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Hypertrophy of the inferior olivary nucleus impacts perception of gravity

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INTRODUCTION

Hypertrophy of the inferior olivary nucleus (ION) is an interesting phenomenon as it reflects a secondary response to an interruption ofafferent connections resulting in increased and abnormally synchronized neuronal activity (Best and Regehr, 2009; Shaikh et al., 2010). Herein we report on a patient with hypertrophy of the ION secondary to ponto-mesencephalic hemorrhage, perceived vertical shifted from clockwise to counter-clockwise deviations within 4 months. We hypothesize that synchronized oscillations of ION neurons induce a loss of inhibitory control, leading to hyperactivity of the contralateral DN and, as a result, to perceived vertical roll–tilt to the side of the over-active DN.

Keywords: vestibular, Guillain–Mollaret triangle, subjective visual vertical, brainstem

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Correction

Lesions along the central tegmental tract may result in ocularpatal tremor (Matsuo and Ajax, 1979; Deuschl et al., 1990) and hypertrophy of the ipsilateral ION (Ruigrok et al., 1990) with its enlarged neurons developing abnormal soma-somatic gap.
junctons (Koeppen et al., 1980; De Zeeuw et al., 1998; Goyal et al., 2000). ION hypertrophy is not just a histopathological finding but can also be visualized in vivo by MR-imaging (Kitajima et al., 1994; Goyal et al., 2000). Previous work suggests that the ION is involved in coordination and timing of movements and motor learning (De Zeeuw et al., 1998). Here we evaluate whether secondary hypertrophy of the ION leads to contralateral SVV tilt indicating hyperactivity of the contralateral DN in line with the current understanding of the Guillain–Mollaret triangle.

MATERIALS AND METHODS

Informed written consent was obtained after a full explanation of the experimental procedure to the participant. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects. SVV measurements were obtained on a motor-driven turntable (Acutronic, Jona, Switzerland) at day 16, month 4, and month 38 after symptom onset. To evaluate the SVV, the patient was asked to align a luminous arrow (time limit per trial: 15 s; 24 trials per position) along perceived vertical in different whole-body-roll orientations (upright, ±45°, ±90° ear-down) in a random order. The arrow projection started 10 s after the turntable came to a full stop. The arrow starting position deviated randomly between 28 and 72° clockwise (CW) or counter-clockwise (CCW) relative to true earth-vertical. For comparison, SVV adjustments (taken at angles between upright and ±90° every 15°) from a group of healthy normal subjects (n = 7) using a similar paradigm were used (Tarnutzer et al., 2009).

RESULTS

A 65-year-old male patient complaining of acute-onset gait unsteadiness presented with horizontal gaze palsy, impaired upgaze, left trigeminal hypesthesia, and left-sided sensorimotor impairment. Clinically, no signs of a (partial) OTR could be seen. An emergency head CT-scan revealed bilateral ponto-mesencephalic bleeding. Brain MRI obtained 14 days after symptom onset showed a predominantly right-sided ponto-mesencephalic dorsal hemorrhage, including the medial vestibular nuclei bilaterally, the right superior and lateral vestibular nucleus, the right (and probably also the left) MLF, and the central tegmental tract bilaterally (Figures 2A,B). No cerebellar or thalamic structures were damaged.

Subjective vertical visual estimations when upright obtained 16 days after symptom onset deviated ipsilaterally (relative to the right ION) by 0.7 ± 0.3° (mean ± 1 SD) for clockwise (CW) arrow rotations and by 4.3 ± 3.9° for counter-clockwise (CCW) arrow rotations, whereas in all roll-tilted positions roll under-compensation (SVV deviations toward the direction of body-roll) – being increased compared to deviations in healthy controls – was noted (Figure 3). A diagnostic work-up revealed no cause for the hemorrhage and the patient was discharged home.

At follow-up (month 4) the patient complained of progressive difficulty walking and fixing with the eyes. Neurologic examination revealed increased gait ataxia and new vertical–torsional pendular nystagmus. MRI showed increased signal and hypertrophy of the right ION (Figures 2C–E). SVV measurements revealed large contralateral (relative to the right ION) deviations when upright being clearly distinct for CW (−20.3 ± 10.5°) and CCW (−10.2 ± 4.5°) arrow rotations. For left-ear-down positions, adjustment errors remained in the same range as in the acute stage, while errors were shifted to roll over-compensation (SVV deviations away from the direction of body-roll) for right-ear-down roll.

