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Letter to the Editor

Eyes and hands oscillation in HIV-associated neurocognitive disorder: A case report

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Dear Editor,

In patients with HIV-associated neurocognitive disorder (HAND), movement disorders, including tremor or broken-eye-movement are reported [1]. However to our knowledge, there are no reports that evaluated details of movement disorders in HAND. We present a patient with HAND who was evaluated the development of opsoclonus and hand tremor. After treatment with combined-antiretroviral-therapy, these symptoms ameliorated and thalamic lesion on MRI disappeared. In addition, increased cerebellar blood flow was visualized by applying subtraction ictal SPECT co-registered to MRI (SISCOM) [2].

A 51-year-old Japanese man with 4-year history of bilateral shaky hands was admitted to our hospital for progressive dementia. Although his hand shakiness was previously diagnosed as essential tremor (ET) at another clinic, arotinolol hydrochloride and clonazepam were ineffective. Five years ago he was fired for 20 years-job due to poor performance. One year before admission, he caused several car accidents and problematic behaviors such as stalking women. Furthermore, he changed jobs frequently. There was no previous drug abuse, and no relevant family history of movement disorder.

His general examination revealed red papules and brownish pigmentation on the trunk and extremities, and right inguinal lymphadenopathy. Neurological examination showed saccadic eye oscillations on horizontal and vertical gaze, and postural- and action-induced tremulous movements of the hands (Supplementary Video S1, pre-treatment).

Neuropsychological examination were as follows; WAIS-III, a total IQ of 58; MMSE, 18/30; TMT-A, 194 s; TMT-B, 229 s; Kohs' block design test, 23-point; Rey-Osterrieth complex figure test, copy-score, 34/36; recall-score 6. His scores were 2SD below demographically corrected normative means in IQ, especially verbal comprehension, working memory and processing speed.

Serum investigations revealed positive HIV-Ag/Ab and a CD4+ T-cell count of 26.6/μL, and RNA-polymerase chain reaction (PCR) showed an HIV-1 load of 2.2×10^6 copies/m. Cerebrospinal fluid (CSF) was clear with the following findings: monocytes, 1 cell/mm^3, protein, 45 mg/dl; glucose, 65 mg/dl (serum glucose, 123 mg/dl); HIV-1 RNA-PCR, 5.5×10^4 copy/ml; β2-microglobulin, 4.0 μg/ml; and no abnormal cells. There was no evidence of other infection including HTLV-I, hepatitis B/C, herpes simplex/zoster/cytomegalovirus, JC-virus, tuberculosis, Treponema, Cryptococcus, and Toxoplasma. In addition, thyroid function, lactate, pyruvate, Vitamin B1/B2/B12/folate, and antibodies including anti-nuclear, anti-SS-A/B, anti- CLß2GPI, anti-cardiolipin, anti-GAD, and anti-neutrophil (PR3/MP4-ANCA) were all within normal range.

Surface EMG of the left extensor carpi radialis and an accelerometer placed on the index fingertip demonstrated continuous rhythmic hand oscillation in wrist-extended tonic posture (Fig. 1A). There was no cortical component enlargement on SEP and no elicited long loop reflex, indicating the absence of cortical hyperexcitability. The movement was considered to be a tremor rather than myoclonus. The peak frequency of the hand tremor was 8 Hz (Fig. 1B).

The direction of his eye oscillation appeared to be horizontal, vertical and diagonal like torsional movement. It spontaneously occurred in not only gaze shifting but also in fixating. In downward gaze, the left and right eyes transiently moved independently to opposite directions (slow-motion replay in Supplementary Video S1). An electrooculogram (EOG) performed using a conventional digital EEG machine revealed reproducible synchronized oscillations of the eyes in both horizontal and vertical directions (Fig. 1C). Superimposition of 6 horizontal EOG results showed clear reproducibility (Fig. 1D). We diagnosed the patient with opsoclonus according to Leigh and Zee [3]. The frequency of eye oscillation was 10 Hz.

Brain MRI revealed atrophy of the bilateral hippocampi and amygdalae, dilatation of the bilateral ventricles suggesting white matter atrophy that was consistent with those described in patients with HAND [4], and scattered hyperintensity lesions in the bilateral thalami on FLAIR/T2-weighted images (Fig. 1E) resembling previous report [5]. There were no abnormalities on diffusion-weighted image (DWI), and no contrast enhancement.

Based on these evaluations, we made a diagnosis of opsoclonus and hand tremor with HAND-HAD (HIV-1 associated dementia) according to Frascati criteria [6]. The patient was transferred to the regional core hospital for AIDS according to the guidelines of the Japanese Government.

