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CLINICAL INVESTIGATION

Idiopathic third and sixth cranial nerve neuritis

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Abstract

Purpose To present cases with idiopathic third and sixth cranial nerve neuritis.

Study design Retrospective observational study

Methods The results of high resolution pre- and post- cranial nerve magnetic resonance images (MRI) with three-dimensional sequences for visualizing cranial nerves in patients with third, fourth, and sixth cranial nerve palsies who were treated at the Neuro-ophthalmology Department of Samsung Medical Center were reviewed. Patients with cranial nerve enhancement confirmed by experienced radiologists were identified. The medical records of these patients were reviewed, and their demographics, clinical presentations, laboratory results, and clinical outcomes were analyzed.

Results Of 265 patients with third, fourth, and sixth cranial nerve palsy, 60 were identified by high resolution MRI as having enhancement of the corresponding cranial nerve. Among these, 17 patients with infiltrative, granulomatous, or tumorous lesions were excluded. In addition, 28 patients with identifiable causes of cranial nerve palsy, such as Miller-fisher syndrome, virus infection, or radiation-induced neuropathy, as well as patients with vasculopathic risk factors, were also excluded. Ultimately, a total of 15 patients with idiopathic third and sixth cranial nerve neuritis were included in this study. The mean age of these patients was 43 ± 15 years. Eight patients had sixth cranial nerve palsy, six third cranial nerve palsy (two partial and four complete), and one patient with complete third and sixth cranial nerve palsy. Nine patients received steroid treatment. Eleven patients recovered fully within a period ranging from a few days to one year. Two patients were much improved up to 1 month after initial presentation, but were then ultimately lost to follow-up. Another patient was lost to follow-up after the initial work-up. The other patient lost to follow-up had partially recovered during the first 6 months.

Conclusions We present patients with idiopathic third and sixth cranial nerve neuritis. They tended to respond well to steroid treatment and to have good prognoses. In order to better understand the long-term prognosis of cranial nerve neuritis and possible association with other neurologic disorders, a larger scale and longer-term study is needed.

Keywords Idiopathic cranial nerve neuritis · Third cranial nerve palsy · Fourth cranial nerve palsy · Sixth cranial nerve palsy

Introduction

Third, fourth, and sixth cranial nerve palsy are common in neuro-ophthalmology practice and may be caused by a variety of conditions. Microvascular ischemia is presumed to be one of the leading causes of acquired ocular motor cranial nerve palsy, particularly in older patients [1]. Serious neurological pathologies, including neoplasm involving the central nervous system, are reported to be the cause in a wide range of 1–15% of cases of ocular motor cranial nerve palsy [2–5]. The other causes of third, fourth, and sixth nerve palsy vary and include inflammation such as that associated with Tolosa-Hunt syndrome, multiple sclerosis, stroke, various vascular lesions, and infection. Despite the availability

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of magnetic resonance imaging (MRI), the causes of ocular motor palsy remain undetermined in 13–35% of cases [1, 6–8].

The recent use of three-dimensional steady-state free precession sequences and modified fully-refocused steady-state sequences, such as constructive interference in steady state (CISS)/fast imaging employing steady-state acquisition cycled phases (FIESTA-C)/balanced fast field echo (B-FFE), enables the augmented visualization of cranial nerves in vivo. These techniques have enabled more accurate diagnosis through the enhanced visualization of each cranial nerve.

In this study, we present cases with idiopathic third and sixth cranial nerve neuritis. Patients with vasculopathic risk factors were excluded so as to rule out ischemic neuropathies. We present the natural history, as well as the results of full ophthalmologic and neurologic assessments, high-resolution MRI, and laboratory results, and the clinical courses of these patients.

