NEUROPHYSIOLOGICAL TESTS IN MULTIPLE SCLEROSIS. A SYNTHETIC OVERVIEW

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ABSTRACT

Background*: The variability of symptoms and signs caused by central nervous system (CNS) lesions make multiple sclerosis difficult to recognize, delaying its diagnosis and treatment. The diagnosis is made only after many months or years, initially giving rise to misunderstanding and inappropriate treatments.The diagnosis relies on clinical, neuroradiological (MRI), neurobiological (CSF) and neurophysiological investigations.*

Methods*: Visual (VEP), brainstem auditory (BAEP), somatosensory (SSEP) and motor (MEP) evoked potentials, the blink reflex (BR) and lastly the conditioned eyeblink reflex may reveal lesion sites which are clinically silent or inaccessible to other diagnostic modalities with different sensitivities.*

Results*: These tests are sensitive, reliable, objective and reproducible neurophysiological tools for assessing CNS function. They are inexpensive and not influenced by the wishes of patients, and are widely available. In addition, they can be performed when other methods of investigation (e.g., MRI) are contraindicated, as in patients with pacemakers or metal implants. The sensitivity of EPs follows the descending order: VEPs > L-SSEPs > L-MEPs > U-SSEPs > U-MEPs > BAEPs > BR.*

Conclusion*: All EPs performed simultaneously are sensitive and reliable diagnostic tools with up to 95% sensitivity in the diagnosis of demyelinating diseases.*

Keywords*: Evoked potentials, Somatosensory evoked potentials, Visual evoked potentials, Motor evoked potentials, Blink reflex.*

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Introduction

The variability of symptoms and signs caused by central nervous system (CNS) lesions make multiple sclerosis (MS) difficult to recognize, delaying its diagnosis and treatment. Currently, diagnosis relies on clinical, neuroradiological (MRI), neurobiological (CSF) and neurophysiological investigations to identify multiple foci of demyelination in the CNS at different stages of evolution (temporospatial dissemination of injuries)[1-4].

Evoked potentials consist of electrophysiological CNS responses to a variety of sensory stimuli. In clinical practice, they require different tests comprising:

Visual evoked potentials (VEPs)
Brainstem auditory evoked potentials (BAEPs)
Somatosensory evoked potentials (SSEPs)
Motor evoked potentials (MEPs)
Blink reflex (BR).

Each of these investigations may reveal lesion sites which are clinically silent or inaccessible to other diagnostic modalities with different sensitivities. They contribute to the diagnosis by identifying abnormal signs when clinical data are equivocal, and serve to monitor neurological changes over time. These tests are sensitive, reliable, objective and reproducible neurophysiological tools for assessing CNS function. They are inexpensive and not influenced

