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The late blink reflex response abnormality due to lesion of the lateral tegmental field

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Summary
We report on a blink reflex abnormality observed in two normal patients, which provides additional information on the central pathways mediating this reflex. Autopsy was performed in one patient and MRI in the other. In the first patient there was a small lesion at the dorsal middle third of the lateral tegmental field and in the second patient at the level of the dorsal lower third of the medulla oblongata. In both patients the common finding was the absence of the late response (R2) ipsilateral to the side of the lesion, while the R2 response on the unaffected side was normal regardless of the side of the supraorbital nerve stimulation. The R1 responses were normal. This type of blink reflex abnormality has not been reported before and is referred to by us as ‘tegmental type’ of R2 abnormality. The results led to the conclusions that: (i) the crossed and uncrossed ascending trigemino-facial connections are mediated through the lateral tegmental field; (ii) the uncrossed trigemino-facial connection originates at the level of at least the lower medulla oblongata; (iii) the contralateral R2 response is established by way of an ascending pathway, which crosses the midline at the level of at least the lower third of the medulla oblongata.

Keywords: blink reflex; lateral tegmental field; pons; medulla oblongata

Introduction
About 100 years ago, the British physician Overend elicited the blink reflex by tapping one side of the forehead (Overend, 1896). The underlying mechanisms of this reflex remained obscure until Kugelberg (1952) analysed the blink reflex electromyographically by electrically stimulating the supraorbital nerve. He showed that the reflex consists of two responses. The first or early response, R1, is unilateral and occurs at a latency of about 10 ms ipsilateral to the side of the stimulation of the supraorbital nerve. Clinically this response is not visible. The second or late response, R2, is bilateral and appears after a latent period of about 30 ms. The R2 responses cause the actual closure of the eyelids.

The blink reflex is now established as an important reflex in clinical studies (Ongerboer de Visser and Cruccu, 1993; Hopf, 1994). Abnormalities of the blink reflex have been reported in, among others, various trigeminal nerve lesions, such as occur in infectious diseases (Goor and Ongerboer de Visser, 1976), traumatic injuries (Kimura et al., 1970, Goor and Ongerboer de Visser, 1976), trigeminal neuralgia (Ongerboer de Visser and Goor, 1974; Cruccu et al., 1990), tumours (Kimura et al., 1970) and neuropathies (Ashworth and Tait, 1971; Kimura, 1971; Auger and McManis, 1990). Blink reflex abnormalities were also found in brainstem and hemispheric disorders (Ongerboer de Visser and Moffie, 1979; Ongerboer de Visser, 1981; Berardelli et al., 1983; Kimura et al., 1985; Hopf et al., 1991; Ongerboer de Visser and Cruccu, 1993; Valls-Solé et al., 1996), in association with diseases of the extrapyramidal system (Messina et al., 1972; Agostino et al., 1988), dystonic disorders (Berardelli et al., 1985; Tolosa et al., 1988; Nakashima et al., 1990; Aramideh et al., 1995; Eekhof et al., 1996) and following lesions of the facial nerve, such as Bell’s palsy (Kimura, 1969). In the latter disorder, the blink reflex has also been used for prognostic evaluation (Kimura et al., 1976).

The common afferent limb of the reflex components is the ophthalmic division of the trigeminal nerve (Kugelberg 1952; Shahani, 1970; Ongerboer de Visser and Goor, 1974; Cruccu et al., 1987). The facial nerve is the common efferent limb (Kimura, 1969; Dengler et al., 1982). The central pathway, through which the blink reflex responses are mediated, are
still incompletely understood. Previous studies have shown that impulses for the R1 response are conducted through the pons and are relayed via an oligosynaptic arc, probably consisting of one or two interneurons, located in the vicinity of the main sensory nucleus of the trigeminal nerve (Shahani and Young, 1972; Kimura, 1975; Ongerboer de Visser, 1983; Holstege et al., 1986). For the R2 responses, it has been established that afferent impulses are conducted through the descending spinal tract of the trigeminal nerve in the pons and medulla oblongata before they reach the caudal spinal trigeminal nucleus (Kimura and Lyon, 1972; Ongerboer de Visser and Kuypers, 1978). From there, impulses are relayed via the medullary pathway, which ascends bilaterally to reach the facial nuclei in the pons. These trigemino-facial connections are thought to pass through the lateral tegmental field, which lies medial to the spinal trigeminal nucleus [in the cat, Holstege et al. (1977); in the human, Ongerboer de Visser and Kuypers (1978)]. However, the type of abnormality of the R2 response due to a lesion that affects mainly the lateral medullary tegmental field has not yet been reported. Furthermore, it is still unclear at which level the fibres mediating impulses for the R2 responses cross the midline.

