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Case report

Hyperekplexia in a patient with a brainstem vascular anomaly

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Objectives – To describe a patient with a clinical picture suggestive of idiopathic hyperekplexia (IH), who was later found to harbour a subtle brainstem vascular anomaly. *Patient* – A 35-year-old man, 4 years earlier, developed sudden jumping and falling in response to unexpected sensory stimuli. *Results* – Neurological examination was normal. Electromyography showed an excessively large and non-habituating motor startle response. There were no mutations of the α_1 subunit of the inhibitory glycine receptor which cause hereditary hyperekplexia. Although all these findings were consistent with a diagnosis of IH, a blink reflex study showed an enhanced recovery curve suggestive of a brainstem lesion. A detailed MRI study revealed a subtle vascular anomaly involving the lower brainstem. *Conclusion* – This is the first report of sporadic hyperekplexia related to a brainstem vascular anomaly. Subtle damage to the brainstem should always be excluded in patients with sporadic hyperekplexia, regardless of the coexistence of additional clear-cut neurological symptoms.

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Key words: startle reflex; hyperekplexia; magnetic resonance imaging; genetics; electromyography; vascular malformation

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Hyperekplexia is a rare involuntary movement disorder which is characterized by the pathological exaggerations of the normal startle reflex that persists throughout the lifetime of the patient (1). Both the pathological and normal startle reflexes are the result of a single efferent pathway originating in the lower brainstem, and have the same pattern of muscular activity (2, 3). Compared with the normal startle reaction, however, the abnormal response is greatly exaggerated in amplitude, more extensive in distribution, and habituates poorly to repeated sensory, particularly auditory, stimuli (2, 3). Hyperekplexia may occur in two forms: a minor form in which there is only an exaggerated startle response; and a major form characterized by additional clinical manifestations, such as transient stiffness (1). Either form may interfere with normal activities, and sometimes may be dangerous (1).

Typically, hyperekplexia is a hereditary disorder (1), which may display either an autosomal dominant or, exceptionally, a recessive inheritance resulting from mutations in the gene encoding the α_1 subunit of the inhibitory glycine receptor (GLRA1) (4, 5).

Nonetheless, patients with sporadic hyperekplexia (SH) have also been described (1, 4, 6, 7). They are indistinguishable from the hereditary cases, except for the absence of a family history of startle phenomena and GLRA1 mutations (4). According to the underlying brainstem pathology, SH may be classified as idiopathic or symptomatic (2). The latter usually show clear-cut neurological symptoms, and have been associated with different brainstem lesions including trauma, Arnold-Chiari malformation, abscess, encephalitis, multiple sclerosis, anoxia, and infarct/haemorrhage (reviewed in Ref. 2).

Here we report the clinical, neurophysiological and genetic findings for a 35-year-old man with a

clinical picture suggestive of idiopathic SH, who was later found to harbour a subtle brainstem vascular anomaly.

Case report

The patient, a 35-year-old right-handed man, with no family history of involuntary movements or other neurological disorders, had been in good health until 4 years earlier, when he developed sudden jumping and falling in response to unexpected noises, visual stimuli, and more rarely, touches or taps to the body. The jumping occurred daily but never spontaneously, and was augmented when the patient was nervous. Because of repeated falling, the patient injured himself on several occasions, and once he fractured his left forearm. Consciousness was preserved throughout the attacks of jerking.

General and neurological examinations were normal, except for the sudden jumping and falling in response to unexpected sounds, visual stimuli or taps to the body. The most violent jumps consisted of a blink, grimace, flexion of the head over the chest, shoulder abduction, and flexion of the elbows, hips and knees with consequent falling to the floor. There were no tonic spasms, spontaneous or sustained jerking, echolalia, echomimia, or automatic obedience.

Haematological and biochemical investigations, serum folate and vitamin B_{12} levels were all normal. A cerebrospinal fluid examination revealed a normal glucose and protein concentration; oligoclonal banding was absent. An autoantibody screen including anti-nuclear, anti-DNA, anti-mitochondrial, anti-microsomal, anti-endomysial, anti-gliadin, anti-Purkinje cell, anti-neuronal nuclear type 1 and 2, and anti-glutamic acid decarboxylase was negative.

A Doppler ultrasound study of the carotid and vertebrobasilar extracranial arteries was normal.

Electrophysiological studies

Awake and sleep EEG recordings, motor and sensory nerve conduction velocities of several nerves of the upper and lower limbs, brainstem auditory and cortical somatosensory evoked potentials from the median nerves, and quantitative eye movement testing were all normal. On EEG recording, the startle response consisted of an initial spike recorded from the centroparietal vertex followed by a short-lasting train of slow waves, and then by desynchronization of background activity lasting 3 s.

