

## PAPER

# Hyperekplexia and stiff-man syndrome: abnormal brainstem reflexes suggest a physiological relationship

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Exaggerated reflex startle (hyperekplexia), often associated with serious falls, is a common feature of two rare neurological diseases, familial hyperekplexia (FH) and the stiff-man syndrome (SMS). In both FH and SMS, excessive startle is frequently associated with an awkward, hesitating gait disorder and with a fear of open spaces ("space phobia").<sup>1–6</sup>

FH is an inherited neurological disorder that manifests itself shortly after birth with severe generalised muscle stiffness ("stiff baby syndrome") and exaggerated startle to external stimulation and emotional upset. In most patients, muscle stiffness subsides during the first year, but jerky startle to acoustic and tactile stimulation may persist for life.<sup>1</sup> In most families, FH follows an autosomal dominant trait and is associated with mutant alleles of the gene encoding the  $\alpha 1$ -subunit of the inhibitory glycine receptor (GLRA1) on chromosome 5q31.2.<sup>7–9</sup> Hyperekplexia may also occur as an idiopathic motor disturbance with late onset (acquired idiopathic hyperekplexia, AH) or associated with other neurological signs in a variety of brainstem or extrapyramidal diseases (symptomatic hyperekplexia).<sup>4, 10</sup>

SMS is an acquired disorder that is characterised by intense stiffness of trunk and proximal limb muscles superimposed with spasms, and by the absence of firm neurological signs. Most patients complain of exaggerated startle to acoustic and tactile stimulation. About 70% of patients have circulating autoantibodies against glutamic acid decarboxylase (GAD-Ab), the enzyme synthesising the major inhibitory transmitter GABA.<sup>3, 6</sup> This suggests that SMS is an autoimmune disease with disordered GABAergic motor inhibition<sup>11</sup> affecting spinal cord, brain stem, and motor cortex.<sup>12–15</sup>

Most likely, exaggerated startle in FH is due to defective glycinergic inhibition. However, the physiologic mechanisms underlying similar phenomena in AH and SMS are

**Background and objectives:** Hyperekplexia and the stiff-man syndrome (SMS) are both conditions with exaggerated startle suggesting abnormal brainstem function. Investigation of brainstem reflexes may provide insight into disturbed reflex excitation and inhibition underlying these movement disorders.

**Patients and methods:** Using four-channel EMG, we examined four trigeminal brainstem reflexes (monosynaptic masseter, masseter inhibitory, glabella, and orbicularis oculi blink reflexes) and their spread into pericranial muscles in five patients with familial hyperekplexia (FH), two with acquired hyperekplexia (AH), 10 with SMS, and 15 healthy control subjects.

**Results:** Both FH/AH and SMS patients had abnormal propagation of brainstem reflexes into pericranial muscles. All patients with hyperekplexia showed an abnormal short-latency (15–20 ms) reflex in the trapezius muscle with a characteristic clinical appearance ("head retraction jerk") evoked by tactile or electrical stimulation of the trigeminal nerve, but normal monosynaptic masseter reflexes. Inhibitory brainstem reflexes were attenuated in some FH/AH patients. Four of 10 patients with SMS had similar short-latency reflexes in the neck muscles and frequently showed widespread enhancement of other excitatory reflexes, reflex spasms, and attenuation of inhibitory brainstem reflexes.

**Conclusion:** Reflex excitation is exaggerated and inhibition is attenuated in both stiff-man syndrome and familial or acquired hyperekplexia, indicating a physiological relationship. Reflex transmission in the brainstem appears biased towards excitation which may imply dysfunction of inhibitory glycinergic or GABAergic interneurons, or both.

speculative.<sup>16</sup> We therefore electromyographically investigated reflex excitation and inhibition at the brainstem level. We examined four brainstem reflexes, all of which are well established in clinical or electrodiagnostic testing: the monosynaptic masseter reflex, the masseter inhibitory reflex, the glabella reflex, and the blink reflex.