In this paper, the clinical and blink reflex findings in two patients with a medullary lateral tegmental field lesion are reported, enabling us to describe a new type of the R2 response abnormality and to provide additional information on the medullary pathways involved in the generation of the late blink reflex responses. MRI was performed in one patient and autopsy in the other.

**Methods**

A comprehensive description of the technique used to elicit the blink reflex and the normative data has been reported earlier (Ongerboer de Visser and Cruccu, 1993). The blink reflex was evoked with the subject in supine position and the eyes open. Supramaximal stimulation of the supraorbital nerve was delivered transcutaneously. The cathode was placed over the supraorbital notch on one side and the anode ~2 cm higher and laterally to avoid spread of current to the contralateral supraorbital nerve. The supraorbital nerves on both sides were stimulated successively. Reflex responses were recorded simultaneously by coaxial needle electrodes inserted into the orbicularis oculi muscles of the lower eyelids or by surface electrodes on the lower eyelids on both sides. The shocks were delivered at intervals of ≥7 s and between spontaneous blinks. A difference in latency between the right and left sides exceeding 1.5 ms for the R1 response and 8.0 ms for the R2 response was considered abnormal (Ongerboer de Visser and Goor, 1974).

The blink reflexes were recorded in both patients shortly or immediately after the neurological examination, which was performed by an independent neurologist.

Both patients gave informed consent to the procedure, which was approved by the Ethical Committee of the Academic Medical Centre in Amsterdam.

**Case reports**

Figure 1 shows a schematic representation of the sites of lesions.

**Patient 1**

A 61-year-old hypertensive woman suddenly experienced diminished sensation of the left side of the body, followed by dysphagia and dysphonia. Physical examination revealed an alert woman with a blood pressure of 190/110 mm Hg and a regular pulse rate of 76/min. There was a right-sided Horner. The right corneal reflex response was absent after stimulation of either side, while a touch of the right or left cornea elicited a normal response in the left orbicularis muscle. The strength of the facial muscles was normal on both sides. There was paresis of the right soft palate. The face showed no sensory deficit and the sense of motion and vibration were normal on the left side. Other sensory modalities were disturbed in the limbs and trunk on the left side. The strength of the extremities was normal. The plantar reflexes were flexor.

Seven months later the patient died from a myocardial infarction. An autopsy was performed.
Fig. 2 Blink reflexes in the first patient with a lesion on the right side. The upper three pairs of traces represent reflex responses in the right (R) and left (L) orbicularis oculi muscles after stimulation of the right supraorbital nerve (R*). No ipsilateral R2 response can be recorded on the right side after stimulation of the right supraorbital nerve. The ipsilateral right R1 response and contralateral left R2 responses are elicited normally. The lower three pairs of traces represent reflex responses in the left (L) and right (R) orbicularis oculi muscles after stimulation of the left supraorbital nerve (L*). Normal ipsilateral R1 and R2 responses are recorded on the left side, while no contralateral right R2 response can be recorded after stimulation of the left supraorbital nerve.

**Blink reflex findings**

Stimulation of the left supraorbital nerve, contralateral to the side of lesion, elicited an ipsilateral R1 response with a latency of 10 ms and an ipsilateral R2 response with a latency of 34 ms (Fig. 2). No contralateral R2 response could be recorded. Stimulation of the right side evoked an ipsilateral R1 with a latency of 10 ms, whereas no ipsilateral R2 response could be elicited. The contralateral R2 had a normal latency of 30 ms.