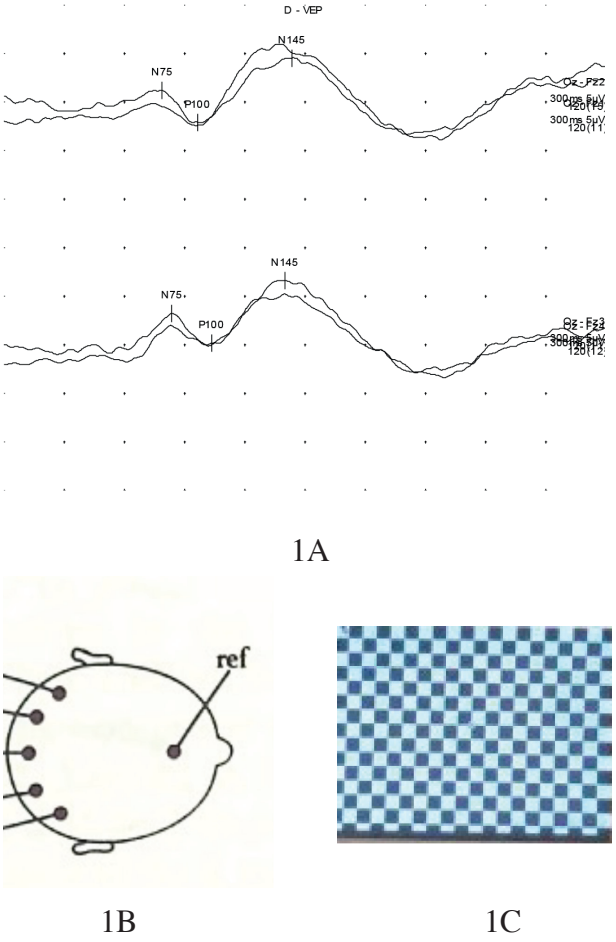
by the volition of patients, therefore useful also in the differential diagnosis of functional disorders[5] and are widely available. In addition, they can be performed when other methods of investigation (e.g., MRI) are contraindicated, as in patients with pacemakers or metal implants. As these potentials are of minimum size, from fractions of a microvolt in the case of BAEPs to a few microvolts, the appropriate test is required to detect the potentials and distinguish the background noise during recording. This is done by averaging, namely the acquisition of multiple responses of the same stimulus in numbers that make them stand out to identify the potentials valid for specific diagnostic purposes. The improved signal-to-noise ratio is the extent of squared responses acquired: 100 = 10, 400 = 20, 900 = 30. Two acquisition trials should be made to confirm the validity and reproducibility of the results.

Visual evoked potentials

Visual evoked potentials (VEPs) are defined as variations in the bio-electric potential of the occipital cortex evoked by visual stimuli. Used initially by flash stimulation, a checkerboard pattern is usually adopted as stimulation, giving a check size of approximately 60 or 15 seconds of visual angle, so the light and dark are reversed alternately without changes in contrast (1-2 Hz). Monocular stimulation is used and is presented to the subject sitting 1 m away from the source of the stimulus. Responses are collected over Oz, O1 and O2 using the standard EEG electrode placement. Accurate implementation of the VEP test should take into account visual acuity, dioptric correction of any deficiency (use of corrective lenses), adequate environmental blackout, the validity of the visual stimulus in terms of brightness and contrast, and patient cooperation with proper setting of the visual target. The waves most commonly recorded are the N75, P100 N145. Clinical practice is mainly confined to the P100 bilaterally, considering its latency, amplitude and symmetry, even if a slight inter-ocular differences of latency and amplitude are well described and may be compatible with neuroanatomical asymmetries of the occipital lobes in humans.

VEP measurement is more sensitive than clinical examination and MRI in exploring prechiasmatic disorders of the visual pathways, allowing a good evaluation of the optic nerve. VEP changes persist long after the recovery of function. The costs of the test are much lower than those of MRI thereby allowing serial evaluations that do not harm visual function and can resolve any doubts over clinical abnormalities of uncertain significance. A normal VEP test will rule out major changes in the optic nerves (Fig. 1).

Factors that may influence the VEP include:



1A

1B 1C

Fig. 1: **A**. 30 ms/division. Standard responses of normal VEPs (N75, P100, N145). **B**. Location of active and reference electrodes for standard responses. The active electrode (O_3) is located along the midline at Oz. The reference electrode is located at location Fz. The locations of the lateral active electrodes, O1_O2_O3_O4_O5 are indicated along with the midline active electrode location, Oz. **C**. Checkerboard pattern reversal.

• Stimulus luminance, contrast, check size, and recording montage significantly affect the latency and amplitude of P100 of pattern-reversal visual evoked potential (PR-VEPS)[7].

• Gender (women have a slightly shorter latency of P100 "Females in some series have been shown to have slightly shorter P100 latency and

larger P100 amplitude than males[7]

• Age: up to one year of age the P100 can have a latency of 160ms and may be slowed in patients over 60 years.

• Variability of parameters (amplitudes, latencies and morphology) of VEP with the depth of anesthesia and types of anaesthetic and sedative agents[8].

• A loss of visual acuity of 1/10 does not significantly alter the response.

