Subclinical brainstem involvement in peripheral polyneuropathies
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Objectives
The objective of this study was to investigate the subclinical brainstem involvement in patients presenting with peripheral polyneuropathy (PN).

Patients and methods
Patients with various disorders presenting with clinical manifestations of PN were evaluated by routine sensory and motor nerve conduction studies and only patients with electrophysiologically documented PN were included in this study. Patients with a previous history of cranial nerve lesions and stroke were excluded. Seventy-eight patients and 30 age-matched and sex-matched healthy individuals were included for the evaluation of blink reflex (BR). BRs were obtained after bilateral electrical stimulation of the supraorbital nerve for quantitative analysis of three responses, early ipsilateral component (R1), late ipsilateral (R2i), and late contralateral (R2c).

Results
R1, R2i, and R2c latencies were prolonged and of low amplitude in diabetic patients with PN. Fifty percent of cancer patients with PN had abnormally delayed BR responses. R1 was delayed in 58.3% of patients with chronic renal failure and it was associated with prolonged R2i and R2c latencies in 41.6% of those patients. In 53.8% of patients with hypothyroidism, R2i and R2c latencies were prolonged whereas R1 latency was normal. Sixty percent of patients with hereditary motor sensory neuropathy had prolonged latency of at least one component of the BR responses. Three patients with scleroderma had markedly low amplitude but normal latency BR responses.

Conclusion
Subclinical involvement of the facial, trigeminal nerves, and brainstem may occur in patients with various disorders presenting with PN, which could be identified by easy and noninvasive BR testing.

Keywords: blink reflex, brain stem, peripheral polyneuropathy

Introduction
Peripheral polyneuropathy (PN) is frequent in many metabolic, inflammatory, and neoplastic disorders. Studies suggest that neurological alterations occur at a variety of anatomical levels, including the central nervous system (CNS), although this central involvement is still a debatable issue [1]. Diabetes mellitus (DM) is one of the most common causes of disabling PN. Central nervous neuropathies have been the least studied of those related to DM [1]. Similarly, peripheral neuropathies are among the most common neurologic complications of cancer, but studies on its brainstem complications are scarce. In addition, in chronic renal failure, the high incidence of neurological complications is well established. However, studies on the influence of uremic metabolic disorders on brainstem conduction are insufficient.

In PN, classical nerve conduction studies have focused exclusively on the peripheral nerves. Electrophysiological tests such as the blink reflex (BR) have been used to assess CNS involvement in patients with PN [2]. The diagnostic value of BR has been well established in the assessment of conduction along the peripheral and the central brainstem reflex arc [3]. BR is analogous to the corneal reflex. It measures the entire reflex arc between the trigeminal and facial nerves. It involves stimulation of the ophthalmic branch of the trigeminal nerve, from where afferents travel to the pons, mesencephalon, and cerebral cortex to make final connections with the facial nerve. In response to stimulation, these afferents trigger the response that can be recorded ipsilateral and contralateral to the site of stimulation. Stimulation of the ophthalmic nerve produces an early ipsilateral phasic component (R1) (representing a pontine reflex), a late ipsilateral tonic component (R2i), and a late contralateral tonic component (R2c) (representing a more complex reflex arc including the pons and the lateral medulla) [4].

The aim of this study was to investigate the subclinical BR alterations in patients with various disorders presenting with PN.

Patients and methods
Patients with various disorders presenting with clinical manifestations of PN (sensory disturbances, pain, and
Peripheral sensory and motor electrophysiological studies were recorded using surface recording electrodes (Neuropack; Nihon Kohden Corporation, Tokyo, Japan), with an analysis time of 20 ms for sensory and 50 ms for motor studies. Studies were carried out in a warm room at a temperature between 25 and 29°C. Sensory and motor nerve conduction velocities, sensory nerve action potential, and compound muscle action potential (CMAP) amplitudes of bilateral sural nerves, bilateral sensory median and ulnar nerves, bilateral posterior tibial motor nerves, and bilateral ulnar motor nerves were determined. Motor conduction studies of the posterior tibial nerve were performed by supramaximal stimuli applied at the ankle and the popliteal fossa. The recording electrodes were placed over the ankle and the tendon of the abductor hallucis muscle. For the ulnar motor nerve, supramaximal stimuli were applied at the wrist, below and above the elbow. The recording electrodes were placed over the belly and tendon of the abductor digit minimi muscle. Abnormalities were defined as slowed velocity, low amplitude, or an absent response in at least two nerves [5].