**Pathological findings**

An infarction was located in the medullary lateral tegmental field between the oliva inferior nucleus and the spinal trigeminal complex on the right side (Fig. 3). Rostrally, the lesion extended slightly rostral to the inferior olivary nucleus and caudally to the level of the (internal arcuate) crossing fibres of the medial lemniscus. The lesion included the caudal portion of the nucleus ambiguus and the spinothalamic tract.

**Patient 2**

A 50-year-old hypertensive man suddenly experienced an unusual sensation of the left side of the body, followed by dizziness and gait disturbances. Physical examination revealed a cooperative man with a blood pressure of 230/120 mmHg and a regular pulse rate of 84/min. There was a Horner on the right side. The eye movements were normal. The right corneal reflex response was diminished after touching the right cornea. The strength of the facial muscles was normal. All sensory qualities were disturbed on the left side of the body. The face showed no sensory deficit. The strength of the extremities was not altered. The tendon reflexes were normal and the plantar reflexes were flexor.

**Blink reflex findings**

Stimulation of the left supraorbital nerve, contralateral to the side of lesion, elicited an ipsilateral R1 response with a latency of 11 ms and an ipsilateral R2 response with a latency
Fig. 3 Autopsy in the first patient showing an infarction in the medullary lateral tegmental field between the inferior olivary nucleus and the spinal trigeminal complex on the right side.

of 38 ms (Fig. 4). No contralateral R2 response could be recorded. Stimulation of the right side evoked an ipsilateral R1 with a latency of 10 ms, whereas no ipsilateral R2 response could be elicited. The contralateral R2 had a normal latency of 38 ms.

MRI findings
A right-sided infarction was located laterally in the caudal medulla oblongata (Fig. 5). The lesion involved the lateral part of the lateral tegmental field and interrupted some of the internal arcuate fibres and the spinothalamic tract.

Discussion
The two patients reported here had an abnormal late blink reflex response, referred to by us as ‘tegmental type’, that has not been reported previously. This was characterized by the absence of the R2 response ipsilateral to the side of the lesion after stimulation of the supraorbital nerve on either side, while the R2 response on the unaffected side was normal regardless of the stimulation side. This type of R2 response abnormality was caused by a total interruption of the crossed and uncrossed trigeminofacial reflex pathways that ascend on the side of lesion. In both patients the R1 responses were normal on both sides.

In intrinsic brainstem lesions four other types of blink reflex abnormalities have been described earlier (A–D in Fig. 6). The first type of blink reflex abnormality is characterized by the isolated absence of R1 or a delayed R1 response that can be observed in pontine lesions (A in Fig. 6, Kimura, 1970). The second type of abnormality is due to a lesion of the descending spinal tract (B2 in Fig. 6) and can be recognized by bilateral absence or delay of the late response following stimulation of the supraorbital nerve ipsilateral to the side of the lesion (Kimura and Lyon, 1972; Ongerboer de Visser and Kuypers, 1978). In this type of R2 abnormality the medially located lateral tegmental field is intact and stimulation of the supraorbital nerve contralateral to the side of lesion elicits normal bilateral responses. The R1 response is also absent or delayed at the side of the lesion when the lesion affects the trigeminal nerve at its entrance into the pons (B1 in Fig. 6), but is normal in medullary trigeminal tract lesions. The third type of abnormality can be observed when a lesion affects the facial nucleus or the intrapontine part of the facial nerve fibres (C in Fig. 6), while clinical or
Tegmental blink reflex abnormality

Fig. 4 Blink reflex responses in the second patient with a lesion on the right side. The upper three pairs of traces represent reflex responses in the right (R) and left (L) orbicularis oculi muscles after stimulation of the right supraorbital nerve (R*). No ipsilateral R2 response can be recorded on the right side after stimulation of the right supraorbital nerve. The ipsilateral right R1 response and contralateral left R2 responses are elicited normally. The lower three pairs of traces represent reflex responses in the left (L) and right (R) orbicularis oculi muscles after stimulation of the left supraorbital nerve (L*). Normal ipsilateral R1 and R2 responses are recorded on the left side, while no contralateral right R2 response can be recorded after stimulation of the left supraorbital nerve.