• Carbamazepine and sodium valproate prolong P100 latencies.

• The recommended sweep length is 250 ms, 400-500 responses should be averaged at times and at least two trials should be acquired, if not more.

The most common VEP alteration in MS is demyelination, typical of retrobulbar optic neuritis, resulting in significant slowing of latency and/or alteration of the morphology of the P100 of the injured side In addition to prolonged latency secondary to demyelination the amplitude of the evoked potentials can drop too, secondary to retrograde nerve degeneration. This impairment is sensitive to early (1-2 months) treatment with methylprednisolone. The frequency and extent of alterations obviously depend on the number and location of the lesions: over 90% in definite MS[9-13].

Brainstem auditory evoked potentials

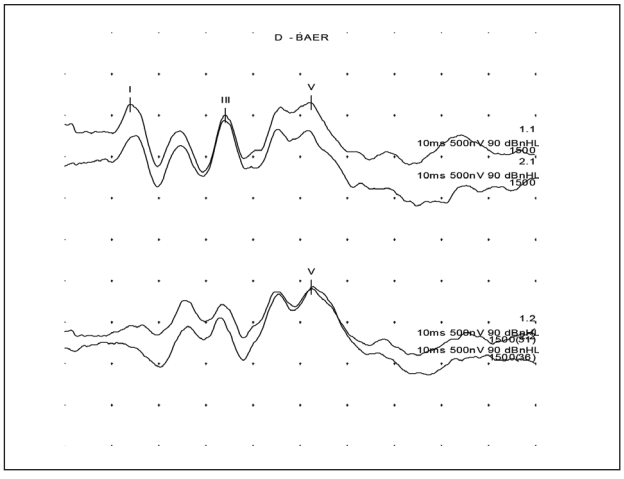


Fig. 2: 1.0 ms/division. Recording montage of the brainstem auditory evoked potentials: The principal 5 BAEP peaks are identified by numeral I-V. Both ipsilateral (superior) and contralateral (inferior) ear channel are shown, both recorded with a vertex reference.

Brainstem auditory evoked potentials (BAEPs) are induced by acoustic stimuli 1000-2000 (click) with monaural stimulation (contralateral ear receives masking noise) consisting of a series of seven waves, of which only the first five are normally measured in clinical practice (Fig. 2).

The generators are currently postulated to be as follows:

• Wave I - Action potential of the VIII cranial nerve

• Wave II - Cochlear nucleus

• Wave III - Ipsilateral superior olivary nucleus

• Wave IV - Nucleus or axons of lateral lemniscus

• Wave V - Inferior colliculus

Technical aspects:

• Stimulus clicks, length 100 to 200 ms, frequency: 5-20 clicks/s, intensity 90 dB above threshold perception clicks.

Recording montage: Usually, a two-channel montage; recording electrodes on the earlobes: channel 1: Cz (vertex, reference) -ipsilateral earlobe (Ai),channel 2: Cz (vertex, reference) -contralateral earlobe (AC), band pass filter: 100 Hz -3000, sweep 10 ms, averaging: 1000-2000 responses.

The main features evaluated in BAEPs are:

• The presence of waves I-V

• Their latencies and peak to peak amplitude

• The interpeak latencies I-III, I-V and III-V

• The amplitude ratio V/I

Evaluation of test intensity/latency (= low-intensity stimuli reduced amplitude and increased latency of waves)

Wave II may also be lacking in normal subjects and IV can be incorporated into the complex IV/V (normal variant).

Unlike VEPs, BAEPs are not affected by sedation, barbiturates or general anaesthesia. Purves et al.[9] reported 45% abnormal VEPs, 35% abnormal SSEPs and 14% abnormal BAEPs in MS patients without brainstem signs such as internuclear ophthalmoplegia or impaired oculomotion (diplopia), from the pons to the lower midbrain, sites of structures involved in BAEP generation. Combining all three investigations, 97% of patients with definite MS, 86% of patients with probable MS, and 63% of patients with possible MS had abnormal findings in at least one of these tests. Literature studies (Chiappa, Maurer) report between 47% and 90% of abnormalities in definite MS, with lower rates (50%) in probable or suspect MS[9,14,15].