Methods

Patients aged 20 to 65 years with third, fourth, and sixth cranial nerve palsy who were treated at the Neuro-ophthalmology Department of Samsung Medical Center from March 2016 to July 2018, were identified using a patient identification log. A retrospective review was performed according to the tenets of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Samsung Medical Center. Patients were identified by experienced neuro-radiologists as having definite cranial nerve enhancement of the corresponding nerve in high resolution MRI. Of these, patients with any abnormal enhancement beyond third, fourth, or sixth nerve, such as space occupying lesions, hemorrhages, infarctions, vascular abnormalities, and periventricular or white matter lesions, were excluded. In addition, patients with identifiable causes of cranial nerve palsy such as restrictive strabismus, previous extraocular muscle surgery, or other disorders that could affect their ocular alignment such as myasthenia gravis, Graves' disease, Miller-fisher syndrome, viral infection involving the central nervous system, or radiation-induced neuropathy were also excluded. Thus, third, fourth, and sixth cranial nerve neuritis were defined as having cranial nerve palsy with high resolution MRI findings which showed enhancement confined to the cranial nerve without any other identifiable cause of the cranial nerve palsy. In addition, patients with vasculopathic risk factors such as smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia, or coronary artery disease that had either been previously or newly diagnosed during the examinations were excluded in this study, in order to rule out the possible inclusion of ischemic neuropathies.

In the initial visit, all patients underwent a full ophthalmologic assessment, including a visual acuity examination, an evaluation of their ocular alignment status, slit-lamp biomicroscopy and fundus examination. High resolution pre- and post- cranial nerve MRI with three-dimensional sequences was performed. MRI was performed using a 3-T system (Magnetom Skyra; Siemens Healthineers) for all patients with a 32-channel phased-array head coil. 2D axial turbo spin-echo T2-weighted imaging was performed in order to visualize the entire brain with the following parameters: repetition time, 4620 ms; echo time, 97 ms; field of view, 240 × 188 mm; matrix, 512 × 410; and section thickness, 5 mm. Proton density (PD)-weighted images were obtained using a three-dimensional sampling perfection with application-optimized contrasts using different flip angle evolution (SPACE) sequences to visualize the cisternal segment of the cranial nerves. The slab thickness (6.4 cm) of the 3D-SPACE sequence was measured from the anterior commissure to the cervicomedullary junction. The detailed parameters of the 3D-SPACE sequence were as follows: repetition time, 1000 ms; echo time, 32 ms; flip angle, 120°; field of view 170×170 mm; matrix, 320×320; section thickness, 0.5 mm; and acquisition time, 6 min, 57 s. An additional three-dimensional constructive interference steady state (CISS) sequence was performed in order to visualize the cisternal segment of the fourth cranial nerve with the following parameters: repetition time, 8.30 ms; echo time, 3.62 ms; flip angle, 50°; field of view, 150×150 mm; matrix, 512×512; section thickness, 0.25 mm; and acquisition time, 7 min, 56 s. The slab thickness (1.5 cm) of the 3D-CISS sequence was from the lower midbrain to the upper pons, including the inferior margin of the inferior colliculus. Following the intravenous injection of 0.1 mmol/kg of gadobutrol (Gadovist; Bayer Pharma AG), three-dimensional magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequence with fat saturation was obtained in order to visualize the nerve surrounded by a venous plexus using the following parameters: repetition time, 1900 ms; echo time, 3.19 ms; flip angle, 10°; field of view, 170×170 mm; matrix, 256×256; section thickness, 0.5 mm; and acquisition time, 5 min, 50 s. The slab thickness (8 cm) of the 3D-MPRAGE sequence was measured from the body of lateral ventricle to the cervicomedullary junction. The following tests were also performed: a test for complete blood cell count with differential, a chemistry panel, electrolytes, lipid profile, C-reactive protein level, erythrocyte sedimentation rate, vitamin B12, folate, prothrombin time, activated partial thromboplastin time, fibrinogen, proteins C, protein S, homocysteine, serum angiotensin converting enzyme, lupus anticoagulants, antinuclear antibody, anticardiolipin antibodies, serologic tests including a syphilis and human immunodeficiency virus 1–2 test, thyroid

stimulating hormone receptor antibody, acetylcholine receptor antibody, ganglioside antibody panels, and chest radiography.