Abbreviations: HAND, HIV-associated neurocognitive disorder; SISCOM, subtraction ictal SPECT co-registered to MRI; $GABA_A$, gamma-aminobutyric acid A

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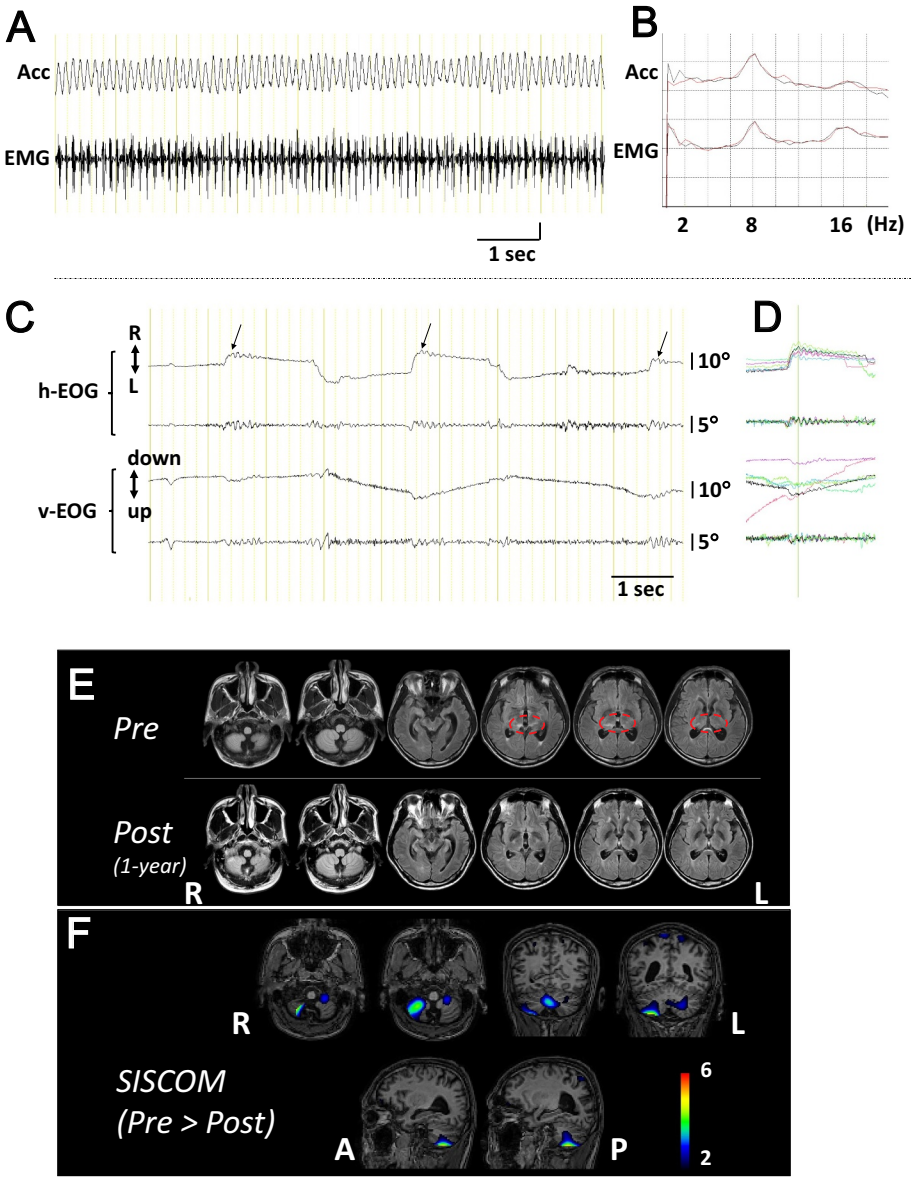

