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Startle Responses in Hereditary Hyperekplexia

Marina A. J. Tijssen, MD; Lydia M. Voorkamp, MD; George W. Padberg, MD, PhD; J. Gert van Dijk, MD, PhD

Background: Patients with hereditary hyperekplexia have excessive startle responses that are accompanied by transient stiffness and also continuous stiffness in infancy. A point of mutation has been identified for the major form of hereditary hyperekplexia in the gene encoding the α1 subunit of the glycine receptor.

Objective: To measure startle reflexes and autonomic responses in the major form of hereditary hyperekplexia in the original Dutch pedigree.

Design: Startle reflexes and autonomic responses were examined by administering 3 series of 20 auditory stimuli at intervals of 10 seconds (90 and 113 dB) and 60 seconds (113 dB).

Setting: The Department of Neurology and Clinical Neurophysiology at the Leiden University Hospital, Leiden, the Netherlands.

Subjects: Nine patients with the major form of hyperekplexia and 20 healthy controls. Of the 9 patients, 5 took medication. The patients are part of the Dutch hyperekplexia pedigree.

Main Outcome Measures: Startle responses were quantified with latency periods and areas of electromyographic bursts of the orbicular muscle of the eye, sternocleidomastoid and biceps muscles, and the thenar muscles. Autonomic reactions were measured with psychogalvanic responses and beat to beat changes of blood pressure and heart rate.

Results: The electromyographic bursts of the 4 muscles occurred in similar order in both patients and controls. The onset of the latency periods in the patient group was significantly (P<.001) prolonged in patients who took medication. Without medication, patients had shorter latency periods of the sternocleidomastoid muscle (P=.003) than controls. The electromyographic burst occurred significantly more often in patients than in controls (P<.001). The areas of the bursts were significantly larger in patients than in controls (P<.001); the degree of habituation was significantly stronger in patients than in controls (P<.001). The amplitude of the psychogalvanic response was increased in hyperekplexia, and the degree of habituation was significantly weaker in patients than in controls. Blood pressure and heart rate did not clearly react in either group.

Conclusions: Motor startle responses are stronger and show more habituation in patients with hereditary hyperekplexia than in controls. The excessive responses include the psychogalvanic response. Increased responses do not necessarily indicate decreased habituation in hyperekplexia.

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Hyperekplexia, or startle disease, is an autosomal dominant disorder characterized by exaggerated startle reactions to unexpected, particularly auditory, stimuli. In the Dutch hyperekplexia family, 2 forms were recognized. The major form is characterized by excessive startle reactions followed by a short period of general stiffness, during which voluntary movements are impossible. In this form, a general stiffness occurs during the first years of life. Patients with the minor form suffer from an excessive startle response, without stiffness. The genetic defect of hyperekplexia has recently been located on chromosome 5q33-q35 and identified as a point mutation in the α1 subunit of the glycine receptor. This locus and the abnormality of the glycine receptor have been confirmed for the major form in the Dutch pedigree, but not for the minor form.

The afferent and efferent systems of the startle reflex in hyperekplexia are identical to those of the normal startle response, involving a similar or the same generator in the lower brain stem, probably in the medial bulbopontine reticular formation. Two differences from controls have been
SUBJECTS AND METHODS

SUBJECTS

Nine patients (6 men and 3 women) with the major form of hyperekplexia of the pedigree described by Suhren and colleagues were included in the study. Of the 20 healthy controls, there were 10 men, aged 26 to 65 years (mean age, 40.5 years) and 10 women, aged 26 to 63 years (mean age, 40.3 years). Of the 9 patients, 5 were taking medication (Table 1). Controls took no medication. The study was approved by the Medical Ethical Committee of the Leiden University Hospital. All subjects gave their informed consent.

METHODS

Startle responses were elicited by delivering tones binaurally through earphones. Subjects stood quietly and wore a parachute harness attached to the ceiling to prevent injury in case of a fall. The subjects were instructed to count the stimuli to keep them alert.

