Electrophysiological investigations in cranial hyperkinetic syndromes

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Publication date
2000

Citation for published version (APA):

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Chapter 6
General discussion.

Neurophysiological investigations of specific brain stem structures provide information on the functional state of its anatomical pathways at different levels within the brain stem.\textsuperscript{113} Electrodiagnostical studies, such as the blink reflex, are playing an increasingly important role in the diagnosis of movement disorders. These studies have provided evidence for the organic nature of dystonia. In this thesis, the term cranial hyperkinetic syndromes is introduced to indicate those disorders, which are characterized by involuntary contractions of the muscles innervated by the cranial nerves. The focus of the thesis is the application of neurophysiological investigations in patients suffering from blepharospasm, torticollis spasmodica, hemifacial spasm and in patients who developed synkinetic movements of facial muscles after Bell's palsy. Involuntary facial muscle contractions, orbicularis oculi blink reflex responses, blink reflex recovery curves, orbicularis oris reflex responses and ephaptic transmission were recorded and analyzed. The objectives were to improve reflex recording techniques for differential diagnostic purposes and to obtain insight into underlying pathophysiological mechanisms of these cranial hyperkinetic syndromes.

Reflex responses.

As mentioned in the introduction, R1 is a periocular reflex and probably alerts the subject to a threatening event near the eye, with only minimal habituation and even facilitation when attention is heightened.\textsuperscript{19} In contrast, R2 is a cutaneous reflex with interneurons which receive multimodal connections. These interneurons may activate the efferent pathway even without direct afferent activation, as they react to novel stimulation of visual, auditory and somatosensory systems, without stimulation of the trigeminal nerve.\textsuperscript{93,94,116} The close interaction of blinks with eye movements suggests that R2 may be involved in saccades to regions of interest: momentary eye closure may aid in a quick change of gaze direction.\textsuperscript{143} This explains the low threshold of R2, its initial long latency, which shortens with stronger stimulation, and the various stimuli by
which it can be evoked. Because novel stimuli are involved, R2 shows such strong
habituation (also multimodal). Habituation is caused by local factors such as presynaptic
inhibition and by cortical influences. Blink reflex recovery curve studies
suggested that the basal ganglia are involved too.

In our study of reflexes in the orbicularis oculi and orbicularis oris muscles after stimula-
tion of the supraorbital nerve, we could evoke R1 or R2 or both in orbicularis oris in
16 of 22 control subjects. The features of responses in these two muscles differed from
each other.
Amplitudes were smaller in the orbicularis oris muscle. Variability of the response
amplitudes in the orbicularis oris muscle was large and six subjects showed no responses
at all. These findings may point to either an increased cortical control on the ventral
part of the facial nucleus or to a large interindividual difference in development of
necessary reflex pathways, or both.

Blink reflex recovery curves.

By studying the blink reflex recovery curves, we answered several methodological
questions. We ascertained that a stimulation current of three times R2 threshold is
better than two times, in terms of smaller variability of the evoked responses in the
control group. Peak amplitude measurements are better than area measurements. While
in peak amplitude measurement the averaged and rectified peak amplitudes of R1 and
R2 are used for recovery curve calculation, area measurements offer information about
peak and duration of the R1 and R2 responses. Results were better, because variability
in the group of control subjects was smallest with peak amplitude measurement. How-
ever, there was not much difference between stimulation with two or three times R2
threshold, and between area and peak amplitude measurement.

Recovery index.

We calculated one variable, the recovery curve index, which enabled us to construct a
cut-off level for a normal recovery curve. This variable was calculated as the mean of
recovery curve values at interstimulus intervals of 0.21, 0.3 and 0.5 seconds, and a
cut-off value of the mean in controls plus 2 SD was chosen.
Reflex studies in cranial hyperkinetic syndromes.

Blepharospasm.

Many studies have shown structural lesions in the basal ganglia in patients with dystonia. The integration of activity of the direct and indirect pathways of the basal ganglia provides a gating influence upon premotor structures such as the thalamus, mesencephalic tegmentum and superior colliculus. In this way the basal ganglia exercise an inhibitory tone on brainstem interneurons, which may regulate the sensitivity of these structures to cortical activity. Normal blink reflexes in the orbicularis oculi and orbicularis oris muscle implicate that the blink reflex pathways function normally, at least during spasm-free intervals.

