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HYPERTROPHIC OLIVARY DEGENERATION AFTER BRAINSTEM HAEMORRHAGE – A CASE REPORT

Razvan Alexandru Radu[1,3], Luiza Maria Ionita[1], Elena Oana Terecoasa[1,3], Andreea Nicoleta Marinescu[2,3], Cristina Tiu[1,3]

[1]Department of Neurology, University Emergency Hospital Bucharest, Romania
[2]Department of Radiology and Medical Imaging, University Emergency Hospital Bucharest, Romania
[3]"Carol Davila" University of Medicine and Pharmacy Bucharest, Romania

ABSTRACT

Insidious neurological deterioration may develop months to years after a lesion involving the Guillain-Mollaret triangle due to hypertrophic olivary degeneration. Lesions involving the dento-rubro-olivary pathways may lead to pseudo-hypertrophy of the inferior olivary nucleus with subsequent neuronal degeneration. A number of clinical syndromes have been linked to hypertrophic olivary degeneration. Cases of gait ataxia, Holmes tremor and symptomatic palatal and oculo-palatal tremor were associated with this condition. We hereby report a case of disabling Holmes tremor and gait ataxia associated with palatal tremor in a 45-year-old patient with a prior brainstem haemorrhage.

Keywords: hypertrophic olivary degeneration; brainstem haemorrhage; Holmes tremor; palatal tremor; case-report

INTRODUCTION

Hypertrophic olivary degeneration (HOD) is a rare and peculiar condition defined as a de-afferentation of the inferior olivary nucleus (ION) of the medulla (1). Pseudo-hypertrophy of the ION was first described by Oppenheim in 1889. Later on, during the first decades of the twentieth century, it was associated to palatal myoclonus and to lesions of the dento-rubro-olivary pathway by Guillain, Mollaret, Foix and others (2).

Cases of ataxia, Holmes tremor, palatal and oculo-palatal myoclonus have been linked to HOD after brainstem lesions and a number of different clinical syndromes have been described in the literature (3). Symptomatic palatal and oculo-palatal tremor was attributed to HOD and differentiated from the essential sporadic variant by Deutschl et al.(4). Furthermore, Sperling and Hermann have described a rarely encountered syndrome of progressive ataxia and palatal tremor associated with HOD in the absence of any structural causative lesions in the Guillain-Mollaret triangle (5).

Cerebrovascular diseases involving the brainstem are recognized as the main causes of HOD and brainstem cavernomas and vascular malformations have been frequently associated with this condition (6). However, cases due to demyelinating diseases, intracranial neoplasms, surgery, radiotherapy, encephalitis, PML and even to metronidazole intoxication were reported (3,6).

Classically MRI characteristics suggestive of HOD are: increased T2 signal intensity confined to the ION (with or without enlargement), lack of contrast enhancement or diffusion restriction and presence of a causally related lesion involving the Guillain-Mollaret triangle. There seems to be a temporal evolution of MR lesions corresponding to the pathologic findings. Thus, increased T2- and proton density weighted signal of the olivary nucleus can be detected at least one month after the occurrence of the initial pathologic lesions. Hypertro-

Author for correspondence:
Elena Oana Terecoasa, Splaiul Independentei 169, Sector 5, Bucharest, Romania
E-mail: oana_ter@yahoo.com

phy of the ION usually appears 6 months after the initial insult and resolves approximately three to four years later. Finally, hyperintensity without hypertrophy of the ION persists indefinitely (7).

These features are chronologically superimposed to histopathological changes described as separate stages: 1 – mild olivary enlargement with neuronal hypertrophy and 2 – hypertrophy of both neurons and astrocytes (8). The peculiarity of this trans-neuronal degeneration is characterized by the vacuolization of neurons and subsequent glial reaction leading to an early stage hypertrophy instead of the atrophy.

