Electrophysiological investigations in cranial hyperkinetic syndromes
Eekhof, J.L.A.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Download date: 27 Dec 2018
Chapter 3

Electromyography and recovery of the blink reflex in involuntary eyelid closure: a comparative study.

Aramideh M, Eekhof JLA, Bour LJ, Koelman JHTM, Speelman JD and Ongerboer de Visser BW.

Abstract.

Electromyographic (EMG) activity of orbicularis oculi and levator palpebrae muscles was recorded to study the origin of involuntary eyelid closure in 33 patients. The evoked blink reflex in all patients and in 23 controls was also studied. To examine the excitability of facial motoneurons and bulbar interneurons in individual patients and to compare the results with EMG findings, R1 and R2 recovery indices were calculated in all subjects, as the average of recovery values at 0.5, 0.3, and 0.21 second interstimulus intervals.

Based on EMG patterns, the patients were divided into three subclasses: EMG subclass 1, 10 patients with involuntary discharges solely in orbicularis oculi muscle; EMG subclass 2, 20 patients with involuntary discharges in orbicularis oculi and either involuntary levator palpebrae inhibition or a disturbed reciprocal innervation between orbicularis oculi and levator palpebrae; EMG subclass 3, three patients who did not have blepharospasm, but had involuntary levator palpebrae inhibition in association with a basal ganglia disease. The total patient group showed an enhanced recovery of both R1 and R2 components compared with controls.

Although 30 out of 33 patients had blepharospasm (EMG subclasses 1 and 2), R1 recovery index was normal in 64% and R2 recovery index was normal in 54%. Patients with an abnormal R2 recovery index had an abnormal R1 recovery index significantly more often. All patients from EMG subclass 1 had an abnormal R2 recovery index, whereas all patients from EMG subclass 3 had normal recovery indices for both R1 and R2 responses. Seventy five per cent of the patients from EMG subclass 2 had normal recovery indices.
The results provide further evidence that physiologically blepharospasm is not a homogeneous disease entity, and indicate that different pathophysiological mechanisms at the suprasegmental, or segmental level, or both are involved. Keywords: dystonia, blepharospasm, blink reflex recovery.


Introduction.

Blepharospasm is a form of focal dystonia, with an aetiology and underlying pathophysiological mechanisms that are still obscure. Blepharospasm may occur in diseases of the basal ganglia or in association with upper brain stem abnormalities. In most patients, however, it is idiopathic in origin.

One investigation technique that has contributed to our understanding of blepharospasm is the recorded blink reflex recovery, which indicates the state of excitability of the facial motoneurons and bulbar interneurons. Electrical stimulation of the supraorbital nerve elicits a blink reflex that consists of two components; an early ipsilateral response, R1, mediated through the pons by an oligosynaptic pathway and a late bilateral response, R2, relayed through a polysynaptic medullary pathway. Motoneurons of the facial nerve constitute the final common path for both responses.

The recovery curve, also known as excitability cycle, of R1 and R2 responses can be obtained by applying two stimuli, conditioning and test, to the supraorbital nerve at different interstimulus intervals. The excitability of the blink reflex circuit may then be assessed by comparing the size of the test response with that of the conditioning response, which is partly dependent on the functional integrity of the suprasegmental structures.

In healthy subjects, the R2 test response shows pronounced suppression at shorter interstimulus intervals, whereas patients with cortical lesions may exhibit an enhanced habituation and patients with basal ganglia disorders a diminished habituation (enhanced recovery) of the response. Previous work has shown an enhanced recovery of the R2 response in patients with blepharospasm, which suggests hyperexcitability of the bulbar interneurons.

By simultaneous recording of the electromyographic (EMG) activities from the orbicularis oculi and levator palpebrae muscles, we have shown that patients with blepharospasm are not a homogeneous group, because differing abnormalities of EMG patterns are found among these patients.
Table 1. General characteristics of the patients examined.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>33</td>
</tr>
<tr>
<td>Women/men</td>
<td>22/11</td>
</tr>
<tr>
<td>Mean age (y) (range)</td>
<td>67 (37-88)</td>
</tr>
<tr>
<td>Mean age at onset (y) (range)</td>
<td>57 (25-77)</td>
</tr>
<tr>
<td>Mean duration of illness (y) (range)</td>
<td>9 (1-20)</td>
</tr>
<tr>
<td>Type of dystonia:</td>
<td></td>
</tr>
<tr>
<td>focal (n)</td>
<td>17</td>
</tr>
<tr>
<td>segmental (n)</td>
<td>13</td>
</tr>
<tr>
<td>Treatment at time of study:</td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin type A (n)</td>
<td>7</td>
</tr>
<tr>
<td>Medication (n)</td>
<td>3</td>
</tr>
</tbody>
</table>