On the same day of peripheral electrophysiological studies, BR testing was performed, where the participants were supine and their eyes gently closed. The right and left supraorbital nerves were stimulated electrically with bipolar surface electrodes according to the method described by Kimura [6]. The stimulus duration was 0.2 ms. The signal was filtered with a range of 20 Hz–3 kHz, the sweep speed was 10 ms/division, and gain was 200 µV. To avoid habituation, four to six stimuli were applied randomly to each side with a minimum of 20 s interstimulus interval without patient awareness of stimuli application time. Stimulus intensity was two to four times higher than the threshold. The BR responses were recorded bilaterally by an active surface electrode placed on the inferior lateral aspect of the orbicularis oculi muscle (Occ) with a reference electrode placed just lateral to the lateral canthus ipsilaterally and the ground electrode was placed over the chin. The onset latencies (ms) of the evoked response were measured from the stimulus artifact to the initial deflection from baseline. For each participant, at least three R1 and three pairs of R2 were recorded and the shortest latencies were determined [6]. In addition, direct motor response of the facial nerve was recorded from the Occ muscle bilaterally after stimulation of the facial nerve anterior to the mastoid. The CMAP latency and amplitude were recorded.

Statistical evaluation

The SPSS 17.0 package program was used to carry out the statistical evaluation. Data were expressed as mean ± SD. The onset latencies of BR responses were considered to be abnormal if they were more than 2.5 SD of the mean value of the healthy controls. Comparison between the patient and control groups was performed using an independent-samples t-test. The significance level was defined as P 0.05 or less.

Results

Patients with DM type 2, neoplastic disorders, chronic renal failure, hypothyroidism, hereditary motor sensory neuropathy (HMSN), and scleroderma were included in this study. Peripheral nerve conduction studies confirmed sensory or sensorimotor PN in the patients studied (Table 1). There was abnormal sural, median, and ulnar sensory conduction (absent sensory nerve action potential, reduced amplitude, and reduced sensory conduction velocity), posterior tibial motor conduction (reduced motor conduction velocity and reduced amplitude), and ulnar motor conduction (reduced motor conduction velocity). There was no significant difference between the patients and control groups in the direct facial nerve motor response. The mean CMAP amplitude of the direct facial nerve response was 2.6 ± 0.7 and 2.4 ± 0.9 mV in patients and controls, respectively. The mean latency was 3.9 ± 0.5 and 3.8 ± 0.4 ms in patients and controls, respectively. None of the patients had abnormal facial nerve conduction to Occ muscle bilaterally.

All control participants showed an ipsilateral R1 response with a mean latency of 10.5 ± 0.8 ms, a second ipsilateral R2i response with a mean latency of 31.4 ± 3.3 ms, and a contralateral R2c response with a mean latency of 31.6 ± 3.7 ms (Fig. 1a). Accordingly, abnormal response latencies were set as follows (mean + 2.5 SD): R1 response latency more than 12.5 ms, R2i response latency more than 39.7 ms, and R2c response latency more than 40.9 ms. Reflex responses varied considerably in peak-to-peak amplitude from one individual to the other. Consequently, amplitude changes could not be evaluated in the patient group [2]. None of the participants had absence of BR responses.
Table 1 Sensory and motor conduction parameters in studied patients with various polyneuropathies