Electromyographic startle response

Electromyographic (EMG) recording was made using bipolar silver chloride electrodes placed 2 cm apart longitudinally over the orbicularis oculi, masseter, sternocleidomastoid, biceps, rectus abdominis, and tibialis anterior muscles bilaterally. The patient was examined while sitting relaxed in a chair. Startle responses were elicited by auditory tone bursts of 1000 Hz frequency, 50 ms duration and 95 dB presented binaurally through earphones and delivered randomly every 60–180 s for 12 trials to test for reflex habituation. Muscle jerks were recorded by triggering the computer at the start of the stimulus. The sampling rate was 1500 Hz per channel. Reflex latencies were measured by the visual inspection of single trials on a computer display. The startle reaction was also recorded in 5 age and sex matched controls.

Cranial and limb muscles were activated in the typical sequence of the startle reflex (2, 3), and relatively little habituation was apparent over the 12 trials (Fig. 1). The mean onset latencies of the EMG responses were longer than those observed in the controls. Indeed, in the latter the mean onset latencies of orbicular muscles of the eye, sternocleidomastoid and masseter were 32.5 ms (range: 26 to 40; standard deviation [SD] $\pm$5), 62.9 ms (range: 48 to 81; SD $\pm$9), 64.2 ms (range: 49 to 85; SD $\pm$12), respectively. The limb muscles were rarely activated.

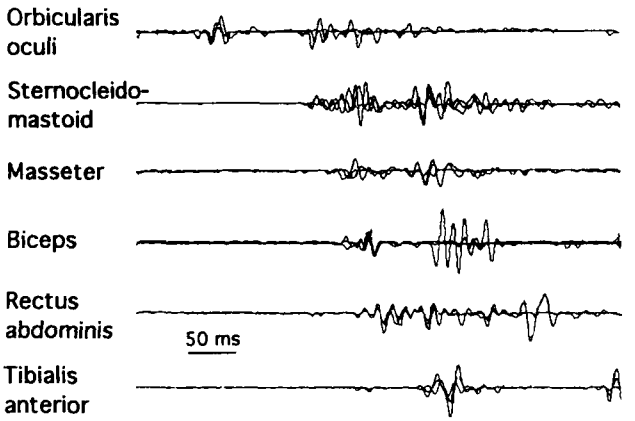


Fig. 1. Pattern of EMG activity of the abnormal startle response elicited by auditory stimulation. Three unrectified single trials are superimposed. Following the auditory blink reflex (mean latency: 71 ms, range: 67 to 89), the earliest EMG activity was recorded at the sternocleidomastoid (176 ms), and then in masseter (210 ms), and trunk (rectus abdominis: 215 ms) and limb (brachial biceps: 234 ms; tibialis: 275 ms) muscles.

Blink reflex study

The study revealed an enhanced recovery curve after stimulation of either side. Thus, the R2 response was recovered by >90% for an interstimulus interval of 500 ms bilaterally [normal values of recovery at 500 ms: ~10% (8; authors' personal experience)].

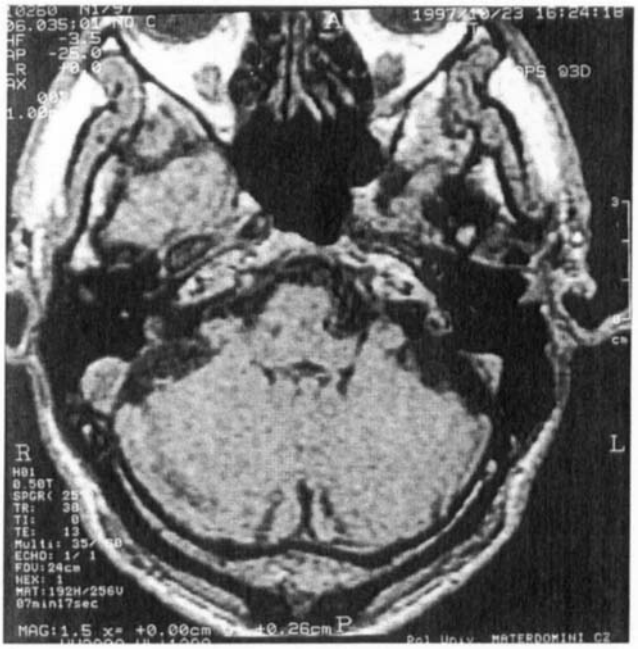
Genetic study

Genomic DNA was extracted with an automated DNA extractor (Applied Biosystems, Foster City, CA, USA). The presence of G1192A, G1192T and T1112A mutations in exon 6 of the α_1 subunit GLRA1 (4, 5) were excluded by restriction enzyme digestion following amplification by the polymerase chain reaction. We also failed to detect any mutations in exon 6 and exon 7 of the α_1 subunit of GLRA1 gene with single-stranded conformational polymorphism (4).