electromyographic examination should reveal paresis of the facial muscles (Ongerboer de Visser and Goor, 1976). The early and late blink reflex responses ipsilateral to the side of lesion are either absent or delayed regardless of stimulation side. The fourth, mixed type of reflex abnormality can be recorded when a lesion involves the descending spinal trigeminal tract, spinal trigeminal nucleus and the crossed fibres that ascend ipsilaterally to the side of lesion (Fig. 6D, Ongerboer de Visser and Kuypers, 1978). In this type, stimulation of the supraorbital nerve on the affected side evokes delayed or absent bilateral R2 responses, and stimulation of the unaffected side elicits a normal ipsilateral R2 and a delayed or absent contralateral R2 response. The R1 responses are normal regardless of the stimulation side.

With respect to the central pathways involved in the generation of R2 responses, the anatomical levels of the lesions in our patients are of major importance (Fig. 1; E in Fig. 6). In both patients the common finding was a tegmental type of R2 response abnormality due to lesions in the lateral tegmental field. In the first patient the lesion was located in the dorsal middle third of the medulla oblongata, while the more caudal lesion in the second patient was present in the dorsal lower third of the medulla oblongata. This observation leads to two conclusions. First, the ascending trigeminofacial reflex pathway, connecting the spinal trigeminal nucleus to the ipsilateral facial nucleus, must originate at the level of the lower medulla oblongata. Secondly, the contralateral R2 response must be established by way of an ascending trigeminofacial pathway that crosses the midline at the level of at least the lower third of the medulla oblongata.

In an earlier report (Ongerboer de Visser and Kuypers, 1978), it was suggested that crossed and uncrossed trigeminofacial pathways conducting impulses for the contralateral and ipsilateral R2 responses, respectively, are located in the lateral tegmental field of the brainstem. The autopsy findings in our first patient provide evidence for this assumption as the lesion, which altered the generation of the late responses, involved the lateral tegmental field and spared the medial tegmental field and the trigeminal complex.

In the cat, Holstege et al. (1986) have demonstrated that a cell group in the medial part of tegmentum, around the level of the hypoglossal nucleus, projects to the facial nerve motor neurons bilaterally. These neurons are not only connected to the orbicularis oculi motor neurons, as in the human, but also innervate the so-called retractor bulbii motoneurons that play an important role in the eye protection reflexes. Moreover, in the cat, this medially located medullary interneuronal cell group also projects to another interneuronal cell group in the pons, which in turn projects to the retractor bulbii and the orbicularis oculi motor neurons. This latter group of interneurons may be involved in the generation of the R1 and R2 responses of the blink reflex.

The results of the present study lead to the following conclusions: (i) a lesion involving the lateral tegmental field, anywhere from the caudal medulla oblongata to the pontomedullary level, may cause a tegmental type of R2
Fig. 5 In the second patient, sagittal T2-weighted spin-echo MR image (top) shows a hyperintense lesion, and axial T1-weighted spin-echo MR image (bottom) a hypointense lesion in the caudal medulla oblongata on the right side, involving the lateral part of the lateral tegmental field and some of the internal arcuate fibres and the spinothalamic tract.
abnormality characterized by the absence of the R2 response ipsilateral to the lesion and a normal R2 response contralateral to the lesion, both regardless of the stimulation side; (ii) in patients with this type of R2 response abnormality the sensory modalities of the face and the strength of the facial muscles are normal on clinical examination; (iii) the uncrossed, ascending trigeminofacial pathway originates at the level of at least the lower medulla oblongata; (iv) the contralateral R2 response is established by way of an ascending trigeminofacial connection that crosses the midline at the level of at least the lower third of the medulla oblongata.

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Fig. 6 Schematic representation of various lesions within the brainstem (A–E) and corresponding blink reflex response abnormalities in the right (R) and left (L) orbicularis oculi muscles after stimulation (*) of the supraorbital nerves. Blink reflex responses are either delayed (left column) or absent (right column). The A, B1, B2, C and D types of abnormalities have been reported earlier and the E type is recorded in the present study. See the text for comments on different types of reflex abnormalities. For abbreviations see Fig. 1.
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