<table>
<thead>
<tr>
<th>Distal latency (ms)</th>
<th>Amplitude (motor: mV, sensory: μV)</th>
<th>Conduction velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right posterior tibial nerve</td>
<td>6.3 ± 1.0</td>
<td>3.3 ± 3.3</td>
</tr>
<tr>
<td>Left posterior tibial nerve</td>
<td>7.4 ± 0.8</td>
<td>3.8 ± 2.4</td>
</tr>
<tr>
<td>Right ulnar nerve (motor)</td>
<td>3.8 ± 1.2</td>
<td>3.5 ± 1.9</td>
</tr>
<tr>
<td>Left ulnar nerve (motor)</td>
<td>3.3 ± 1.0</td>
<td>4.2 ± 2.4</td>
</tr>
<tr>
<td>Right sural</td>
<td>–</td>
<td>3.5 ± 2.1</td>
</tr>
<tr>
<td>Left sural</td>
<td>–</td>
<td>3.3 ± 2.8</td>
</tr>
<tr>
<td>Right median (sensory)</td>
<td>–</td>
<td>5.3 ± 3.3</td>
</tr>
<tr>
<td>Left median (sensory)</td>
<td>–</td>
<td>6.1 ± 2.9</td>
</tr>
<tr>
<td>Right ulnar (sensory)</td>
<td>–</td>
<td>4.2 ± 3.8</td>
</tr>
<tr>
<td>Left ulnar (sensory)</td>
<td>–</td>
<td>4.5 ± 3.7</td>
</tr>
</tbody>
</table>

Figure 1

Blink reflex responses in a normal control participant (a) (normal latency and amplitude), in a leukemic patient (b) (low-amplitude left R1 response, low-amplitude left R2i and R2c, lower traces), and in a scleroderma patient (c) (R1, R2i, and R2c of low amplitude bilaterally). Three traces were superimposed. Upper traces were recorded from right orbicularis oculi whereas lower traces were recorded from left orbicularis oculi.
Sixteen cancer patients presenting with sensory (nine patients) and sensorimotor axonal (seven patients) PN were included. There were 12 women and four men, age range 47–56 years. They had leukemia (eight patients), cancer colon (four patients), lung cancer (two patients), and ovarian malignancy (two patients); all were on vincristine treatment. Eight (50%) patients had abnormally delayed R1 (12.7 ± 0.15 ms), R2i (39.9 ± 2.1 ms), and R2c (42.3 ± 3.2 ms) responses (Table 2). One leukemic patient without clinical facial palsy had abnormally delayed, low-amplitude left R1 response coexisting with low-amplitude left R2i and R2c responses (Fig. 1b).

Twelve chronic renal failure patients undergoing hemodialysis (the mean level of serum creatinine was 10.6 ± 2.7 mg/dl and blood urea nitrogen was 70.1 ± 24.4 mg/dl) with sensorimotor axonal PN (100%) were enrolled. There were four women and eight men, age range 40–60 years. Patients were examined 24 h after the last dialysis treatment. Early and late BR responses showed abnormally delayed latencies (R1: 13.0 ± 0.6 ms, R2i: 42.1 ± 1.1 ms, R2c: 45.2 ± 1.5 ms). R1 was delayed bilaterally in seven patients (58.3%) whereas it was associated with prolonged R2i and R2c latencies in five patients (41.6%) (Table 2). No correlation was found between BR response abnormalities and disease duration.

Twelve patients had symptoms and signs of hypothyroidism associated with serum triiodothyronine (T3) and thyroxin (T4) below the normal limit (2.3–4.2 pg/ml and 0.8–1.8 ng/l, respectively), with a thyroid-stimulating hormone above normal (0.5–4.7 μIU/ml) [8]. There were nine women and three men, age range 33–48 years and disease duration ranging from 1.5 to 5 years. Peripheral electrophysiological studies showed evidence of sensory demyelinating PN (slowing of sural, median, and ulnar nerves sensory conduction velocity). In seven patients (53.8%), analysis of BR showed prolongation of R2i and R2c latencies whereas R1 latency was normal (R1: 11.0 ± 0.6 ms, R2i: 40.7 ± 1.2 ms, R2c: 42.2 ± 1.0 ms) (Table 2).

Ten patients with HMSN (seven patients had HMSN type I and three patients had HMSN type II). All were men, age range 32–41 years. Six patients (60%), five with type I HMSN and one with type II HMSN, had prolonged latency of at least one component of the BR responses (R1: 12.9 ± 1.4 ms, R2i: 41.1 ± 2.2 ms, R2c: 44.1 ± 0.5 ms) (Table 2).

Three scleroderma female patients had vasculitic axonal sensorimotor PN. The BR responses were normal in latencies (right supraorbital nerve stimulation; R1: 12.0, R2i: 38.0, R2c: 39.4, left supraorbital nerve stimulation; R1: 12.2, R2i: 36.40, R2c: 38.20). However, their amplitudes were markedly reduced (Fig. 1c).