Hypertrophy of the ION is thought to be the effect of reduced cerebellar inhibitory output from the dentate nucleus. Due to the particular expression of soma-somatic gap junctions between ION neurons, removal of cerebellar inhibition is thought to produce hypertrophy, increased electrotonic coupling and synchronized oscillations. These oscillations might be the trigger of the oculo-palatal myoclonus. However, a recent study showed that an abnormal cerebellar function is needed in order to maintain these phenomena. Thus, a dual mechanism mediated by cerebellar and ION dysfunction was proposed for the genesis and maintenance of oculo-palatal myoclonus and of other signs and symptoms associated with HOD (9).

To date there is no universally effective pharmacological therapy for the treatment of HOD associated symptoms (2,9). We report a case HOD after brainstem haemorrhage associated with severe functional decline and disability. This case report was prepared according to the CARE Guidelines (12).

CASE REPORT

A 45-year-old Caucasian man was admitted in our department for postural and action tremor of the right limbs, gait disorder and loss of balance with insidious onset (Fig. 1).

His past medical history was consistent with a left sided ponto-mesencephalic haemorrhage 18 months before and arterial hypertension (Fig. 2). At the time he suffered the haemorrhage he was a smoker and a chronic alcohol consumer. He quit smoking and stopped drinking alcohol after stroke. Repeated cerebral MRI three months after the index event showed a posterolateral left-sided pontine lesion suggestive of a cavernoma (Fig. 3).

The patient initially made a good recovery. Neurologic examination performed three months after the brainstem haemorrhage showed mild left-sided peripheral facial palsy, mild right-sided hemiparesis, mild ataxia of all limbs and slurred speech. The disability was mild and the patient was considered to have a modified Rankin score of two points. His clinical condition remained stable for the following ten months. Afterwards, he complained of progressive deterioration of his walking ability due to tremor and loss of balance. At the time he presented to our department (18 months after the onset of the brainstem haemorrhage and 5 months after his condition began to worsen) he could barely walk due to severe gait ataxia and disabling postural and action tremor mainly affecting his right limbs.

Neurological examination at admission showed: severe truncal ataxia, gait ataxia, ataxia of all limbs, rotatory nystagmus on vertical gaze, severe cerebellar dysarthria, palatal myoclonus, Holmes tremor affecting the right limbs, subtle left-sided pe-