Results

Of the 265 patients with third, fourth, and sixth cranial nerve palsy, 60 patients were identified by experienced neuro-radiologists as having definite cranial nerve enhancement on high resolution MRI. Among these patients, 17 with infiltrative, granulomatous, or tumorous lesions were excluded. In addition, 13 patients with identifiable causes of cranial nerve palsy, such as Miller-fisher syndrome (4) or suspected Guillain-Barre syndrome (3) based on ganglioside antibody test results; varicella zoster virus infection (1) based on the results of polymerase chain reaction; and radiation-induced neuropathy (2), traumatic neuropathy (3), and 15 patients with vasculopathic risk factors were also excluded. As a result, a total of 15 patients with idiopathic third and sixth cranial nerve neuritis were ultimately included in this study (Table 1). The mean age was 43 ± 15 years (range 21–65 years). Nine (60%) of these patients were men and six (40%) were women. All patients were Asian. Eight patients exhibited right-sided palsy, five left-sided palsy, and two bilateral palsy. There were eight patients with a sixth cranial nerve palsy, six with a third cranial nerve palsy (with two being partial and four being complete), and one patient with complete third and sixth cranial nerve palsy. Among these 15 patients, no patient showed neurologic symptoms or signs other than those of third or sixth cranial nerve palsies, excepting pain. Seven (47%) patients had headache or ocular pain upon initial presentation.

The locations of the cranial nerve enhancement are described in Table 1. Among the 15 patients, one with third nerve palsy showed enhancement in the sixth nerve in addition to the palsied third nerve. The other patient with both third and sixth nerve palsies showed enhancement only in the third nerve. In two of the 15 patients, the fluorescent antinuclear antibody test (FANA) results were positive. Another one patient had anti-SSA (Ro) antibodies. However, none of these patients had other symptoms or signs which met the diagnostic criteria of rheumatologic disorder.

Five of the six patients with third nerve palsy received intravenous methylprednisolone treatment with oral taper; the other patient with third cranial nerve palsy did not receive steroid treatment owing to his fast (within days) recovery. Of the 8 patients with sixth cranial nerve palsy, three received oral prednisolone for three to four weeks while the other five did not receive any treatment, either because their symptoms had started to improve prior to the confirmation of the diagnosis or because they refused steroid treatment. The remaining patient with both third and sixth cranial nerve palsies received oral prednisolone for four weeks.

The mean follow-up duration was 10 ± 13 months (range 1–48 months). Eleven patients fully recovered within a period ranging from days to 1 year. Two patients were much improved up to 1 month after the initial presentation, but were ultimately lost to follow-up. One

Table 1 Demographics and clinical findings of patients with third and sixth cranial nerve neuritis

Case no., sex (F/M)	Age (years)	Cranial nerve involved	Site	Complete vs. partial	Presence of pain (+)	Location of the cranial nerve enhancement
1, M	21	3rd	Right-sided	Complete	+	Distal cavernous sinus, proximal extracranial segment
2, M	30	3rd	Bilateral	Partial	–	Bilateral cavernous sinus
3, M	45	3rd	Left-sided	Complete	–	Cisternal segment
4, F	46	3rd	Right-sided	Complete	+	Cisternal segment
5, F	65	3rd	Right-sided	Complete	+	Cavernous segment of third nerve and Cisternal segment of sixth nerve
6, M	55	3rd	Left-sided	Partial	+	Cisternal segment
7, F	55	3rd, 6th	Bilateral	Complete	+	Cavernous segment of third nerve
8, M	28	6th	Right-sided		+	Dorello's canal
9, F	31	6th	Right-sided		+	Dorello's canal
10, M	41	6th	Right-sided		–	Cisternal segment
11, M	48	6th	Left-sided		–	Cisternal segment
12, M	33	6th	Right-sided		–	Cavernous sinus
13, F	64	6th	Left-sided		–	Dorello's canal
14, M	63	6th	Right-sided		–	Cisternal segment
15, F	21	6th	Left-sided		–	Dorello's canal, Cavernous sinus

no number, *F* female, *M* male

patient was lost to follow-up after the initial work-up. The remaining patient recovered partially within 6-months. The detailed clinical course of each patient is described in Table 2. Figures 1, 2, 3 and 4 present the MRI images of various cases, in which enhancements were confined to the corresponding cranial nerves without the presence of any other lesions.

