SHORT REPORT

Pontine hyperperfusion in sporadic hyperekplexia

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Objective: To explore with neuroimaging techniques the anatomical and functional correlates of sporadic hyperekplexia.

Methods: Two elderly women with sporadic hyperekplexia underwent neurophysiological assessment, MRI of the brain and proton magnetic resonance spectroscopy (¹H-MRS) of the brainstem and frontal lobes. Regional cerebral blood flow was investigated with single photon emission tomography (SPECT) during evoked startles and at rest.

Results: Both patients showed excessively large and non-habituating startle responses. In both patients, MRI showed impingement of the brainstem by the vertebrobasilar artery, lack of frontal or brainstem abnormalities on ¹H-MRS and hyperperfusion in the dorsal pons and cingulate cortex, and superior frontal gyrus at SPECT during evoked startles.

Conclusions: In our patients with hyperekplexia, the vertebrobasilar arteries were found to impinge on the brainstem. Neurophysiological findings and neurofunctional imaging of evoked startles indicated a pontine origin of the movement disorder modulated by activation in cortical, especially frontal, areas. The neurofunctional correlates of evoked startles in human sporadic hyperekplexia are similar to those observed for the startle circuit in animals.

The startle reflex is a craniocaudal spreading wave of flexor movements along the neural axis that is elicited by an abruptly occurring sensory event. A pathological exaggeration of the normal startle reflex to unexpected stimuli, particularly sounds, is the hallmark of both hereditary and symptomatic hyperekplexia, whose clinical features arise from a functional disturbance of the brainstem startle relay.¹

In animals, the neural circuit mediating the acoustic startle reflex involves three synapses located on the cochlear root, the nucleus reticularis pontis caudalis (PnC) and the spinal motor neurons.² Activation of an area in the medial pons corresponding to PnC has been reported during the startle reflex in normal humans by means of brain imaging studies.³

We report neurophysiological and brain MRI evaluations with proton magnetic resonance spectroscopy (¹H-MRS) and single photon emission tomography (SPECT) of two elderly women with sporadic hyperekplexia.

PATIENTS

Two women, 67 and 68 years old, presented with excessive startles to sudden stimuli such as a telephone ringing, a door closing or an unexpected visual stimulation since adolescence and age 58 years, respectively. Over the past 2 and 4 years, sudden jumps had increased during the day, on a few occasions accompanied by a fall, and during the night, particularly when going off to sleep. Neither patient had a family history of

exaggerated startle. Diffusely increased deep tendon reflexes on neurological examination were found in both patients.

Sudden acoustic, visual and tactile (glabella tapping) stimuli elicited a stereotyped jerking with blinking, facial grimacing, flexion of the head, trunk and lower limbs and abduction at the shoulders, with a feeling of anxiety and, sometimes, an outcry.

In both patients, laboratory investigations, including serological tests for vasculitis and serum and CSF antibodies to transglutaminase, glutamic acid decarboxylase, ganglioside, sulphatide, myelin associated glycoprotein, onconeural antibodies Hu, Yo, Ri amphiphysin and glutamate receptors, were normal. Neuropsychological examination was normal. Genetic analysis of GLRA1 did not reveal any mutation except for a silent G1322C nucleotidic change (GenBank XM_032738) in patient No 1.

Several spontaneous and evoked jerks were polygraphically recorded (fig 1). The onset latency of the evoked jerks varied from 25 ms to 60 ms, but with a similar order of muscle recruitment on jerk locked back averaging: electromyographic (EMG) activity started in the sternocleidomastoideus and then spread to the orbicularis oculi, the masseter, the deltoideus and the axial and lower limb muscles, a blink-like orbicularis oculi EMG activity preceding the evoked ones (fig 1).

Both patients also presented with spontaneous and evoked nocturnal jerks on falling asleep that vanished with the appearance of spindles and K complexes, at which time they were replaced by typical periodic limb movements during sleep in patient No 2. Periodic limb movements while awake were recorded in both patients.

