Clinicoanatomical Correlation of Upbeat Nystagmus: Report of a Case

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Upbeat nystagmus is an uncommon neurologic sign. The causal link between the lesion site and the generation of upbeat nystagmus is intriguing and deserves detailed investigation. We report a patient with systemic lupus erythematous (SLE) who developed upbeat nystagmus with an exponentially decreasing slow phase velocity, indicating involvement of the vertical position-to-velocity neural integrator. Magnetic resonance imaging (MRI) revealed a high signal intensity lesion on T2-weighted (T2WI) and diffusion-weighted images at the site compatible with the location of nucleus intercalatus, the most caudal of the perihypoglossal nuclei. The upbeat nystagmus subsided two months later and follow-up MRI three months later showed disappearance of the previous lesion. We propose that the nucleus intercalatus might play a pivotal role in the human ocular-motor control system. **(Mid Taiwan J Med 2002;7:183-8)**

Key words

MRI, nucleus intercalatus, upbeat nystagmus,

INTRODUCTION

Upbeat nystagmus has been reported in patients with lesions in midbrain, pontomesencephalic junction, caudal parts of the medulla, and cerebellar vermis [1-7]. Most of the reported cases had additional complex symptoms and their images often showed extended lesions making it difficult to clarify the precise lesion contributing to the generation of upbeat nystagmus [3,4,8]. In addition, detailed electrophysiological recording of the nystagmus usually depended on previous reports, which hindered us from understanding the pathophysiology of this rare disorder. We report a patient with upbeat nystagmus, in whom a tiny median medullary lesion was illustrated on MR images. The causal link between the nystagmus and the lesion was intriguing and worthy of investigation.

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CASE REPORT

A 31-year-old female was admitted to our hospital because of acute onset upward oscillopsia for three days. She had had SLE for five years and received regular medication including hydroxychloroquine (400 mg, daily), prednisolone (5 mg, daily), and azathioprine (50 mg, daily). She developed acute onset of dizziness and severe vomiting on April 14th, 2001. These symptoms subsided spontaneously the next day. However, recurrent dizziness, vertigo, nausea, vomiting, and unsteady gait in association with sorethroat, headache, and cold sweats developed in the early morning of April 19th, 2001. She began to have upbeat oscillopsia on April 20th, 2001, although the other symptoms gradually ameliorated. The coarse of upbeat oscillopsia was not altered by change of posture but seemed more vigorous on upward gazing.

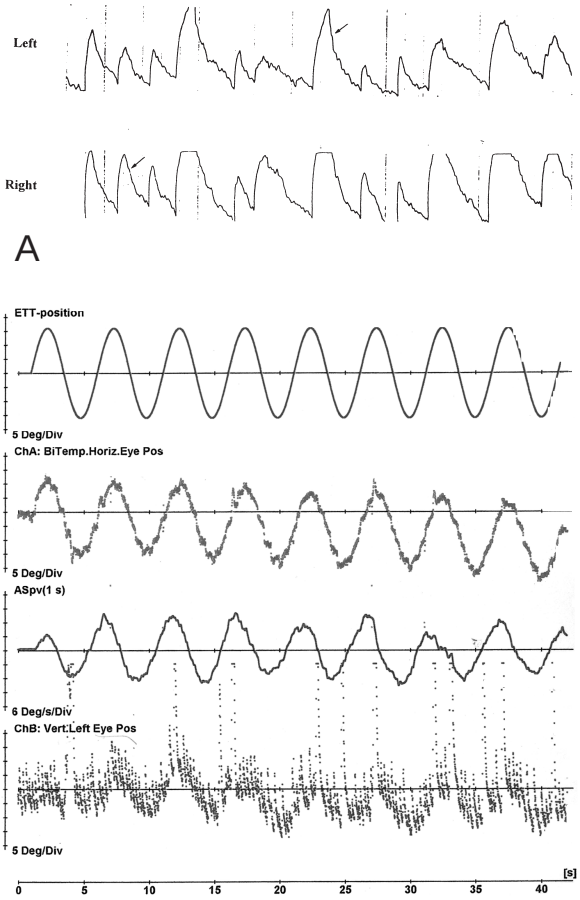

Fig. 1. A: Vertical eye movement recording with EEG (reversed FP1 and FP2 waveform) demonstrates the upbeat nystagmus. The frequency is 2-3 Hz. The slow phases show an exponentially decaying waveform (arrow). B: The ENG recordings of eye tracking test: the upper most line is the tracking line for the testing target; the second is the horizontal eye tracking of the testing target; the third is the horizontal velocity of this eye tracking test; the fourth line is the vertical velocity. We can see the marked saccadic pursuits of the eye tracking test from the second eye tracking line and more significant nystagmus in upward gazing from the fourth line.