Three series of 20 stimuli were given: the first series comprised 90-dB tones delivered at 10-second intervals, the second, 113-dB tones at 10-second intervals, and the third, 113-dB tones at 60-second intervals. The 3 series were executed in identical order, with at least a 5-minute pause between the series. The effects of stimulus intensity and stimulus interval on habituation were studied.

Electromyographic Recording

Electromyographic (EMG) activity was recorded, with Ag-AgCl cup electrodes using the belly-tendon system, from the orbicular muscle of the eye, the sternocleidomastoid and biceps muscles, and the thenar muscles on the right side. Electromyographic signals were acquired with a 4-channel EMG (Viking II, Nicolet Instrument Corporation, Madison, Wis), with a bandpass of 20 Hz to 20 kHz. Periods of 250 milliseconds were sampled and stored for later analysis. The beginning, end, area, and onset of latency periods of the EMG bursts were determined.

Autonomic Recording

Psychogalvanic responses (PGRs) were recorded with Ag-AgCl electrodes attached to the palm and dorsum of the right hand. The signal was recorded on paper with an electroencephalogram.

The PGR recording was adjusted during the test according to the magnitude of the response. As psychogalvanic activity showed spontaneous fluctuations, it was quantified by measuring the difference between minimum and maximum peaks during an 8-second period after the stimulus.

Beat to beat systolic and diastolic blood pressure and heart rate were measured in the left arms of the patients with a continuous measurement device (Finapres, Ohmeda, Bilthoven, the Netherlands); these signals were also recorded on paper. The minimum and maximum results, the differences of which were regarded as measures of autonomic reactions, of the 3 parameters (systolic blood pressure, diastolic blood pressure, and heart rate) were measured during a 6-second poststimulus period.

Data Analysis

Differences in onset of the latency period of EMG bursts of the 4 muscles between the patient and control groups were investigated using a 2-tailed Student t test. For analysis of the onset of the latency period, only the first response in each series was used. The frequency of the occurrence of bursts, for all responses, were compared between the groups using the χ² test. Differences in the areas of EMG responses between the groups were analyzed with repeated measures analysis of variance (RM-ANOVA). The areas of EMG responses were skewed and the square root transformed before the analysis. An RM-ANOVA was performed with the sum of the square roots of the areas of the 4 muscles during the series with the response as a variable, and the group (patient or control) as a factor. This was separately performed for every series. The influence of the type of series was investigated with RM-ANOVA in the patient group, the control group, and the combined group.

The degree of habituation could be defined as absolute or relative in comparison with the response to the first stimulus. Since it was not clear which method was preferred, both approaches were used. Absolute changes were calculated by subtracting the area of a response from the response to the first stimulus; relative changes were calculated by expressing areas as percentages of the measure of the first response. An RM-ANOVA was performed on these transformed responses, with group as a factor. Autonomic variables were investigated with RM-ANOVA.

The influence of medication on the parameters in the patient group was analyzed by comparing the startle parameters between the patients who took medication and those who did not within the patient group.

Statistical analysis was performed using a statistical systems package (NCSS, Kaysville, Utah). P<.05 was considered significant.
autonomic responses in hyperekplexia are also affected. Recently, it was shown that patients with hyperekplexia had a reduced peak velocity of horizontal saccadic movements, without signs of diminished cortical influence, indicating that the abnormality was located in the brain stem. These data suggest that abnormalities need not be restricted to motor startle responses.

The aim of this study was to investigate the magnitude of motor and autonomic responses and the degree of habituation in patients with the major form of hereditary hyperekplexia.

RESULTS

No complications occurred; none of the subjects fell during the procedure.

EMG FINDINGS

The latency periods differed between patients who took medication and those who did not (Table 2). The latency periods for the orbicular muscle of the eye and the sternocleidomastoid and biceps muscles (P < .001) were significantly prolonged in patients who took medication. The latency periods of the muscles of the patients who did not take medication were compared with those of controls: the latency period of the sternocleidomastoid was shorter in patients (P = .003). Mean latency periods increased in the order of the orbicular muscle of the eye, the sternocleidomastoid, the biceps, and then the thenar muscles in all patients regardless of medication use (Table 2).

