SPINOCEREBELLAR DEGENERATION AND SLOW SACCADES IN THREE GENERATIONS OF A KINSHIP: CLINICAL AND ELECTROPHYSIOLOGIC FINDINGS

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Slow horizontal saccadic eye movements (SEM) were first reported in patients with spinocerebellar degeneration (SCD) by Wadia and Swami [34]. The syndrome is characterized by an autosomal dominant pattern of inheritance, a slowly progressive course, ataxia, scanning speech, and slow horizontal SEM with lack of nystagmus. Since this initial observation, other cases of SCD with slow SEM have been reported [1, 7, 16, 21, 23, 24, 25, 28, 30, 32, 33, 34, 35, 37]. The major anatomical substrate for SEM is the pontine paramedian reticular formation (PPRF)[8, 9, 18, 20], which is also probably the origin of phasic REM sleep [17, 39]. Although there has been no clear evidence of a common origin of these functions, a recent report of absent REM stage of sleep and slow SEM in patients which spinocerebellar degeneration implies possible common mechanisms [25].

We have studied four members (three generations) of a family with spinocerebellar degeneration and slow horizontal SEM to further determine the physiological characteristics of their eye movements; and to determine electrophysiologically the degree of impairment of diverse anatomical structures of the central and peripheral nervous systems. Our studies included: all-night polysomnograms, recordings of eye movements (particularly SEM); optokinetic and vestibular stimulation, audiograms, auditory brainstem evoked responses, peripheral nerve conduction studies, cortico-somatosensory evoked potentials and visual evoked responses.

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CACE REPORTS

Data concerning clinical, neurological and laboratory findings of the patients studied are summarized in table 1. The pedigree and degree of clinical involvement are depicted in figure 1. All the patients had full extraocular movements without nystagmus and except for the slow saccadic eye movements, cranial nerve examination was normal. Weakness was not evident, deep tendon reflexes were present and normal, and plantar responses were flexor in all the patients. Sensory examinations were normal in all patients to touch, pain and position stimuli. Vibratory sensation was slightly decreased

Data	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	60	25	22	9
Age at onset symptoms (years)	50	25	19	7
Sex	Male	Female	Female	Male
Slow horizontal saccades	+++	+++	+++	++
Ataxia and scanning speech	+++	+++	+++	0
Muscle tone	Normal	Slightly flaccid	Slightly flaccid	Normal
EKG	Normal	Left ventricular hypertrophy	Normal	Normal
Echocardiogram	Normal	Mitral valve prolapse	Mitral valve prolapse	Normal

Table 1 — Clinical and laboratory manifestations of SCD and slow saccades in three generations of a kinship. Grading system: 0, absent; + mild; ++ moderate; +++ severe.

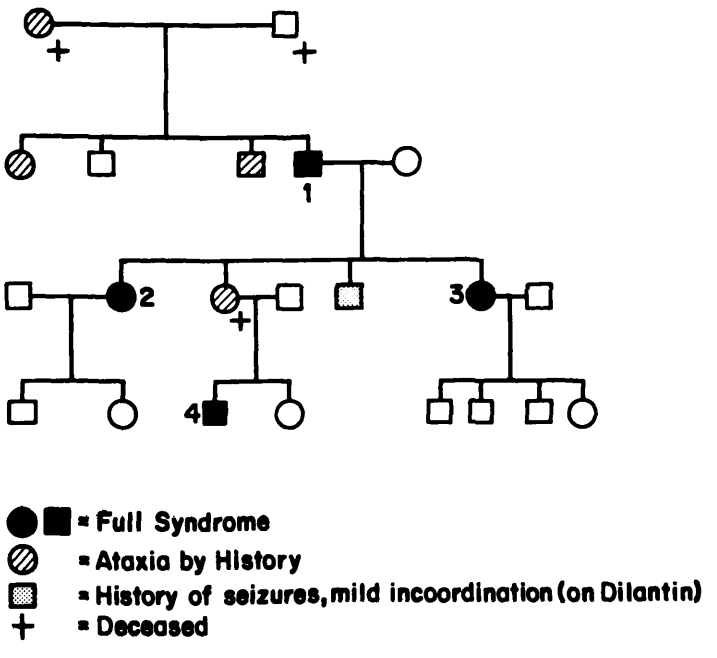

Fig. 1 — Pedigree of family showing 4 cases of spinocerebellar degeneration with slow SEM from 3 generations suggesting autosomal dominant inheritance.

