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OTONEUROLOGIC AND AUDIOLOGIC FINDINGS IN FIBROMYALGIA

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ABSTRACT. Patients with fibromyalgia were studied with otoneurological and audiological tests. Altogether 168 patients (141 women) participated. Vertigo/dizziness was reported by 72% of the patients. Sensorineural hearing loss was found in 15% of the cases. Auditory brainstem responses (ABR) and oculomotor tests were applied, and statistical comparisons between patients and controls were performed. Significant differences were found for the absolute latency of wave V and for the I–V and III–V interpeak latencies, indicating brainstem dysfunction. Abnormal ABR recordings were found in 30% of the cases. In the oculomotor study the mean velocity gain for the smooth pursuits and the mean saccadic latency were significantly different between patients and controls. Abnormal saccades were seen in 28% and pathological smooth pursuit eye movements in 58% of the patients. Electronystagmography was pathological in 45% of the cases. The findings indicate that CNS dysfunction frequently occurs in patients with fibromyalgia, although proprioceptive disturbances might also explain some of the abnormalities observed.

Key words: auditory brainstem response, electronystagmography, fibromyalgia, hearing loss, oculomotor tests, saccadic eye movements, smooth pursuit eye movements.

INTRODUCTION

Although fibromyalgia is a syndrome of unknown aetiology and pathophysiology, diagnostic criteria have been formulated and the syndrome is looked upon as a fairly well-defined condition (27). Widespread and chronic muscular pain is a cardinal symptom, but fatigue and symptoms of autonomic dysfunction are also commonly reported (28).

In advanced cases, symptoms which can be indicative of cerebral dysfunction, e.g. sleep disturbances, headache, disturbed memory and difficulties with concentration, may be present. Hallucinosis, probably caused by cerebral irritation and not part of a functional mental disorder, has been reported (14). In a study of regional cerebral blood flow in patients with fibromyalgia with the 133 Xe inhalation technique, regional flow reductions were observed in a high percentage of cases (15). These studies could indicate that CNS dysfunction is likely in advanced cases of fibromyalgia.

Disturbances of the eye motor function have been reported in patients with fibromyalgia. Ödkvist et al. (18) found abnormalities affecting smooth pursuits and electronystagmography. Rosenhall et al. (20) found disturbances of the saccades in 42% of cases and of the smooth pursuits in 89% of cases in patients with fibromyalgia with dysaesthesia. One explanation for oculomotor disturbances is CNS dysfunction involving the systems generating, executing or regulating the eye movements. However, erroneous proprioceptive signals may also cause disturbances of the oculomotor function (4). A further indication of a CNS dysfunction is the abnormal auditory brainstem responses (ABR) observed in 30% of patients with fibromyalgia (21). However, these observations have been made in selected cases of non-consecutive patients who had fibromyalgia with dysaesthesia.

The present study, which includes the patients of the earlier studies cited above (20, 21), is a report of otoneurological and audiological test results of all patients, fulfilling the diagnostic criteria if fibromyalgia, referred to a rehabilitation clinic during 1983–93.

SUBJECTS

From a population of patients with pain problems, mainly chronic, idiopathic pain, referred to a rehabilitation clinic for pain treatment and/or vocational guidance, 168 patients fulfilling the criteria of fibromyalgia were selected for the present study.

Initially, the criteria proposed by Yunus et al. in 1981 (28) were used. These criteria implicate generalized aches and pains or prominent stiffness, involving three or more anatomical sites for at least 3 months, with at least five

typical and consistent tender points, and with no secondary causes. After 1990 the criteria proposed by the American College of Rheumatology (27) were used. These include pain perceived in all four quadrants of the body for at least 3 months, and having at least 11/18 tender points at specific anatomic sites.

Of the 168 patients, 141 were women (mean age 45.1 years, range 21–73 years) and 27 men (mean age 46.0 years, range 23–61 years). Almost all cases were on long-term sick leave or on an early pension because of the pain syndrome. They were, except from a few cases, blue-collar workers. Immigrants from rural districts in former Yugoslavia and Greece constituted 56% of the patients.