In the present study, we examined the recovery of R1 and R2 responses and EMG activity of orbicularis oculi and levator palpebrae muscles in patients with involuntary eyelid closure. The aim of the study was: (1) to evaluate the state of excitability of facial motoneurons and bulbar interneurons in individual patients with a certain EMG abnormality; (2) to see whether there is a correlation between clinical data, EMG subclass, and recovery values, and (3) to provide additional information on possible underlying pathophysiological mechanisms of blepharospasm.

Materials and methods.

Thirty three patients, 22 women and 11 men (mean age 67 (range 37-88) years) with involuntary eyelid closure were studied. Table 1 summarises the clinical data of the patients. At the time of the study, seven patients were already under treatment with botulinum A toxin (Dysport) but in all patients voluntary and reflex activity of the orbicularis oculi could easily be recorded. The control group consisted of 23 subjects (six women and 17 men) with a mean age of 49 (range 18-73) years.

The method of EMG recording from orbicularis oculi and levator palpebrae muscles has been reported previously.\textsuperscript{5,6} Blink reflex studies were performed with the subject lying supine. Electrical stimuli were applied to the supraorbital nerve at the supraorbital foramen. Surface recording electrodes were placed over the lower portion of orbicularis oculi ipsilateral to the stimulation site. A Grass stimulator was used to apply constant current pulses with a duration of 0,2 ms. The early and late blink reflexes were evoked with stimulus intensity adjusted to three times the threshold of the R2 response. Subjects were requested to close their eyes gently during stimulation, and responses with artefacts due to involuntary movements were rejected. Paired stimuli (conditioning and test) were delivered at interstimulus intervals of 0.5, 0.3, and 0.21 seconds and six trials were performed at each interval. Between successive trials, a rest period of at least 30 seconds was maintained to avoid habituation of the response. The low pass filter was set at 3 kHz and the high pass filter at 1 Hz.
Figure 1. (A) Rectified and averaged (6x) EMG responses at intervals 0.5, 0.3 and 0.21 seconds between the conditioning and test stimuli in a patient from EMG subclass 1. Recovery curve for R1 (B) and R2 (C) in the same patient. The recovery of R1 and R2 responses are enhanced at all three intervals. ISI = interstimulus interval; t/c ratio = test response/conditioning response.
(6 dB/oct). The sweep time was kept at 200 ms. All responses were stored digitally on a PDP 11/73 computer. In an off-line analysis procedure, performed fully automatically, reflex responses were digitally band-pass filtered within a range of more than 100 Hz to minimise DC-offsets and slow eye drifts and below 900 Hz to reduce the high frequency noise. The responses were then full-wave rectified and the average of six trials was computed for each interstimulus interval. Peak amplitude of R1 was calculated within a window from 10 to 25 ms to avoid stimulation artefact, and that of R2 within a window from 32 to 90 ms. The average rest activity level was established within a window from 150 to 200 ms and subtracted from the average response. For each subject, R1 and R2 recovery values were obtained by calculating the size of the test response as a percentage of the conditioning response at each interstimulus interval.

R1 recovery index was calculated in each subject as the mean value of peak amplitude recovery, obtained at interstimulus interval of 0.5, 0.3, and 0.21 seconds. The R2 recovery index was calculated in the same way. The upper limit of normal for R1 and R2 was defined as the mean + 2.5 SD.

Statistical analysis.

A correlative study was performed between the clinical data, EMG subclasses, and blink reflex recovery indices by means of Kruskall-Wallis and $\chi^2$-square tests with the SPSS statistical program. Differences and correlations were considered significant at p-values < 0.05.

Results.

Table 2 summarises the results of the recorded EMG and blink reflex recovery.

EMG findings.