## METHODS

### Patients and controls

We investigated five patients with FH (2–36 years of age) from three families, two patients with AH (16 and 33 years of age), 10 patients with SMS (31–73 years of age), and 15 healthy control subjects (CS; 21–53 years of age). The subjects or, where legally required, their parents gave informed consent to participate in electrophysiological studies. All FH patients participating in this study carried point mutations of the GLRA1 gene. The two patients with AH had no neurological abnormality other than hyperekplexia, gait disturbance, and space phobia, as well as normal ancillary findings including brain MRI, CSF analysis, and screening for GAD-Ab. Four patients with FH and both AH patients were on symptomatic treatment with clonazepam (0.75–6 mg per day) or diazepam (6 mg per day). All SMS patients had stiffness of the legs and trunk; one patient had additional involvement of the neck and arms. In none of them did stiffness or spasms involve the face. In eight of the 10 SMS patients, radioimmunoassay testing disclosed serum antibodies directed against GAD. Nine patients with SMS were under current symptomatic treatment with diazepam (5–60 mg per day), clonazepam (7 mg per day), intrathecal

**Abbreviations:** AH, acquired hyperekplexia; CS, control subject; FH, familial hyperekplexia; MAS, masseter; OOC, orbicularis oculi; SCM, sternocleidomastoid; SMS, stiff-man syndrome; TRA, trapezius

**Table 1** Survey of abnormal reflex excitation and inhibition in patients with familial or acquired hyperekplexia or with stiff-man syndrome

Stimulus		FH/AH (n = 7)	SMS (n = 10)
<b>Abnormal reflex excitation</b>			
Tap to chin	Monosynaptic MAS reflex exaggerated	0/7	2/10
Pulse to V3	Short-latency spread into TRA/SCM	7/7	2/10
	Short-latency spread into TRA/SCM	7/7	0/10
Tap to glabella	Short-latency spread into TRA/SCM	7/7	4/10
	Widespread reflex spasms	0/7	5/10
Pulse to V1	Short-latency spread into TRA/SCM	7/7	0/10
	Widespread reflex spasms	0/7	5/10
Any	Widespread reflex spasms	0/7	5/10
<b>Abnormal reflex inhibition</b>			
Tap to chin	Loss of reflex inhibition in TRA/SCM	1/7	3/10
	MAS post reflex silent period incomplete/delayed	2/7	3/10
Pulse to V3	Loss or delay of S2 component of MAS inhibition	2/7	1/10
	Elevated reflex thresholds for MAS inhibition	0/7	7/10
Tap to glabella	Loss of OOC inhibition	0/7	2/10

MAS, masseter; OOC, orbicularis oculi; SCM, sternocleidomastoideus muscles; TRA, trapezius; V1/V3, first/third trigeminal nerve branch.

baclofen (60–925 µg per day), or tizanidine (16 mg per day), or a combination of these drugs.

### Procedure

Subjects rested on a comfortable couch in supine position with their eyes closed. The glabella reflex was elicited by gently tapping the root of the nose with a micro switch-equipped tendon hammer. The masseter reflex and the masseter post reflex silent period were evoked by tapping the tip of the chin. The blink reflex was elicited by electrical stimulation of the left supraorbital nerve (square wave shocks, pulse width 0.2 ms). The masseter inhibitory reflex was evoked by electrical stimulation of the lower lip. In the case of electrical stimulation, we first determined the individual reflex thresholds by a stepwise current increase or decrease. We defined the threshold as the lowest required stimulus intensity to consistently reproduce at least one reflex component. We then elicited the orbicularis oculi blink and the masseter inhibitory reflexes with a stimulus intensity of 2–3 × reflex threshold. Because of altered reflex thresholds,

considerably higher stimulus intensities were required in some SMS and FH/AH patients.

In addition to the reflex effects in the respective target muscle, we investigated the spread of reflexes into neighbouring muscles. Therefore, we recorded brainstem reflexes simultaneously from the orbicularis oculi (OOC), masseter (MAS), trapezius (TRA), and sternocleidomastoid (SCM) muscles on the left side using surface electrodes (diameter 7 mm) attached over the respective muscles (filter setting 100–3000 Hz). Four reflexes were elicited consecutively at intervals exceeding 30 s and electronically superimposed.

Normal values were obtained from the 15 CS subjects (fig 1). Quantitative data are presented as absolute values or arithmetic means with 1 SD. The level of significance was set at  $p < 0.001$ .

