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Short Communication

Olivary hypertrophy improved by steroid treatment: Two case reports with unique presentations

Masahiro Ohara[a], Nobuo Sanjo[a,*], Takaaki Hattori[a], Jun Oyama[b], Meiko Hamada[a,c], Kokoro Ozaki[a,d], Takanori Yokota[a]

[a] Department of Neurology and Neurological Science, Graduate School of Medical and Dental Science, Tokyo Medical and Dental University, Japan
[b] Department of Diagnostic Radiology and Nuclear Medicine, Graduate School of Medical and Dental Science, Tokyo Medical and Dental University, Japan
[c] Department of Neurology, Ome Municipal General Hospital, Japan
[d] Diagnostics and Therapeutics of Intractable Diseases, Intractable Disease Research Center, Graduate School of Medicine, Juntendo University, Japan

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ABSTRACT

Olivary hypertrophy (OH) is the secondary degeneration of the inferior olivary nucleus (ION). It is observed one month after the onset of a primary lesion within the dento-rubro-olivary pathway and is usually associated with oculopalatal tremors. Here, we report two unique cases with rare autoimmune diseases leading to OH development with progressive cerebellar ataxia, both of which improved with steroid treatment. The first patient was a 59-year-old man with slowly progressive dysarthria and ataxic gait without palatal tremor. Anti-*N*-methyl-D-aspartate (NMDA) receptor antibody was positive in the CSF, supporting a diagnosis of anti-NMDA receptor encephalitis. The second patient was a 56-year-old man who developed dysarthria, ataxia, gait disturbance, and palatal tremor. He was diagnosed with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), based on presence of a punctate contrast-enhancing lesion in the middle cerebellar peduncle, pons, and cerebellum on magnetic resonance imaging (MRI). Brain MRI in both patients demonstrated high signal intensity regions in the bilateral IONs. Semi-quantitative volume analysis of MRI revealed significant reduction in ION volume after steroid treatment and accordingly cerebellar ataxia was improved in both cases. Clinical and radiological features of the two cases were unique, indicating potential novel etiologies in the pathophysiology of OH associated with cerebellar ataxia.

1. Introduction

Olivary hypertrophy (OH), also known as hypertrophic olivary degeneration, is a distinctive magnetic resonance imaging (MRI) finding of high signal intensity and enlargement of the inferior olivary nucleus (ION), observed on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. In case of symptomatic OH, the neural cells in the dento-rubro-olivary pathway, originally referred to as the Guillain-Mollaret triangle (GMT), is thought to gradually degenerate within several weeks to few months after the onset of a primary disease/condition, including stroke, tumor, vascular malformations, trauma, drug use, demyelinating diseases, and surgery (Samuel et al., 2004; Gu et al., 2015). These findings are pathologically indicative of secondary degeneration of the ION (Lapresle and Hamida, 1970). Most often, OH is associated with pathognomonic symptoms known as oculopalatal tremors (OPT) (Tilikete and Desestret, 2017; Konno et al., 2016).

Occasionally, patients with OH present with cerebellar ataxia in conjunction with palatal tremor (PT). These patients have a clinical diagnosis of progressive ataxia with palatal tremor (PAPT) (Samuel et al., 2004). In patients exhibiting PAPT, no structural lesion is usually observed in the GMT (Gu et al., 2015). A previous study reported that 44% of the patients with OH had no lesion in the GMT, whereas 53% of the patients were diagnosed with PAPT (Gu et al., 2015). However, the lack of evidence to elucidate the pathophysiology of OH in patients

Abbreviations: OH, Olivary hypertrophy; MRI, magnetic resonance imaging; ION, inferior olivary nucleus; FLAIR, fluid-attenuated inversion recovery; GMT, Guillain-Mollaret triangle; OPT, oculopalatal tremor; PT, palatal tremor; PAPT, progressive ataxia and palatal tremor; GAD, glutamic acid decarboxylase; TPO, thyroid peroxidase; TG, thyroglobulin; CSF, cerebrospinal fluid; NMDA, *N*-methyl-D-aspartate; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

* Corresponding author at: Department of Neurology and Neurological Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.