Table 2 Treatment and clinical outcomes of patients with third and sixth cranial nerve neuritis

Case no., sex (F/M)	Age (years)	Cranial nerve involved	Site	Treatment	Follow-up duration (months)	Clinical outcome at the final visit
1, M	21	3rd	Right-sided	IVMP + oral taper	6	Improved until 6 months
2, M	30	3rd	Bilateral	No treatment	6	Completely recovered within days
3, M	45	3rd	Left-sided	IVMP + oral taper	4	Completely recovered within 2 months
4, F	46	3rd	Right-sided	IVMP + oral taper	48	Completely recovered within 3 months
5, F	65	3rd	Right-sided	IVMP + oral taper	28	Completely recovered within 2 months
6, M	55	3rd	Left-sided	IVMP + oral taper	12	Completely recovered within 12 months
7, F	55	3rd, 6th	Bilateral	Oral steroid	12	Completely recovered within 12 months
8, M	28	6th	Right-sided	Oral steroid	1	Much improved until 1 month and lost to follow-up
9, F	31	6th	Right-sided	Oral steroid	5	Completely recovered within 3 months
10, M	41	6th	Right-sided	No treatment	1	Much improved until 1 month and lost to follow-up
11, M	48	6th	Left-sided	No treatment	1	Completely recovered within days
12, M	33	6th	Right-sided	No treatment	3	Completely recovered within days
13, F	64	6th	Left-sided	No treatment	2	Completely recovered within 1 month
14, M	63	6th	Right-sided	No treatment	–	Lost to follow-up after initial work-up
15, F	21	6th	Left-sided	Oral steroid	14	Completely recovered within 3 months

no number; *F* female; *M* male; *IVMP* intravenous methylprednisolone

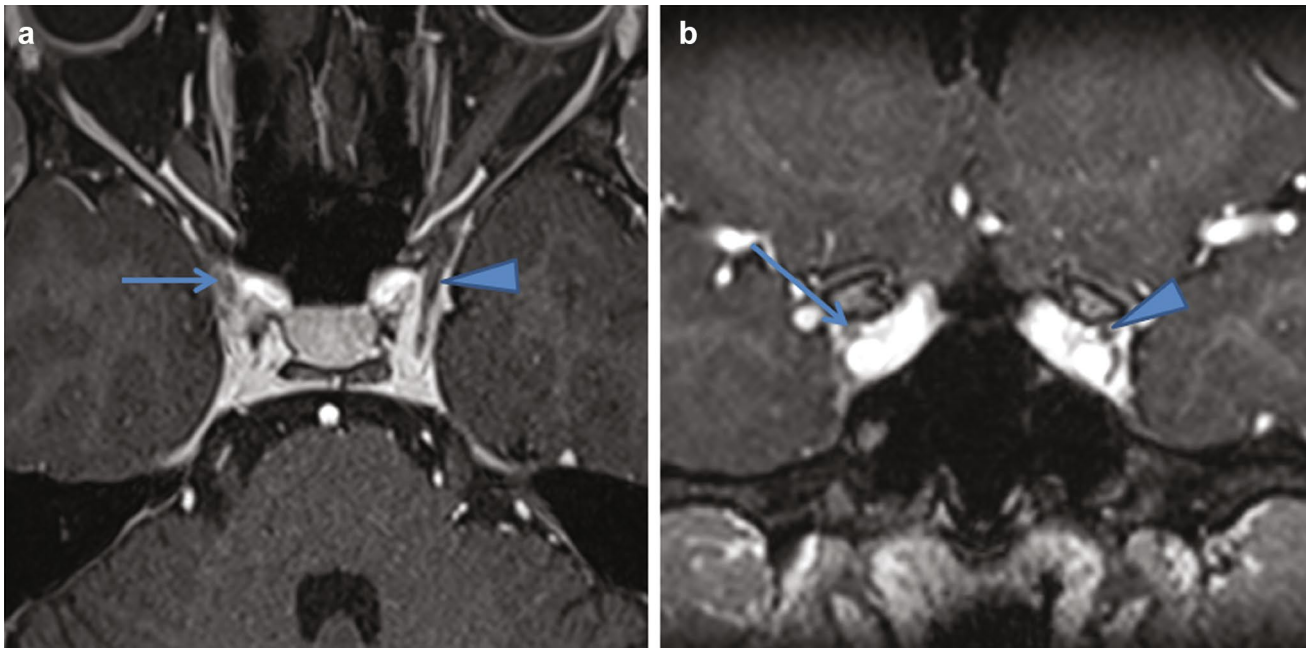

Fig. 1 Patient with right oculomotor nerve palsy. Axial (**a**) and Coronal (**b**) 3D-MPRAGE images demonstrate abnormal enhancement of cavernous sinus segment of right 3rd cranial nerve (arrow). Please note that the normal contralateral 3rd cranial nerve (arrowhead) does not show enhancement