Many patients with blepharospasm show ophthalmologic abnormalities, which may lead to a relatively increased sensorimotor cortical activity. When basal ganglia gating of interneurons is intermittently disturbed, blink reflexes may show abnormalities during spasms.

The whole patients' group showed an enhanced recovery of R2 response, which in respect to the assumption of Kimura indicates hyperexcitability of brain stem interneurons. All patients with pure blepharospasm had an abnormal R2 recovery index. Involuntary levator palpebrae inhibition, also known as apraxia of eyelid opening, is a condition characterized by patients' inability to open the eyes on command. This can not easily be distinguished from blepharospasm and it may accompany blepharospasm in some patients. Patients with involuntary levator palpebrae inhibition all had a normal R2 recovery index. These findings indicate that blepharospasm is not a homogeneous disease entity, and point to different pathophysiological mechanisms at different levels.

Torticollis spasmodica.

We examined blink reflexes in patients with isolated torticollis spasmodica, without involvement of facial muscles. Blink reflex responses were normal and our results were similar to those of Nakashima et al. In their study, those patients with torticollis spasmodica as a part of a generalized dystonia had an increased R2 amplitude on the affected side. Therefore, blink reflex pathways appear to be normal in torticollis spasmodica as a focal dystonia.

In contrast, the abnormal R2 recovery curves and indices in these patients indicate that brainstem interneurons involved in blink reflexes are hyperexcitable in a proportion of patients with torticollis spasmodica, although to a lesser extent than in blepharospasm patients. The gating influence of the basal ganglia in torticollis is probably executed by a thalamocortical route.
Hemifacial spasm and post Bell's palsy synkinesia.

Different reflexes were evoked in patients with hemifacial spasm and compared to those recorded in patients who developed synkinetic movement between the branches of the facial nerve after Bell's palsy, so-called post Bell's palsy synkinesia (PBS).

Reflexes.

We found normal blink reflexes during spasm free intervals in patients with hemifacial spasm and, therefore, were unable to reproduce the results found by Nielsen.\textsuperscript{105} He claimed that abnormal blink reflexes are required for ephaptic transmission. He was the only author, who found these abnormalities. Indeed, the various abnormalities as published by several authors,\textsuperscript{10,48,105} fail to show a consistent pattern. Although other studies have presented evidence in favour of ephaptic transmission,\textsuperscript{118,123} the extensive intraoperative studies of Möller and Jannetta appear to offer more evidence in favour of motoneuron hyperexcitability.\textsuperscript{95,96,97,98,99,100} Other evidence for increased motoneuron excitability comes from studies, where ipsilateral facial nerve stimulation is avoided.\textsuperscript{43,93} One may conclude that blink reflex latencies and amplitudes in orbicularis oculi can vary considerably and as the blink reflex activates only a small proportion of the facial motoneuron pool,\textsuperscript{85} it may not be the most suitable test to examine hyperexcitability. Hyperexcitability of motoneurons leads to a massive motoneuron response to relatively weak stimulation. Supramaximal nerve stimulation in blink reflex studies elicits already maximal amplitudes of the excited (partial) motoneuron pool, so there remains only a small margin for further amplitude enlargement.

There is no doubt that blink reflex amplitudes and latencies are often abnormal in post Bell's palsy synkinesia.\textsuperscript{83,140} This is a sign of damage to the facial nerve. We showed an increased R1 latency and a lower CMAP amplitude in the mental muscle on the affected side.

Recovery curves.

Our finding of abnormal R1 and R2 recovery curves is consistent with motoneuron hyperexcitability, according to Kimura's criteria.\textsuperscript{82} Valls-Solé et al\textsuperscript{138} found only abnormal R2 recovery curve values.

R1 and R2 recovery curve indices were abnormal in individual patients with hemifacial spasm on the affected as well as on the unaffected side. When results of recovery curve indices in blepharospasm and torticollis are considered, these dystonias show no qualitative differences compared to hemifacial spasm. In fact, in this latter disorder no more than 17% of patients showed abnormal R1 and R2 indices on the affected side, and 46% had an increased R2 index. A reactive increased inhibition of interneuron input in the facial nucleus may prevent massive motoneuron activation in many patients and this may lead to apparently normal recovery indices.
Abnormal R2 recovery curve values on the unaffected side in patients with hemifacial spasm were also shown by Valls-Solé et al.\textsuperscript{138} In our study, 35\% of patients with hemifacial spasm had an abnormal R2 recovery index on the unaffected side. Apparently, hyperexcitability may also occur on the unaffected side. An explanation might be that there is retrograde activation of a blink center, which activates contralateral motoneurons. This resembles the compensatory overactive blink controller as proposed by Baker et al.\textsuperscript{13}

