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Central Nervous System Involvement in Early Syphilis

Part II. Correlation between Auditory Brainstem Responses (ABR) and Cerebrospinal Fluid Abnormalities

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Twenty-six consecutive patients with secondary or early latent syphilis, all with normal neurological findings, were studied with auditory brainstem responses (ABR), cerebrospinal fluid (CSF) analysis and an assay for immune complexes in serum and CSF. Seven of the 26 patients studied had a pathological ABR pattern and 14 had one or more pathological CSF tests. Fifteen patients had circulating immune complexes in serum. No patient had demonstrable immune complexes in CSF. A significant correlation was found between an abnormal ABR pattern and pathological CSF findings—but not between pathological ABR and presence of immune complexes. ABR seems to be a sensitive method for detection of early asymptomatic CNS involvement in syphilis. *Key words: Early syphilis; Auditory brainstem responses; Cerebrospinal fluid; Immune complexes.* (Received February 1, 1983.)

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Auditory brainstem electrical responses (ABR) constitute a sensitive test for minor lesions in the brainstem (18). Sound stimulation gives rise to electrical potentials emanating in the auditory pathways in the brainstem. In normal individuals, five ABR waves (Wave I, II, III, IV and V) have been characterized (8). Abnormalities in the ABR pattern can be found in patients with, e.g., intra-axial brainstem tumours, brainstem infarction, and multiple sclerosis. In a recent paper, Rosenhall & Roupe (14) described the wave patterns in patients with secondary and advanced syphilis. Decreased amplitudes and prolonged latencies were often found, indicating occult lesions in the brainstem. The aim of this investigation was to estimate the frequency of pathological ABR findings in early syphilis and to determine whether these disturbances were correlated to cerebrospinal fluid (CSF) abnormalities or to circulating immune complexes.

PATIENTS

Thirty-two patients with secondary or early latent syphilis were seen at the Department of Dermatology, Sahlgren's Hospital, Gothenburg, from November 1980 to October 1982. Six patients were not included in the study as they had received treatment with antibiotics (2 patients) or refused lumbar puncture (4 patients). The study group thus comprised 26 patients, 24 men (20–69 years, mean 39 years) and 2 women (18 and 42 years). All but 6 of the men were homosexuals. Seventeen patients had clinical manifestations and serology consistent with secondary syphilis (9) and 9 patients had early latent syphilis, which means that they had positive syphilis serology but no clinical signs of syphilitic

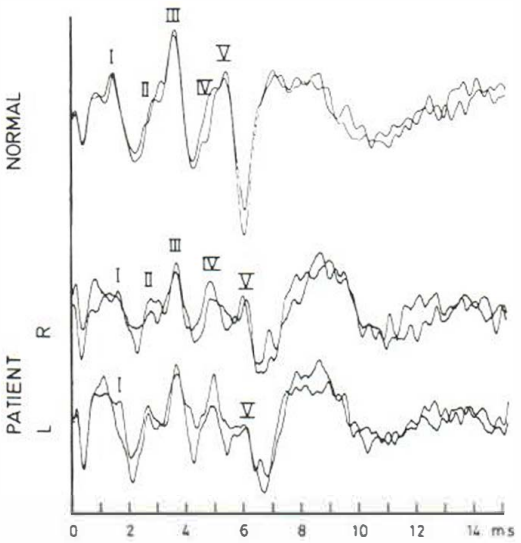

Fig. 1. ABR recordings from a 43-year-old man with early latent syphilis (lower recordings). R = right ear, L = left ear. The different waves I–V can be identified on the graph. The latency of wave V and the I–V interval are significantly prolonged on both sides. The upper ABR curves are recorded from a normal control.

disease. The diagnosis was based on anamnestic data and/or serological tests indicating an infection of less than 2 years' duration. In 6 of 9 patients with early latent syphilis the findings suggested an infection of more than 6 months' duration, while in 3 cases a more recent infection was probable. Neurological examination, lumbar puncture, blood sampling and ABR examination were performed in all patients before instituting therapy. CSF findings for 24 of these patients have been presented in an earlier report (12).

METHODS

ABR (auditory brainstem responses)

ABR audiometry was performed in a sound-proof room. Unfiltered clicks with a peak energy of about 1 kHz were administered via TDH-39 earphones. 1 024 or 2 048 stimuli with alternating phase were presented monaurally. The clicks were presented at an intensity of 80 dB hearing level (115 dB peak equivalent sound pressure level) with a repetition rate of 25 per second and in some instances of 10 per second as well. The responses were picked up with two surface self-adhesive silver/silver chloride electrodes, one placed on the forehead and the other on the ear-lobe. The signals were filtered using a 150–2 500 Hz band pass filter and conveyed to a Nicolet 527 signal averager. Two identical stimulus rounds were superimposed on each graph, and forehead positive deflections weredelineated upwards.