Somatosensory evoked potentials

Somatosensory evoked potentials (SSEPs) consist of a series of waves with peaks of different polarity recorded in the peripheral, spinal and cortical regions as a result of mixed or sensory nerve stimulation. SSEPs are considered to result of an ascending sensory volley from the peripheral nerves to the posterior column spinal pathways; from nucleus cuneatus and nucleus gracilis the volley cross and ascend in the medial lemniscal pathways to thalamic nuclei, before to reach the somatosenory cortex. For stimulation using short-lasting rectangular pulses (0.1-0.3 ms), electrodes are placed on the skin overlying the mixed nerve with the cathode placed proximally at a distance of 3 cm from the anode. The short-latency SSEP is considered to be generated predominantly from volleys traversing the large-fibre sensory system of the lemniscal pathways. Usually mixed nerves are stimulated to record large amplitude responses (dependent on the number of fibres and antidromic motor nerve fibre activation).

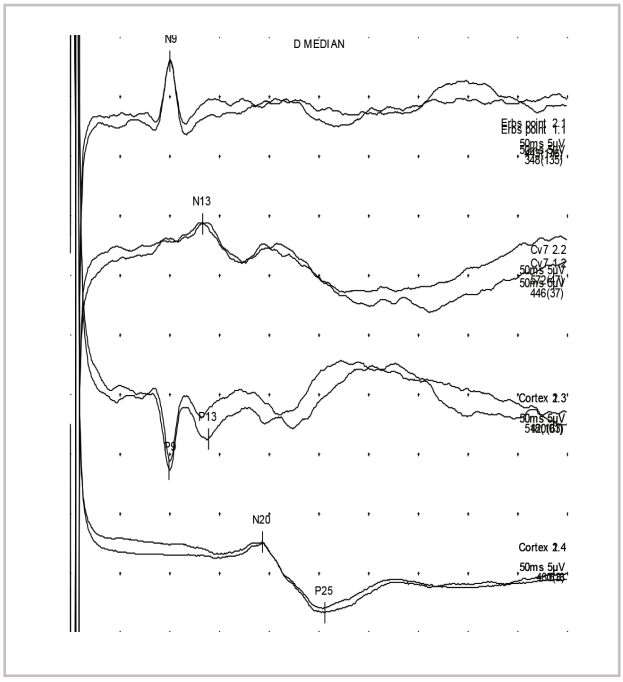


Fig. 3: Median nerve somatosensory evoked potentials 5 ms/division. Obligate peaks and recording montages following stimulation of the median nerve. Erb's Point ipsilateral/controlateral (EPi/EPc), 7th Cervical Spine (Cv7), Far fields potentials 3th tracings, center of frontal pole (Fz), Cerebral Cortex (C).

Repeated stimulation is carried out at the motor threshold with activation of Ia fibres of the median nerve in the upper limbs (C6 root), or better, of the ulnar nerve (C8 root) along the disynaptic lemniscal pathways: spinal ganglion-nuclei of Goll and Burdach-VPLc (contralateral thalamus); the lower limbs are stimulated at the posterior tibial nerve at the ankle or the peroneal nerve in popliteal fossa, medial to the biceps femoris tendon (L5 root). The lemniscal and partly extralemniscal pathways are involved in the generation of SSEPs. Stimulations of both the median nerve at the wrist (Fig. 3) and the tibial nerve at the ankle (Fig. 4) provide recordings in the peripheral nervous system (Erb point or popliteal fossa, N9 or N7 respectively, spinal cord ("near fields" N13 or N22 in C7 or L1 respectively), and cortex ("near fields" in CPC or Cz, international system for recording and editing 10-20)[16-24]