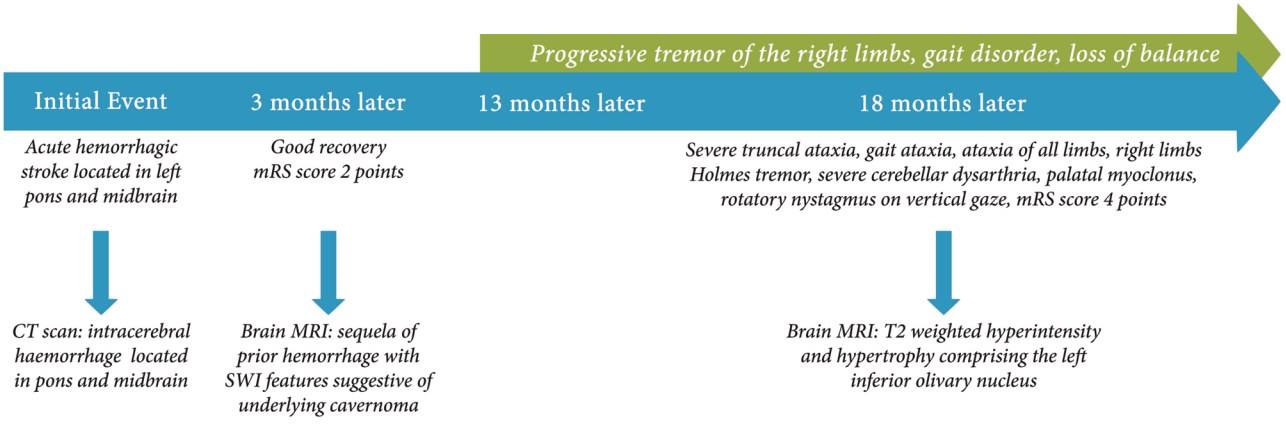

FIGURE 1. *Patient Timeline*

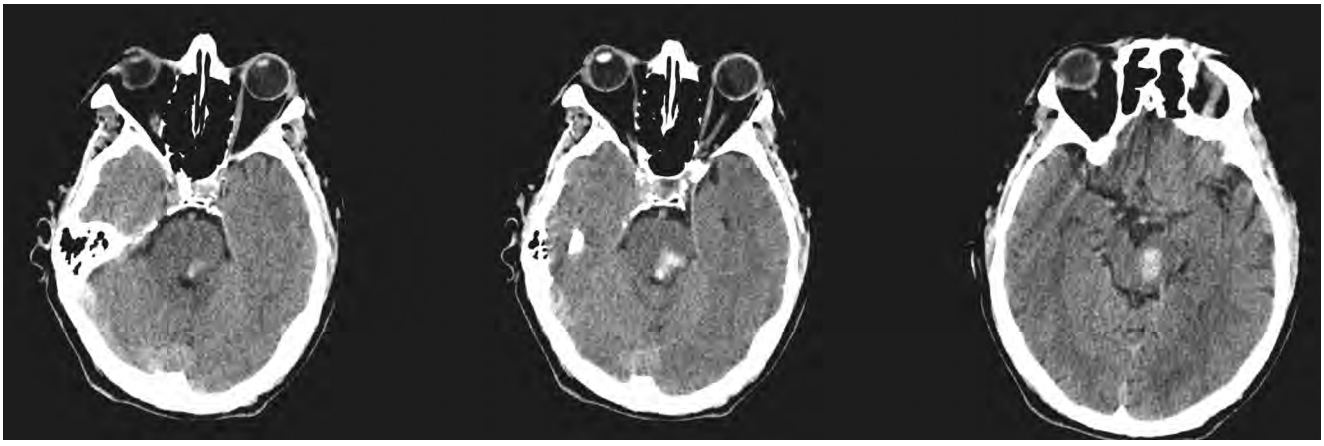

FIGURE 2. *Brain CT at the time of the haemorrhagic stroke – left-sided ponto-mesencephalic hyperdensity consistent with acute brainstem haemorrhage*

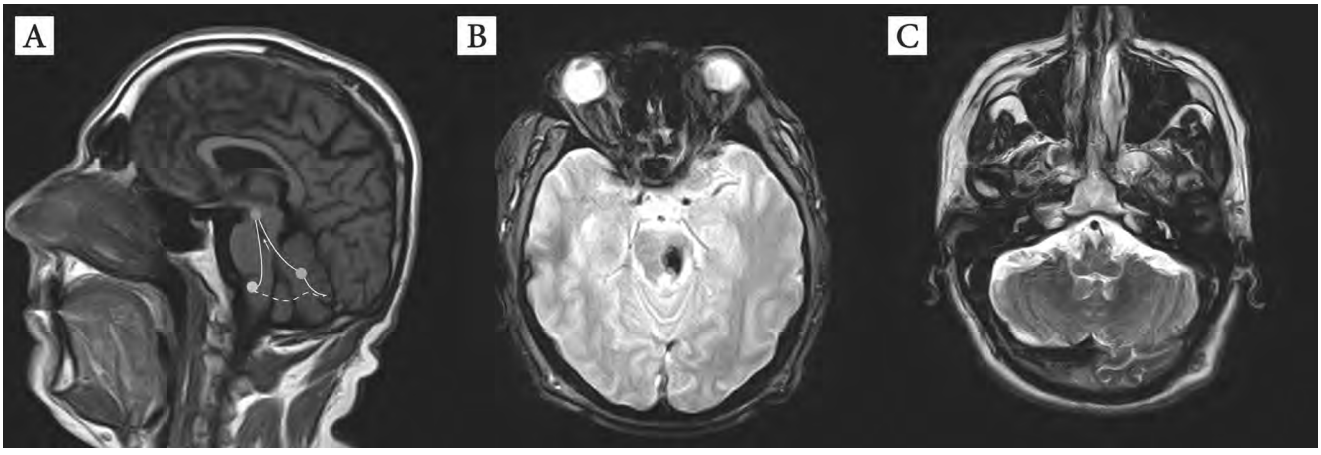

FIGURE 3. *Brain MRI performed 3-months after the initial brainstem haemorrhage.*

