Visual evoked potentials in neurosyphilis

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SUMMARY The visual evoked potential (VEP) to pattern reversal was recorded in 79 patients with neurosyphilis. Sixteen patients (20%) had abnormal VEP latencies with a predominance of pathological VEP values in the group of tabes dorsalis (50%) as compared to general paresis (18%) or meningo-vascular forms (13%). A comparison of the frequency of abnormal VEP with that of other ophthalmological tests (visual acuity, visual field, central campimetry, pupillary reactions, dark adaptation, optic fundus) yielded no diagnostic superiority of VEP.

From experience with the analysis of visual evoked potentials (VEPs) in multiple sclerosis it has become evident that this procedure is a sensitive method for detecting lesions of the optic nerve or of the posterior parts of the visual pathways, even in cases where the lesion could not be established clinically.1,2 It has been shown that a delayed VEP is not specific to one particular disease as pathological VEP’s have been observed in other diseases such as pernicious anaemia3 or hereditary ataxias.4

In neurosyphilis, pathological neuro-ophthalmological findings such as pupillary abnormalities, optic neuritis, or optic atrophy may contribute to the diagnosis.5,6 The question arises as to whether or not the analysis of VEP can contribute to the assessment of involvement of the optic nerve by neurosyphilis. The post-World War II trend of a continuous decrease in the number of cases of primary and secondary syphilis owing to the introduction of penicillin therapy was reversed in the early 1960s, resulting in a slow gradual increase in the rate of primary and secondary syphilis.7 Even higher numbers of cases of neurosyphilis may occur since about 80% of cases remain unreported.8

Owing to the introduction of antibiotics a change in the symptoms of neurosyphilis has taken place.9 Tabes dorsalis and general paresis have become rare, but there has been a relative increase in meningo-vascular or unclassifiable forms which has caused increasing diagnostic difficulties. Moreover, asymptomatic neurosyphilis or neurosyphilis with rather uncharacteristic symptoms frequently precedes symptomatic neurosyphilis.8 Neurosyphilis, especially in its asymptomatic form, can only be definitely diagnosed by CSF examination. In such cases an attempt to find additional neurological symptoms and signs always must be made. The purpose of this study has been to assess the clinical value of the pattern evoked visual responses in a large group of patients with various manifestations of neurosyphilis and to correlate the results with other neurological and ophthalmological findings.

Methods and Materials

Control subjects. Thirty healthy volunteers (medical personnel, 16 women and 14 men, average age 39 years) served as controls for the determination of normal values of visual evoked potentials.

Patients. Ninety-four patients (15 asymptomatic patients with positive blood serology and 79 neurosyphilis patients with positive CSF findings) were investigated during a period of 18 months. (For details see table). The majority of the patients had been registered at the Neurological University Clinic over a prolonged period of time, and were requested to visit for regular check ups. In all patients the following laboratory examinations were performed on blood serum and CSF: (a) Fluorescent-Treponema-antibody-absorption-test (FTA-ABS); (b) Treponema-Pallidum-Haemaglutination-test (TPHA) and, in ambiguous cases, (c) Treponema-Pallidum-Immobilisation-test (TPI) according to Nelson. In cases of positive blood serology and negative CSF tests a seropositive syphilis was assumed. Neurosyphilis, however, was assumed only when, in addition to positive serological and CSF findings (TPHA, FTA-ABS, TPI), at least two of the following three criteria were fulfilled: (a) Pathological neurological findings which could not be attributed to any other neurological disorder, (b) increased cell counts and elevations of CSF protein (IgG or total protein), (c) Positive effects of antibiotic therapy
Table 1  Subdivision of the syphilitic patients investigated

<table>
<thead>
<tr>
<th>Patients</th>
<th>N (Women/Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosyphilis (total)</td>
<td>79 (27/52)</td>
</tr>
<tr>
<td>Syphilitic meningitis</td>
<td>5 (-/5)</td>
</tr>
<tr>
<td>Asymptomatic neurosyphilis</td>
<td>7 (3/4)</td>
</tr>
<tr>
<td>Meningovascular neurosyphilis</td>
<td>23 (8/15)</td>
</tr>
<tr>
<td>General paresis</td>
<td>16 (3/13)</td>
</tr>
<tr>
<td>without tabetic symptoms</td>
<td>8 (1/7)</td>
</tr>
<tr>
<td>with tabetic symptoms</td>
<td>8 (2/6)</td>
</tr>
<tr>
<td>Tubes dorsalis</td>
<td>14 (6/8)</td>
</tr>
<tr>
<td>Special courses</td>
<td>3 (1/2)</td>
</tr>
<tr>
<td>Unclassifiable neurosyphilis</td>
<td>11 (6/5)</td>
</tr>
<tr>
<td>Seropositive syphilis</td>
<td>15 (7/8)</td>
</tr>
</tbody>
</table>

(normalisation of the CSF-findings or amelioration of the clinical symptoms or both).

