (32).

CONCLUSION

The overall incidence of neurological complications in patients with IE is about 30%, a vast majority of these patients have left sided valvular disease; in 15-25% the neurological deficit is the onset symptom of IE. More virulent organisms, such as staphylococcus and enterococcus are associated with a higher frequency of complications. Because the neurological manifestations of IE may be so protean in nature, the neurologist need to consider IE as a possible diagnosis in every patient with fever and stroke. IE can occur in persons unknown to have predisposing heart disease, this is particularly true in elderly patients subjected to invasive procedures leading to nosocomial infection, and in drug abusers. CT and MRI are useful radiological techniques in the diagnosis of neurological sequlae of IE. Cerebral angiography should not be delayed in patients suspected to have a mycotic aneurysm. The corner stone of management of IE is early institution of appropriate antibiotic therapy, which prevents or diminishes the risk of neurological complications. Anticoagulants should be avoided in patients with native valve endocarditis because of the risk of hemorrhagic intracranial complications. Anticoagulants should be continued in patients with prosthetic valve IE who do not have evidence

of intracranial hemorrhage. Despite the advances in the diagnosis and management of IE, patients with neruological complications continue to have an unfavourable prognosis. Early diagnosis of IE and prompt antibiotic therapy reduces the incidence of neurological complications.

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