On examination, her consciousness and mental status were normal. Cranial nerve examination revealed primary position upbeat nystagmus. Saccadic eye movements on a vertical plane revealed upbeat nystagmus with an overshooting phenomenon, and horizontal pursuit eye movements were saccadic. Her eye movements were full and there was no diplopia, tinnitus, or hearing impairment. Decreased optokinetic nystagmus (OKN) was observed when the target moved upwards. There was no motor weakness of the limbs. Deep tendon reflexes were normal and plantar responses were flexor. Sensation and cerebellar functions were intact.

Electronystagmographic recording showed primary position upbeat nystagmus with an exponentially decreasing velocity waveform in slow phases. Saccadic pursuits, more apparently noted on upward gazing (Fig. 1), dysmetria saccade, and poor OKN were also illustrated by electronystagmography. Caloric recordings revealed bilateral visual suppression. Pure tone audiogram, brainstem evoked potentials and blinking reflexes were normal. Laboratory data, including CBC/DC, basic biochemistry (SGOT, SGPT, BUN, creatinine, blood glucose, electrolytes, uric acid), and thyroid function tests (serum TSH and serum free T4) were unremarkable. Positive anti-nDNA, ANA (homogenous 1:640 ×) and decreased C4 levels (10.2 mg/dL, normal limit: 16-47) were detected, though C3 levels, anti-ENA I (SM & RNP Ab) and anti-cardiolipin IgG Ab were not contributory. Cerebrospinal fluid (CSF) data showed polyclonal gammopathy by protein electrophoresis and immunoelectrophoresis. The white blood cell (WBC) count and protein levels in CSF were normal. Brain MRI showed a tiny lesion with high signal intensity on T2-weighted images (Figs. 2A, 2B) and diffusion-weighted images (DWI) in the middle of the caudal medulla oblongata (Fig. 2C). Under the tentative impression of an ischemic event caused by SLE-related vasculitis, we administrated prednisolone and gabapentin to the patient at a daily dose of 20 mg and 300 mg, respectively. Her oscillopsia ameliorated 2 days later and gabapentin was discontinued. Although the frequency of upbeat nystagmus diminished, the amplitude of nystagmus became larger after the cessation of gabapentin. Thus, gabapentin was readministrated and the dose was increased to 600 mg daily for another 5 days. The frequency and the amplitude of her nystagmus diminished dramatically with this

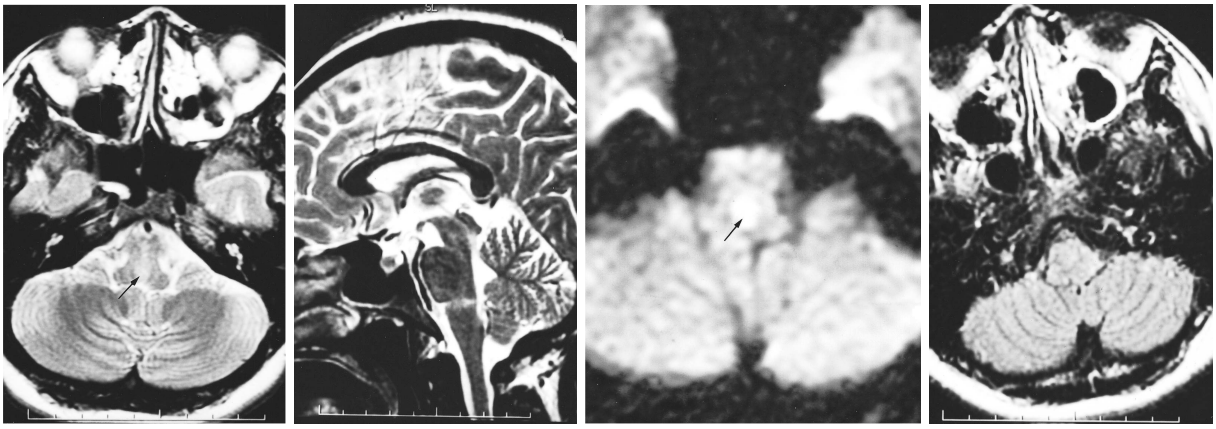

Fig. 2. A: T2WI (TR:4500, TE:101/Ef) brain magnetic resonance image in axial section shows a small lesion in the middle of the caudal medulla oblongata. The site compatible to the location of nucleus intercalatus is involved (arrow). B: The sagittal section of brain MRI on T2WI (TR:4500, TE:75/Ef) also illustrates the small lesion. C: The lesion in the middle of the caudal medulla oblongata (nucleus intercalatus) is bright-up on diffusion-weighted images (arrow), indicating acute cytotoxic edema. D: Follow-up brain MRI (axial section on FLAIR density, TR:9002, TE:142/Ef) three months later showed no visible lesion in the medulla oblongata.

regimen and it almost disappeared two months later. Follow-up brain MRI three months later showed no visible lesion in the medulla oblongata (Fig. 2D).