According to the classification by Hoff and Weingarten all patients with neurosyphilis were placed into one of the following categories: (1) Syphilitic meningitis (pleocytosis of 15 to 1000/3 cells and meningism), (2) Asymptomatic neurosyphilis (pleocytosis and increase of CSF IgG, absence of neurological symptoms), (3) Meningovascular syphilis (localised or general neurological symptoms), (4) General paresis, (5) Tubes dorsalis (locomotor ataxia), (6) Specific forms: syphilitic amyotrophy, syphilitic spastic spinal paralysis (Erb type), pachymeningitis cerebri hyperplastica and (7) Nonclassifiable forms (which could not be associated with any of the above mentioned forms without forcing the evidence). General paresis and tabs dorsalis, as well as the specific forms, were categorised as tertiary forms. In some cases the distinction between tabs dorsalis and general paresis was ambiguous, especially in cases in which the psycho-organic syndrome did not clearly dominate the clinical picture as the primary symptom, and the constellation of symptoms would also have justified the classification of the patient’s affliction as tabs dorsalis.

Electrophysiological investigation (VEP)

The average VEP response to pattern reversal stimuli was recorded in the dark from both eyes as well as from each eye separately in all patients. A slide of a checkerboard pattern was projected via a mirror mounted on a pen motor upon a screen placed 1 m in front of the subject, the entire stimulating field subtending 30° to the eye. The movement of the mirror was adjusted, so that the pattern moved alternately one square to the right or to the left every 500 ms. The subjects were told to fix their eyes upon a light spot projected into the middle of the checkerboard screen. The sizes of the individual white or black squares were about 1°. The luminance of the white squares was 55cd/m², that of the black ones was 5·5cd/m².

The VEPs were recorded from scalp electrodes via pre-amplifiers with a frequency response of 3 dB down at 2·5 kHz, time constant 0·1 ms. The electrode placement was 5 cm above the inion referred to the vertex. One hundred and twenty-eight responses (64 patterns to the right and 64 to the left) were averaged via a Nicolet-averager (type SW-71B) and latency of the P2 component was measured and photographed from the oscilloscope. Each test was repeated at least once to confirm an abnormal finding.

Conrad, Benecke, Mpoon, Behrens-Baumann

Ophthalmologic investigations

The following ophthalmologic investigations were performed: (a) visual acuity (V), (b) visual field with white and red marks (VF) (Goldmann perimeter), (c) central campimetry (HAI) (Haist stereoscopy), (d) pupillary reactions (PUP), (e) measurement of dark adaptation (DAA) with the Goldmann-Weekers adaptometer, (f) examination of the optic fundus, especially of the papilla (PAP). Haist marks were only considered pathological when at least two different colours were affected. Argyll-Robertson pupil or absent pupillary reactions were regarded as pathological symptoms. Anisocoria or "unrounded" pupils were not taken as pathological because they may be present as normal variants or after ophthalmologic disorders (for example iritis, senile atrophy of the sphincter pupillae). Pathologic findings of dark adaptation were only bilaterally ascertained, in order to reduce subjective variations of assessment; all examinations of the optic disc were performed by the same investigator.

Results

Classification of patients

A total of 94 syphilis patients were included in this study (table). Out of the total group, five male
patients suffered from a syphilitic meningitis in the secondary stage. Late asymptomatic neurosyphilis was observed in seven patients whereas in 23 patients a meningovascular form of neurosyphilis was assumed, sixteen patients showed clear signs of general paresis (dementia paralytica), eight of them with additional symptoms of tabes dorsalis. Fourteen neurosyphilis patients were classified as suffering from tabes dorsalis, three cases were rare specific forms of neurosyphilis (syphilitic amyotrophy, syphilitic spastic paraparesis (Erb type), pachymenigitis cervicalis hyperplastica). Eleven patients could not definitely be placed in one of the above mentioned categories and were considered as suffering from nonclassifiable neurosyphilis.

**Visual evoked potentials**

The upper limit of the normal range for the latency to the peak of the major positive potential of the VEP was defined as the mean + 2 SD, that is 107.5 ms. For each subject the longest latency of P2 from the two eyes was used.