A) Sagital T1-weighted sequence illustrating the Guillain-Mollaret triangle, green bullet-dentate nucleus, blue bullet – red nucleus, orange bullet – inferior olivary area. Tracts connecting these structures are depicted with a full-white line. The spaced line illustrates olivocerebellar fibers travelling through the inferior cerebellar peduncle to the cerebellar cortex. Besides the sequela of the old ponto-mesencephalic hemorrhage depicted by the arrow, there are no other abnormal changes.

B) Axial Susceptibility Weighted Imaging showing blooming artefact consistent with old haemorrhage and a possible underlying cavernoma.

C) Axial T2-weighted sequence showing normal aspect of the inferior olivary area.

ripheral facial palsy and right-sided hypoesthesia. The severe action tremor and truncal ataxia were considered by the patients the most troubling manifestations. He did not complain of oscillopsia or palatal myoclonus and did not report distinctive ear clicks. He was in usual good shape despite being severely limited in his walking ability and could still perform isometric exercises and an impressive number of push-ups.

A brain MRI scan performed in an outpatient clinic two months before admission revealed increased T2/FLAIR signal intensity and enlargement of the left inferior olivary area, with decreased T1 signal intensity, no diffusion abnormality and no contrast enhancement. These findings were not present on prior brain MRI and CT scans performed with the occasion of the brainstem haemorrhage. The MRI scan performed during the hospitalization showed a similar aspect of the olivary lesion thereby excluding a possible malignancy or an inflammatory aetiology of the lesion. Lack of contrast enhancement and hypertrophy of the ION supported the diagnosis of hypertrophic olivary degeneration (Fig. 4 and 5). Laboratory work-up during hospitalization was unremarkable and blood pressure monitoring showed values within normal range.

Based on the imaging and clinical data we made a diagnosis of secondary hypertrophic olivary degeneration and initiated levodopa therapy. However, he did not respond to monotherapy with levodo-