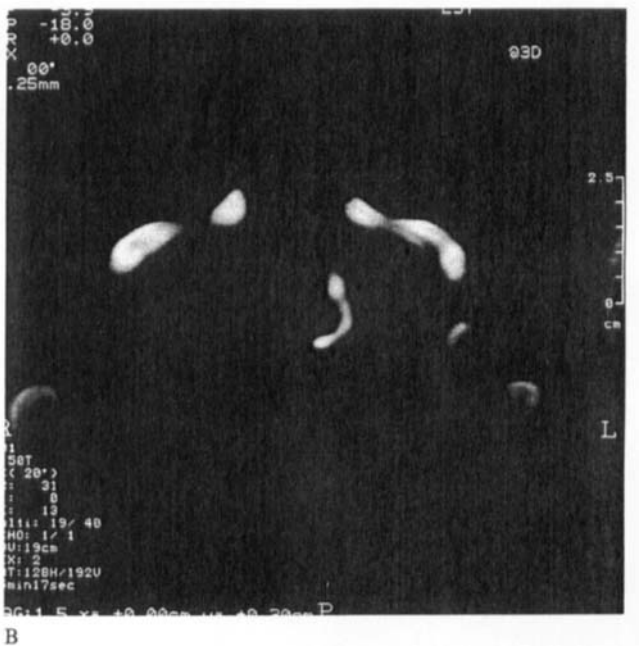
Magnetic resonance imaging (MRI) study

Axial long TR/TE MR and corresponding 3D phase-contrast MR angiography demonstrated that the left vertebral artery impacted the pons on the left side at the cerebellopontine angle (Fig. 2A, B). In addition, on MR angiography, there was a marked tortuosity of both vertebral arteries mainly on the left side (Fig. 3A, B). The left vertebral artery also described a brusque angle and crossed the midline before joining the contralateral one to form the basal artery (Fig. 3A, B).

Daily treatment with 3 mg of clonazepam was started with moderate benefit, but a higher dosage was not tolerated. In agreement with the findings of Dooley & Andermann (9), the addition of 1 g of sodium valproate daily led to a dramatic improvement in his jerking.



A



B

Fig. 2. Observe the left vertebral artery impacting upon the pons on the left side at the cerebellopontine angle, as illustrated by axial long TR/TE MR (A) and corresponding axial 3D phase-contrast MR angiography (B).

Discussion

The patient described here fulfilled the neurophysiological criteria which have been so far utilized for the diagnosis of minor hyperekplexia (10). Indeed, in accordance with the EMG findings observed in patients with the minor form of hereditary hyperekplexia, our patient showed delayed motor startle latencies in comparison with those in the controls (10). Moreover, EMG recording showed an excessively large and non-habituating motor startle response, with the classical and stereotyped order of muscle recruitment (2, 3, 10), that readily differentiated it from both the reflex myoclonus (11) and jerks of psychogenic origin (12). The latter are characterized by variable latency, longer duration, and variable patterns of muscle recruitment (12).

A genetic study failed to reveal any GLRA1 mutations, which have been shown to cause autosomal dominant and recessive familial hyperekplexia (4, 5). This finding together with the negative family history strongly supports the suggestion that our patient is affected by SH (4).