Fig. 1. A: An accerelogram (Acc, upper trace) and surface electromyogram (EMG, lower) during left wrist extension. Acc was put on the left index fingertip, and EMG was placed on the left extensor carpi radialis. Eight hertz rhythmic fine tremor was documented. B: Power spectra of Acc and EMG in A. Results of two different analysis (former and latter half of raw data) were superimposed. Frequency resolution was set to 0.5 Hz. C: Horizontal and vertical electrooculogram (h- and v-EOG) during horizontal eye saccades. In both h- and v-EOGs, eye position and differential waves of eye position were shown. Time constant was set to 2 s for eye position (upper), and 0.03 s for differential waves (lower). Countable 10 Hz rhythmic oscillation were found in gaze terminal not only horizontal, but also vertical direction. Oscillatory amplitude in rightward saccades seemed larger in amplitude as compared with leftward. High frequency filter was set to 40 Hz, and notch filter of 60 Hz was applied. D: Superimposition of EOG with reference to first oscillatory waves (arrow in C) in 6 rightward saccades. The oscillation was reproducible in phase and frequency. The scale is same as C. E: Brain MRI FLAIR images of brain *Pre-* (upper) and *Post-* (lower) treatment. In the *Pre*-treatment, atrophy of bilateral hippocampi and amygdalae, and hyperintensity lesions in bilateral thalami were found. In contrast to that, thalamic lesion disappeared in *Post*-treatment (1-year later). F: Blood flow increase in Pre-treatment as compared with Post. By using Subtraction ictal SPECT co-registered to MRI (SISCOM) method, statistical difference of cerebral blood flow between *Pre-* and *Post-* (1-year later) treatment was analyzed and the results were superimposed the patient's own T1 MRI. Right cerebellum and vermis were found to be activated in *Pre*-treatment. Color scale indicates *Z*-value. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

One year after the diagnosis, the patient's opsoclonus and hand tremor had disappeared in response to HIV therapy (Supplementary Video S1, post-treatment). The patient's activities-of-daily-livings restored and MMSE-score improved to 23/30. Therefore we were convinced that his tremor was not latent ET but due to HIV-infection to CNS. The thalamic lesions on MRI disappeared (Fig. 1E). ^{123}I-IMP-SPECT was performed before and 1 year after the diagnosis. The SISCOM technique [2] showed increased perfusion in the right cerebellum and vermis at pre-treatment compared to 1-year later (Fig. 1F).

The patient was considered particularly interesting due to the presence of 2 different oscillation locations and frequencies, i.e., 8 Hz in the hands and 10 Hz in the eyes. These symptoms disappeared after HIV treatment. There were reversible abnormalities of the bilateral thalami on MRI and of the right cerebellum and vermis on SISCOM. Functional neuroimaging evidence is rare in this condition, but the cerebellar activation during opsoclonus in this patient seems consistent with a previous fMRI study in 2 patients with severe opsoclonus [7].

While the pathogenesis of opsoclonus remains unclear, the cerebellum is known to play an important role. Dysfunction of the fastigial nuclei in the cerebellum and omnipause neurons is thought to be involved [3]. More recently, a clinical report described drug-induced gamma-aminobutyric acid$_A$ (GABA$_A$) dysfunction leading to eye oscillations and body tremor in 2 patients, and GABA$_A$ receptors are known to be located on forebrain, omnipause, olivary, and cerebellar neurons [8]. One patient in that study had an 8-Hz hand tremor, as in our patient, suggesting that hand tremor may be caused by dysfunction of the cerebellar-brainstem network. Since hand tremor in our patient had been present for 4 years, SISCOM demonstrated a chronic cerebellar functional abnormality. CSF findings showed no active CNS inflammatory process. The increased blood flow may not have been due to inflammation, but rather to the disinhibition causing the eye and hand oscillation.

The role of the thalamus in opsoclonus is more controversial than that of the cerebellum. Regarding the control mechanism of somatomotor and eye movement, growing evidence suggests the importance of the thalamus as a relay station in cerebello-brainstem-thalamo-cortical-networks [9,10]. The ventrolateral and ventroposterolateral thalamus receive cerebellar output, and their nuclei project to motor-related cortical areas [10]. Furthermore, thalamotomy alleviates tremor by disconnecting abnormal cerebellar drive through the thalamus and premotor cortex [9]. The thalamus may therefore play a role in this disorder.

In conclusion, our patient's findings may elucidate the significance of the thalamus and cerebellum in the pathogenesis of opsoclonus and hand tremor. The frequencies of these conditions in our case were 10 Hz and 8 Hz, respectively. Further investigations are expected to clarify whether these discrepant frequencies are a common feature of this condition.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.07.030.

Informed consent

Written informed consent for publication of clinical details and videos was obtained from the patient himself and his mother. This is a retrospective and observational case report and is not applicable for the ethics committee approval.

Authors' contribution

AS, SY, KN, KT performed neurological/neurophysiological evaluation for diagnosis. EO, YS made radiological evaluation. KI, AO evaluated and treated for HIV. AS, SY, conceived the study design and drafted the manuscript. TO supervised the interpretation for eye movement findings and EOGs in the study. All co-authors revised the manuscript critically and approved the final version of the manuscript.

Declaration of Competing Interest

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