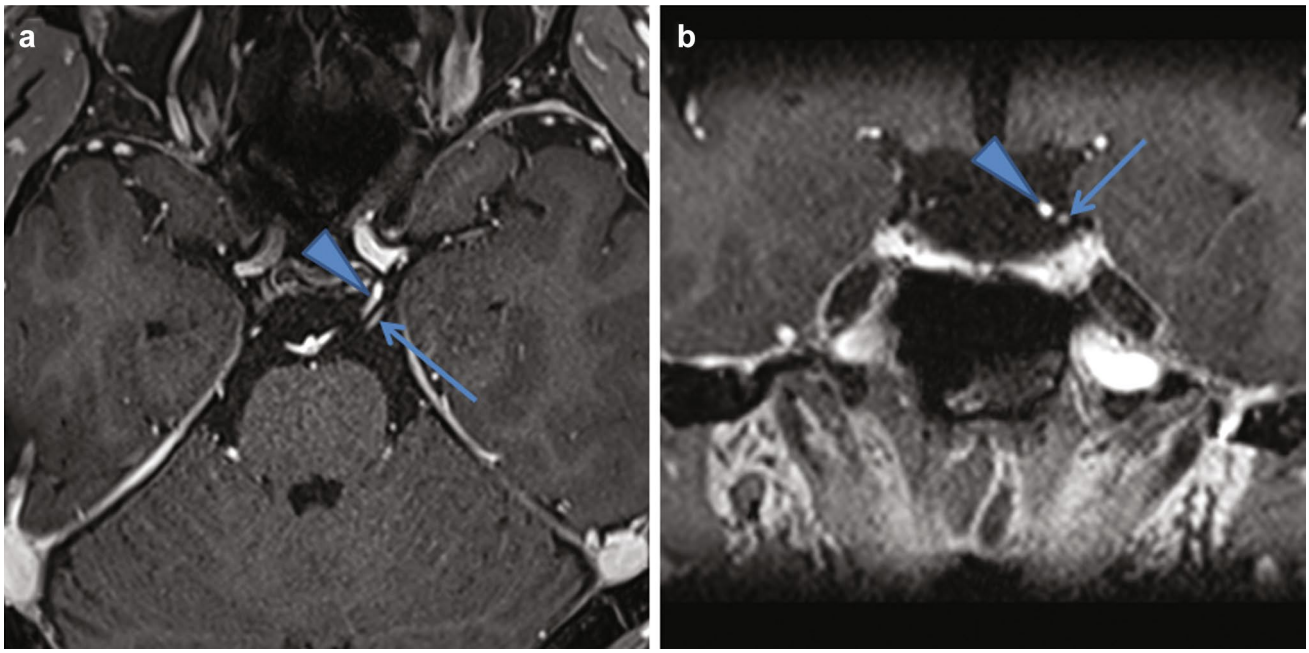

Fig. 2 Patient with left oculomotor nerve palsy. Axial (**a**) and coronal (**b**) 3D-MPRAGE images demonstrate abnormal enhancement of the cisternal segment of left 3rd cranial nerve (arrow) on the inferolateral aspect of the posterior communicating artery (arrowhead). The cisternal segment of right 3rd cranial nerve does not show enhancement and is not visible on this images