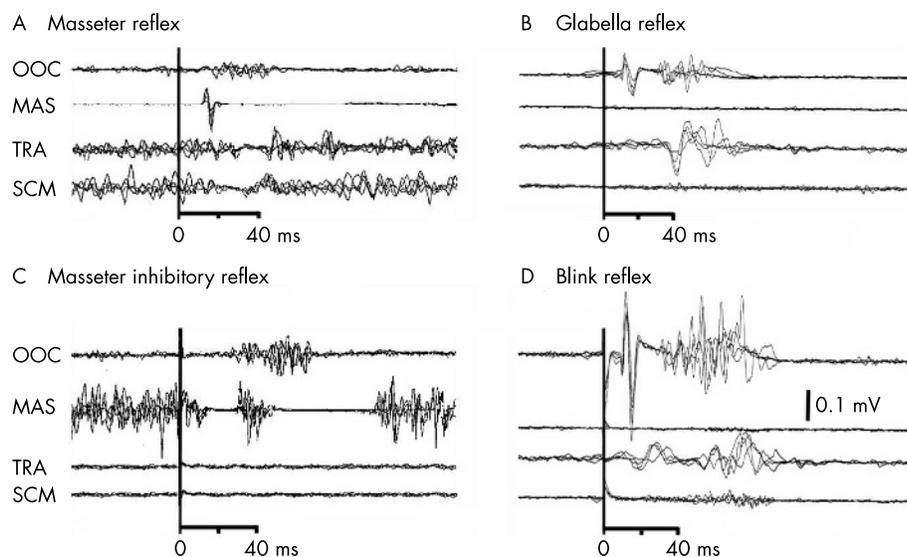
## RESULTS

### Familial hyperekplexia Reflex excitation

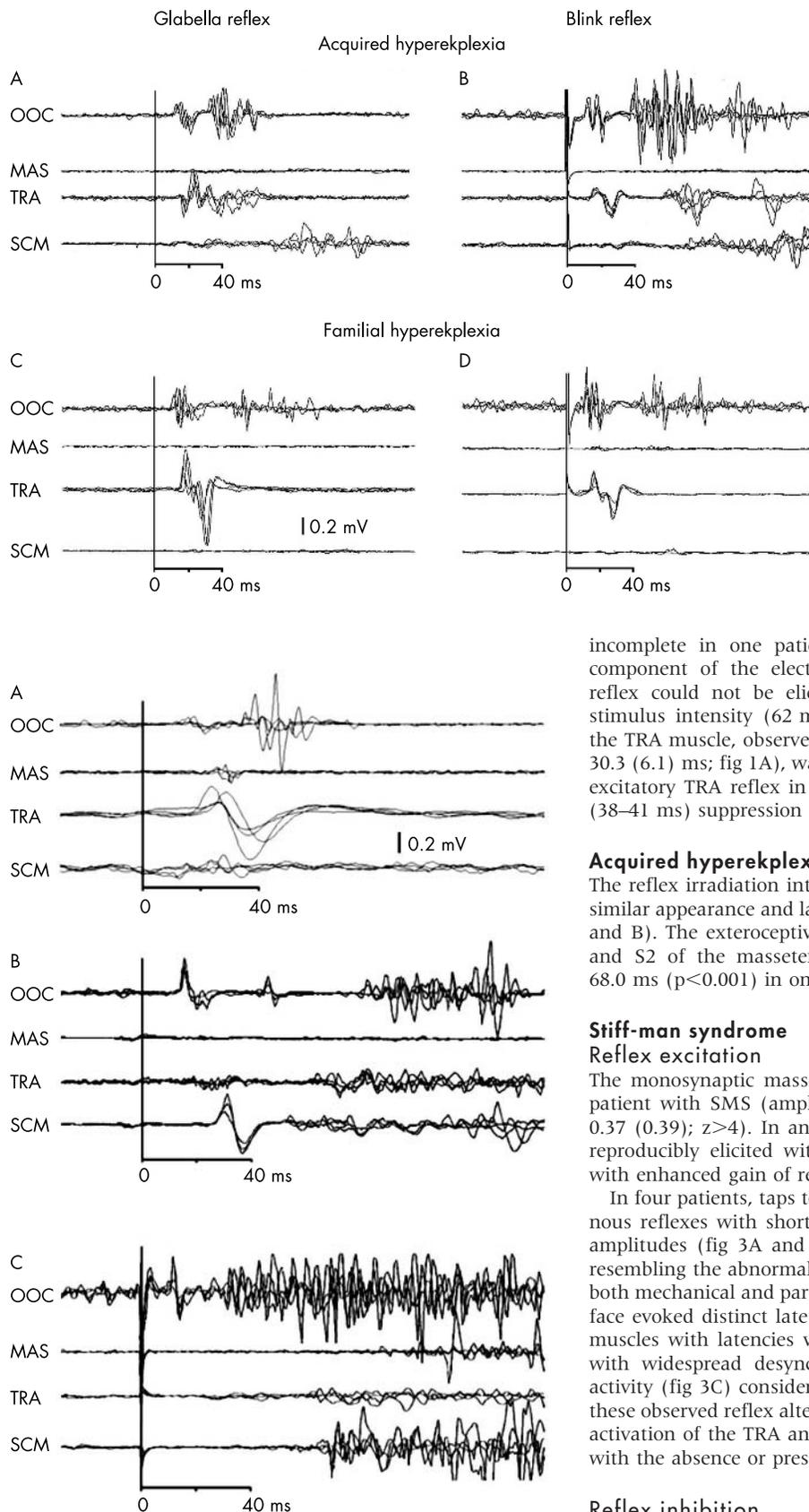
The blink, glabella, and monosynaptic masseter reflexes were normal. However, all patients had abnormal irradiation of excitatory reflexes into the neck muscles: both electrical and mechanical stimulation elicited highly synchronised short-latency reflex activity in the TRA muscle (table 1, fig 2C and D). The reflex latency was shorter with taps to the jaw (12.6–16.0 ms) than to the glabella (13.7–22.1 ms), and the amplitudes higher and more stable with mechanical than with electrical stimulation. A second, less synchronised component followed inconstantly at around 50 ms. In all FH patients, a synchronised but unstable reflex in the SCM muscle accompanied the TRA reflex with slightly longer latencies after taps to the chin (16.2–25.5 ms) and to the glabella (17.6–25.2 ms). Such activation of the neck muscles was only sporadically observed in the CS: upon elicitation of the blink reflex, two CS had early trapezius reflexes at a similar latency (20 ms; fig 1D) but with smaller amplitudes, and four CS exhibited late responses (latency around 60 ms).