in the toes of patients 1 and 2. The following laboratory studies were normal in these patients: complete blood count, blood sugar, BUN, electrolytes uric acid and proteins, serum creatinine, phosphokinase, serum glutamic and oxalacetic transaminase, cholesterol, triglycerides, lactate, piruvate, protein electrophoresis, serum B_{12}, folic acid, carotene and vitamin A, T_3, T_4, urinalysis; cerebral spinal fluid cells, protein and sugar (except cases 3 and 4 in which no lumbar puncture was done). Mental status, chest x-ray and CAT scan of the head were normal in all patients. A bone marrow biopsy done in case 2 was normal. A muscle biopsy done in the left vastus lateralis muscle of case 2 revealed scattered atrophic angular fibers but no evidence of fiber type grouping.

MATERIALS AND METHODS

EYE MOVEMENTS — Horizontal eye movements were examined with a Beckman oscillographic recorder. System sensitivity was 10μV/mm pen deflection with electrical activity filtered (minus 3dB points 0.016 and 100 Hz.). Silver-silver chloride electrodes were positioned in the horizontal optic axis adjacent to the outer canthi of both eyes with ground at the forehead. Electrode resistance was established at less than 5,000 ohms. The following test battery was administered: calibration, horizontal saccadic eye movement, pendulum tracking, optokinetic stimulation, examination for presence of gaze nystagmus, and caloric stimulation. The velocity and quality of SEM were measured while having the patients visually fixate on small red lights flashing between 20° right and midline, 20° left and midline, and 20° right and 20° left of midline at a flash rate of 0.5/sec. Pursuit eye movements were recorded while the patient followed a pendular target in the horizontal visual plane. Optokinetic stimuli were projected in both right and left directions at increasing stimulus velocities. Gaze at stationary targets in the horizontal visual plane was recorded at angles of 15° and 20° to the right and left of primary eye position. The caloric test was performed by irrigating each auditory canal with 44°C water for 30 seconds3. Approximately 100 seconds after onset of the irrigation the patients were asked to open their eyes and visually fix on a target placed one meter directly in front of them.

AUDIOMETRIC EVALUATION — Peripheral hearing was evaluated by pure tone audiometric screening tests at octave frequency intervals ranging from 250 to 8,000 Hz. 15.

AUDITORY BRAINSTEM RESPONSE (BAER) — Stimuli consisted of a series of 70 dBnHL 14 clicks presented monaurally to the subject via a headphone (TDH-39) at a rate of 10/sec. Recordings were obtained from silver-silver chloride electrodes at the vertex referred to ipsilateral earlobes with a forehead ground. Electrode resistance was established at less than 2,000 ohms. EEG activity was filtered (minus 3dB points: 100 Hz and 3,000 Hz) and amplified 10,000 times. The electrical activity, time locked to the stimulus, was averaged (Nicolet 1072) over the first 10.24 msec. following stimulus onset at a sampling rate of 25,000 Hz. Two replicated averages of 2,048 sweeps of the auditory brainstem response were summed prior to measurement of absolute peak and interwave latencies.

POLYSOMNOGRAMS — In a specially prepared sound-attenuated bedroom, EEG, eye movements (EOG), submental and anterior tibialis electromyograms and electrocardiograms were recorded. Recordings were scored in accordance with the recommendations of Rechtschaffen and Kales26 in 1968.

SOMATOSENSORY EVOKED POTENTIAL (SSEP) — Both near and far field somatosensory evoked potentials were studied. The cerebral responses were recorded with silver disc surface electrodes applied to the scalp with collodion. The active electrode for recording potentials generated by stimulation of the posterior tibial nerves was placed 2 cm. behind Cz (International EEG Electrode Placement System). The active electrodes for recording of stimuli from the median nerves were placed 7 cm. below that of the posterior tibial nerve active electrode along a line drawn from that electrode to the external auditory meati contralateral to the side stimulated. The median nerve reference electrode was placed mid distance between the lower limb recording and reference electrodes. Electrode resistances were less than 5,000 ohms. Stimulation sites for the lower extremities were the posterior tibial nerves behind the medial malleoli12. The upper limb stimulation was applied over the median nerves immediately above the wrist folds. The stimuli were square wave electrical pulses of 100 msec. duration with voltage sufficient to produce a minimal visible muscle twitch of the thenar areas or short flexion of the toes. A Teca TE-4 Electromyograph and NS-6 stimulator were used as recording and stimulating equipment. The potentials were amplified through a TECA AA6 MKIII Amplifier with filters set at 0.8 and 800 Hz. and averaged by a TECA DAV-6 computer with analog-to-digital conversion of 8 bits complimented by 8 point interpolator. The number of sweeps were averaged 128 to 512. The potentials were recorded on fiber optic paper and subsequently analyzed. For far field somatosensory evoked potential, the recording electrode was placed 2 cm behind Cz with reference over the shoulder contralateral to the upper extremity being stimulated11. The ground electrode was the same as described for the near field technique. From 1,000 to 2,000 sweeps were averaged and the filters were set at 10 and 2,500 Hz. The absolute peak latencies of all potentials were measured.