Table 1. Patients With Hyperekplexia

<table>
<thead>
<tr>
<th>Age, y/Sex</th>
<th>Type of Medication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>28/F</td>
<td>Clonazepam, 2 mg 3 times a day</td>
</tr>
<tr>
<td>33/M</td>
<td>Clonazepam, 2 mg 3 times a day</td>
</tr>
<tr>
<td>34/M</td>
<td>...</td>
</tr>
<tr>
<td>46/M</td>
<td>Phenobarbital, 75 mg twice a day</td>
</tr>
<tr>
<td>51/M</td>
<td>...</td>
</tr>
<tr>
<td>54/M</td>
<td>...</td>
</tr>
<tr>
<td>61/F</td>
<td>Diazepam, 7 mg twice a day, 2 mg once a day</td>
</tr>
<tr>
<td>66/F</td>
<td>Clonazepam, 2 mg twice a day</td>
</tr>
</tbody>
</table>

* Ellipses indicate that medication was not used.

Table 2. Latency Periods of Electromyographic Bursts in Patients and Controls*

<table>
<thead>
<tr>
<th></th>
<th>Patients Taking Medication</th>
<th>Patients Not Taking Medication</th>
<th>/ Test</th>
<th>Controls</th>
<th>/ Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of possible responses</strong></td>
<td>15</td>
<td>12</td>
<td>...</td>
<td>60</td>
<td>...</td>
</tr>
<tr>
<td>Orbicular muscle of the eye</td>
<td>48.7±9.9 (14)</td>
<td>27.5±2.1 (11)</td>
<td>&lt;.001</td>
<td>35.3±0.8 (46)</td>
<td>.4</td>
</tr>
<tr>
<td>Sternocleidomastoid muscles</td>
<td>68.9±11.5 (13)</td>
<td>44.3±2.8 (11)</td>
<td>&lt;.001</td>
<td>68.8±5.5 (18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Biceps muscles</td>
<td>105.8±24.5 (12)</td>
<td>56.4±2.9 (11)</td>
<td>&lt;.001</td>
<td>119.3±9.45 (2)</td>
<td>.7</td>
</tr>
<tr>
<td>Thenar muscles</td>
<td>139.0±28.3 (7)</td>
<td>106.5±12.3 (7)</td>
<td>.06</td>
<td>84.8±32.4 (1)</td>
<td>.6</td>
</tr>
</tbody>
</table>

* All data are expressed in milliseconds (mean±SE) unless otherwise indicated. The numbers in parentheses indicate the number of the first stimuli of the 3 series that were followed by an electromyographic response; the number of possible responses reflects the number of patients taking and not taking medication (5 and 4, respectively) and controls (20); for each, the first stimulus of the series of each of the 3 series was taken into account. P values for latency periods refer to the t test; ellipses, not applicable.

†P values between patients taking medication and those who did not.

‡P values between patients not taking medication and controls.

The frequency of the occurrence of an EMG burst for all 4 muscles was significantly higher in the patients who did not take medication than in those who did (P < .002) (Table 3). The frequency of occurrence was significantly higher for all 4 muscles in the patients who did not take medication than in controls (P < .008). The louder tone elicited more responses (series 1 vs 2) in both the patient (those taking and those not taking medication) and the control groups for the orbicular muscle of the eye and the sternocleidomastoid muscles (P < .001). For these comparisons, the responses of the biceps and thenar muscles were disregarded because there were too few responses in the control group. The longer interval elicited more responses (series 2 vs 3) in the whole patient group for the same 2 muscles (P < .001). In the control group, the difference was not significant.

HABITUATION OF STARTLE RESPONSES

The 4 different muscles had a similar pattern of habituation, and, therefore, the areas of the muscles were summed. The summed area of the 4 muscles was significantly different between the patients who took medication and those who did not (P = .33) for the 3 series combined. In all the patients, a significant reduction of area occurred during the series of 20 stimuli (P < .001). There was no interaction between the 2 types of patients (P = .76) for each series separately as well as the 3 series combined. Therefore, we analyzed the amplitude measurements of the 2 types of patients as pooled data.