### Reflex inhibition

Besides these excitatory reflex abnormalities, pre-activation of the pericranial muscles revealed lost or diminished inhibitory reflexes in the FH subjects: the exteroceptive suppression of the OOC, intercalated between the R1 and R2 components of the blink reflex<sup>17,18</sup> in all CS (latency (SD) 21.7 (1.5) ms), was delayed in one patient (30.0 ms,  $p < 0.001$ ). Similarly, the masseter post reflex silent period was



**Figure 1** Normal patterns of brainstem reflexes recorded simultaneously from the orbicularis oculi (OOC), masseter (MAS), trapezius (TRA), and sternocleidomastoideus (SCM) muscles. In each panel, four reflex responses are superimposed. In A, voluntary pre-innervation of the TRA and SCM during elicitation of the masseter reflex allows identification of the inhibitory reflex components in these muscles. Reflex activation of the TRA in the glabella or the blink reflex, though uncommon in normal subjects (table 1), is shown here for comparison with the abnormal reflex patterns in patients with FH/AH (fig 2) and SMS (fig 3). The vertical calibration (bottom right) applies to all registrations.



**Figure 2** Abnormal spread of the glabella and blink reflexes in a patient with acquired hyperekplexia (A, B) and in a patient with familial hyperekplexia (C, D). Abbreviations as in fig 1. In contrast to the control subjects, short-latency reflex activation of the TRA is regularly observed in both conditions. The vertical calibration in C applies to all registrations.