According to the EMG patterns, patients were divided into three subclasses. Ten patients belonged to EMG subclass 1, in whom EMG recording showed involuntary discharges in the orbicularis oculi alone, with normal tonic activity of levator palpebrae and normal reciprocal innervation of orbicularis oculi and levator palpebrae. EMG subclass 2 consisted of 20 patients. Besides involuntary discharges in orbicularis oculi, EMG recording in these patients disclosed either episodes of involuntary inhibition of tonic activity of levator palpebrae or a disturbed reciprocal innervation of orbicularis oculi and levator palpebrae. EMG subclass 3 consisted of three patients.
Figure 2. (A) Rectified and averaged (6x) EMG responses at intervals 0.5, 0.3 and 0.21 seconds between the conditioning and test stimuli, in a patient from EMG subclass 2. Recovery curve for R1 (B) and R2 (C) in the same patient. The recovery of R1 and R2 responses are normal at all three intervals. ISI = interstimulus interval; t/c ratio = test response/conditioning response.
Abnormality in these patients was characterized by solely involuntary inhibition of levator palpebrae, with normal activity of orbicularis oculi and normal reciprocal innervation of orbicularis oculi and levator palpebrae muscles. These three patients had, therefore, no blepharospasm.

**Blink reflex findings.**

**Controls.**

There was pronounced variability in R1 recovery from one subject to another at different interstimulus intervals. The mean recovery of R1 at the 0.5 second interval was 69% and this increased to 78% at 0.21 seconds. Table 2 shows R1 and R2 recovery indices. The mean value of the R1 recovery index was 78% (range, 36%-120%), and the upper limit of normal was 135%. The R2 recovery curve showed less variability. By contrast with R1, recovery of R2 gradually decreased from 29% at the 0.5 second interval to 15% at 0.21 seconds. The R2 recovery index had a mean value of 22% (range 11%-42%), and the upper limit of normal was 43%.

**Patients.**

In five patients, the R1 recovery index could not be calculated because the amplitude of R1 was too low with respect to the noise. Recovery of R1 gradually increased from 117% at the 0.5 second interval to 137% at 0.21 seconds. Table 2 shows R1 and R2 recovery indices for the total patient group and for the three EMG subclasses. The R1 recovery index in the patient group differed significantly from that in the control group (p < 0.001). Recovery of R2 gradually decreased from 50% at the 0.5 second interval to 31% at 0.21 seconds. R2 recovery index in the patient group was significantly higher than that in the control group (p < 0.001). Considering the individual data, 18 of 28 patients (64%) had a normal R1 recovery index, and 18 of 33 patients (54%) had a normal R2 recovery index (table 2). A significant number of patients with an abnormal R1 recovery index also had an abnormal R2 recovery index (p = 0.01, Yates corrected test).

Considering the data from different EMG subclasses, the R1 recovery index differed statistically from control subjects in EMG subclass 1 (p < 0.001, table 2) and less so in EMG subclass 2 (p < 0.05). The R2 recovery index differed statistically from control subjects only in EMG subclass 1 (p < 0.001). All the patients from EMG subclass 1 had an abnormal R2 recovery index, and 50% of them also had an abnormal R1 recovery index. Dystonia of other cranial or cervical muscles was found significantly more often in EMG subclass 1 (p < 0.01, table 2).

Figure 1 shows an example of abnormal R1 and R2 recovery curves in one of the patients from this group. All three patients from EMG subclass 3 had normal R1 and
Table 2. Mean values of R1 and R2 recovery indices in patients and controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>No of subjects</th>
<th>Focal segmental dystonia</th>
<th>Mean R1 index (range)</th>
<th>No of abnormal R1 indices</th>
<th>Mean R2 index (range)</th>
<th>No of abnormal R2 indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>23</td>
<td>-</td>
<td>78 (36-120)</td>
<td>22 (11-42)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Patients:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>33</td>
<td>382</td>
<td>125 (35-227)**</td>
<td>10 †</td>
<td>42 (6-108)**</td>
<td>15</td>
</tr>
<tr>
<td>EMG subclass</td>
<td>1</td>
<td>10</td>
<td>184</td>
<td>161 (73-278)**</td>
<td>5</td>
<td>60 (45-79)**</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>20</td>
<td>165</td>
<td>118 (35-215)*</td>
<td>5</td>
<td>32 (6-108) NS</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>96 (74-107) NS</td>
<td>0</td>
<td>31 (28-37) NS</td>
</tr>
</tbody>
</table>

The recovery indices are given in percentages.

* p < 0.05; ** p < 0.001 vs controls. † R1 could not be recorded in five patients, two from EMG subclass 1 and three from EMG subclass 2. NS: statistically not significant.

R2 recovery indices, whereas all had associated basal ganglia disease; one had progressive supranuclear palsy, and two had multiple system atrophy. Interestingly, 15 patients (75%) from EMG subclass 2 had a normal R2 recovery index. Figure 2 shows normal R1 and R2 recovery curves in one of the patients from this group.

Discussion.