The different ABR waves were identified (Fig. 1). The latency of wave V and the interval between waves I and V (I–V interval, or interpeak latency) were used to determine the function of the auditory pathways in the brainstem. The I–V interval is considered to be the most reliable parameter for evaluating the auditory brainstem function.

The interaural time difference of wave V (IT_5) was also calculated. An IT_5 of 0.4 msec or greater was considered abnormal (15). The amplitudes of the different waves were also measured. A ratio between wave V and wave I of 0.5 or less was considered a borderline finding indicating central auditory dysfunction (17).

When evaluating ABR audiometry it is of importance to know the hearing of the patients. Pure-tone audiometry was therefore performed in all patients.

ABR control group

The ABR results in the patients were compared with those from a control group of 500 healthy individuals used in our ABR laboratory for normative purposes. The control group contains ABR recordings from people with normal hearing and from individuals with different types of cochlear hearing loss. This control group was divided into subgroups according to sex, age and hearing. Seven such subgroups were used in this study (Table I).

The ABR of each patient was compared with ABR data from the matching control subgroup, thus

taking into account sex, age and hearing. The mean values of the wave V-latency and the I–V interval +2 SD ($p<0.05$) from each control subgroup were considered to be normal.

Cerebrospinal fluid

The CSF samples (15–20 ml) were obtained by lumbar puncture under standardized conditions. At the same time 10 ml of blood was obtained. The samples were stored at 5°C until analysis. No blood-contaminated CSF samples were included.

The cell number was estimated and a cytological examination was performed as described earlier (12). Protein was determined *ad modum* Lowry et al. (11). Albumin and immunoglobulin G were assayed by immunoelectrodiffusion as described by Laurell (10). The IgG index was calculated *ad modum* Tibbling (21) and CNS IgG synthesis according to Tourtellotte's formula (22). The protein pattern was analysed by agar gel electrophoresis (23).

Serological techniques

The Wasserman (WR) and Venereal Disease Research Laboratory (VDRL) tests were used as screening tests for syphilis, while the fluorescent treponemal antibody absorption (FTA-ABS) test (4) constituted confirmation. These tests were performed on CSF and blood simultaneously.

Immune complexes

Demonstration of circulating immune complexes was performed by incubating 2×10^6 normal granulocytes prepared as described by The et al. (20) with 100 µl of the patient's serum and 50 µl of fresh normal human serum as a complement source, for 90 min. Tests were considered positive only when more than 10% of the granulocytes showed immune complexes. Control serum was drawn from 250 healthy blood donors. Six of these individuals (2.4%) had detectable immune complexes.

Statistical analysis

Pitman's non-parametric permutation test (2) was used to analyse correlations between CSF and ABR pathology (normal CSF =0, slight CSF pathology = 1 and pronounced CSF pathology = 2).

RESULTS

Except for symptoms like headache (5 patients) and tiredness (11 patients) none of the patients had any neurological symptoms and all were found normal in the neurological examination.

ABR

Nineteen patients had normal ABR recordings obtained from both ears. Six of the patients studied had prolongation of the I–V interval (interpeak latency), three in one ear only and three in both ears (Fig. 1). In most instances the latency of wave V was prolonged as well.

Table I. *Controls and patients divided into subgroups according to sex, age and hearing*
Values given are numbers of ears tested. In all patients and most controls, both ears were tested

Males			Females		
Age (years)	Controls	Patients	Age (years)	Controls	Patients
Normal hearing					
16–25	34	8	16–25	34	2
26–35	42	12			
36–45	17	10			
High frequency hearing loss					
20-65	131	14	20–60	38	2
66–	107	4			

The values of these parameters exceeded control subgroup means +2 SD. Two of the patients with unilateral abnormality had abnormal IT_5 as well.

Altogether three patients had decreased amplitudes of wave V, two in one ear and one in both ears. This latter patient had a ratio between wave V and wave I of 0.50 for the right ear and of 0.48 for the left ear. This pattern, which is pathological, was consistent in many averaged sweeps. However, this patient had normal wave latencies. As a conclusion, seven patients (27%) had abnormal ABR recordings. Four had pathological interpeak latencies, one had reduction of the wave V amplitude and two patients both latency- and amplitude abnormalities. Of the patients with abnormal ABR four had secondary syphilis and three early latent syphilis.