The sum of the area of the 4 muscles was larger in patients than in controls (P < .001). The reduction in area during the series of stimuli was larger in patients than in controls (Figure 1): the area changed significantly during the series (P < .001), and this alteration differed significantly between patients and controls (P < .001). This held for each series separately as well as for the pooled series. The series significantly influenced the sum of the area in the control group (P = .004) and the patients and controls (P = .009) but not in the patient group (P = .06): the 113-dB tone elicited more responses than the 90-dB tone, and the 60-second interval elicited more responses than the 10-second interval. The reduction in area during the series was not significantly influenced by
the type of series (controls, \( P = .98 \); patients, \( P = .08 \); whole group, \( P = .6 \)) (Figure 2).

These values were based on the absolute values of the area of the EMG response. The EMG response was also analyzed relative to the response to the first stimulus. The differences between the groups were also significant \( (P = .004) \); responses changed during the series \( (P < .001) \), but the interaction was not significantly different \( (P = .5) \) (Figure 1).

### AUTONOMIC RESPONSES

The PGRs were not significantly different between the 2 types of patients \( (P = .48) \). They decreased during the series in both patient types \( (P < .001) \), and there was no interaction between the patients who took medication and those who did not \( (P = .86) \). The PGRs were therefore analyzed for all patients.

The PGRs were significantly larger in patients than in controls for each of the series \( (P = .007) \). They decreased during the series of stimuli, but were significantly less in patients than in controls \( (P < .001) \) (Figure 3). The differences between patients and controls with regard to the decrease in PGRs were not uniform for the 3 series. In series 1, the PGRs of patients decreased more than those of controls \( (P < .001) \); in series 2, they decreased less than those of controls \( (P < .001) \); and in series 3, no significant difference was found \( (P = .05) \).

The differences between minimal and maximal results of the systolic and diastolic blood pressure and heart rate measurements in patients and controls were only significant for diastolic blood pressure \( (P < .05) \). Differences in heart rate, but not in systolic or diastolic blood pressure, changed during the stimulus series \( (P < .01) \). There were no interactions (ie, any changes during the series did not differ between patients and controls for heart rate and systolic or diastolic blood pressure).

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**Table 3. Frequency of the Electromyographic Bursts in Patients and Controls**

<table>
<thead>
<tr>
<th></th>
<th>Patients Taking Medication</th>
<th>Patients Not Taking Medication</th>
<th>( t ) Test</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of possible responses</td>
<td>300</td>
<td>240</td>
<td>...</td>
<td>1200</td>
</tr>
<tr>
<td>Orbicular muscle of the eye</td>
<td>61</td>
<td>84</td>
<td>.02</td>
<td>64</td>
</tr>
<tr>
<td>Sternocleidomastoid muscles</td>
<td>27</td>
<td>63</td>
<td>&lt;.001</td>
<td>5</td>
</tr>
<tr>
<td>Biceps muscles</td>
<td>19</td>
<td>35</td>
<td>.002</td>
<td>1</td>
</tr>
<tr>
<td>Thenar muscles</td>
<td>6</td>
<td>17</td>
<td>&lt;.001</td>
<td>1</td>
</tr>
</tbody>
</table>

*All data are presented as the percentage of all responses in a group that were followed by an electromyographic response, except for the number of possible responses, which indicates the number of patients taking and not taking medication (5 and 4, respectively) and controls (20); for each, the 20 stimuli of the 3 series were taken into account. \( P \) values for the frequency of occurrence refer to the \( t \) test; ellipses, not applicable.

\( \dagger \) \( P \) values between patients taking and not taking medication.

\( \ddagger \) \( P \) values between patients not taking medication and controls.