We investigated the recovery of R1 and R2 components of the blink reflex in patients with involuntary eyelid closure, as one single group or divided into three subclasses according to the EMG patterns of orbicularis oculi and levator palpebrae muscles. Patients with EMG subclass 1 had involuntary discharges solely in orbicularis oculi muscle. EMG subclass 2 consisted of patients with involuntary discharges in orbicularis oculi, accompanied by either involuntary inhibition of levator palpebrae motor activity, or a disturbed reciprocal innervation of orbicularis oculi and levator palpebrae. In an earlier report we proposed the term "blepharospasm-plus" to designate those patients with this type of EMG abnormality. The patients from EMG subclass 3 had solely involuntary inhibition of levator palpebrae also known as apraxia of eyelid opening with no clinical or EMG signs of blepharospasm. We included these patients in the present study because the differentiation between blepharospasm and involuntary levator palpebrae inhibition is not always easy to
make clinically and synchronous EMG recording from orbicularis oculi and levator palpebrae is often required.6

In controls, R1 recovery showed some variability between subjects at all three inter-stimulus intervals. From 0.5 to 0.21 second intervals, R1 recovery showed a gradual enhancement, with relatively less suppression at 0.3 seconds. By contrast, R2 recovery showed almost no interindividually variability and from 0.5 to 0.21 second intervals there was a gradual increase in suppression. Also, in the total patient group the recovery of R1 differed from that of R2. There was often an absolute increase of R1 test response when the interval was shortened from 0.5 to 0.21 seconds, whereas the R2 test response diminished at shorter intervals. Such a difference in the properties of R1 and R2 responses has also been found in other studies.14,125,131 The same facial nerve motoneurons generate both responses and the final efferent pathway is common. Therefore, the difference in the recovery behaviours of R1 and R2 responses, in both the controls and patients, should be caused by the bulbar interneurons. Yet it cannot entirely be explained by the difference in the number of bulbar interneurons through which these responses are relayed, and is probably also dependent on the individual properties of the interneurons, their relation to one another, and the suprasegmental drives on them. A difference in presynaptic inhibition at the primary cutaneous afferent terminals34,129 also cannot be excluded.

The enhanced recovery of the R2 response found in the total patient group confirms the results of previous authors.16,30,114,135 We also found an increased recovery of the R1 response, whereas Tolosa et al135 noted a normal R1 recovery and the other authors did not report on the features of R1 recovery in patients with blepharospasm.16,30,114 Although these conflicting results and the lack of information on this issue may require further investigation, some features of the recorded blink reflex are in favour of an enhanced excitability of the oligosynaptic pathway through which the R1 response is transmitted. Willer et al144 reported on the existence of a crossed trigemino-facial connection, and showed that a contralateral R1 response can easily be obtained in healthy subjects when the test stimulus was preceded by an adequate conditioning stimulus. Yet after single stimulation of the supraorbital nerve, Berardelli et al16 recorded a contralateral R1 response in six of 16 patients with blepharospasm. Based on these data, it seems that at least the crossed oligosynaptic route mediating the contralateral R1 response is hyperactive in some patients with blepharospasm. Therefore, we agree with the conclusion of Tolosa et al135 that the facial motoneurons themselves are not hyperactive in patients with blepharospasm. We presume instead that the interneurons involved in the generation of both the R1 and R2 responses may be hyperexcitable.

The pathways through which the basal ganglia can modulate the blink reflex are unknown. It seems, however, that the basal ganglia exert an inhibitory influence on the bulbar interneurons, even if it occurs indirectly via cortical pathways because lesions of these pathways can suppress the blink reflex.15,84,112 Evinger et al49 showed that apomorphine, a dopamine receptor agonist, and nicotine, which releases dopamine in the striatum, increase the latency of the R2 response without altering the
latency of the R1 response. In their recent paper, Basso et al.\textsuperscript{14} showed that partial or even complete lesions of the substantia nigra and ventral tegmental area in rats do not modify the R1 recovery at all, whereas R2 recovery shows pronounced excitability. Accordingly, in patients with Parkinson's disease R1 recovery is normal,\textsuperscript{2,82} R2 recovery is enhanced,\textsuperscript{2,46,82} and R2 latency is shortened.\textsuperscript{82} Furthermore, patients with Huntington's disease exhibit a decrease in blink reflex excitability\textsuperscript{3,46} and an increase in the latency of the R2 response,\textsuperscript{3,22,46} comparable with those findings in patients with hemispheric lesions. By contrast, R1 recovery was enhanced in our patients and the previous studies showed that the latency of R2 is normal in patients with blepharospasm.\textsuperscript{16,30,114,135} Based on these findings, two important conclusions can be drawn.