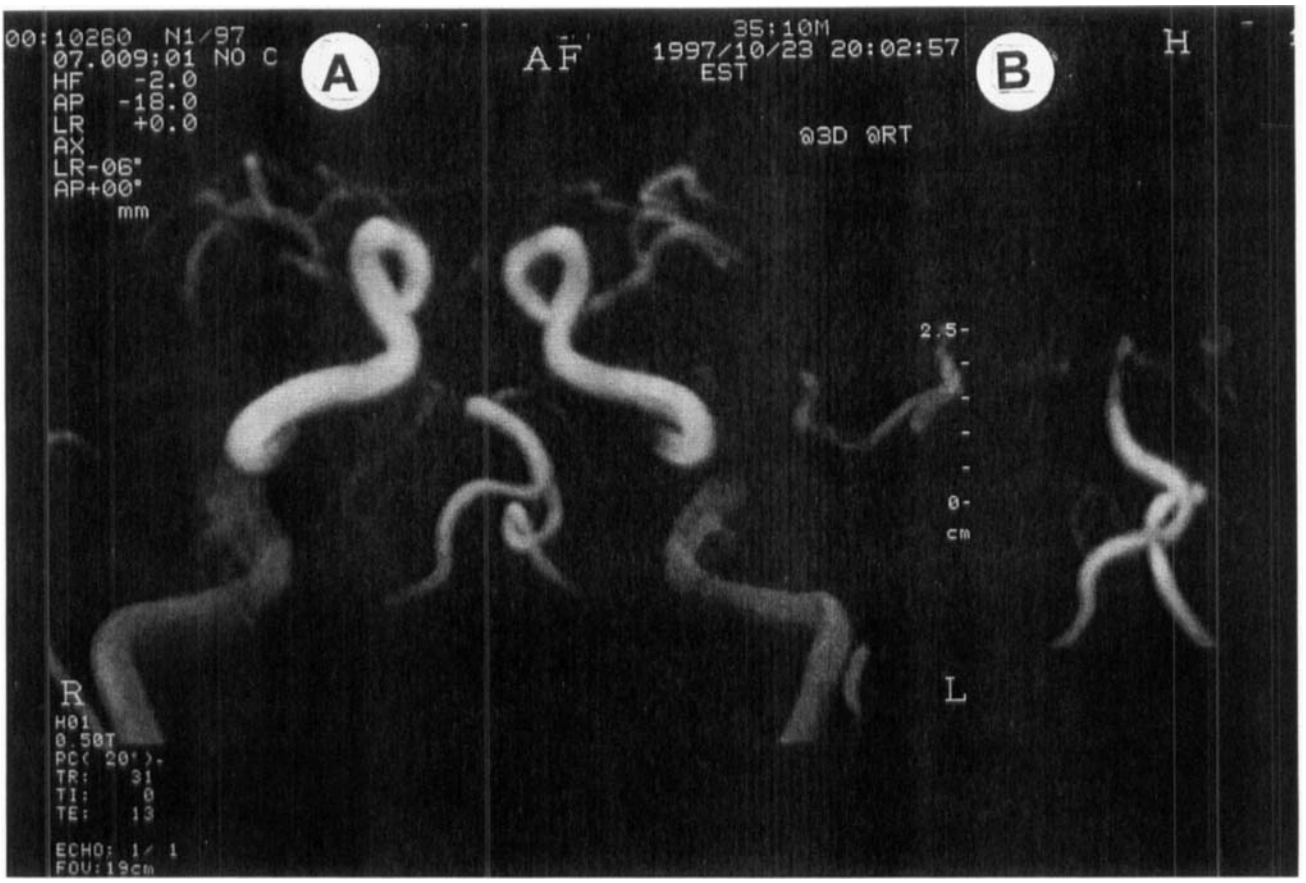


Fig. 3. 3D MR angiography. Notice the marked tortuosity of both vertebral arteries mainly on the left side (A). The vertebral artery also described a brusque angle (A) and crossed the midline (B), before joining the contralateral one to form the basal artery.

SH has been divided in idiopathic or symptomatic (2). Most SH cases reported were symptomatic of brainstem lesions (2, 13), whereas only a few patients with idiopathic SH have been described (1, 6, 7). Notably, most of the latter cases were reported by Gastaut & Villeneuve (6) in 1967, raising the question whether, at least in some of them, a more exhaustive neurophysiological and imaging study would have detected a subtle brainstem lesion.

In our patient, indeed, a blink reflex study showed an enhanced recovery curve highly suggestive of a brainstem lesion (14). Moreover, MRI investigation revealed a subtle vascular anomaly affecting the lower brainstem, which is considered to be the site of origin of both normal and pathological startle responses (3, 4). These findings, taken together, suggest that this vascular anomaly is responsible for the excessive startle response in our patient. The mechanism by which this vascular anomaly could have damaged the brainstem remains unclear, but a mechanical compression of those nervous structures mediating the startle response by the abnormal loop and kinking of the vertebral arteries may have a causal role.

To our knowledge, this is the first report of SH due to a vascular vertebrobasilar anomaly. Based on the present observation, it may be argued that subtle damage to the brainstem should always be excluded in patients with SH, regardless of the coexistence of additional clear-cut neurological symptoms.

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