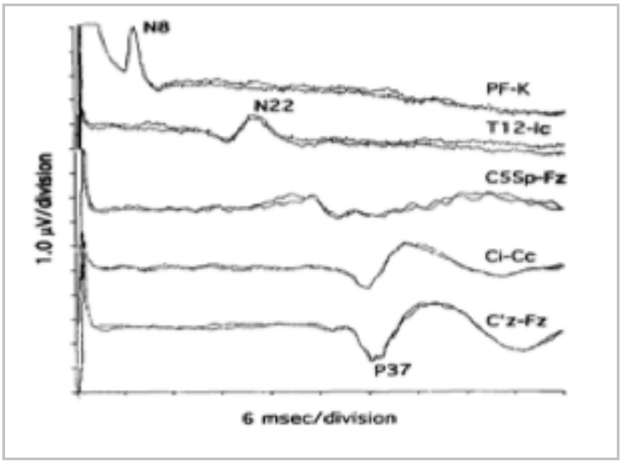


Fig. 4: Posterior tibial nerve somatosensory evoked potentials. 6 ms/division. Obligate peaks and recording montages following stimulation of the posterior tibial nerve. 12th thoracic vertebra(T12), popliteal fossa (PF), knee (K), 5th Cervical Spine (C5Sp), center of frontal pole (Fz), ipsilateral/controlaterale cortex (Ci/Cc), center of frontal pole (Fz).

Recording and montages

Surface electrodes are usually used (needle electrode in particular conditions, as in intra-operative monitoring). The central scalp electrodes should be located 2 cm posterior to the C3 and C4 positions of the 10-20 international system of EEG electrode placement.

Upper extremities(fig. 3):
Channel 1 - EPi-EPc
Channel 2 - C5S-EPc
Channel 3 - CPi-EPc
Channel 4 - CPc-Cpi
Sep-Arm Far Field

Lower extremities (fig.4):
Channel 1 - PF-K, the knee channel
Channel 2 - T12S-IC
Channel 3 - Fpz-C5S
Channel 4 - CPz-Fpz
Channel 5 - CPi-Fpz

Sep-Leg_Routine

Increasing the frequency of stimulation results in decreased amplitude and increased latency. For recording, surface electrodes (Ag/AgCl) should be securely fastened. Needle electrodes can be used in special cases to overcome skin impedance (which may reduce the current voltage of stimulation).

Recording a good Erb point or cauda equina potential (that certifies proper and effective nerve stimulation), it is important to allow measurement of central conduction times and bilateral comparative latency evaluation. Like BAEPS, barbiturate doses (sufficient to render the EEG isoelectric) and general anaesthesia do not significantly alter the SSEPs. Besides potential "near field" there are also the so-called "far field" potentials recorded in the scalp, but with a non-cephalic reference with constant latency and amplitude regardless of the location of the electrode. The postulated generators of the various waves, in chronological order of appearance, are (in brackets the far field potentials)[19]:

• Generators of median SSEPs: Erb point = brachial plexus; N11, N13 = dorsal column, nucleus cuneatus; (P14 = medial lemniscus); (N18 = rostral brainstem, thalamus); N20 = primary sensory cortex; P22 = primary motor cortex;

• Generators of tibial SSEPs: N22 = dorsal grey and root entry zone at the lumbosacral spine; N30 = nucleus gracilis; (P31 = brain stem, ipsilateral to P14); (N34 = rostral brain stem, ipsilateral to N18); P40 = primary sensory cortex.

• Useful SSEP parameters: Peripheral conduction time (wrist -Erb point/N9 latency); N9-N13 (plexus-posterior horns CT); N13-N20 (cervical-cortical CT); P14-N20 (lemniscus-cortical CT); P14-N18 (functional study of brain stem like BAEPs); N22-N30 (intraspinal CT); N22-P40 (lumbar-cortical CT).