METHODS

MRI and proton magnetic resonance spectroscopy

MRI was performed on a 1.5 T system. In both patients the routine protocol was supplemented by magnetic resonance angiography and single voxel ¹H-MRS, with a point resolved proton spectroscopy sequence (PRESS, TR = 2000 ms, TE = 272 ms). In both patients an 8 ml voxel was placed in the frontal mesial cortex and subcortical white matter. A 8 ml voxel was also acquired in the basis pontis in case No 2 and a 4.5 ml voxel in the medulla in case No 1. A local database of 13 healthy volunteers was used as a reference for the frontal spectra whereas reference normal values for the pontine and medullary spectra were previously reported.⁴ Finally, axial three dimensional T1 weighted turbo gradient echo images were obtained for co-registration with the SPECT images.

Single photon emission tomography

SPECT was obtained by intravenous injection of 740 MBq ethyl-cisteinate-dimer labelled with technetium-99m (^{99m}TcECD).

Abbreviations: DI, difference image; EMG, electromyography; ¹H-MRS, proton magnetic resonance spectroscopy; PnC, nucleus reticularis pontis caudalis; rCBF, regional cerebral blood flow; SPECT, single photon emission tomography

Figure 1 (A) Polygraphic recording of spontaneous and evoked jerks by means of sudden loud noise (beep), tactile (glabella tapping) and visual (flash) stimuli in patient No 1. (B) Electromyographic (EMG) average of five spontaneous (patient No 1) and audiogenic (patient No 2) jerks. The same pattern of muscular recruitment is present except for an initial EMG burst on the orbicularis oculi in the audiogenic jerks in patient No 2. EMG activity was seen first in the sternocleidomastoideus (broken line in A and B) quickly followed by the orbicularis oculi and the masseter rostrally and the deltoid and the tibialis anterior caudally (arrows). Delt, deltoid; Interc, intercostalis; L, left; Mylo, mylohyoid; Orb Oc, orbicularis oculi; R, right; Rectus Abd, rectus abdominis; Rectus Fem, rectus femoris; SCM, sternocleidomastoideus; T-A Resp, thoraco-abdominal respirogram; T-L Parasp, thoracolumbar paraspinalis; Tib Ant, tibialis anterior.

within 10 s after the last of a series of acoustic repetitively evoked jerks (46 in patient No 1 and 48 in patient No 2) over 1 h. During the 5 min immediately after the injection, 10 other jerks were evoked. Image acquisition started 30 min later, using a double detector Vertex system (ADAC Laboratories, Milpitas, California, USA). High resolution collimators were used with 64 views acquired (pixel size 2.96 mm² and 60 s per view). Images were reconstructed with a slice thickness of 3.75 mm by iterative algorithm with Butterworth prefiltering (cut-off = 0.45; order number = 10).

Control SPECT was obtained 1 week later using the same dose of the tracer, SPECT system and with the patients lying quiet and awake with closed eyes, and in the absence of startles.

To explore areas of possible increased perfusion during hyperreflexia, image registration and subtractions of startle and rest SPECT were performed using a previously described method.^{5,6}

The scan centre points were placed on the anterior commissure and the two scans were realigned and resliced by means of Statistical Parametric Mapping 2 realignment function.

Startle and rest scans were first normalised to adjust for differences in administered dose. Rest scans were then subtracted from the scans obtained during startle to obtain a difference image (DI) whose values corresponded to the per cent changes in perfusion showing possible areas of changes in regional cerebral blood flow (rCBF) associated with startle.

To co-register DI to magnetic resonance images with Statistical Parametric Mapping 2, using a normalised mutual information algorithm,⁷ startle scans were used to determine the co-registration parameters which were applied to DI. Only the areas of increased rCBF exceeding a 25% threshold in signal intensity and a 0.5 ml threshold in voxel cluster extent were superimposed on T1 high resolution magnetic resonance images. Localisation of suprathreshold areas was facilitated by means of automatic anatomical labelling.⁸

RESULTS

MRI and ¹H-MRS

MRI in patient No 1 showed diffuse widening of the inter-hemispheric and convexity CSF spaces consistent with chronic subdural hygroma without any brain signal abnormality. In addition, the left vertebral artery impinged on the ventral medulla causing a mild leftwards torsion of the medulla (fig 2). Spinal MRI was normal.

