



Vestibular Hyperreflexia and Opsoclonus in Acute Hepatitis A Virus Infection

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Dear sir,

Opsoclonus refers to a burst of involuntary, arrhythmic, to-and-fro saccadic oscillations in multiple planes without an intersaccadic pause [1, 2]. Opsoclonus usually results from autoimmunity from preceding infections or dormant neoplasm [3, 4]. Opsoclonus often presents with other neurological symptoms and signs such as dizziness, myoclonus, ataxia, and mental confusion [3, 4]. In this study, we report vestibular hyperreflexia in a patient with opsoclonus-myoclonus syndrome as a rare complication of acute hepatitis A virus (HAV) infection.

A previously healthy, 52-year-old woman presented with fever, myalgia, and general weakness for a week. The patient was febrile with a body temperature at 38.6 °C. The initial serologic tests revealed 1390 IU of aspartate transaminase (reference range [RR]=0–40), 1090 IU of alanine transaminase (RR=0–40), and 586 IU of r-glutamyl transpeptidase (RR=8–35). Viral hepatitis was diagnosed with the anti-hepatitis A IgM antibody in the serum (4.41,

RR=negative). Two days after hospitalization, the patient reported vertigo, oscillopsia, and unsteadiness. The neurological examination at that time revealed ocular flutter and marked truncal and limb ataxia. Head impulse tests (HITs) were unavailable due to frequent fixation losses. Bithermal caloric tests revealed hyperactive responses in both ears (477°/s of summated slow phase velocities induced by warm and cold stimulations in both ears, Fig. 1a). One day later, the patient lapsed into confusion and started to show intermittent myoclonic jerks in all extremities. Meanwhile, the ocular flutter evolved into opsoclonus by additionally involving the vertical and torsional planes (Fig. 1b and Video). Brain MRIs showed no responsible lesion, and cerebrospinal fluid examination showed an albuminocytologic dissociation (1/mm³ of WBCs and 87.5 mg/dL of protein). Whole body and brain fluorodeoxyglucose-positron emission tomography and serologic tests for the paraneoplastic antibodies and tumor markers were all negative. After administration of 1 g per day of intravenous methylprednisolone and 0.4 mg/kg per day of immunoglobulin for 5 consecutive days, the patient gradually regained alertness. The myoclonus also improved over 2 weeks, and opsoclonus and ataxia disappeared 1 month after the initial presentation. Based on the clinical presentation, laboratory results, and response to the immune-modulating treatments, the patient was finally diagnosed with opsoclonus-myoclonus syndrome due to HAV-associated autoimmune encephalitis.

Until now, diverse parainfectious causes have been described in relation to opsoclonus, including herpes simplex, Epstein-Barr, varicella-zoster, human immunodeficiency, mumps, and Zika viruses [1, 2]. Along with those, HAV-associated opsoclonus was also reported once [7].

Of interest, our patient showed vestibular hyperreflexia on caloric tests. Previously, vestibular hyperreflexia was once described with HITs (hyperactive head impulse sign) in a patient with ocular flutter [8]. To the best of our knowledge, however, vestibular hyperreflexia on caloric tests has not been reported in patients with opsoclonus or ocular flutter. Vestibular