All demyelinating processes involving the medial lemniscus or dorsal column can cause prolonged latencies or lack of SSEP development. This may occur in 80% of MS patients even in the absence of sensory signs and symptoms. Obviously, the percentage will rise in those patients with sensory symptoms or signs, particularly when assessing SSEPs of the lower limbs, which are more likely to be affected by demyelinating lesions as they have a longer nervous route. Upper extremity SSEPs are abnormal in 60% of all patients with definite, probable or possible MS, and in 40% of asymptomatic patients with MS. The most common pathological changes are extensions of the central latencies. One third of SSEP abnormalities in MS are unilateral; if bilateral, the abnormalities are often asymmetric[20-24].

Motor evoked potentials

Transcranial magnetic stimulation (TMS) is a technique used to measure corticospinal tract changes at any level of the motor pathway. TMS has shown a significant prolongation of central motor conduction time (CMCT) in MS patients. The stimulator consists of tightly wound well-insulated copper coil. As a result of the small magnetic field induced by the coil, a secondary electric field circulating in the opposite direction to the magnetic field is produced. Painless TMS has replaced electric stimulation gaining general diffusion in the study of motor evoked potentials (MEPs).

MEPs are the excitatory effects elicited by TMS; the silent period is a transient suppression of motor activity after a TMS-induced muscle response during muscle contraction. MEPs are characterized by the parameters of threshold, latency, amplitude, duration and morphology. They are recorded by surface electrodes positioned on the muscle under examination and are amplified by an electromyograph. TMS stimulates the corticospinal tract and peripheral motor neurons thereby allowing measurement of MEPs. The spinal nerve roots are stimulated by positioning the coil on the cervical spine (upper limbs) or lumbar region (lower limbs). The MEP latency obtained gives the peripheral latency. The CMCT can be calculated by subtracting the MEP latency from the central latency.Clinical signs show a good correlation with CMCT abnormalities (Fig. 5). Calculation of CMCT should be slightly overestimated to include the root conduction time: i.e., the peripheral component should be calculated using the technique of F-wave recording [F-M-1]/2), which allows the exact CMCT to be measured by removing it from the total the root conduction time[25-26].

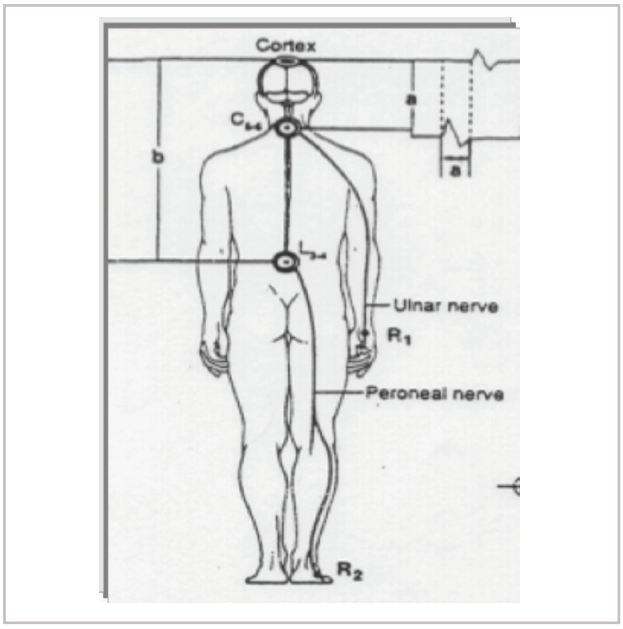


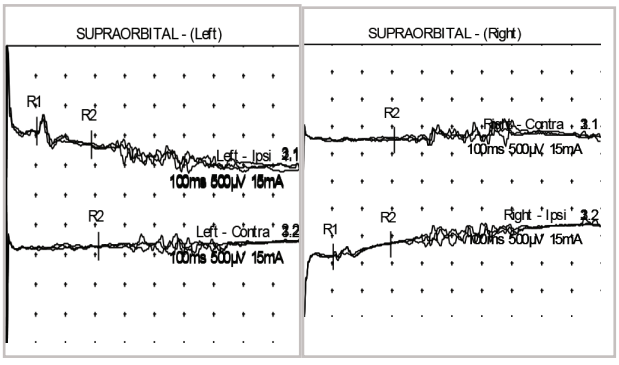
Fig. 5: Central and peripheral magnetic stimulation for central motor conduction time (CMCT) evaluation.