Firstly, it is conceivable that dopaminergic activity of at least the substantia nigra may not control the state of activity of facial motoneurons directly or indirectly, through the oligosynaptic reflex pathway, and that the enhanced R1 recovery in our patients as a group should have some other origin. Secondly, it is possible that alterations in basal ganglia activity influence the bulbar interneurons somehow differently in patients with idiopathic blepharospasm from those patients with known diseases of the basal ganglia such as Parkinson's disease.

A causal relation between hyperexcitability of interneurons and the occurrence of involuntary discharges in orbicularis oculi becomes less evident when we consider the data of R1 and R2 recovery indices in individual patients or in patients from different EMG subclasses. Our results showed a normal R1 recovery index in 64% and a normal R2 recovery index in 54% of the total patient group, despite the fact that 30 out of 33 patients had involuntary discharges in orbicularis oculi, whether or not in combination with involuntary levator palpebrae inhibition (EMG subclasses 1 and 2). An abnormal R1 recovery index occurred significantly more often in patients with an abnormal R2 recovery index. An interesting finding was that all patients with blepharospasm alone (EMG subclass 1), had an abnormal R2 recovery index and 50% also had an abnormal R1 recovery index. On the other hand, those patients with involuntary discharges in orbicularis oculi with either involuntary levator palpebrae inhibition or a disturbed reciprocal innervation of orbicularis oculi and levator palpebrae (EMG subclass 2), often had normal R1 and R2 recovery indices. At the time of this study, seven out of 20 patients from EMG subclass 2 were already under treatment with botulinum A toxin. It is unlikely that this influenced the recovery values in these patients, because previous studies\textsuperscript{50,139} showed no difference in the blink reflex excitability in patients with blepharospasm before and after such treatment. Furthermore, it is also unlikely that patients with blepharospasm alone may have had a severe form of orbicularis oculi muscle dystonia, because as noted by Pauletii et al.,\textsuperscript{114} there is no correlation between the severity of dystonia and the excitability of the blink reflex. The most probable explanation is a difference in underlying pathophysiological mechanisms. There may be a dissociation of the suprasegmental controls resulting in involuntary orbicularis oculi contraction, whether or not accompanied by disturbed levator palpebrae muscle activity, which cannot be examined by simply eliciting the blink reflex.
Dissociation between innervation of emotional and voluntary movements of the facial musculature is well recognised in patients with central facial paresis, and with thalamic or pallidal lesions.\textsuperscript{101,102} Symptomatic blepharospasm may occur in disorders of the basal ganglia but never, to our knowledge, as an isolated abnormality. Conversely, no study has yet provided clear evidence for any pathology of the basal ganglia and their involvement in the generation of involuntary contractions of the eyelids in patients with idiopathic blepharospasm. On the other hand, Siegel et al\textsuperscript{128} reported on cells, located within a portion of the medial reticular formation, which showed discharges in relation to the closing movements of eyelids. The authors mentioned that some of these cells probably project directly to the facial cells and some may relay their outputs over multisynaptic pathways. In another report, Siegel et al\textsuperscript{127} also proposed that local interaction of these medial reticular formation cell populations may allow synthesis of the simple reflex movements generated in the brainstem.

We suggest that besides the abnormal drives exerted by the basal ganglia, disorders of the segmental structures may also contribute to the enhanced excitability of the blink reflex responses and to the generation of blepharospasm. This assumption may explain why the recovery of R1 and R2 responses was often enhanced in patients with blepharospasm alone, who also often had dystonia of other cranial muscles without additional clinical features pointing to abnormal basal ganglia activity.

All three patients from EMG subclass 3, with involuntary levator palpebrae inhibition, had normal R1 and R2 recovery indices. These patients also had abnormalities of, among others, the basal ganglia. Therefore, certain disorders of the basal ganglia may influence the tonic activity of levator palpebrae muscle without altering the excitability of the blink reflex. We are unaware of any previous reports on this issue.

In conclusion, the results of the present paper are in agreement with our earlier findings,\textsuperscript{4,5,6} and provide further evidence that, physiologically, blepharospasm is not a homogeneous disease entity. They indicate that various pathophysiological mechanisms at the suprasegmental, or segmental, level, or both, are involved.

We thank Drs L Volger and A Hilgevoord for their help in statistical analysis.