Exclusion criteria were earlier CNS infections, head trauma with unconsciousness and abuse of alcohol and drugs. According to extensive files available, no cases of toxicomania or other abuses seemed to be at hand. Specific neurological disease was excluded by a thorough clinical examination carried out by a senior internist with special interest in neurology (GÖ). All patients were also examined by an orthopaedic surgeon who excluded orthopaedic disease as a cause of the pain. Rheumatologic or other inflammatory disease was excluded by laboratory test procedures and clinical examination.

The patients (and the controls) were instructed verbally and by letter to stay off all medication for 48 h prior to the test procedures. Measurements of metabolites of different drugs were not performed, however.

METHODS

The hearing of each patient was measured using pure tone and speech audiometry according to standard procedures. A history of dizziness/vertigo and disturbances of the equilibrium was taken. All tests were performed by trained audiologists.

Auditory brainstem response (ABR)

All patients were tested with ABR, an evoked response method which records the function of the cochlear nerve and the auditory pathway in the brainstem. In 157 cases, equipment based on a Nicolet 527 signal averager was used; 1024 clicks with alternating polarity were presented monaurally by TDH-39 earphones. The intensity level was 80 dBnHL, and the repetition rate 25 stimuli/s. The signals were bandpassed (150–2500 Hz) and averaged. In 11 cases a Madsen 2250 ERA was used. Rarefaction 1000 half-sine waves with an intensity level of 80 dBnHL and a repetition rate of 20 stimuli/s was used. The filter settings were 150–2000 Hz.

There are different patterns of ABR abnormalities indicating retrocochlear or brainstem pathology. The following parameters were studied in this investigation: (a) the absolute latencies of waves I, III and V; (b) interpeak latencies (IPLs) between waves I and V (I–V IPL), I and III (I–III IPL) and III–V (III–V IPL); (c) the interaural time difference (ITD) of wave V and the I–V IPL (ITD) and (d) the amplitude of wave V in relation to the amplitude of wave I (V/I ratio). Normative criteria for the latency parameters were established using a control group, see below. ITDs of $\geq$0.4 ms were regarded as pathological (23). Regarding the amplitude parameter the criterion adopted by Starr & Achor (24) was used. This implies that an amplitude ratio wave V/wave I of $\leq$0.5 is regarded as abnormal.

Control group for ABR

One-hundred-and-twenty-four apparently healthy subjects were enrolled as controls for ABR; 81 women (mean age 44.6 years, range 21–75 years) and 43 men (mean age 40.7 years, range 22–75 years). The controls were tested with the same Nicolet equipment as a majority of the patients. All had normal hearing ($\leq$20 dB) in the frequency range 0.25–2 kHz and normal hearing or, at most, a slight hearing loss (<40 dB) at frequencies 3–6 kHz.

Oculomotor tests

All except two patients were given oculomotor tests, which monitor the neurological systems responsible for the eye motor function.

Voluntary horizontal smooth pursuit eye movements (slow, tracking eye movements) with gaze angle of 40° and target velocities of 10°/s, 20°/s and 30°/s were recorded. Six smooth pursuits for each direction and target velocity were averaged. The velocity gain (the ratio between the velocity of the eye movement and the velocity of the target) was calculated.

Voluntary horizontal saccades (rapid eye movements) with gaze angles of 20°, 40° and 60° were recorded. Seven to eight saccades for each of the gaze angles and for both directions were averaged. The maximal velocity and the accuracy of the saccades were calculated for all subjects tested. The latency (the reaction time from the change of the target to the initiation of the eye movement) was calculated for 91 of the patients.

Control group for oculomotor tests

The control group for oculomotor tests comprised 90 apparently healthy individuals with neither chronic pain nor vertigo. There were 48 women (mean age 43.1 years, range 21–76 years) and 42 men (mean age 40 years, range 21–76 years). The normal subjects were tested with the same methodology and the same equipment as the patients.

Electronystagmography (ENG)

ENG was performed on 85 of the patients. ENG measures the vestibular function, both the peripheral in the labyrinth, and the central in the vestibular nuclei, the vestibulocerebellum and other locations. Horizontal eye movements were recorded with a Siemens-Elema Mingograph 34 ink-jet recorder. The presence of spontaneous nystagmus with and without gaze fixation, of gaze nystagmus and of positional nystagmus was observed. A bithermal caloric test was performed with water temperatures of 30° C and 44° C. Unilateral weakness of the caloric response or the presence of directional preponderance was calculated. Inability of visual suppression of the caloric nystagmus was noted. The normative criteria suggested by Coats (5) were used.