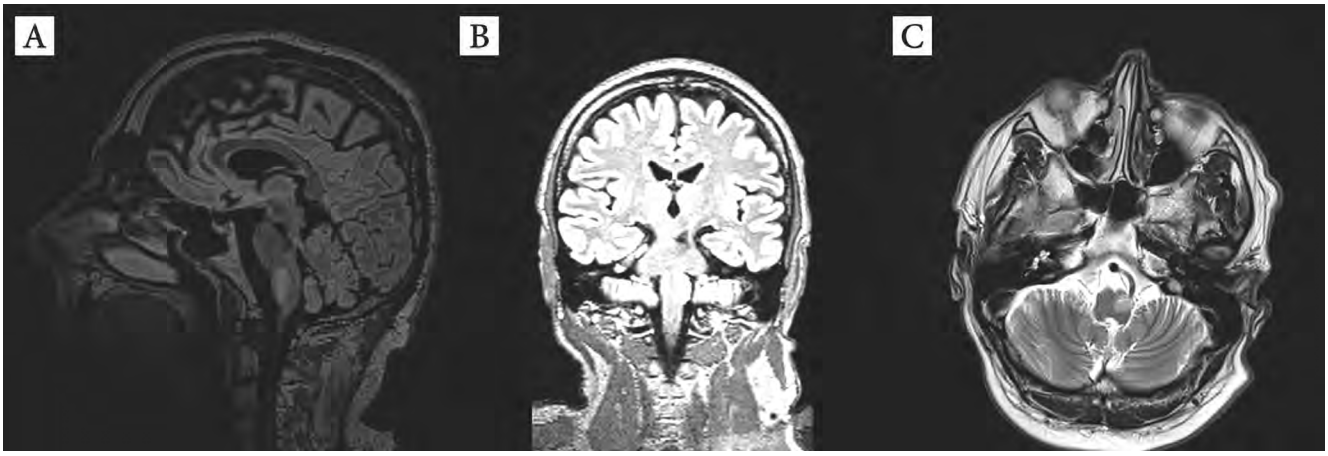

FIGURE 4. *Brain MRI performed 16-months after the brainstem haemorrhage showing hyperintensity and enlargement of the inferior olivary nucleus, ponto-mesencephalic hypointensity consistent with the old haemorrhage.*
A) Sagital FLAIR-weighted sequence B) Coronal FLAIR reconstruction C) Axial T2-weighted sequence.

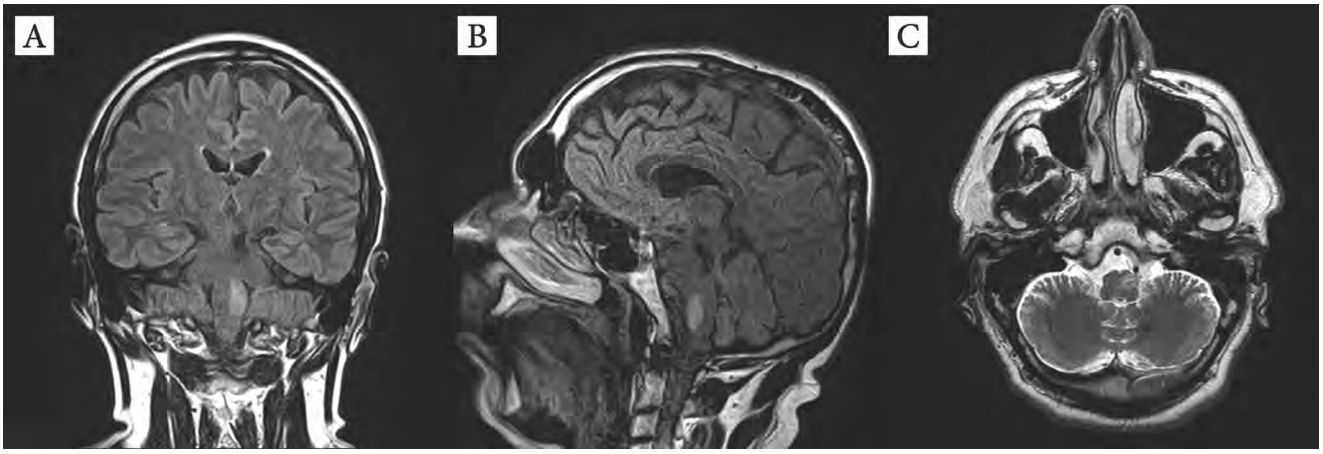

FIGURE 5. *Brain MRI performed 18-months after the brainstem haemorrhage showing similar aspect with the MRI performed two months before.*
A) Coronal FLAIR-weighted sequence B) Sagital FLAIR-weighted sequence C) Axial T2 weighted sequence.

pa (which was titrated up to 500 mg/day) so during the next months we subsequently tried lamotrigine (titrated up to 75 mg/day) and clonazepam (titrated up to 2 mg/day) but the patient reported no improvement in his symptoms. Furthermore, clinical examination did not show any improvement of his tremor, ataxia or gait disorder so we decided to stop medical therapy with the above mentioned drugs due to lack of efficacy. The patient currently has a modified Rankin score of 4 and did not further deteriorate. He is not bothered by the palatal myoclonus and does not report oscillopsia but has a significant impairment of activities of daily living due to gait and limb and action tremor.

DISCUSSION

The clinical picture of this patient together with the temporal profile of the signs and symptoms is suggestive for secondary degeneration of the ION. The typical palatal tremor and vertical nystagmus were largely asymptomatic but he was mainly burdened by the gait ataxia and by the development of postural and action tremor suggestive of Holmes tremor. The clinical course with initial improvement after the brainstem haemorrhage followed by insidious secondary deterioration is similar to other reported cases of HOD (13-15).