In patient No 2, MRI showed a few small focal hyperintensities in the left centrum semiovale and a small focal hyperintensity in the left paramedian posterior basis pontis. The basilar artery mildly impinged on the left portion of the anterior surface of the basis pontis and the medulla was slightly rotated towards the left. Spinal MRI was normal.

On ¹H-MRS, no metabolite ratio exceeding 2 SD below or above the mean in the control subjects was observed in the frontal lobe or brainstem in the two patients.

SPECT

Visual evaluation of the SPECT scans did not reveal any area of hyperperfusion during startle or of hypoperfusion at rest.

DIs (fig 2) in both patients showed focal areas of increased perfusion in the dorsal portion of the pons and in the cingulate gyrus and superior frontal gyrus bilaterally and in the left parietal inferior gyrus. Patient No 2 showed additional areas of increased perfusion in the anterior cingulate gyrus bilaterally, in the left putamen and left thalamus and in the inferior temporal gyrus bilaterally.

DISCUSSION

Two women had exaggerated non-habituating startle responses to unexpected, particularly sound, stimuli, compatible with hyperreflexia. Several lines of evidence support a brainstem origin of this movement disorder in our patients. In both patients the vertebrobasilar arteries impinged on the left portion of the medulla or pons and there was torsion of the medulla, as previously reported in other symptomatic cases of

Figure 2 Axial source image for magnetic resonance angiography (top) demonstrates impingement of the left vertebral artery on the ventral medulla (arrow). Startle/rest single photon emission tomography (SPECT) image subtraction superimposed on T1 weighted image (bottom) shows foci of increased regional cerebral blood flow (rCBF) in the posterior portion of the medulla and pons (A–C), superior frontal gyrus (D, F) and cingulate cortex (D,E) bilaterally, and left parietal inferior gyrus (D). The area of apparently increased blood flow in the left orbit is due to a greater amount of free (unbound) Tc99m pooling in the vascular spaces in the startle SPECT compared with the rest of the SPECT.

hyperekplexia.^{9–10} The EMG responses to taps of the glabella and the pattern of muscular recruitment, while typical of hyperekplexia, are features compatible with a relay within the brainstem.^{11–12} Finally, SPECT during evoked startles demonstrated increased rCBF in the dorsal portion of the pons, indicating abnormal brainstem function (with exaggerated arousal), consistent with the location of the pontine reticular nucleus and converging with animal and human data demonstrating its activation during startle.^{2–3}

While increased rCBF in the temporal regions in patient No 2 could reflect the auditory afferences during the startling procedure, the increased rCBF in other cortical regions seems to indicate implication of the frontal brain areas in the pathophysiology of the startle responses in our patients. In particular, activation of the cingulate and superior frontal gyrus during startle is in line with the observation that the motor output of hyperekplexia, originating at a brainstem level, is modulated by coactivation of these cortical areas.^{13–14}

Neuroanatomical studies of the circuitry and cortical modulation of the startle reflex¹⁵ demonstrate that exaggeration of the reflex arises when the “top-down” inhibitory functions of the frontal cortex on either the startle circuit (ie, PnC) or on the amygdala, or both, are taken offline.^{16–17}

Indeed, frontal lobe dysfunction was found on neuropsychological evaluation, EEG and SPECT at rest in sporadic hyperekplexia by Gaitatzis *et al.*¹⁸ Apart from the SPECT findings, in our patients the only clue to frontal lobe damage was the MRI findings in one case of chronic subdural hygroma. The latter is however often an incidental non-specific finding.

In conclusion, we suggest that in our sporadic cases of hyperekplexia, presumably associated with vascular compression of the ventral lower brainstem, startles were generated at a pontine level, as shown by the SPECT hyperperfusion during startle. The startle-related increased cortical activity in our patients could reflect a neuromodulatory cortical, especially frontal, effect with disinhibition of the brainstem startle circuit.

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