Statistical evaluation

Comparisons were made between the patients and the controls using the Mann-Whitney U test. Women and men were analysed separately. As regards ABR, comparisons were performed for the latency parameters (absolute latencies, IPLs and ITDs). A hearing loss induces a latency shift,

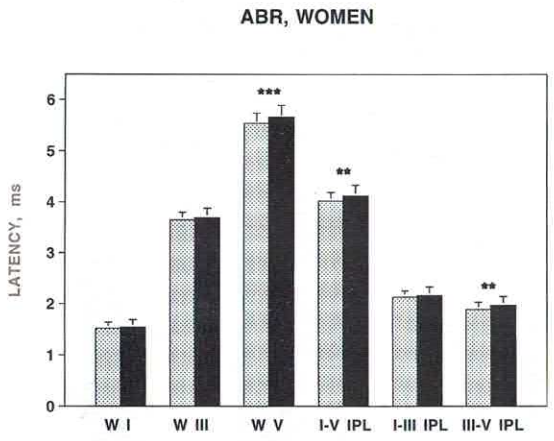

Fig. 1. Comparison between female patients (black bars) and matching controls (grey bars) for the different ABR parameters measured. Mean values and SDs are given. The absolute latency of wave V and the I–V and III–V interpeak latencies differ significantly between the groups. The asterisks represent the level of significance.

which makes a neurological evaluation of the ABR difficult in hearing-impaired subjects. For this reason only subjects with no or only minor hearing loss were included (≤20 dB in the frequency range 0.25–2 kHz and <40 dB at the frequencies 3–6 kHz). Since the latencies are also dependent on the equipment used, only patients tested with the Nicolet device were included; 128 women and 24 men fulfilled these criteria and were selected for the statistical ABR evaluation.

The following oculomotor test parameters were selected for statistical evaluation: the mean smooth pursuit gain for the target velocity 20°/s, and for saccades the mean velocity, accuracy and latency for the gaze angle 60°. Averaged values for right- and left-directed eye movements were used.

The results of ABR and oculomotor tests for each patient were also compared with the normative standards used in our laboratory. These normative standards are based on healthy

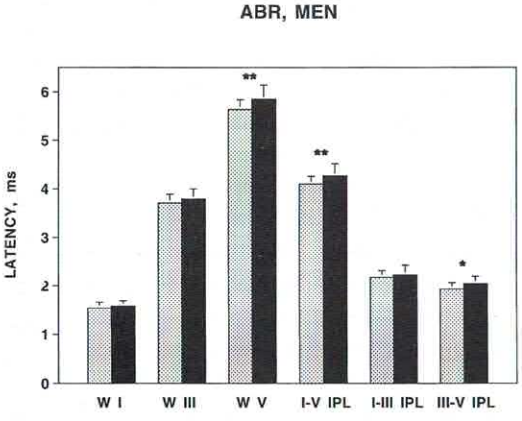

Fig. 2. Comparison between male patients (black bars) and controls (grey bars) for the different ABR parameters studied. Wave V and the I–V and III–V IPLs were significantly different, the same finding as in the female group.

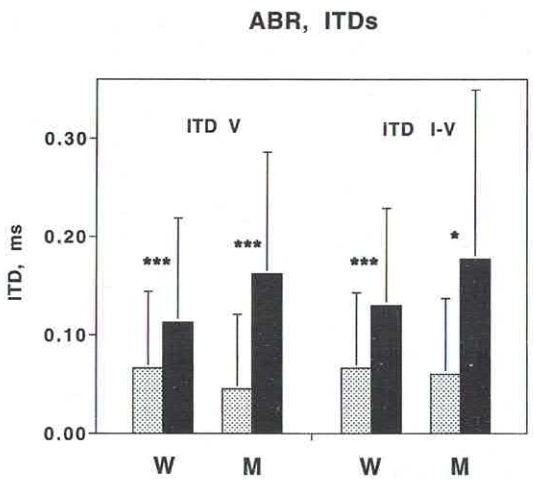

Fig. 3. Interaural time differences for wave V (ITD V) and for the I–V IPL (ITD I–V). Comparison between patients (black bars) and controls (grey bars) for women (W) and men (M). Mean values and SD's are given. Statistically signifcant differences were observed for both parameters for both genders.

controls (including the control groups used in the present study) taking into account age, sex and hearing loss. Normal mean ±2 SD was regarded as a normal test result, and individual deviations from the norms were registered.