Table 2 Blink reflex latencies in normal control participants and in patients with various polyneuropathies

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of participants</th>
<th>Number of patients with abnormal responses</th>
<th>R1 (ms) (mean ± SD)</th>
<th>R2i (ms) (mean ± SD)</th>
<th>R2c (ms) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal controls</td>
<td>30</td>
<td>0</td>
<td>10.5 ± 0.8</td>
<td>31.4 ± 3.3</td>
<td>31.6 ± 3.7</td>
</tr>
<tr>
<td>Diabetic PN</td>
<td>25</td>
<td>R1: 15, R2i: 14, R2c: 12</td>
<td>12.9 ± 1.7</td>
<td>39.56 ± 3.7</td>
<td>42.18 ± 4.0</td>
</tr>
<tr>
<td>Cancer-related PN</td>
<td>16</td>
<td>8</td>
<td>12.75 ± 0.1</td>
<td>39.97 ± 2.1</td>
<td>42.3 ± 3.2</td>
</tr>
<tr>
<td>Uremic PN</td>
<td>12</td>
<td>R1: 7, R2i: 5</td>
<td>13.0 ± 0.6</td>
<td>42.1 ± 1.1</td>
<td>45.2 ± 1.5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12</td>
<td>R2i and R2c: 7</td>
<td>11.0 ± 0.8</td>
<td>40.7 ± 1.2</td>
<td>42.2 ± 1.0</td>
</tr>
<tr>
<td>HMSN</td>
<td>10</td>
<td>6</td>
<td>12.8 ± 1.4</td>
<td>41.1 ± 2.2</td>
<td>44.1 ± 0.5</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>3</td>
<td>3</td>
<td>12.2 (low amplitude)</td>
<td>36.4 (low amplitude)</td>
<td>38.2 (low amplitude)</td>
</tr>
</tbody>
</table>

HMSN, hereditary motor sensory neuropathy; PN, peripheral polyneuropathy.

Discussion

In the current study, BR was found to be altered in patients with DM type 2, cancer-related polyneuropathy, chronic renal failure, HMSN type I and II, scleroderma, and hypothyroidism. BR alterations were first described in a large series of patients with polyneuropathy in 1982 by Kimura [2]. He analyzed the BR of patients with Guillain–Barre syndrome, chronic inflammatory polyneuropathy,
Fisher syndrome, HMSN types I and II, and diabetic polyneuropathy. Lesions of the trigeminal nerve involve the afferent limb of the BR arc and eliminate or delay both the early ipsilateral and the late bilateral reflex responses to supraorbital nerve stimulation on the involved side. Facial nerve lesions affect the efferent limb of the BR arc and abolish or delay the early and the late ipsilateral responses to supraorbital nerve stimulation on the involved side, whereas the late reflex response on the side opposite to the lesion will be unaffected, irrespective of the stimulation side. Pontine lesions can cause unilateral or bilateral delay of early reflex components, whereas the late reflex components can be delayed or normal, depending on whether or not the late reflex pathways are interrupted as they pass through the pons in the trigeminal spinal tract. Lesions of the medulla do not affect the early reflex responses, particularly if the spinal trigeminal tracts and nuclei are involved. Thus, if analysis of the late reflex responses fails to show evidence of peripheral trigeminal or facial nerve deficit, alterations of the early reflex component of the BR are generally indicative of a pathologic condition of the pons [9]. The latency of R1 represents the conduction time along the trigeminal and facial nerves and pontine relay. A bilateral delayed early R1 response indicates bilateral subclinical dysfunction of the trigeminal and/or facial nerve [6]. The polysynaptic R2 response latency reflects excitability of interneurons and synaptic transmission in addition to axonal conduction [2,6].