**Figure 3** Abnormal glabella (A, B) and blink (C) reflex patterns in three patients with SMS: short-latency responses of the TRA (A, B) and SCM (B), abnormal synchronisation of the second OOC reflex component (B), and reflex spasms in the OOC and SCM (C). Abbreviations as in fig 1. The vertical calibration in A applies to all registrations.

incomplete in one patient. In the same patient, the S2 component of the electrically evoked masseter inhibitory reflex could not be elicited, even at maximum tolerable stimulus intensity (62 mA). Moreover, reflex inhibition of the TRA muscle, observed in all CS after a chin tap (latency 30.3 (6.1) ms; fig 1A), was overrun by the hypersynchronous excitatory TRA reflex in FH and followed by a long-lasting (38–41 ms) suppression of the ongoing EMG activity.

**Acquired hyperekplexia**

The reflex irradiation into the TRA and SCM muscles had a similar appearance and latency as in patients with FH (fig 2A and B). The exteroceptive suppression of the OOC was lost and S2 of the masseter inhibitory reflex was delayed to 68.0 ms ( $p < 0.001$ ) in one patient with AH.

**Stiff-man syndrome  
Reflex excitation**

The monosynaptic masseter reflex was exaggerated in one patient with SMS (amplitude 2.19 mV, mean (SD) for CS: 0.37 (0.39);  $z > 4$ ). In another, the masseter reflex could be reproducibly elicited with taps to the glabella, compatible with enhanced gain of reflex transmission.<sup>19</sup>

In four patients, taps to the glabella elicited hypersynchronous reflexes with short latencies (24.8–28.5 ms) and high amplitudes (fig 3A and B) in the TRA and SCM muscles, resembling the abnormal reflexes in FH/AH. In five patients, both mechanical and particularly electrical stimulation of the face evoked distinct late reflex effects in the TRA and SCM muscles with latencies varying between 35 and 71 ms and with widespread desynchronised and long-lasting muscle activity (fig 3C) considered reflex spasms.<sup>19</sup> The presence of these observed reflex alterations, in particular the early reflex activation of the TRA and SCM muscles, was not associated with the absence or presence of GAD-Ab.

**Reflex inhibition**

In three patients the latency of the masseter post reflex silent period was delayed beyond 20 ms (mean (SD) for CS: 12.4 (2.3) ms;  $p < 0.001$ ;  $z > 3$ ). The electrically evoked masseter inhibition had normal latency and duration, but required abnormally high stimulus intensities: in five patients, the

reflex threshold was greater than 41 mA (compared to 19.4 (4.4) mA in CS;  $p < 0.001$ ). Taps to the chin failed to induce reflex inhibition of the TRA in two patients, and of the SCM (latency in CS, 21.0 (4.5) ms) in one SMS patient. Both reflex effects were regularly observed in CS (fig 1A). Similarly, the exteroceptive inhibition of the OOC muscle was abolished in two patients with SMS.

## DISCUSSION

In patients with FH/AH and SMS, the patterns of normal brainstem reflexes with their irradiation into pericranial muscles are distinctively altered. In both motor disturbances, we found enhanced reflex excitation and attenuated reflex inhibition. Exclusively in patients with SMS, moreover, we observed hyperactive masseter reflexes and widespread reflex spasms. While some of the presented abnormalities of excitatory reflexes have been documented in other reports,<sup>16 20–22</sup> this is the first study to systematically evaluate inhibitory brainstem reflexes in patients with FH/AH and SMS. Our findings show that in both disorders reflex transmission through the brainstem is biased towards excitation.

Our study has certain limitations. First, most examined patients were on treatment with benzodiazepines or baclofen which could have altered reflex transmission and possibly given false EMG findings. However, as these drugs are known to attenuate reflex excitation and enforce inhibition,<sup>23–25</sup> one might expect a higher prevalence of reflex abnormalities in untreated patients rather than falsely positive findings. Second, no normative data for brainstem reflexes exist in children. However, personal experience and anecdotal reports<sup>9</sup> suggest that the patterns and latencies principally resemble those in adults. Third, the low prevalence of both syndromes and the small number of examined patients limit the ability to generalise our findings.