Abnormal R2 recovery curves have been described in patients with Bell's palsy, with or without residual weakness. The curves were more abnormal in patients with weakness than in those who recovered completely. Furthermore, those who had a residual weakness had more abnormal recovery curves on the affected than on the unaffected side.\textsuperscript{132}

\textit{Reflexes in orbicularis oris muscle.}

We found increased amplitudes of R1 and R2 on the affected side in the orbicularis oris muscle in hemifacial spasm and of R1 amplitude in patients with PBS. Supraorbital nerve stimulation in these patients was apparently able to activate a larger part of the available motoneuron pool in the ventral facial nucleus than in controls. This may indicate a loss of cortical control on the ventral nucleus.

Responses in the orbicularis oris after supraorbital nerve stimulation are found by most authors in hemifacial spasm and in patients with PBS.\textsuperscript{10,83,140} Not all of our patients showed these responses. Our inclusion criterion for synkinesia was synchronous muscle activity in the orbicularis oculi and orbicularis oris muscles, recorded with needle electrodes, either on lip pouting or squeezing of the eyes. Our patient group with PBS had their symptoms for one or two years after the palsy.

\textit{Lateral spreading.}

We showed lateral spreading in all patients with hemifacial spasm and in 50\% of patients with PBS. This suggests that part of the pathophysiological mechanisms in these disorders are similar, although traditionally hemifacial spasm is attributed to facial nerve root compression and PBS to faulty nerve regeneration. Lateral spreading was first considered as an indication of ephaptic transmission\textsuperscript{104} and later as a sign of motoneuron hyperexcitability.\textsuperscript{95}

Pathological studies of the facial nucleus in hemifacial spasm are lacking. Animal studies after facial nerve damage indicate nerve regeneration.\textsuperscript{12,134} In PBS, there is an evident damage to the myelin of the facial nerve, with or without axonal damage,\textsuperscript{83,140} starting in its course through the petrous portion of the temporal bone, and there is a persistent synkinesia, while in hemifacial spasm the nerve damage is limited to focal loss of myelin more proximally at the nerve root level\textsuperscript{24,119} and synkinesia is a transient phenomenon, as it disappears after removal of the facial nerve root compression.\textsuperscript{42,106} Another difference between both disorders in our study was the occurrence of bursts of repetitive, high frequency spontaneous motor unit discharges in affected muscles in hemifacial spasm,
often triggered by movement, while short muscle action in PBS was limited to actual movement of muscles on the affected side. We proposed that this difference may be due to vascular compression acting as a stimulus to the facial nerve root. Nielsen\textsuperscript{107} called this mechanism ectopic stimulation in hemifacial spasm, and Harner\textsuperscript{65} described neurotonic discharges in the facial nerve when it was touched during posterior fossa operations.

Since in our study lateral spreading has been recorded in 50% of patients with PBS, it may indicate that this phenomenon should not be considered as pathognomonic for hemifacial spasm. Needle EMG recording is also required to show high-frequency spontaneous discharges as can be recorded in hemifacial spasm.

We have shown that lateral spreading cannot always be recorded from all facial nerve branches, but it may be restricted to one facial nerve branch. This observation indicates that changes in the facial nucleus may be limited to one subdivision within the facial nucleus.

Dendrites extend through the whole facial nucleus.\textsuperscript{53} Slight damage to the facial nerve may already cause loss of dendritic synapses of the facial nerve nucleus. These are then replaced by astrocytic cell processes, wrapped around the neuronal body. This phenomenon is called synaptic stripping and it reduces the total number of synapses.\textsuperscript{62} A reduction in number of inhibitory synapses may explain the increased incidence and amplitudes of R1 and R2 in the orbicularis oris muscle in patients with hemifacial spasm. Furthermore, the phenomenon of synkinesia can also be explained by the same assumption that there is an excitatory overflow due to decreased synaptic inhibition.

