J Neurol (2012) 259:372–374
DOI 10.1007/s00415-011-6170-2

LETTER TO THE EDITORS

Vertical pendular nystagmus and hypertrophic inferior olivary nuclei degeneration: an "odd couple"

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Received: 12 June 2011 / Revised: 1 July 2011 / Accepted: 2 July 2011 / Published online: 16 July 2011

Dear Sirs,

A 56-year-old man had a hypertensive pontine hemorrhage (Fig. 1a), which resulted in bilateral internuclear ophthalmoplegia, pseudobulbar palsy, and spastic ataxic tetraparesis. Three months after a stroke, while neurological deficits were recovering, the patient manifested progressively blurred vision and oscillopsia, corresponding to a vertical conjugate pendular nystagmus (PN) (video). Electronystagmography showed a 3-Hz frequency and 2–3° amplitude sinusoidal curve, with up- and down-phases symmetric for direction and velocity, without null zones and torsional or gaze-evoked components. PN was not modified by eye covering, saccades, head thrust, 20 diopter prisms, optokinetic maneuvers, and sleep.

Brain MRI (Fig. 1b, c) showed an hemosiderin-and ferritin-lined cleft confined to the dorsal pontine tegmentum and the central tegmental tract. MR-T2-WI images showed a symmetric enlargement of the inferior olivary nuclei with high signal intensity (Fig. 1c, d), which is the typical appearance of the hypertrophic inferior olivary nuclei degeneration (HIOND).

PN did not improve with baclofene (up to 60 mg/day), pregabalin (up to 600 mg/day), memantine (up to 40 mg/day), clonazepam (up to 3 mg/day), lamotrigine (50 mg/day) worsened the condition. PN remained unchanged at 1 year of follow-up.

The radiological hallmarks of the HIOND are the symmetric olivary enlargement with high T2 signal intensity (Fig. 1d), and the presence of distant lesions in specific locations: contralateral cerebellar dentate nucleus, contralateral superior cerebellar peduncle, ipsilateral dorsomedial red nucleus, and ipsilateral pontine tegmentum [1].

The HIOND, as demonstrated in pathological studies since the beginning of the 20th century [2], is a unique form of neuronal degeneration associated with enlargement, rather than atrophy. Olivary nuclei "hypertrophy" is due to the combination of astrocytosis, gemistocytes, and neuronal vacuolar cytoplasmic enlargement [2], due to abnormal soma-somatic gap junctions, hypertrophic thick neuritis, and demyelination [3]. As the association with specific remote lesions is constant, the HIOND is considered the effect (through transneuronal or transsynaptic degeneration) of the damage of the dentatorubral tract (connecting the dentate nucleus with the controlateral red nucleus) and the central tegmental tract (connecting the red nucleus to the ipsilateral inferior olive). The ensemble of these nuclei and tracts is known as the dentatorubral–olivary pathway or "Guillain-Mollaret triangle" (GMT). A recent study with diffusion tensor imaging (DTI) demonstrated signal changes in all anatomical components of the GMT in patients with HIOND at different stages [3], even when standard MRI is negative. In particular, PN has been related to the damage of the paramedian cerebellar tract projections to the pontine tegmentum and to the consequent denervation of the dorsal cap of the inferior olive. Tegmental pontine lesions, in the case of bilateral PN and

Electronic supplementary material The online version of this article (doi:10.1007/s00415-011-6170-2) contains supplementary material, which is available to authorized users.