RESULTS

Dizziness and vertigo

Seventy-two percent of the patients complained of dizziness or vertigo. Most of them (48% of all patients) had slight, diffuse dizziness causing no or only minor discomfort. Four percent of all patients complained of constant, severe dizziness. Eighteen percent complained of attacks of rotatory or nautical vertigo. Disturbance of the gait without dizziness or vertigo was reported by 2% of the patients.

Hearing loss

Sensorineural hearing loss, not related to aging, exposure to occupational noise or middle ear disease, was found in 25 of the 168 patients (15%). Slight hearing loss was most common (10%, 16 cases), moderate hearing loss was found in 4% (6 cases) and severe hearing loss in 1% (2 cases).

ABR

There were no statistically significant differences for either women or men between the patients and the

Table I. *Numbers and percentages (within parenthesis) with abnormal ABR recordings. The different types of pathological patterns are given. I–V IPL/wave V: prolongation of the interpeak latency between waves I and V and prolongation of the absolute latency of wave V. ITD: prolongation (≥0.4 ms) of the interaural difference between wave V of the right and left ears. Pathological latencies: abnormalities of I–V IPL/wave V and/or ITD. Wave-V Amplitude: reduction of the amplitude of wave V*

ABR Abnormalities		
Total	51	(30.3%)
Pathological latencies (I-V IPL/V/ITD)	44	(26.2%)
Pathological I-V IPL/Wave V	32	(19.0%)
Pathological ITD	17	(10.1%)
Pathological Wave-V Amplitude	12	(7.1%)

controls for waves I and III. Wave V was significantly lengthened in the patient group ($p < 0.001$, women and $p < 0.01$, men). The I–V IPL was also prolonged in the patient group ($p < 0.01$, women and men). The I–III IPL was similar in both patients and controls. The III–V IPL was significantly prolonged in the patient group ($p < 0.001$, women, and $p < 0.05$, men) (Figs 1 and 2). The interaural time differences were also significantly longer in the patient group (ITD V $p < 0.01$, women, and $p < 0.001$, men; ITD I–V IPL $p < 0.001$, women, and $p < 0.05$, men) (Fig. 3). Fifty-one of the 168 patients (30%) had abnormal ABR recordings. The I–V IPL/wave V latency was significantly prolonged in 19% of the cases and the ITD was abnormal in 10%.

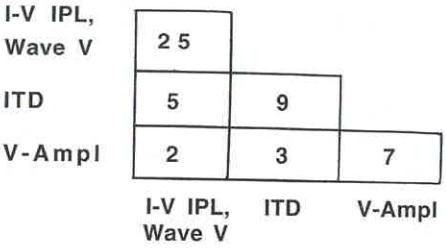

Fig. 4. Combination of different ABR abnormalities in patients with fibromyalgia. I–V IPL, wave V = prolongation of the interpeak latency between waves I and V and prolongation of the absolute latency of wave V. ITD = prolongation (≥0.4 ms) of the interaural difference between wave V of the right and left ears. V-Ampl = reduction of the amplitude of wave V.

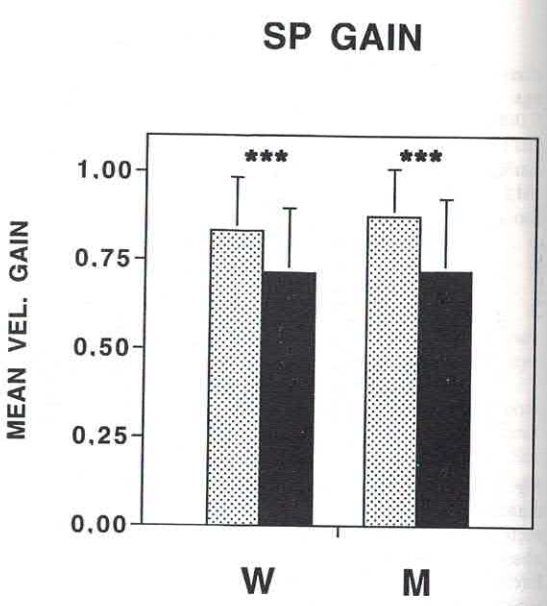

Fig. 5. Smooth pursuits, velocity gain, mean values and SDs. Black columns = patients; grey columns = controls. W = women, M = men. A strongly significant difference between patients and controls was found for both women and men.