### Abnormal brainstem reflexes in familial hyperekplexia

In our study, the most prominent reflex alteration was the hypersynchronous short-latency reflex in the TRA muscle. Because of its characteristic clinical appearance, we will refer to it as the “head retraction reflex”.<sup>16 26</sup> The fact that it can be elicited by electrical stimulation of the trigeminal nerve suggests that this trigemino-cervical reflex belongs to the cutaneo-muscular reflexes.<sup>27</sup> Its latency and pattern resemble the trigemino-facial blink reflex. By analogy, we assume that similar neuronal pathways link the trigeminal sensory nuclei with the spinal motor nuclei of the accessory nerve.<sup>28 29</sup> The presence of a trace of this reflex in some CS (fig 1D)<sup>30</sup> and—as revealed by needle electrode recordings—also in the deep neck muscles of normal subjects<sup>31</sup> suggests that the head retraction reflex may be rudimentarily present, but physiologically suppressed in normal subjects. Since this reflex is the most prominent, and often the only firm neurological sign of FH,<sup>1 2</sup> a disorder of the inhibitory glycine receptor,<sup>7 9</sup> it is tempting to speculate that disinhibition of this reflex in FH is due to defective glycinergic inhibition. The presence of a clinically and electrophysiologically similar head retraction reflex in patients with AH suggests that FH and AH share physiological abnormalities.

### Abnormal brainstem reflexes in the stiff-man syndrome

The head retraction reflex was also present in four of 10 patients with SMS corresponding to a prevalence of about 50% in a recent large cohort study.<sup>16</sup> Another characteristic finding observed only in our patients with SMS, but described in patients with tetanus or in hemimasticatory spasm,<sup>32 33</sup> were widespread reflex spasms. None of the SMS

patients investigated had clinical involvement of the face, and the neck was involved in only one. Therefore the high prevalence of abnormal trigeminal reflexes suggests sub-clinical involvement of the brainstem. Excitability of the reflex circuits between the trigeminal sensory nuclei and the motor nuclei of the cranial nerves is modulated by segmental and suprasegmental inputs.<sup>34 35</sup> Increased brainstem inter-neuronal excitability in SMS patients as revealed by enhanced blink reflex recovery cycles was ascribed to altered inhibitory drive from the basal ganglia or to cortical hyperexcitability.<sup>12 36</sup> Intrinsic pathology of brainstem interneurons was considered unlikely, because the masseteric exteroceptive silent period in patients with SMS has been reported as normal.<sup>32 36</sup> Our findings differ from the reported data in that a considerable proportion of patients with SMS do have abnormal masseteric inhibitory components suggesting primary dysfunction of the inhibitory interneurons at brainstem level.

### A physiological relationship?

Reflex transmission through the brainstem is biased towards excitation in both SMS and FH. Both motor disturbances also have in common the presence of a head retraction reflex.<sup>16</sup> Such similarities suggest a physiological relationship. Are these similarities a reflection of a shared synaptic disease process between SMS and FH?

In FH, a genetic disorder with mutated glycine receptors, abnormalities of brainstem reflexes are most likely due to diminished glycine inhibition.<sup>37</sup> SMS, however, is currently understood as a disorder with impaired GABAergic synaptic transmission.<sup>11 38</sup>

Biochemical and physiological links between SMS and FH not yet understood are that cerebrospinal fluid levels of free GABA are reduced in FH<sup>39</sup> and segmental glycinergic inhibitory circuits are impaired in SMS.<sup>13 14</sup> A simple explanation for such a relationship might be that the inhibitory transmitters, GABA and glycine are simultaneously present in the trigeminal subnuclei<sup>40–43</sup> and are both involved in the trigeminal reflex transmission.<sup>3</sup> This hypothesis is corroborated by the observation that in various species, and presumably also in human beings, GABA<sub>A</sub> and glycine receptors show a widespread co-localisation in the central nervous system.<sup>44–47</sup>

## CONCLUSIONS

Patients with the familial or acquired forms of hyperekplexia and patients with the stiff-man syndrome share physiological abnormalities: brainstem reflex excitation is exaggerated whereas reflex inhibition is attenuated. This is likely due to defective inhibition, mediated by GABAergic and glycinergic brainstem interneurons. We conclude that both transmitters are co-localised in polysynaptic reflex pathways of the brainstem.

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