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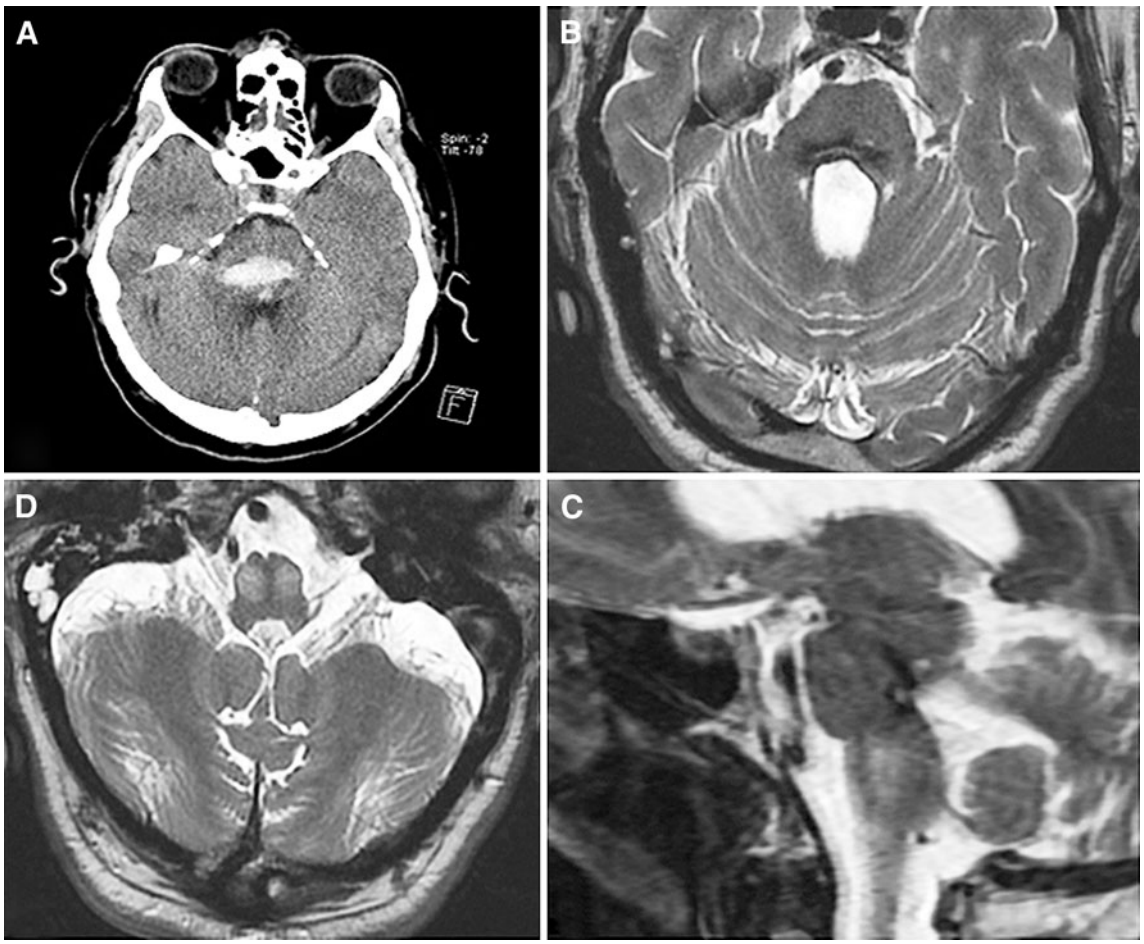

Fig. 1 **a** Brain-CT: the pontine hemorrhage at the onset. **b** T2-MRI: hemosiderin deposits in the pontine tegmentum 3 months after the onset. **c** T2-MRI: residual hemorrhage in the pons and olivary hyperintensities in the bulb. **d** T2MRI: inferior olivary hyperintensities (HIOND)

HIOND, are usually symmetric and consequent to a hypertensive hemorrhage [4].

Besides PN, HIOND could associate to palatal myoclonus, ocular myoclonus, or dentate-rubral tremor.

The 1 to 6-month delay by which PN and the other tremors follow the onset of the pontine hemorrhage suggests a deafferentation mechanism. The physiopathological hypothesis for the HIOND-related syndromes might be the loss of an inhibitory tonic control, which the dentatorubral pathways exert on the oculomotor or other brainstem nuclei. The generator might be located next to the oculomotor nucleus or in the cerebellar nuclei, and transmits directly to the mesencephalic centers of the vertical gaze. A specific role of the inferior olivary nuclei in generating PN has also been advanced [5].

Drugs affecting GABAergic transmission are known to reduce PN amplitude in patients with multiple sclerosis [6]. The increment of PN in our patient with lamotrigine remains an unexplained phenomenon.

Prognosis for cessation of PN after pontine hemorrhage seems poor with drugs. Motor-driven prisms oscillating images in lockstep with PN are experimental devices that might reduce oscillopsia.

In a few patients, PN and palatal tremor were reported to diminish or cease spontaneously after several years [7], a finding which seems to parallel HIOND progression to complete olivary atrophy within 3–8 years [8]. New experimental studies focusing on HIOND physiobiology (in patients with DTI-MRI or autopsy studies, and in animal models) should be designed to achieve further knowledge of brainstem rhythmic generators and their neurotransmitters.

Conflict of interest The authors declare that they have no conflicts of interests and that they have no grants to disclose for this study. The manuscript has not been published elsewhere and has not been submitted simultaneously for publication to another source. There is no ghost writing by anyone not named on the author list.

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