MEP duration is increased in patients with definite MS, which is compatible with the increased temporal dispersion of the impulses reaching the spinal motor neuron pool. A correlation between CMCT and manual dexterity has been reported in patients with definite MS. MEP studies can be useful to monitor the clinical response to treatment. CMCT decreases toward normal values in patients who show clinical improvement after steroid treatment. A good correlation is also found in longitudinal assessments, including slowing of CMCT stages of relapse, with subsequent improvement after corticosteroid treatment[27]. The sensitivity of evoked potentials in detecting silent lesions follows the descending order: VEPs> Lower extremity SSEPs > Upper extremity SSEPs > MEPs > BAEPs.

Blink reflex

The blinking reflex is recorded using surface electrodes following stimulation of the supraorbital branch of the trigeminal nerve. The reflex includes afferent (trigeminal nerve) and efferent (facial nerve) components and usually consists of a response ipsilateral to the stimulus (R1) and a bilateral R2 response, with latencies of about 10 and 35 ms respectively (Fig. 6)[28]

The usefulness of the blink reflex is its ability to capture both lesions of the oligosynaptic afferent R1 response and the efferent ipsi or contralateral (R2) polysynaptic pathways[29-31].



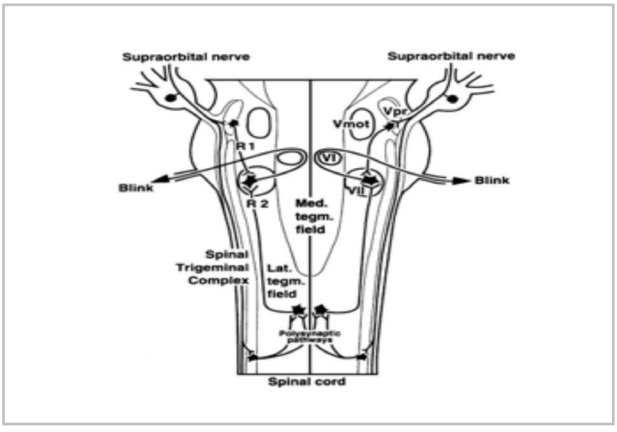


Fig. 6: Blink reflex (A left, B right) and reflex circuits (C) (36, modified).

Possible lesion locations are:

• The main sensory nucleus of the fifth cranial nerve (delayed or absent R1, R2 normal)

• The spinal fifth cranial nerve (normal R1, R2 delayed or absent from the affected side)

• Bulbar ipsilateral interneurons (normal R1, R2 ipsilateral impaired or absent, contralateral R2 present)

• Contralateral bulbar interneurons (R1 and R2 ipsilateral normal, contralateral R2 altered).

The first two lesions prevail in MS. An earlier study of 260 patients with longer disease duration showed a delayed R1 in 66% of relapse-remitting MS (RR-MS), 56% of patients with multiple sites of CNS involvement without relapse or recurrence of a localized lesion, and 29% of patients with suspected MS. R1 was altered in 78% of patients with pontine lesions, 57% of patients with other brain stem lesions, and 40% with neither brain stem signs nor symptoms[29].

Subsequent studies showed similar results[32-36]. The blink reflex detects lesions of the short pontine pathway. Blink reflex abnormalities are less common than those disclosed by other

neurophysiological investigations, but they reveal subclinical sites of pontine demyelination and hence contribute to early disease diagnosis.