CSF analyses

Fourteen of 26 patients had pathological results in one or more of the following CSF variables: cell count, cytology, IgG index, IgG synthesis, electrophoresis and serological syphilis tests in CSF. For details, see (12).

Five patients (4 with early latent and one with secondary syphilis) had a more pronounced CSF pathology, with signs of intrathecal immunoglobulin production (increased IgG index and/or IgG synthesis), pathological electrophoresis pattern, positivity in serological syphilis tests, increased cell number and pathological cytology.

Nine patients had increased cell count and/or pathological cytology but no signs of intrathecal immunoglobulin production and all were non-reactive in WR, VDRL and FTA-abs in CSF.

Thus, of the 26 patients studied, 12 had normal CSF findings, while 9 exhibited slight and 5 more pronounced pathological findings.

Immune complexes

In 10 of 17 patients with secondary syphilis and 5 of 9 patients with early latent syphilis, circulating immune complexes were detected in serum. No patient had demonstrable immune complexes in CSF.

Correlation between CSF and ABR pathology (Table II)

One of 12 patients with normal CSF had a pathological ABR pattern, compared with 2 of 9 patients with slight CSF pathology and 4 of 5 patients with pronounced CSF pathology.

There was a significant correlation ($p<0.05$) between CSF and ABR pathology.

Correlation between immune complexes in serum and ABR pathology

Five of 7 patients with an abnormal ABR pattern and 10 of 19 patients with a normal ABR pattern had detectable circulating immune complexes.

There was no significant correlation between pathological ABR and presence of immune complexes in serum.

Table II. *Correlation between ABR and CSF pathology in 26 patients with early syphilis*

	ABR	
CSF	Normal	Pathological
Normal $n=12$	11	1
Slight pathology, $n=9$	7	2
Pronounced pathology, $n=5$	1	4
Total	19	7

DISCUSSION

Early invasion of the central nervous system in syphilis is usually asymptomatic (9). The first sign of involvement has been described as a basal meningitis (19). Sporadic involvement of the cranial nerves has been reported (3, 24). When using more detailed methods of examination, a high incidence of neurological signs such as depression of pallesthesia (7), changes in pupils and light reactions (1) has been described.

Rosenhall & Roupe 1981 (14) found brainstem dysfunction, according to the ABR findings, in patients with early syphilis.

In the present study, 7 of the 26 patients (27%) were found to have pathological ABR. ABR abnormality might indicate either a lesion of the cochlear nerve or dysfunction of the upper part of the brainstem. The former condition is generally associated with hearing loss of retrocochlear type. Syphilis might cause basal meningitis, which could possibly affect the cochlear nerve and cause retrocochlear hearing loss. In this study, 3 of the patients with abnormal ABR had normal hearing. The remaining 4 patients with abnormal ABR had high-frequency hearing loss which was only slight to moderate and with no indication of retrocochlear origin. Moreover, Rosenhall & Roupe (14) reported the results of impedance audiometry and sound localization tests, both of which are very sensitive to retrocochlear lesions, in patients with syphilis. These tests proved normal in the patients studied, indicating that the eighth cranial nerve was not affected. There is thus reason to believe that the ABR abnormalities found in the present study indicate brainstem dysfunction, which is consistent with the preliminary findings in a separate group of patients (14).

In a previous study (including 24 of the present patients) the CSF findings in early syphilis were presented in detail (12). Stimulation of the immune system within the CNS early in the course of syphilis was demonstrated. In secondary syphilis the predominant finding was a pleocytosis, mainly reflecting lymphocytic activation. In early latent syphilis, 35% of the patients exhibited signs of intrathecal immunoglobulin production and specific antibodies.

The study of pathogenetic mechanisms involved in syphilis is of importance for our understanding of different manifestations of the disease. Immunological mechanisms, both cellular and humoral (13), are involved in the disease process. In secondary syphilis, circulating immune complexes have been demonstrated (5, 16) and some of the clinical manifestations seem to reflect an immune complex deposition (6).

In the present study, circulating immune complexes in serum could be demonstrated in 60% of the patients before treatment. In no instance could any of these immune complexes be detected in CSF.

Of 26 patients with secondary or early latent syphilis, all with normal neurological findings, 7 showed an abnormal ABR pattern indicating brainstem dysfunction. These disturbances were significantly correlated to abnormalities in the CSF. No significant correlation was found between pathological ABR and circulating immune complexes in serum.

The finding of a correlation between immunological activity in CSF and ABR pathology in the patients studied confirms that the subclinical lesions in the CNS detected by ABR reflect a syphilitic immunopathological process.

Besides CSF analysis, ABR seems to be a sensitive method for the detection of early asymptomatic CNS involvement in syphilis.

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