The patient returned for regular follow-up visits and 38 months after symptom onset the SVV was re-measured. On clinical examination vertical–torsional pendular nystagmus and gait ataxia were unchanged. SVV in upright position revealed large a large trial-to-trial variability of adjustment errors for both CW (−3.8 ± 24.6°) and CCW (14.1 ± 14.0°) arrow rotations. Again SVV errors depended on the direction of arrow rotation (Figure 3), but now arrow roll adjustments showed under-compensation for both directions. While roll under-compensation for left-ear-down positions were unchanged compared to previous recordings, adjustment errors for right-ear-down positions shifted back from roll over-compensation to roll under-compensation.

DISCUSSION

In this case report we describe for the first time a significant shift in the internal estimate of direction of gravity associated with hypertrophy of the ION. A roll–tilt bias in estimated direction of gravity is generally explained by an asymmetric lesion along the ascending
bilateral CVP (Brandt, 2000). In the acute stage, the SVV in this patient deviated rightward, i.e., toward the side of the predominant hemorrhage. Thus we assume that the loss of the right vestibular nuclei (known to result in ipsilesional SVV deviations; Dieterich and Brandt, 1993; Brandt, 2000) is the main contributor to the SVV adjustment errors measured at day 16. However, interruption of the left MLF may also contribute to the SVV tilt because MLF-lesions lead to contralateral SVV deviations (Dieterich and Brandt, 1993; Brandt, 2000). The shift in SVV from an ipsilateral (i.e., rightward) to a contralateral (i.e., leftward) SVV deviation observed at month 4 is most likely associated with hypertrophy of the right ION at that stage since the DN is under control of the contralateral ION (Pearce, 2008).

In the case presented here the predominantly right-sided ponto-mesencephalic hemorrhage interrupted the right central tegmental tract, which most likely explains the hypertrophy of the right-sided ION at follow-up. In the following we provide a hypothetical explanation for the switch from acute ipsilateral (with regards to the side of ION hypertrophy at follow-up) to chronic contralateral SVV deviations as a result of the hypertrophy of the ION. We conjecture that the switch in SVV tilt is a consequence of removing GABA-mediated inhibitory modulation of the ION neurons provided through the central tegmental tract (Best and Regehr, 2009). As a consequence synchronized oscillations of large groups of neurons in the ION are then sent to the cerebellar cortex and the deep cerebellar nuclei through climbing fibers (Shaikh et al., 2010) and result in a loss of the inhibitory control provided through this pathway (Leigh and Zee, 2006). This mechanism may lead to an over-excitation of the DN contralateral to the hypertrophic ION and consequently to a tilt toward the side of the over-active DN. Over-excitation of the DN leading to a shift in SVV toward the side of the stimulated DN is analogous to the reported contralesional SVV shifts in case of an inhibition (e.g., by stroke or bleeding) of the DN (Baier et al., 2008).

The relative improvement of SVV errors at month 38 despite the fact that the clinical findings (gait ataxia, vertical–torsional pendular nystagmus) persisted and MR-imaging continued to show an increased signal on T2-weighted sequences and hypertrophy of the right ION may indicate distinct mechanisms of adaptation of the involved networks. While the pendular nystagmus is governed by brainstem circuits, estimating direction of gravity is a cognitive task based on multisensory cortical integration, possibly situated...
within the temporo-peri-Sylvian vestibular cortex (Kahane et al., 2003). Based on the improvement of SVV accuracy and the ongoing nystagmus we hypothesize that long-term adaptation has led to a re-weighting of the different sensory input signals used for generating the internal estimate of direction of gravity. Thereby the otolith signal might be weighted less and consecutively the internal estimate of direction of gravity is less biased. However, SVV measurements at month 38 have to be interpreted with caution, as they varied considerably more from trial-to-trial compared to day 16 and month 4.

In summary, this case report further supports the crucial role of the DN in processing vestibular information and how it is modulated by the ION. It suggests that over-excitation of the DN by disinhibition of the ION can result in functional impairment of estimating the direction of gravity. In short, inhibition of the DN (e.g., by an ischemic cerebellar lesion including the DN) leads to SVV tilt away from the affected DN (Baier et al., 2008) and over-excitation of the DN – as reported here – leads to SVV tilt toward the affected DN.

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