E-mail addresses: oharnuro@tmd.ac.jp (M. Ohara), n-sanjo.nuro@tmd.ac.jp (N. Sanjo), takaaki-hattori@umin.ac.jp (T. Hattori), ooymmrad@tmd.ac.jp (J. Oyama), k-oznuro@tmd.ac.jp (K. Ozaki), yokonuro@tmd.ac.jp (T. Yokota).

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without any lesions in the GMT or in those without a clinical diagnosis of PAPT indicates the existence of novel etiologies of OH.

Alternatively, an increased signal intensity of the IONs is known to persist for years to decades (Goyal et al., 2000). However, the enlargement of the IONs initially manifests on MRI approximately 6 months after an acute event and will disappear after 3 to 4 years (Goyal et al., 2000). There is a possibility that some OH patients can be treated because previous reports have shown that autoimmune diseases (e.g., multiple sclerosis) and inflammation (e.g. encephalitis) sometimes lead to OH (Konno et al., 2016). However, to our knowledge, there has been no report of patients with OH who responded to treatment. Here we describe two patients with rare autoimmune diseases that led to the development of OH with cerebellar ataxia. These patients uniquely improved after steroid treatment for their primary diseases.

2. Methods

MRI studies were performed using 3-T system (Signa HDxt 3T; GE Healthcare) and 1.5-T systems (MRT200SP5; Toshiba Medical systems, Signa HDxt 1.5T; GE Healthcare and Vantage; Toshiba Medical systems). MRI images were analyzed on T2-weighted images with the following parameters: TR = 4000 ms, TE = 96.3–98.6 ms, flip angle = 90 degree, acquisition matrix = 384 × 256, 5 mm axial slices in Signa HDxt 3.0 T, TR = 3475–4460 ms, TE = 96.3–100 ms, flip angle = 90, acquisition matrix = 352–384 × 256, 5 mm axial slices in Signa HDxt 1.5 T, TR = 4300 ms, TE = 105 ms, flip angle = 90, acquisition matrix = 320 × 256, 5 mm axial slices in MRT200SP5 1.5T and TR = 4300–4800 ms, TE = 105 ms, flip angle = 90, acquisition matrix = 320 × 256, 5 mm axial slices in Vantage. Signal intensity and size of OH was evaluated using Image J software (https://imagej.net/Welcome) (Supplementary Fig. 1) by modifying the previously reported protocol (Tanaka et al., 2011). To compare the interval changes of OH on MRI with that of described patients, we also evaluated OH in patients with no apparent changes on MRI (Supplementary Table 1).

3. Results

3.1. Case 1

A 59-year-old man was hospitalized for slowly progressive dysarthria and gait disturbance since the age of 56. On admission, he was alert and well-oriented. However, cerebellar ocular motor dysfunction was observed, including left-beating nystagmus in left gaze, hypermetric saccades, and jerky pursuit. Neurological examination revealed dysarthria, limb ataxia dominantly on the right side, and wide-based ataxic gait. PT was not observed. Laboratory testing revealed no specific abnormalities in blood count, C-reactive protein, thyroid function, and serological tests including anti-glutamic acid decarboxylase (GAD) antibody, anti-thyroid peroxidase (TPO) antibody, and anti-thyroglobulin (TG) antibody. Routine cerebrospinal fluid (CSF) study revealed no abnormalities but anti-NMDA-receptor antibody in the CSF was positive. Oligoclonal bands in the CSF were negative. Hyper signal intensity and bilateral enlargement of the IONs were detected on T2-weighted and FLAIR MRI images without any lesions at GMT (Fig. 1A). We speculated that an autoimmune etiology was associated with the symptoms and started oral administration of prednisolone (1 mg/kg). Following administration, dysarthria and ataxia, especially nose-finger test and fast alternating hand movements in the left side, rapidly improved. Follow-up MRI obtained 2 weeks after steroid administration revealed improvement of OH (Fig. 1B).