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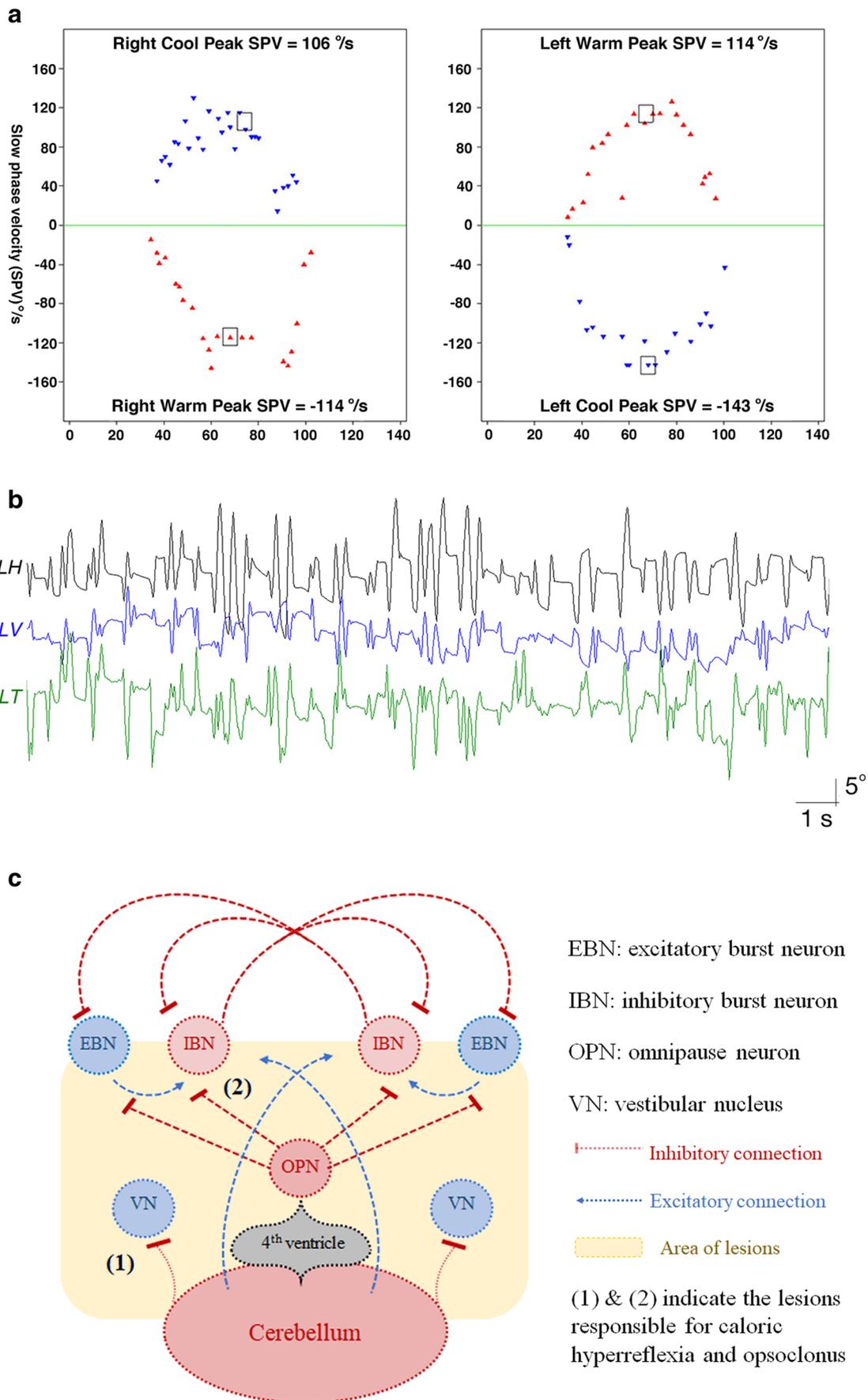
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◀ **Fig. 1** Vestibular hyperreflexia and opsoclonus. **a** Bithermal caloric stimulation induces hyperactive responses in both ears with the sum of the slow-phase velocity (SPV) at 220°/s in the right ear and 257°/s in the left ear (normal range = 37–165). Analysis of SPV was conducted after manual removal of the ocular oscillations due to ocular flutter. **b** Video-oculography (SLVNG, SLMED, Seoul, South Korea) shows fast, involuntary, spindle-shaped to-and-fro saccadic oscillations without an intersaccadic interval in the multiple planes. **c** Schematic illustration of the neural networks responsible for caloric hyperreflexia and opsoclonus observed in our patient. Brainstem and cerebellar dysfunction cause disinhibition of the saccadic burst neurons as well the vestibular nucleus complex (the illustration was simplified from those of the previous studies [5, 6])

hyperreflexia on caloric test or HITs may be ascribed to disinhibition of the vestibular nucleus due to cerebellar dysfunction [9, 10]. Therefore, apart from saccadic oscillations, vestibular hyperreflexia may be an explanation of dizziness, the commonest presenting symptom in patients with opsoclonus [3, 4]. In this patient, vestibular hyperreflexia developed simultaneously with opsoclonus and myoclonus. The mechanism of opsoclonus or ocular flutter and myoclonus can be explained by GABAergic dysfunction in the brainstem-cerebellar network [11, 12]. The floccular Purkinje cells also inhibit the vestibular nucleus partly via the GABAergic pathway [13]. Therefore, vestibular hyperreflexia (disinhibited vestibulo-ocular reflex) may accompany opsoclonus or ocular flutter (disinhibited saccades, Fig. 1c). In summary, opsoclonus can be complicated by HAV infection, and vestibular hyperreflexia may be observed in opsoclonus-myoclonus syndrome.

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Author Contributions Dr. S.U. Lee analyzed and interpreted the data and wrote the manuscript. Drs. H.J. Kim, J. Lee, H.J. Oh, and J.S. Kim analyzed and interpreted the data and revised the manuscript. Dr. J.Y. Choi designed and conceptualized the study, interpreted the data, and revised the manuscript.

Compliance with Ethical Standards

Conflict of Interest Dr. J.S. Kim serves as an associate editor of *Frontiers in Neuro-otology* and on the editorial boards of the *Journal of Korean Society of Clinical Neurophysiology*, the *Journal of Clinical Neurology*, *Frontiers in Neuro-ophthalmology*, the *Journal of Neuro-ophthalmology*, the *Journal of Vestibular Research*, the *Journal of Neurology*, and *Medicine*. Others have no conflicts of interest to disclose.

Ethical Standard This study followed the tenets of the Declaration of Helsinki and was performed according to the guidelines of the Institutional Review Board of Seoul National University Bundang Hospital (B-1802-448-704).

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