HOD is usually produced by a lesion involving the Guillain-Mollaret triangle (1). This functional-anatomic entity is composed mainly by projections of the dentate nucleus that travel to the contralateral red nucleus through the brachium conjunctivum (2). Projections from the red nucleus descend in the central tegmental tract to the ipsilateral olivary nucleus which in turn sends projections to the contralateral cerebellum through the inferior

cerebellar peduncle. Lesions anywhere in this triangle (with the exception of the olivary nucleus and the inferior cerebellar peduncle) will determine secondary hypertrophy of the ION (1,2). Lesions involving only the rubro-olivary bundle, as in our patient, usually lead to ipsilateral HOD, while lesions involving the dento-rubral pathway are responsible for contralateral HOD. Rarely, caudal midbrain lesions affecting the dento-rubral fibers (in the Wernekink `s decussation) may also involve the central tegmental tract and may determine bilateral HOD.

Many of the reported cases developed signs and symptoms suggestive of HOD more than one year after the initial lesion and so did our patient (13–16). Neuropathological and imaging abnormalities are reported early after the initial lesion. However, some patients do not develop symptoms following hypertrophy of the inferior olivary nucleus but the factors that lead to the clinical expression of this condition are not yet clearly defined (7,8). Interestingly, a large retrospective study which selected patients from an imaging database reported symptomatic HOD in 32.6% of the patients presenting imaging features suggestive of HOD. In this database, the proportion of patients who developed clinical signs and symptoms attributed to HOD was higher in the group of patients with imaging evidence of bilateral hypertrophy of the ION than in the group of patients with unilateral imaging signs of ION hypertrophy. The most frequent reported symptom was ataxia followed by palatal tremor, dysarthria and limb tremor (6). The lack of any symptom in some patients with HOD might be explained by the phenomena of neuroplasticity and remodelling. However, symptoms are reported up to five years after the occurrence of the initial lesion of the Guillain-Mollaret triangle, so that, some patients with isolated radiological HOD might develop symptoms years after the radiological signs of HOD became evident. The lack of prospective databases hampers our knowledge about the relevance of imaging findings and the temporal evolution of HOD. A prospective observational study of patients with lesions in the Guillain-Mollaret triangle is therefore needed to enhance our understanding about this disabling condition.

The Movement Disorder Society defines Holmes tremor as a syndrome of rest, postural and intention tremor that is aggravated by movement and emerges from proximal and distal muscle contractions (17). It is usually described after focal brainstem lesions and was previously reported in patients with HOD (10,18,19). The response to pharmacotherapy was usually variable and frequently disappointing in previously reported cases, as was the case of our patient. However, some patients might improve after stereotactic thalamotomy or deep brain stimulation.

The largest published series of patients with Holmes tremor comprised 29 patients. The most frequent etiology was cerebrovascular disease (48.3%) and the moment of tremor onset varied from months to years after the causative lesion, which most frequently involved the midbrain (58.6% of cases). Patients usually developed hemiparesis and ataxia and response to pharmacotherapy was generally disappointing. However, trials of Levodopa, Levetiracetam, Lamotrigine, Clonazepam and Gabapentin are warranted for each patient due to albeit rare but possible improvement (11). In patients without any improvement after medical therapy, evaluation for thalamotomy or deep brain stimulation in experienced centres is recommended. Although, large series of patients treated with these approaches are still lacking.

CONCLUSION

Patients with brainstem ischemia and haemorrhage involving the Guillain-Mollaret triangle may develop an unexpected neurological deterioration months to years after the initial cerebrovascular event due to hypertrophic olivary degeneration. For this reason, these patients should be closely monitored and the occurrence of any symptom suggestive for a dysfunction of the inferior olivary nucleus should prompt further evaluation by neuroimaging studies. Although pharmacological treatment is generally ineffective, different drugs should be tried and in case of no improvement stereotactic thalamotomy or deep brain stimulation could be considered. Prospective clinical and imaging registries together with further pathological studies dedicated to patients with HOD will probably enrich our knowledge about this severely disabling disease.

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