3.2. Case 2

A 56-year-old man was admitted after 2 years of gait disturbance and dysarthria. His symptoms had gradually progressed and other symptoms such as diplopia and dizziness also appeared. On admission, he was alert and well oriented. Neurological examination revealed PT, dysarthria, and limb ataxia. Cerebellar ocular motor dysfunction was also observed, such as gaze-evoked nystagmus, hypermetric saccades, and jerky pursuit. Laboratory examination revealed no specific abnormalities in blood count, thyroid function and serological tests. CSF study showed mild pleocytosis (19/μL, reference range < 5/μL) (95% monocytes), slightly elevated total protein (54 mg/dL, reference range 15–45 mg/dL), and negative culture for tuberculosis, fungi and viruses. Oligoclonal bands in the CSF were negative. MRI images revealed increased signal and enlargement in the IONs bilaterally on T2-weighted MRI, which was contrast enhanced on T1-weighted MR images as punctate lesions affecting the middle cerebellar peduncle, pons, and the cerebellum (Fig. 1C–F). We made a preliminary diagnosis of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) and started steroid pulse therapy with oral prednisolone (1 mg/kg). The scale for the assessment and rating of ataxia (SARA) (Schmitz-Hübsch et al., 2006) showed rapid improvement from 15 points to 9 points within two weeks. In terms of the subscores of SARA, fast alternating hand movements (from 2 points to 0 point), heel-thin slide tests (from 3 points to 0 point), and sitting balance (from 2 points to 1 point) improved. However, PT showed no remarkable response. Finally, the diagnosis of CLIPPERS was confirmed with reference to steroid treatment responsiveness (Pittock et al., 2010). Notably, his symptoms regarding 'progressive ataxia and palatal tremor (PAPT)', were probably associated with CLIPPERS (Deuschl et al., 1994a; 1994b). Follow-up MRI 10 months after steroid administration revealed improvement of OH accompanied by decreased gadolinium enhancement in the pons and the cerebellum (Fig. 1G–I).

3.3. Image evaluation

The results of semi-quantitative analysis of OH are described in Table 1. The ratios of mean gray-scale value of the IONs to the control regions showed no significant difference before and after steroid treatment in both cases. In contrast, the sizes of IONs in cases 1 and 2 were reduced by 20.9% and 12.7%, respectively, after the treatment. There was no apparent change in volumetric reduction in control patients (1.6 ± 3.4% increase) (Table 1).

4. Discussion

We presented two unique patients, one with anti-NMDA receptor encephalitis and the other with CLIPPERS, leading to OH with progressive cerebellar ataxia. Both patients responded to steroids in terms of OH and cerebellar ataxia. To the best of our knowledge, there has been no other report demonstrating an improvement of OH. These clinical and radiological features were obviously distinctive and indicated the possibility that there are some novel etiologies of OH associated with cerebellar ataxia.

The patient with anti-NMDA-receptor antibody had no lesions at the GMT, and chronic cerebellar ataxia without cerebellar lesions was observed. Moreover, cerebellar ataxia and enlargement of the IONs on MRI responded immediately to steroid treatment. It was too short a duration, if only trans-synaptic mechanism was associated with pathophysiology of OH in this patient, as axonal changes via synapses take several weeks to occur. In fact, a previous MRI study showed that OH generally emerges at least 1 month after primary lesion development (Goyal et al., 2000). We speculated that some steroid-responsive inflammatory mechanisms may have localized in the IONs as well as in the cerebellum. Ishihara et al. (2005) reported an autopsy case with OH presenting with cerebellar ataxia that had paraneoplastic encephalitis caused by peripheral T-cell lymphoma (Ishihara et al., 2005). In addition, perivascular lymphocyte infiltration and inflammation were observed around the IONs as well as in the cerebellum, indicating that autoimmune encephalitis might lead to primary inflammation in the IONs and the cerebellum (Ishihara et al., 2005). Therefore, in the first