VISUAL EVOKED RESPONSE (VER) — Visual evoked responses were studied in a darkened room by using 128 stimuli by checkerboard pattern-reversals from a Nicolet Model 1006 black and white pattern generator. The subjects were seated 100 cm. from the screen. The visual field angle arc was 55°. Each eye was stimulated independently. Recordings were made from active silver-silver chloride electrodes placed sagitally at the 02, P2 and C2 scalp location (International EEG Electrode Placement System) referred to the two ear electrodes tied together. The evoked potentials were amplified through GRASS 7P11 amplifiers and six channels of recording were fed to a Nicolet Med 80 computer with 250m/sec window for averaging. The ongoing EEG activity was monitored by graphic readout during stimulation of all channels. A low linear frequency filter setting of 100 HZ was used for all readings. Two averages of 128 stimuli at a rate of 1 per second were obtained on stimulation of each eye. These were summed together for each eye and the latencies were obtained from the summed values. Peak latencies of the potentials were measured.

NERVE CONDUCTION VELOCITY (NCV) — Motor nerve conduction studies of median, ulnar, peroneal and posterior tibial nerves were performed using standard

techniques [4, 31]. A TECA TE-4 electromyograph provided 100 μ/sec. square wave stimulation of supramaximal intensity at a rate of 1/sec. Filter settings were 8-8,000 Hz. Sensory evoked responses were obtained orthodromically from the median nerve using silver ring electrodes and recording at the wrist with silver-silver chloride disc electrodes [6] and from the sural nerve antidromically at the ankle [27] with filter setting of 16-32K Hz. The responses were averaged with a TECA DAV6 averager. Ulnar nerve F-response latency was obtained stimulating at the wrist and recording at the hypothenar eminence [10]. Latency of the tibial nerve H-reflex was determined by stimulating at the popliteal fossa and recording at the median gastrocnemius muscle with reference at the Achilles tendon [5].

RESULTS

Ocular fixation instability (flutter) was noted during calibration in all patients but patient 2. The mean velocity of horizontal saccadic eye movements for all patients was below that of our normal control range (Table 2). Each patient in the study was unable to pursue the pendular target smoothly and required corrective saccades to refixate. None of the four patients was able to produce normal horizontal optokinetic nystagmus responses as evidenced by: saccadic alternation of the slow components [13], low and variable eye velocities, inability to appreciably increase slow-phase velocity with increasing stimulus velocity and poor or absent responses at higher stimulus speeds. Because of these factors, accurate mean measures of the optokinetic responses could not be computed. In eccentric and primary-gaze conditions, horizontal gaze nystagmus was absent in all patients with the exception of patient 1. This patient demonstrated square-wave jerks that were enhanced in the left-gaze and center-gaze positions and suppressed with eye closure and right-gaze. In caloric testing with 44°C with water, all patients showed an extreme tonic deviation of the eyes in the direction of expected slow phase with an absence of nystagmus and reported

Direction	Patient 1	Patient 2	Patient 3	Patient 4	Control Group Mean and Range
Right 20 to center	54.0	75.0	105.0	26.5	243.5 (214 — 285)
Center to right 20	41.5	52.5	93.0	64.5	215.0 (170 — 244.5)
Center to left 20	48.0	58.5	97.5	39.0	235.0 (189 — 265)
Left 20 to center	48.0	45.0	97.5	37.5	197.5 (170 — 213.5)
Right 20 to left 20	64.5	78.0	105.0	52.0	306.0 (244.5 — 344)
Left 20 to right 20	98.0	61.5	112.5	40.5	274.5 (244.5 — 314)

Table 2 — Mean saccadic velocity °/sec. - Mean velocities of horizontal eye movements. Saccadic stimuli consisted of small red lights alternately flashing at a rate of 0.5/sec. between 20° right and middline (20° R-C); 20° left and midline; 20° right and left of midline (20° R-20° L). Controls were twenty neurologically intact subjects of ages 10 to 60 years.

oscillopsia approximately 100 seconds after the onset of irrigation while visually fixing on the target placed in front of them.