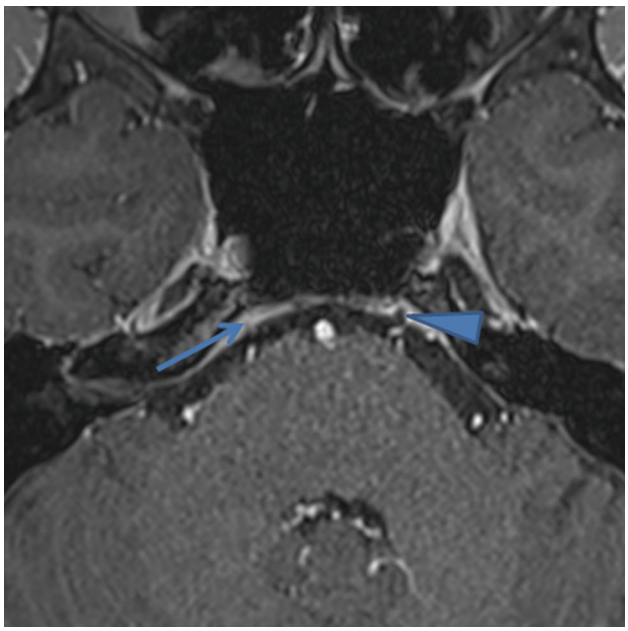

Fig. 3 Patient with right abducens nerve palsy. On axial 3D MPRAGE image, right abducens nerve (arrow) entering Dorello's canal demonstrates enhancement as compared to normal non-enhanced contralateral abducens nerve (arrowhead)

Discussion

The age range of patients with cranial nerve neuritis in this study varied from 21 to 65 years, as did the severity of symptoms. Seven of the 15 patients presented with headache or ocular pain. The pain could vary depending on the location of the inflammation of the nerves. Although the presence of pain may raise suspicion regarding inflammation as a possible cause of cranial nerve palsy, the absence of pain may not be helpful in ruling out cranial nerve neuritis.

Excepting 1 patient who was lost to follow-up after the initial work-up, all other patients showed either complete recovery or partial improvement by the end of the follow-up period; some with and others without steroid treatment. Five patients who did not receive any treatment showed either complete recovery or partial improvement within the first month. Because all patients with complete palsy as well as all patients who failed to show improvement prior to the confirmation of the diagnosis received steroid treatment, we could not evaluate the natural courses of the palsy in these patients.

In this study, we defined cranial nerve neuritis as cranial nerve palsy with definite cranial nerve enhancement of the corresponding nerve in high resolution MRI. Incidental enhancement of cranial nerves has also been reported in asymptomatic patients [9, 10]. However, definite enhancement of cranial nerves, especially in certain locations such as cisternal segment of the third nerve and the seventh nerve outside the facial canal is reported to be pathologic [10, 11]. Mark et al. report that enhancement of the cisternal segment of the third nerve was always abnormal, revealing an underlying inflammatory or neoplastic process [11].