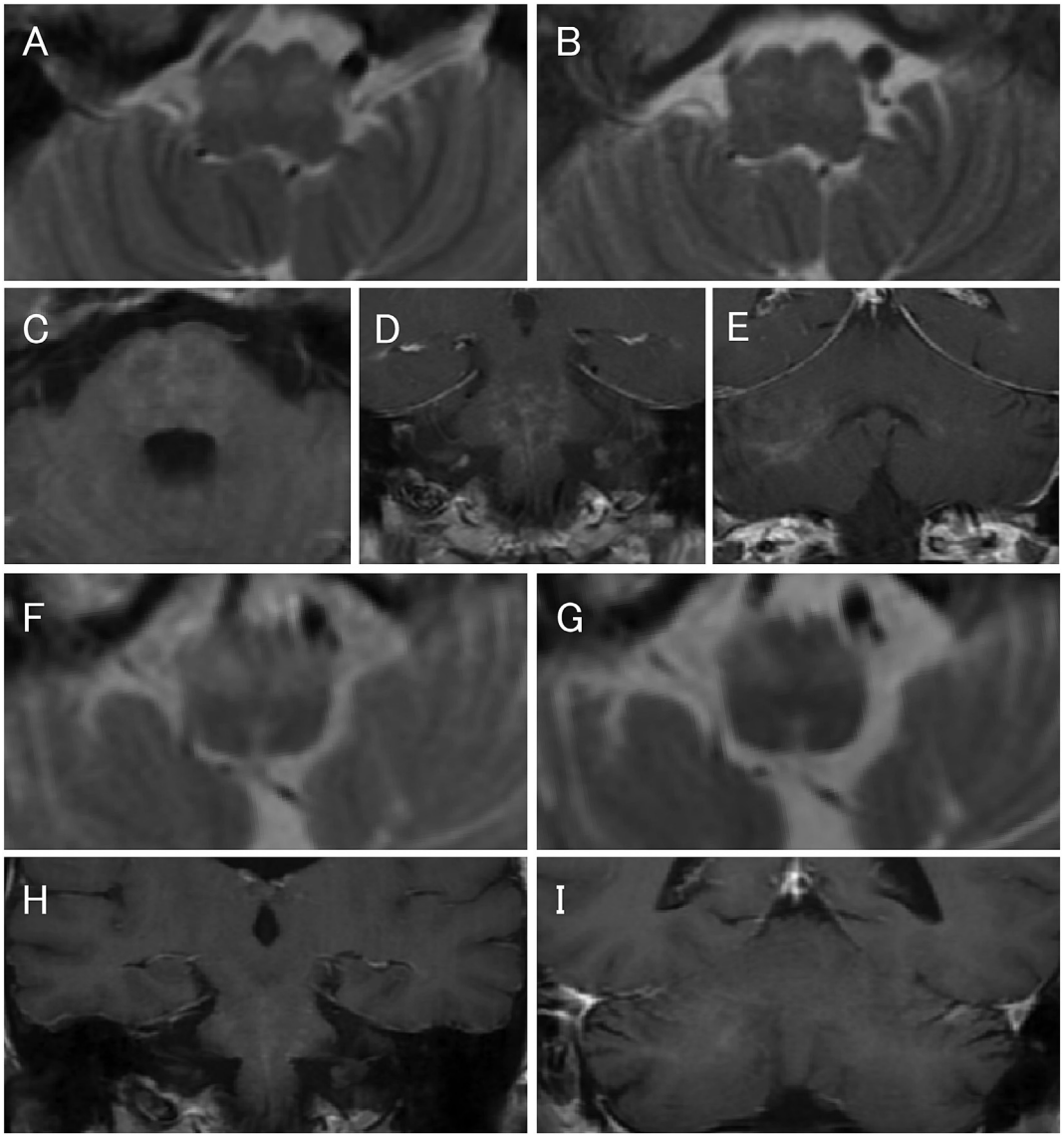

Fig. 1. Brain MRI scans of patients with OH (case 1: A–B and case 2: C–I). A: Axial T2-weighted magnetic resonance images obtained at admission showed enlargement and increased signal intensities of bilateral inferior olives. B: Axial T2-weighted images 2 weeks after the treatment showed improvement of OH. C–E: Contrast-enhanced T1-weighted images obtained on admission showed punctate enhancement affecting the middle cerebellar peduncle, pons and cerebellum. F: First MRI study showed enlargement and increased signal intensities of bilateral inferior olives. G: Follow-up MRI 10 months after steroid administration showed reduction of the enlargement of olives, but signal intensities were not altered. H, I: Contrast-enhanced T1-weighted images obtained two weeks after the treatment revealed diminished enhanced lesions in the pons and the cerebellum.