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**Figure 1.** The absolute (left) and relative (right) decrease in electromyographic (EMG) bursts in patients and controls. The areas of summed EMG bursts (±SEM) of the orbicular muscle of the eye and the sternocleidomastoid, the biceps, and the thenar muscles are shown in patients and controls for the combined series. Absolute EMG response refers to the level of response expressed as the square root of the summed area in millivolts per millisecond. For relative EMG responses, these areas were expressed as a percentage of the response to the first stimulus in a series. Note that the level of the response is initially higher in patients than in controls and the decrease in size during the series is larger for patients than for controls, regardless of whether absolute or relative responses were used.
Figure 2. The influence of loudness and interval time on habituation in patients (left) and controls (right). The level of the response is represented by the square root of the areas in millivolts per millisecond of the summed electromyographic bursts of the orbicular muscle of the eye and sternocleidomastoid, the biceps, and the thenar muscles in patients (left) and controls (right). Responses are shown for all 3 series of 20 stimuli. Series 1: 90-dB tone, 10-second interval; series 2: 113-dB tone, 10-second interval; and series 3: 113-dB tone, 60-second interval. In the patient group (left), the influence of the series on the summed area is not significant, but it is in the control group (right). The reduction in area during the series is not significantly influenced by the type of series in the patients or controls. Note the different scale of the level of response in patients and controls.

Figure 3. Habituation of the psychogalvanic reflex (PGR) in patients and controls. The PGR (±SEM) in patients and controls is shown for the combined series. The level of the PGR is initially higher and decreases less in patients than in controls.

Motor startle responses were more pronounced in patients with the major form of hereditary hyperekplexia than in controls. This finding is comparable with the results of other studies. In both absolute and relative terms, the area of EMG responses showed more habituation in patients than in controls, which is in contrast to earlier studies. One probable explanation could lie in the composition of the patient group, which consisted of patients with the major form of hyperekplexia in the present study. Most of the patients in whom habituation was investigated did not fulfill the criteria for the major form of hyperekplexia. It was recently shown that only the major form should be considered as hereditary hyperekplexia based on linkage studies and mutations in the gene encoding the glycine receptor. A neurophysiological study of the minor form of hyperekplexia showed that the pattern of the startle response is different from both controls and the major form of hyperekplexia: the startle responses showed no habituation to repetitive stimuli. The only other study on habituation in the major form was based on the observation in a single subject that the startle reflex could still be provoked after 20 stimuli. In contrast, the present study provides a quantitative groupwise comparison. We conclude that motor startle responses habituate more strongly in the major form of hyperekplexia.

The frequency of occurrence of the startle responses was increased, and the onset of the latency pe-
period of the sternocleidomastoid muscles was shortened in patients with hyperekplexia. A trend toward the shortened latency periods in hyperekplexia is also apparent in the biceps and the thenar muscles, although the differences were not significant. These shortened latency periods might be a result of increased cortical facilitation.

The amplitude of PGRs, as a measure of autonomic reactivity, was also increased in hyperekplexia. This indicates that the excessive startle reflex is not restricted to a motor response. A recent study on horizontal saccadic movements in patients with hyperekplexia also revealed that the abnormalities in hyperekplexia are not limited to the startle reflex. These abnormalities must be caused by the mutation in the α1 subunit of the glycine receptor, which is found in patients with the major form of hyperekplexia. The glycine receptors containing the α1 subunit are mainly localized in the brain stem and the spinal cord. As the glycine receptor modulates inhibitory effects, a lack of inhibition in hyperekplexia may result in a higher sensitivity of the startle generator with the consequence of exaggerated startle responses.

An interesting finding was the effect of medication on the different parameters of the startle reflex. The use of medication significantly prolonged the onset of latency periods and decreased the frequency of occurrence. No significant influence of medication was found on the area of the burst, the degree of habituation, and the amount and degree of habituation of the PGR. This suggests that initial response size and habituation periods and decreased the frequency of occurrence. No significant influence of medication was found on the area of the burst, the degree of habituation, and the amount and degree of habituation of the PGR. In previous studies, the influence of medication was not measured, although Matsumoto and colleagues mentioned that the only patient who was not taking medication had the shortest onset of latency periods. Medication may cause a delay through decreased facilitation by the cortical facilitation, due to lesions of part of the temporal gyrus and the frontal cortex, has been reported.

The motor response habituated more in patients than in controls, while the reverse held for the habituation of the PGR. This suggests that initial response size and habituation are under different influences. Therefore, we conclude that the magnitude of the initial startle response and its habituation should be regarded as different indexes of pathophysiological conditions in patients with hyperekplexia. The causes of these differences are unknown.

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