The audiograms were normal in all patients except for patient 1, who showed a bilateral sensori-neural loss of hearing at 4KHz, (thresholds of 35 dB for the right and 45 dB for the left ear). This finding was attributed to presbyacusis. Latencies and wave morphology of BAER and VER were within normal limits for all patients when compared with the normal control subjects of our laboratory. Two consecutive overnight polygraphic recordings were obtained from each patient. Total time in bed, total sleep time and sleep latencies were normal for their respective ages. Each patient had distinctive non-REM stages. Although phasic periods of REM were not discernible during any period of REM sleep in patients 1, 2, and 3, it was possible to identify normal percentages of REM stages on the basis of the EEG monitoring and decreased muscle tone (Fig. 2). In patient 1, there was evidence of phasic periods of REM, but the percentage was decreased relative to total REM sleep for his age group 36.

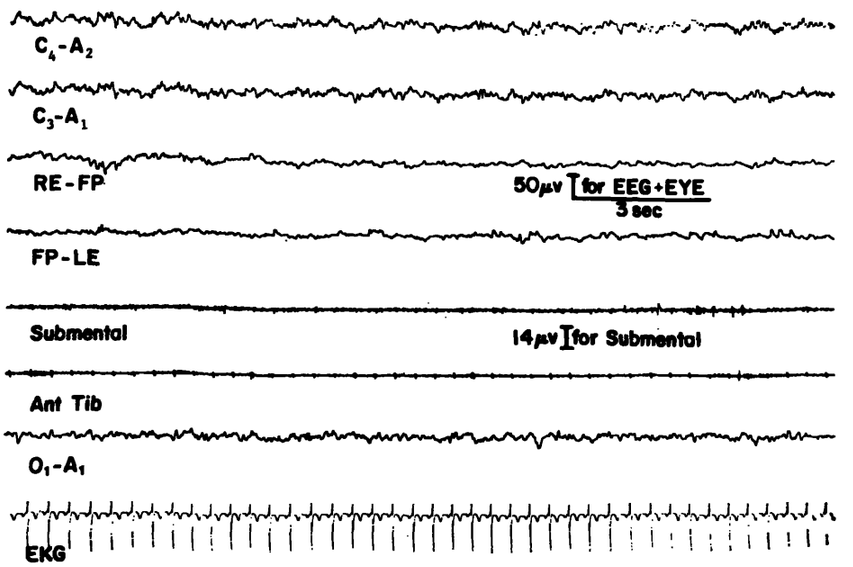

Fig. 2 — Samples of REM stage in case 2. The patient is clearly in REM stage of sleep as documented by EEG slowing (CH-A2, C3-A2), decreased EMG activity in submental and anterior tibial muscle recording yet eye movements are not seen in RE-FP and FP-LE.

All patients had normal motor nerve conduction velocities, but only patient 4 had H-reflexes present. Patient 1 had no response to sural nerve stimulation, but had normal median sensory conduction with a low amplitude response of 5 microvolts. Patient 2 demonstrated low amplitude sensory evoked responses from the sural and median nerves of 2 microvolts and 4 microvolts respectively. Far-field brainstem SSEP showed no responses to stimulation of the median nerves in patients 1, 2, and 4.

Near-field potentials were elicited in patients 1, 2, and 4 with stimulation of the posterior tibial and median nerves. Patient 1 produced poorly defined low amplitude prolonged potentials (45 msec. and 23 msec.) for the posterior tibial and median

nerves respectively. Patient 2 showed no consistent responses from the posterior tibial nerves, but median nerve responses were present with a borderline prolonged latency (20 msec.) and low voltage. Patient 4 showed normal latencies from the right posterior tibial (33 msec.) and right median (19 msec.) nerves; however, the configuration was distorted and amplitude low when these results were compared to published normal values 11, 12.