The latency parameters (I–V IPL, wave V and ITD) were pathological in 26% of all cases. The amplitude of wave V was reduced in 7%. The distribution of the ABR abnormalities is seen in Table I and Fig. 4.

Smooth pursuit eye movements

The mean velocity gain was significantly lower in the patient group than in the control group for both women and men ($p < 0.001$) (Fig. 5). Ninety-six of the 166 patients tested (58%) had pathological smooth pursuit eye movements. In all these cases the mean velocity gain of the 20°/s smooth pursuits was significantly reduced. In 24% of all patients the smooth pursuits were severely abnormal with a mean velocity gain of ≤0.5.

Saccadic eye movements

The statistical evaluation showed a significant difference between the patient group and the control group for women and men for the mean saccadic latency ($p < 0.001$). For the other parameters studied, saccadic velocity and accuracy, no statistical differences between the groups were observed (Fig. 6). Forty-seven of the 166 patients tested (28) had abnormal saccades. The saccadic velocity was disturbed in 18% of the cases. The velocity was reduced in 16% and increased in 2%

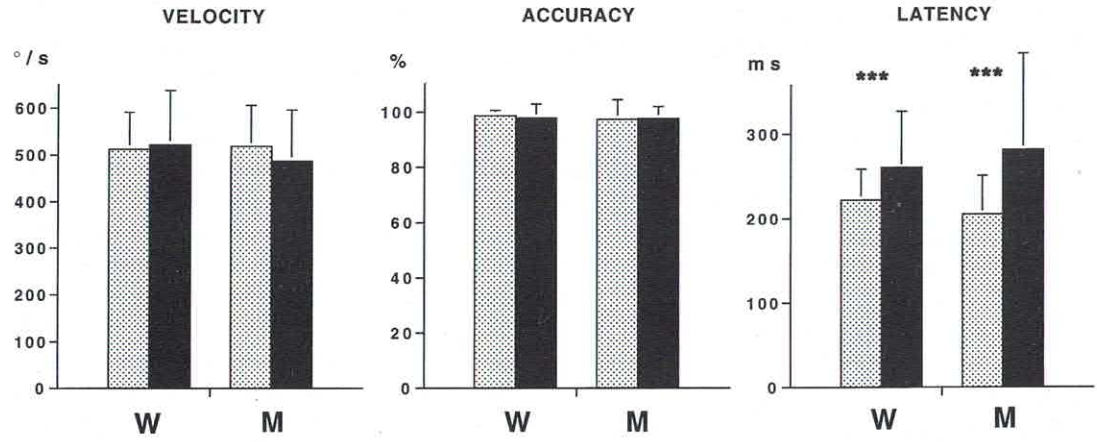

Fig. 6. Results of measurements of three different saccadic eye motor parameters. Mean values and SDs are given for maximal velocity (°/s), accuracy (%), and latency (ms). Black columns = patients; grey columns = controls. W = women, M = men. No significant differences between patients and controls were observed for velocity and accuracy. The latencies were longer for fibromyalgia patients than for controls.

(Table II). The saccadic accuracy was abnormal in 17%. The saccades were hypometric in 16% and hypermetric in 1% (Table II). In 10 cases (6%) both the velocity and the accuracy were pathological. Prolonged latencies were observed in 14 of 91 patients studied (15%).

ENG

In 38 of 85 patients studied (45%) the ENG recordings were abnormal (Table III). Signs of central dysfunction (one or more of the following findings: direction changing positional nystagmus, hyperactivity of the caloric response, directional preponderance and depressed visual suppression) were found in 35% of the cases tested (Table III).