DISCUSSION

According to Myles M. Behrens, "Upbeating nystagmus in the primary position may suggest a lesion of the cerebellar vermis, medulla, or pons" [9]. Several loci, such as the perihypoglossal and inferior olivary nuclei, brachium conjunctivum, anterior cerebellar vermis, pontomedullary junction, and caudal part of the paramedian medulla, have been attributed to the generation of upbeat nystagmus [2-7]. A wide range of diseases may be responsible, including infarct, demyelination, tumor, Wernicke's encephalopathy, and probably inflammatory processes [1,2,8,10,11]. To date, there is no clear conclusion concerning the causal relationship between the lesion site and the emergence of upbeat nystagmus. The MRI findings of the patient in our report revealed a small lesion in the dorsal paramedian caudal medulla at the site of the nucleus intercalatus. The lesion disappeared three months later. Following analyses of the clinical signs and the MRI findings, the nucleus intercalatus lesion was suspected of playing a pivotal role in the generation of upbeat nystagmus. The patient had SLE with positive nDNA and high titer of ANA. The high signal intensity lesion on T2WI and diffusion-weighted images suggested a new infarction which could have been caused by vasculitis with the underlying SLE.

There are some discrepancies concerning the function of the nucleus intercalatus. Munro and Hirose et al suggested that it is a part of the integrator of ocular-motor signals, based on the fact that their patients had nystagmus with an exponentially decreasing slow phase velocity, a condition similar to our patient [3,4,12]. However, Bronstein et al argued that large lesions in Munro and Hirose's patients may have damaged additional neuronal circuits involved in ocular-motor integration allowing them to secure velocity-position plots of single nystagmic beats [12,13]. Our patient showed an exponentially decreasing velocity waveform in slow phase, clinical findings similar to Munro and Hirose's reports. Also, the lesion site of the current patient was concurrent with the findings reported by Janssen and Bronstein et al. The scenario strengthened the evidence that nucleus intercalatus may act as a vertical position-to-velocity neural integrator in the human oculomotor system.

According to Daroff and Troost's classification, large amplitude upbeat nystagmus which increases in intensity on upward gaze and decreases on downward gaze is associated with lesions of the anterior vermis of the cerebellum, and small amplitude upbeat nystagmus which decreases during upward gaze and increases in intensity with downward gaze is associated with lesions of the medullary regions [14]. The current patient had large amplitude upbeat nystagmus characteristic of enhanced nystagmus in upward gaze yet her lesion was located in the medullary region. In addition, overshooting dysmetria of saccadic eye movement was noted in our patient. We propose that part of the function of the nucleus intercalatus is involved in the integration of signals to the cerebellum, particularly the vermis or the flocculus [15].

Visual suppression has long been recognized to be useful in the differentiation of peripheral from central vertigo [16]. The mechanism of visual suppression is not only dependent on the integrity of the floccular inhibition of the vestibulo-ocular reflex (VOR) but also on the numerous cortical and subcortical structures involved in the realization of voluntary ocular movements [17]. The persistence of visual suppression during the caloric test in this case implied that the nucleus intercalatus may not be crucial in the integration of visual suppression during caloric tests.

In this patient, the nystagmus waxed and waned in concordance with the administration and withdrawal of gabapentin. Gabapentin may benefit the management of acquired nystagmus in several ways [18]. First, gabapentin may enhance GABA synthesis by increasing the activity of glutamic acid decarboxylase [19]. In addition, it may also decrease GABA degradation by inhibiting GABA transaminase [20]. The phenomenon sheds light on the notion that GABA is important in the circuits integrated by nucleus intercalatus.

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上躍式垂直眼振的臨床解剖關係：一病例報告

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上躍式垂直眼振是不常見的神經學徵象。其臨床症狀和眞正病灶的解剖關係是有趣且值得進一步探討的課題。這裡提出一位患有紅斑性狼瘡的病人，發生了上躍式垂直眼振，而且其眼振的速度在慢相時呈現指數型降低，顯示控制垂直性的位置-速度神經整合中樞受到影響。此病例的腦部核磁共振影像在T2WI和DWI條件下都可以發現一小的高訊號病灶，位置與intercalatus神經核處相符合。此病患的眼振經過藥物治療，大約於發病二個月後消失，追蹤的核磁共振掃描也顯示之前的高訊號病灶已消失。因此本篇報告認爲intercalatus神經核確實在人類的眼球運動控制系統上扮演重要的角色。（中台灣醫誌 **2002;7:183-8**）

關鍵詞

核磁共振影像，intercalatus神經核，上躍式垂直眼振

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