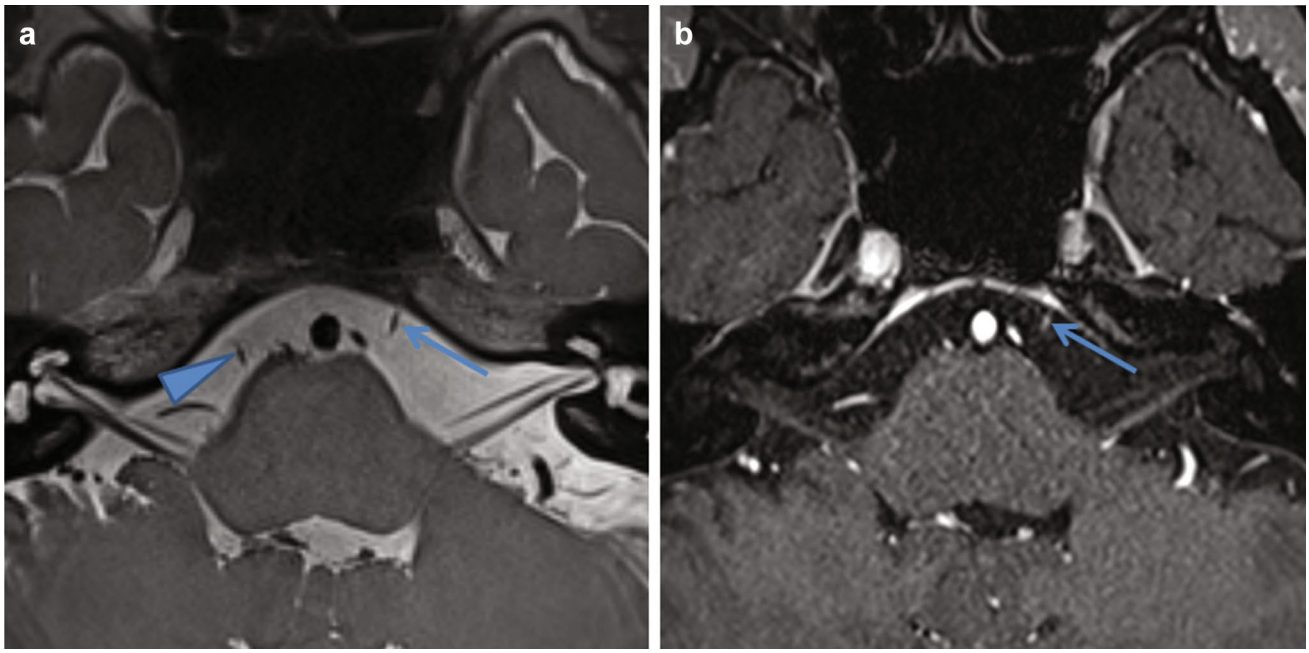

Fig. 4 Patient with left abducens nerve palsy. Axial proton density weighted 3D SPACE image (**a**) and axial 3D MPRAGE image (**b**) demonstrate enhancement of cisternal segment of left abducens nerve (arrow). Contralateral abducens nerve (arrowhead) does not show enhancement

Due to the high prevalence of presumed microvascular ischemia in acquired cranial nerve palsy, particularly in old age, it is crucial to discriminate cranial nerve neuritis from ischemic changes of the cranial nerve. Five of the 15 patients in this study were over 50 years old. Although patients with vasculopathic risk factors had been excluded so as to rule out the inclusion of cases with microvascular causes, age itself could still be a risk factor for ischemic nerve palsy. Unfortunately, ischemic neuropathy and inflammatory neuropathy may be difficult to distinguish in MRI even in the optic nerve, which has a much larger diameter than any of the third or sixth cranial nerves [12]. The benign clinical course is also similar between ischemic or inflammatory third and sixth cranial nerve palsy. Previous studies reported that 73% of patients with presumed microvascular ischemic sixth cranial nerve palsies recovered within six months [3, 13, 14]. One study of 59 cases of presumed microvascular ischemic sixth nerve palsy reported that 86% of patients achieved complete resolution while 14% achieved incomplete recovery [15]. Pain alone cannot be a surrogate indicator for inflammation as Wilker et al. reported that among 87 patients with acute-onset ocular motor cranial nerve palsy with presumed microvascular causes, 62% of events were accompanied by pain [16]. However, high resolution MRI which can visualize each cranial nerve was not performed routinely in the majority of these previous studies, so we cannot rule out the possibility that cases with idiopathic cranial nerve neuritis were previously mistakenly classified as presumed microvascular nerve palsy. As mentioned above, all patients who had vasculopathic risk factors that had either been previously diagnosed or were newly diagnosed in our investigations were excluded from this study. Although a certain proportion of patients, particularly the five patients older than 50 years old, could have had an ischemic nature or a complex nature of ischemia and inflammation, we suggest that there exist cases with idiopathic cranial nerve neuritis independent of or coexisting with ischemia, that tend to respond well to steroid treatment as well as have a good prognosis. In order to confirm and investigate the natural course of this disease category, a larger scale and longer-term study is needed.

This study has several limitations. First, it was retrospective in nature, so not all patients received the same treatment regimen. Second, the follow-up duration was short. A longer-term study is needed in order to better understand the long-term prognosis of the disease. Third, we could not find fourth nerve enhancement because the fourth nerve enhancement is difficult to detect, even on cranial nerve MRI with three-dimensional sequences for visualizing cranial nerves. We hope that further development in MRI techniques could provide better visualization. Fourth, because all data were obtained from one ethnicity, the direct application of these data to other races may need to be qualified.

In conclusion, in this study we present patients with idiopathic third and sixth cranial nerve neuritis. They tended to respond well to steroid treatment and to have good prognoses. In order to reveal the long-term prognosis and the

possible association with other neurologic disorders, a larger scale and longer-term study is needed.

Conflicts of interest K.-A. Park, None; J.-H. Min, None; S. Y. Oh, None; B. J. Kim, None.

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