Diabetic PN is one of the most common complications of diabetes, affecting about 50% of patients [10]. Glycemic control is a pivotal factor in the development of polyneuropathy [11,12]. The incidence of cranial neuropathies is higher in diabetic patients compared with a nondiabetic population [13]. The oculomotor and facial nerves are among the most commonly affected nerves [14]. Studies have detected subclinical facial nerve pathology in 70% of diabetic patients with PN [15]. Thömke et al. [16] indicated that peripheral facial palsy might be the only clinical sign of a pontine infarction in diabetic patients. In this study, significant delay in the BR responses in diabetics with PN was clearly found. These BR abnormalities in diabetic patients who had no any clinical signs of CNS dysfunction prove that diffuse subclinical damage occurs to the CNS, which can be discovered by sensitive neurophysiologic methods such as BR [17]. Our data were in agreement with previous reports that concluded that subclinical facial and trigeminal nerve involvement is not unusual in DM, although it is significantly less frequent than the involvement of limb nerves [18–21]. R1 alterations were attributed to diffuse demyelination of medium thick myelinated A-β fibers that conduct the R1 response along the length of facial and trigeminal nerves in diabetic patients with PN [18], whereas the bilateral delay of R2i and R2c latencies in those patients could be because of diffused pontomedullary dysfunction, mainly at the crossing interneurons level [1–3]. In the current study, no correlation was found between BR abnormalities and disease duration. It seems, rather, that hyperglycemia could play an important role in producing alterations in BR through hyperosmolality as the brain is the organ most susceptible to changes in osmolality [19,22]. This is in agreement with Neau et al. [19], who studied 21 uncontrolled diabetics and found an elongation of the R1 and R2 components of BR. In addition, Stamboulis et al. [23] have shown that in hyperglycemic patients, the BR components had prolonged latencies than normoglycemic patients. In contrast, some results showed alteration in the latency of BR components in normoglycemic and hyperglycemic diabetes patients with a short period of disease evolution [1]. In the present study, BR alterations were higher in patients with more severe generalized sensory and motor peripheral nerve involvement. Also, Guney et al. [18] have found that R1 values in diabetic patients without PN did not differ significantly from normal controls and this was not the same for diabetic patients with PN. Thus, it could be concluded that the severity of PN may be a marker of CNS dysfunction. It should be noted here that the generally low-amplitude BR responses in the diabetic patients studied may be a consequence of the hyperglycemic and/or ischemic axonal loss in the intracranial portion of facial and trigeminal nerves. Also, this ischemic axonal loss is believed to be the cause of markedly reduced BR amplitudes in the three scleroderma patients with vasculitic axonal PN.

Peripheral neuropathies in the cancer patients studied could be because of neurotoxicity of cancer treatment (vincristine-induced symmetric sensorimotor axonal polyneuropathy), paraneoplastic vasculitic distal sensorimotor neuropathy, paraneoplastic sensory neuronopathy, nutritional deficiencies, and metabolic derangements. Chemotherapy may also cause central neurotoxicity, whose incidence and severity are related to the cumulative drug dose or dose intensities [24]. Similarly, other etiologies of cancer induced peripheral neuropathies may have an influence on brainstem conductivity.

In chronic renal failure PN patients undergoing hemodialysis, we detected bilaterally delayed R1 response and this could indicate bilateral dysfunction of the trigeminal and/or facial nerve in the pontine reflex arc, whereas delayed R2i and R2c latencies were suggestive of subclinical interneuron dysfunction in low brainstem reticular formation because of metabolic changes analogous to that of DM. Previous autopsy findings of uremic patients showed focal and perivascular areas of demyelination and necrosis in the bulb region with frequent involvement of the descending root of the trigeminal nerve [25,26].

Thyroid hormone is known to influence the synthesis of myelin [27], which is important for the speed of impulse transmission along the polysynaptic pathways mediating the BR [28]. Also, changes in interneuronal excitability of the BR arc in the brainstem, alteration of cerebral metabolism, and low body temperature in hypothyroidism may be the causes of the R2i and R2c latency abnormalities in the hypothyroid patients studied [27].

In a study of 27 HMSN patients [29], R1 and R2 mean latencies were prolonged in comparison with those of healthy individuals. The medium thick myelinated A-beta fibers conduct the R1 component, whereas R2 is conducted by the nociceptive thin myelinated A-δ
fibers [29]. It seems that the involvement of these fibers in the disease process is responsible for slowing of R1 and R2 responses in HMSN patients.

**Conclusion**

Subclinical involvement of the facial, trigeminal nerves, and brainstem may occur in patients with various disorders presenting with PN, which could be identified by easy and noninvasive BR testing.

**Acknowledgements**

There are no conflicts of interest.

**References**