Table II. *Numbers and percentages (within parenthesis) of pathological saccades. Velocity disturbances include reduced as well as increased velocity (control mean ±2 SD). Dysmetria (poor accuracy) includes hypometric saccades (the amplitude of the main saccade is reduced) and hypermetric saccades (the amplitude of the main saccade is increased). Latency measurements were not performed on all patients, and are therefore not included in the table*

Saccadic Abnormalities		
Total	47	(28.3%)
Velocity disturbances	29	(17.5%)
Reduced velocity	26	(15.7%)
Increased velocity	3	(1.8%)
Dysmetria	28	(16.9%)
Hypometria	26	(15.7%)
Hypermetria	2	(1.2%)

DISCUSSION

A majority of the patients in the present study had vertigo/dizziness. This symptom was not very prominent in most of the patients, however, and was described as a vague, indistinct dizziness. The vertigo was generally not of the type present in peripheral vestibular disorders, e.g. Menière's disease (10, 3). Hearing loss, in most cases slight, was an infrequent finding in the present study group. Since other causes, e.g. presbyacusis, noise-induced hearing loss or middle-ear disease, were excluded as far as possible, the present study suggests a weak correlation between fibromyalgia and hearing loss, a relationship which has been reported earlier (9).

Table III. *Numbers and percentages (within parenthesis) of patients with abnormal ENG. Data regarding different types of pathological patterns are reported*

Electronystagmographic abnormalities		
Total	38	(44.7%)
Positional nystagmus	16	(18.8%)
Spontaneous nystagmus	10	(11.8%)
Caloric hyperactivity	9	(10.6%)
Unilateral weakness	5	(5.9%)
Directional preponderance	4	(4.7%)
Decreased visual suppression	4	(4.7%)

The present study of consecutive patients with fibromyalgia indicated that most of them has otoneurological abnormalities. The symptoms interfered with social activity level and work performance, and most patients were on long-term sick leave and the pain was refractory to physiotherapeutic and ordinary pharmacological treatment. There were far more immigrants than expected from the general population. Immigrants were more often affected but not more severely afflicted than Swedish patients.

Ödkvist et al. (18) and Rosenhall et al. (20, 21) have shown similar results in studies of fibromyalgia patients. In our earlier study the patients had severe fibromyalgia with focal neurological symptoms (hemidysaesthesia). In the later part of the study most of the patients had less severe fibromyalgia, and neurological symptoms and signs were often absent. This latter group showed in this way similarities with the fibromyalgia group studied by Ödkvist et al. (18).

The prevalence of ABR abnormalities was the same (~30%) in this study as in the earlier one (21). Since the material has been extended considerably, a more detailed statistical analysis is possible now. Significant differences were found, for both women and men, between patients and controls for the absolute latency of wave V, for the I–V and III–V IPLs and for ITDs of both wave V and I–V IPL. The III–V IPL reflects the function of the auditory system in the brainstem, between the cochlear nuclei and the superior olive (17). The consistent findings of ABR abnormalities, affecting wave V, the III–V IPL and the ITDs, strongly indicate that dysfunction involving the pons is common in patients with fibromyalgia.

Oculomotor disturbances were more commonly seen in our earlier study of fibromyalgia with dysaesthesia than in the present one (42% and 28% respectively for saccades and 89% and 58% respectively for smooth pursuits). The reason for this is probably that the former represents a group with very pronounced symptoms, while the total group includes patients with somewhat less severe manifestations.

The mean velocity gain was significantly lower in the patient groups than in the control groups. The prevalence of smooth pursuit abnormalities is similar between the present study and that of Ödkvist et al. (18).

Velocity disturbances of saccadic eye movements were seen in 18% of the cases tested. Reduced saccadic velocity was the most common abnormality and can be seen in pontine lesions (19). Increased saccadic velocity, occasionally observed here, has been reported to occur in cases with acute meningo-encephalitis (11). In the present study the saccades were more often hypometric than in our earlier study, in which the saccades commonly had reduced velocity. Saccadic hypometric often reflects cerebellar dysfunction, but a supra-tentorial location of the lesion is also possible (26, 6, 19). Although saccadic abnormalities affecting velocity and accuracy occur frequently, there were no significant differences between patients and controls in the statistical analysis. One explanation is that abnormalities of velocity and accuracy deviate in both directions from normal values (saccades might have either reduced or increased velocity and they can be either hypometric or hypermetric), resulting in increased variability and, consequently, no statistically significant differences between clinical and normative groups.