DISCUSSION

The clinical characteristics of the patients reported here is similar to the form of olivopontocerebellar degeneration initially described clinically and pathologically by Wadia and Swami [34] in 1971. Our studies revealed that although the clinical symptoms of the disease do not appear until the second decade of life, clinical and physiological evidence of slow horizontal SEM may be evident earlier. Electrophysiological data in the present cases, particularly the low amplitude sensory evoked responses and absent H-reflexes, indicate impaired function of sensory axons. Muscle biopsy findings of patient 2 demonstrates involvement of motor axons as well, thus suggesting a peripheral neuropathy not detected clinically. It was striking, however, that no clinically significant sensory abnormalities were detected inspite of the abnormal electrophysiological findings. Stretch reflexes were normal in all patients. The highly abnormal near and far-field somatosensory evoked responses found in these patients may be caused by a peripheral neuropathy, however, we doubt such possibility because, as previously reported [22], in mild neuropathies it has been possible to obtain SSEP. Thus, we believe that these findings more likely indicate involvement of the posterior columns or higher sensory pathways. Impairment of the brainstem mechanisms associated with horizontal SEM, optokinetic nystagmus and caloric nystagmus was substantiated by clinical and electrophysiological findings; particularly the presence of slow horizontal SEM, abnormal horizontal optokinetic responses and the absence of nystagmus following caloric stimulation, although subjective dizziness suggested peripheral vestibular function.

The mechanisms underlying REM sleep have been studied extensively in animals [8, 9, 18, 20], but little is known about the anatomical and physiological substrate of this phenomenon in man. There does appear to be a relationship between SEM and REM. Both forms of eye movement are felt to originate in the PPRF [9, 17, 39]. Absence of phasic periods of rapid eye movements during sleep was found in all but one of our patients. The presence of REM sleep without eye movements was substantiated by characteristic EEG changes, decreased muscle tone, and changes in EKG and respiration. It is likely that the absence of phasic REM and slow SEM in these patients is caused by abnormalities of the PPRF which are also believed to be the cause of the abnormal optokinetic and caloric responses encountered in these patients. Other abnormalities suggesting cerebellar pathology, such as abnormal smooth eye pursuit, were also demonstrated [2, 19, 29, 38].

The neurophysiological data obtained in these studies were of prime assistance in determining functional abnormalities of some brainstem neurons, cere-

bellum, peripheral nerves and, possibly, posterior columns in these patients despite the lack of conclusive anatomopathological studies. Our observations seem to indicate that horizontal SEM, phasic periods of REM sleep and the fast components of optokinetic and vestibular responses are all generated by the same neurons in the PPRF. We also concluded that the changes in muscle tone occurring during REM sleep are not necessarily modulated by the same neurons, in that our patients went through REM sleep despite the lack of phasic rapid eye movements during the REM periods.

SUMMARY

Four members of a family with spinocerebellar degeneration and slow saccadic eye movements are described. Detailed electrophysiological studies revealed abnormalities of neurological pathways not apparent clinically. The patients had slow saccades as mesasured electrophysiologically, as well as absence of rapid eye movements (REM) despite REM stages of sleep. These studies suggest that although saccadic eye movement and REM are mediated through the pontine paramedian reticular formation, other characteristics of REM sleep are not necessarily mediated through the same neurons.

RESUMO

Estudo clínico e eletrofisiológico em três gerações de uma família com degeneração espinocerebelar e movimentos oculares lentos.

Este trabalho apresenta o estudo de quatro membros de uma família com degeneração espinocerebelar e movimentos sacádicos oculares lentos. Estudos neurofisiológicos detalhados mostraram anormalidades em tratos do sistema nervoso central que não eram aparentes ao exame clínico. Além dos movimentos oculares sacádicos lentos também foi possível demonstrar durante o registro poligráfico do sono a ausência completa dos movimentos oculares rápidos do sono REM apesar dos outros parâmetros do sono REM estarem normais. Desta maneira o estudo permite que se tire as seguintes conclusões: os movimentos sacádicos oculares lentos e os movimentos oculares rápidos do sono REM são mediados por mecanismo central comum possivelmente através da formação reticular paramediana da ponte; outras características fisiológicas do sono REM, particularmente a hipotonia muscular, não são necessariamente mediadas pelo mesmo sistema neuronal.

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