*Lues seropositiva:* The range of latency of the P2 component for the 15 cases of latent syphilis, characterised by negative cerebrospinal fluid serology, normal physical condition, and positive blood serology is presented in fig 1. None of the cases with seropositive syphilis had a prolonged latency of the P2 component.

**Neurosyphilis**

(a) *Delayed latency* Of 79 cases of neurosyphilis, 16 patients (20.3%) had pathological VEP's, which were bilateral in ten. The range in all patients with neurosyphilis is illustrated in fig 1. A P2-component failed to appear in one of the eyes in 5 cases due to severe visual loss or blindness resulting from a previous nerve lesion. A more detailed subdivision of the patients with symptomatic forms of neurosyphilis (that is meningovascular form, tabes dorsalis, general paresis) with their relative involvement of pathologic latencies is illustrated in fig 2. Subjects with tabes dorsalis (N = 14) showed the highest incidence of pathological VEP's (N = 50%), whereas 18% of the subjects with general paresis (N = 16) and 13% with meningovascular forms (N = 23) showed pathologic VEP's. A subdivision of the group of patients with general paresis (N = 16) into those with additional tabetic signs (N = 8) and those without revealed that all the observed pathological VEP's occurred among cases with general paresis with additional tabetic signs. (b) *Relation of visual evoked potentials to other ophthalmologic findings* In order to compare the findings of the VEP latencies with those of the other ophthalmological tests (V, VF, HAI, PUP, DAA, PAP) for the different neurosyphilis groups, the results were arranged in the form of contingency tables, making it easy to recognise the frequency in which the different ophthalmological tests yielded convergent or divergent results.

Figure 3A shows that the various ophthalmological tests provided similar rates of pathological findings as the VEP latencies (see upper and lower right square versus left and right upper squares), with the exception of an overproportional share of pathological findings with regard to the Haitz marks.1 It is remarkable, however, that parallel convergent findings of pathological VEP latencies or pathologic ophthalmologic tests or both (right upper square) were observed only in about 30-40% of the cases.

Figure 3B demonstrates that the percentage frequency of pathological findings within the optic
system is clearly higher, when instead of single results of the ophthalmological tests a combination of all test is considered. Reduction of visual acuity (<0.5) could only be established in 6.3%.

Discussion

The present study was undertaken to investigate the diagnostic validity of visual evoked potentials in neurosyphilis. From a total of 79 neurosyphilis patients 20.3% exhibited pathological VEP latencies. Separate evaluation of the different manifestations of neurosyphilis (see table) reveals a clear predominance of pathological VEP values in the group with tabes dorsalis (50%) as compared to general paresis (18%) or meningovascular forms (13%).

Comparing the frequency of pathological values of VEP with that of the other ophthalmological tests (visual acuity, visual field, central campimetry, pupillary reactions, dark adaptation, optic fundus) it becomes obvious that the frequency of pathological findings was similar for each of the different diagnostic methods.

It is striking that the prolongation of VEP latencies in neurosyphilis is less (up to about 30 ms) than in multiple sclerosis (up to about 100 ms). This may be due to different types of lesions in both diseases. The question arises as to why pathological VEPs are more frequent in tabes dorsalis than in the other manifestations of neurosyphilis. Two different types of optic nerve lesions have been described: an earlier inflammatory process involving the perioptic meninges and the pial septae of the optic nerve12-14 and the (later) postneuritic atrophy occurring in tabes dorsalis.12 15 16

The higher incidence of pathological VEPs in the tabetic complex of symptoms is in agreement with the results of Bruetsch17 18 who postulated a positive relation between severity and duration of the inflammation and the extent of destruction from demyelination of the optic nerve. Another study19 on VEP changes in 16 patients with neurosyphilis showed delayed responses in 50% of the patients. These findings cannot easily be compared to our results, since only two cases of tabes dorsalis and one case of general paresis were examined.

It can be concluded that VEPs have no definite diagnostic superiority compared to other ophthalmological tests. This is in contrast to the clinical value of the VEP in the diagnosis of multiple sclerosis. Nevertheless, the present results reveal two interesting aspects: (a) the combination of several ophthalmological examinations including VEP increases the diagnostic accuracy (up to 60%) since, with these tests, different functions within the optic system are examined, (b) the higher percentage of pathologic VEP findings in tabes dorsalis indicates a more frequent involvement of the optic nerves in tabes dorsalis, as compared to other syphilitic manifestations. Furthermore, it should be stressed that pathological VEPs in patients with uncertain neurological symptoms should result in consideration of a diagnosis of neurosyphilis.

References

7. Tramont EC. Treponema pallidum (syphilis). In: Mandell
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