The most frequent cause of hemifacial spasm is a vascular compression at the facial nerve root, but lesions of the facial nerve at other levels or even within the brainstem can produce similar symptoms. This mechanism could be demonstrated in one of our patients, who suffered from Bell's palsy years ago, from which she recovered completely without synkinesia. She developed blepharospasm, and on the affected side she had additional spasms, which were indistinguishable from those of hemifacial spasm. EMG examination revealed lateral spreading on the affected side (unpublished observation). A similar patient has been reported in the literature.\textsuperscript{61} From these observations, it is reasonable to suggest that prior facial nucleus damage and increased interneuron excitability, as has been shown in blepharospasm, can apparently cause symptoms similar to hemifacial spasm. Baker et al\textsuperscript{13} suggested that blepharospasm develops more often after Bell's palsy than would be expected by chance, and they demonstrated eyelid kinematics abnormalities in four patients who showed characteristics of both disorders. No report was made on the study of lateral spreading or registration of spontaneous muscle activity.
Future research.

Blink reflex pathways.

The exact pathway of the blink reflex and its connections to the basal ganglia and cerebral cortex should still be clarified. The question of the existence of a specific blink center (or a blink controller) is narrowly related.

1. The existence of a blink center can be studied in patients with small brainstem lesions, enabling us to correlate electrodiagnostical findings with clinical and anatomical observations.
2. The connection of the basal ganglia and brainstem interneurons involved in blink reflexes can be studied in animals, after specific lesions in regions of interest and with registration of blink reflexes.
3. The difference between blink reflex responses simultaneously measured in the orbicularis oculi, orbicularis oris and mental muscles in control subjects may provide information on the organization of these responses. This may provide arguments in favour of or against Jenny's theory of stronger cortical control on perioral muscles. More information might be obtained by a study of these responses in patients with pseudobulbar palsy.

Blepharospasm.

1. Blink reflexes during spasm-free periods are normal, but it is interesting to study these reflexes also during spasms in the same patient. This may provide evidence of an altered gating during spasms.
2. Blink reflex recovery curves have been studied only unilaterally. By studying recovery indices bilaterally in individual patients, asymmetry between sides may be demonstrated. This can help to confirm or reject the theory of Baker et al\textsuperscript{13}, that a unilateral lesion of the orbicularis oculi and an abnormal adaptation of the blink controller can cause blepharospasm.
3. The multimodal character of R2 response may cause differences in R2 recovery behaviour when different conditioning and test stimuli are applied. Photic conditioning followed by trigeminal test stimulation leads to almost normal recovery, while paired trigeminal stimulation produces decreased habituation.\textsuperscript{78} The authors interpreted this as a larger susceptibility of brainstem interneurons to photic stimulation. A more plausible explanation may be that photic conditioning does not interact with basal ganglia gating in the same way as trigeminal stimulation does. Thus, there may be modality-specific decreased habituation in blepharospasm, because a limited number of sensorimotor channels in the basal ganglia are involved. This can be examined by multimodal paired stimulation, for instance visual-trigeminal, auditory-trigeminal, trigeminal-visual and trigeminal-auditory.
Hemifacial spasm and post Bell's palsy synkinesia.

1. Lateral spreading has not systematically been examined in normal subjects. Therefore, it is possible that some healthy subjects may show lateral spreading and that they may especially be prone to develop hemifacial spasm.

2. Studies of lateral spreading in patients with a history of Bell's palsy with and without synkinesia, and with different stages of severity of synkinesia, may help to clarify the conditions under which lateral spreading can be developed in these patients. The possibility of a transition from Bell's palsy with synkinesia to hemifacial spasm can be demonstrated by a longitudinal study. In case that such a transition exists, diagnostic criteria must be developed for these disorders. MRI scans in these patients can reveal whether a vascular compression accompanies the development of hemifacial spasm. These studies may provide additional information when surgical intervention is required and may be helpful in predicting the outcome.

3. The study of lateral spreading in patients with hemifacial spasm caused by lesions other than vascular compression may provide more insight into underlying pathophysiological mechanisms and may give us information on selection of patients for surgical intervention.

4. Pathological studies of the facial nerve and nucleus in patients with hemifacial spasm are required to study structural changes. These studies may help to give an answer to important questions such as a) does synaptic stripping occur? b) which synapses remain? c) do connections between subnuclei exist? d) how large is the dendritic tree of facial motoneurons in man? and e) does faulty nerve regeneration occur?