The conditioned eyeblink reflex

The delayed conditioned eyeblink reflex, in which an individual learns to close the eyelid in response to a conditioned stimulus (e.g., a tone), relies entirely on the functional integrity of a cerebellar motor circuit that involves the contingent activation of Purkinje cells by parallel and climbing fibres. The delayed paradigm of eyeblink conditioning might be particularly valuable for the detection of subtle abnormalities of cerebellar motor learning that are clinically silent: the test might have predictive value following a clinically isolated syndrome[37].

Summary of the role of neurophysiological tests

The symptoms, course and prognosis of MS show broad interindividual variability. Up to 30% of patients have a "benign" disease course for more than 20 years after the first manifestation. Early diagnosis of MS and assessment of the disease prognosis and course are crucial. Diagnosis relies on the identification of at least two CNS lesions and demyelinating lesions disseminated in time and space. Because the illness is difficult to diagnose on clinical grounds alone, neurophysiological studies, in addition to MRI and CSF evaluations, can yield this information. The diagnostic sensitivity of the individual tests is variable: generally speaking, patients with a longer history of disease have a higher incidence of test abnormalities. The combination of VEPs, SSEPs, BAEPs, MEPs and the blink reflex can detect lesions in a high number (up to 90%) of patients referred for suspected MS and in whom the subsequent diagnosis was definite. Comparisons of the first three evoked potential stimulus modalities have found visual and somatosensory testing to be of approximately equal sensitivity in revealing clinically unsuspected lesions, with auditory testing being one half to one third less sensitive; the three tests are complementary. Combining all of the first three modalities, 97% of patients with definite MS, 86% of patients with probable MS, and 63% of patients with possible MS had abnormal findings in at least one of these tests[39]. VEPs are more sensitive than MRI or physical examination in prechiasmatic lesions, with abnormalities persisting over long periods of time. In demyelinating disease, an abnormal BAEP response is more common in symptomatic patients, but a positive test may sometimes be recorded in the absence of clinical brain stem symptomatology. About 20% of the population tested for a second lesion have an abnormal BAEP and about half of these go on to develop MS in the following one to three years[39].

New MEP techniques using multiple stimulation to determine CMCT[40] or double stimulation of different intensities and at different interstimulus intervals can increase the sensitivity of electrophysiological data on intracortical fibre dysfunction[41-42]. While MRI offers better sensitivity than any single electrophysiological study, combined EPs and the blink reflex can enhance the sensitivity of these tests. EP have mild specificities and give limited information on the aetiology of a lesion and none on the state of possible inflammation, but electrophysiological investigations remain objective diagnostic tools and prognostic measures before and after treatments. Together with the clinical picture and MR imaging, transverse and longitudinal studies have demonstrated a good correlation between EP abnormalities and disability. This suggests that multimodal EPs are a good marker of the severity of nervous damage in MS and may predict the evolution of disability[22,43,44]) to identify patients at high risk of clinical deterioration and guide decisions as to immunomodulatory[45] or immunosuppressive[46] treatment. Immunosuppression could be evaluated by the effects on the patient's clinical status and the resolution of neurophysiological abnormalities (MEPs): IV methylprednisolone administration in RR-MS and suspected MS is followed by a prompt partial resolution of central conduction block paralleled by an improvement in muscle force.

Conclusion

- SSEPs such as MEPs of the lower extremities are more sensitive than those of the upper extremities
- BAEPs are altered more frequently than the BR, especially in patients with signs or symptoms of brain stem lesions
- VEPs and SSEPs are more frequently sensitive than other EPs
- All EPs performed simultaneously are sensitive and reliable diagnostic tools with up to 95% sensitivity in the diagnosis of demyelinating

diseases

• EPs confirm their practical usefulness in patients with pacemakers or metal prostheses or otherwise unable to undergo MRI (such as subjects with claustrophobia)

• The sensitivity of EPs follows the descending order: VEPs > L-SSEPs > L-MEPs > U-SSEPs > U-MEPs > BAEPs > BR.

• Single EPs are insufficient for transverse and longitudinal monitoring of the diagnosis and prognosis of demyelinating diseases, while the multimodal global score is a better tool for experimental and clinical investigations.

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