patient, it is possible that inflammation occurred at the IONs/cerebellum leading to OH with cerebellar ataxia, and thus they responded to the steroid treatment.

PAPT is a subtype of symptomatic PT in which progressive cerebellar degeneration is the most symptomatic feature and usually no structural lesion is observed in the GMT (Samuel et al., 2004; Gu et al., 2015). The second patient demonstrated PAPT-like symptoms, which was probably a symptomatic form of OH. PT did not respond to steroids even though OH was improved, which indicated the possibility that direct inflammation did not develop at the IONs; instead, trans-synaptic degeneration was associated with the pathophysiology of OH. Alternatively, cerebellar ataxia was improved by steroid treatment accompanying radiological improvement of the cerebellar lesions, indicating that cerebellar ataxia was associated with cerebellar inflammatory lesions. In the patient, gadolinium-enhancing lesions at the pons, where central tegmental tracts pass through, were observed on MRI. It is thus assumed, that the primary inflammatory lesions in the central tegmental tract responded to steroid treatment, at which point the ongoing deafferentation sequentially ceased, leading to an eventual improvement in the secondary degenerative hypertrophy of the IONs.

5. Conclusion

The present study indicates the potential discovery of novel etiologies of OH associated with cerebellar ataxia, leading to unique clinical features. It is probable that inflammation or autoimmune responses affecting the IONs and/or the dento-rubro-olivary pathway could lead to development of OH and cerebellar ataxia, which improve with steroid treatment. Moreover, palatal tremor secondary to brainstem lesions and cerebellar ataxia mediated by cerebellar lesions in combination can mimic PAPT syndrome. Further studies are required to confirm the novel etiologies that lead to OH with response to steroid treatment.

Supplementary data to this article can be found online at https://

Table 1
Semi-quantitative analysis of OH.

	Mean gray scale		Pixels (%)	
	Rt. ION/ control region	Lt. ION/ control region	Rt. ION/ medulla	Lt. ION/ medulla
Case 1				
Pre-treatment (Fig. 1A)	1.26	1.23	19.5	20.4
Post-treatment (Fig. 1B)	1.25	1.27	15.2	16.4
Relative change (%)	−1.00	4	−22.1	−19.6
Case2				
Pre-treatment (Fig. 1F)	1.39	1.33	19.6	18.1
Post-treatment (Fig. 1G)	1.39	1.32	18.3	14.7
Relative change (%)	0	−1.00	−6.63	−18.8
Patients with no change (n = 4, the number of IONs = 6)				
Relative change (%) (mean ± SD)	−3.6 (± 2.4)		1.6 (± 3.4)	

ION: inferior olive nucleus, Rt: right, Lt: left.
Pixels (%) were calculated the following formula: pixels in ION/pixels in medulla × 100.
Relative change (%) was calculated the following formula: $(X_{post\text{-}treatment} - X_{pre\text{-}treatment})/X_{pre\text{-}treatment} \times 100$.

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Authors' contributions

Dr. Ohara: acquisition of data, data analysis, drafting the manuscript.

Dr. Sanjo: study concept and design, drafting/revising the manuscript.

Dr. Hattori: revising the manuscript.

Dr. Oyama: acquisition of data, data analysis, revising the manuscript.

Dr. Hamada: acquisition of data, revising the manuscript.

Dr. Ozaki: acquisition of data, revising the manuscript.

Dr. Yokota: drafting/revising the manuscript, study supervision.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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