The only saccadic parameter with significant differences from norms was the latency, which deviated in one direction only from normative values (all patients with deviations had longer latencies than the controls). The latency reflects the reaction time which elapses from the change of the target to the execution of the eye movement. It might measure a more generalized influence on the CNS than the other parameters.

Oculomotor dysfunction, affecting both saccades and smooth pursuits, has been reported in connection with whiplash injuries (13). These abnormalities, which are similar to what has been reported in fibromyalgia, could be secondary to impaired proprioception of neck or could be caused by brainstem lesions.

The interpretation of the findings of abnormal saccades and smooth pursuits as well as abnormal ENG registrations is that of CNS dysfunction, most likely in the posterior fossa. However, disturbances of smooth pursuits and also, to some extent, of saccades, can be seen in patients with tension headache (TH) without neurological signs and symptoms (4). The explanation of this observation is that proprioceptive dysfunction in the neck might cause erroneous signals which could disturb the oculomotor regulation.

The prevalence of smooth pursuit abnormalities was about the same in the TH group (22) and in the group of fibromyalgia patients studied here (53% and 58% respectively). The prevalence of saccadic abnormalities was also about the same in both groups; about 30%. Velocity disturbances were more commonly seen among fibromyalgia patients than among TH

patients (16% and 6% respectively). None of the patients with TH had abnormal ABR recordings (22), in contrast to what was found in the fibromyalgia group.

Ödkvist et al. (18) reported that positional nystagmus, neck torsion nystagmus, hyperactivity in calorics and spontaneous nystagmus often occurs in patients with fibromyalgia. This is in agreement with the findings of the present study. The ENG findings found here generally signal CNS involvement. Directional changing positional nystagmus, hyperactivity of the caloric nystagmus, directional preponderance and decreased visual suppression of the caloric nystagmus indicate central vestibular dysfunction. Spontaneous nystagmus and reduced vestibular function in one ear can be seen in both peripheral and central unilateral vestibular lesions.

The present study suggests that CNS dysfunction often occurs in patients with fibromyalgia according to the results of ABR, the saccade test and ENG. Proprioceptive disturbances of CNS dysfunction are both plausible explanatory factors of the pathological smooth pursuit findings observed here.

The cause of the observed CNS dysfunction is unknown, but some hypothetical mechanisms are possible. One is long-standing medication of drugs, e.g. analgetics, antidepressants, tranquillizers and hypnotics. One important aim of the rehabilitation clinic is to render the patients as free as possible from all kinds of medication, and alternative methods for pain relief are encouraged. According to personal knowledge of the patients and the files available, none of the patients was judged to have any drug dependence, including abuse of analgesics, tranquillizers or alcohol. It can therefore be presumed that the observations described above were not caused by medication or abuse, or by withdrawal of medication during the test session. However, since metabolites of different analgetic compounds were not measured prior to testing, and since data concerning medication earlier in life could not be reliably assessed, it cannot be fully ruled out that recent or earlier medication might have had an influence on the test results.

Chronic fatigue syndrome (or chronic fatigue immune dysfunction syndrome), which seems to be similar to fibromyalgia (8) has been suggested to be caused by infectious agents. Behan et al. (2) coined the term myalgic encephalo-myelitis, and pointed out enterovirus as a possible agent. Herpes viruses and retroviruses have also been discussed as aetiological agents to fibromyalgia, but these suspicions have not been verified (25, 7).

Stress factors have been discussed as inducing CNS dysfunction (1, 12). Such a discussion is relevant concerning fibromyalgia, which has similarities to Post Traumatic Stress Disorder (PTSD), where stress mechanisms are known to be the aetiological factor. In animal experiments, glucocorticoid elevation induced by repeated stress causes neuronal destruction and CNS atrophy (16). It can therefore be speculated that mental stress with its neurohormonal aspects may be both an aetiological and patho-physiological mechanism explaining both the symptoms and signs as well as the otoneurological findings, indicating CNS dysfunction in cases of fibromyalgia.

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