



Letter to the Editor

GABAergic dysfunction in the olivary-cerebellar-brainstem network may cause eye oscillations and body tremor



Opsoclonus and flutter are ocular oscillations consisting of continuous, involuntary, conjugate saccades without intersaccadic intervals. If these saccadic oscillations are purely horizontal, they are called ocular flutter; if they have horizontal, vertical and torsional components, they are called opsoclonus. Behavioral disturbances, cerebellar ataxia, and limb tremor may co-occur. Several infectious, paraneoplastic, metabolic, and toxic etiologies cause these disturbances, but how neural circuits generate the oscillations is not clear. Two main hypotheses for the pathomechanism of opsoclonus/flutter have been proposed on the basis of different clinical and experimental observations. In the first, reduction of glycinergic inhibition generates oscillations in the positive feedback loop between saccadic brainstem burst neurons (Shaikh et al., 2007). In the second, disinhibition of cerebellar fastigial nuclei induces unwanted saccades through excitatory projections to the burst neurons (Wong et al., 2001). However, both theories remain controversial because they were not confirmed by lesion studies in animals, clinical findings, or model simulations (Lemos and Eggenberger, 2013). Analysis of high-resolution eye movement recordings from patients with opsoclonus/flutter might clarify the underlying mechanisms, but these are extremely rare.

Here, novel observations from two patients with opsoclonus and body tremor subsequent to performance-enhancing substance abuse suggest that eye and body oscillations may be generated by a GABAergic dysfunction of the olivary-cerebellar-brainstem network. The study was approved by the local ethics committee and informed consent was obtained from the patients.

Two tennis-players developed opsoclonus/flutter after a few months of self-administration of performance-enhancing substances. Patient 1, a 32-year-old male, presented with rapid onset of behavioral disturbances, vertigo, ataxia, head tremor, and opsoclonus causing visual blur and oscillopsia (Supplementary Video 1). Patient 2, a 34-year-old male, showed rapid progression of limb and axial tremor, vertigo, mood changes, ataxia, and ocular flutter (Supplementary Video 2). Common infectious, toxic, paraneoplastic, and metabolic causes of opsoclonus/flutter were excluded by negative brain MRI, blood, and CSF exams. Both patients reported an analogous typology, supply, and use of the enhancing chemicals, but only patient 1 provided a sample of the compound for testing, which led to the identification of anabolic androgenic steroids (AAS): nandrolone, stanozolol, and testosterone propionate. Treatment with intravenous IgG and benzodiazepine led to recovery in three-to-four weeks in both patients.

In patient 2, limb tremor characterized by tonic motor activity at 8 Hz was recorded by electromyography (EMG) from the

extensor carpi radialis, during maintenance of the antigravity position of the arm (Fig. 1A). High resolution eye movement recordings from the same patient (pt 2) showed fixation interrupted by frequent horizontal saccadic pulses (back-to-back saccades without intersaccadic interval, Fig. 1B, label P), as well as horizontal macro-square-wave jerks (back-to-back saccades separated by intersaccadic intervals). The saccadic intrusions sometimes passed the midline, causing macrosaccadic oscillations around the target (Fig. 1 B, label S). In some cases, saccadic pulses transitioned from sharply peaked pulses to flattened pulses, evolving into macrosaccadic oscillations (Fig. 1C).

The patient also had an exceptional saccadic intrusion consisting of hybrid, spindle-shaped oscillations at 3.6 ± 0.3 Hz with amplitudes ranging from 9° to 37° (Fig. 1D). Saccades in this spindle were separated by an intersaccadic interval on the right side but not on the left side, so that the oscillations appeared as a hybrid of macrosaccadic oscillations on the right side and saccadic pulses on the left side (a *square-pulse* waveform). A similar co-occurrence of hybrid oscillations with and without intersaccadic intervals was seen in an earlier paper, but was not remarked upon (Helmchen et al., 2003).

Reflexive saccades toward horizontal target displacements were hypermetric and followed by saccadic oscillations (Fig. 1E). Small, uncorrelated ocular tremor was present on both horizontal and vertical axes ($p < 0.001$; horizontal: 45.1 ± 19.1 Hz, amplitude = $0.24 \pm 0.15^\circ$ vs. vertical: 39.3 ± 17.7 Hz, amplitude = $0.26 \pm 0.14^\circ$) (Fig. 1F). The velocity/amplitude main sequence for saccades was normal, whereas the oscillations of the ocular tremor did not follow a saccadic velocity/amplitude main sequence (Fig. 1G).

Hypermetric saccades and macrosaccadic oscillations imply an impairment of the ipsilateral fastigial nucleus (Quaia et al., 1999). On the other hand, saccadic pulses indicate hyperexcitability of premotor burst cells and lack of omnipause neurons activation (Shaikh et al., 2007).

In our cases, the AAS association suggests that these impairments might be due to a GABAergic dysfunction. Indeed, AAS affect neuronal activity by both acute and chronic actions on the GABA_A receptors, with effects varying specifically on their α , δ and ϵ subunit composition and GABA concentration (Oberlander et al., 2012). AAS induce allosteric modulation of the channels and alter GABA_A receptor subunit expression and function (Oberlander et al., 2012). Moreover, AAS affect the immune system by altering antibody and cellular functions (Brenu et al., 2011). Thus, AAS might increase the risk of autoimmune pathological mechanisms in the central nervous system, targeting GABA_A receptors. GABA_A receptors, with α subunit composition vulnerable to AAS, are present on the forebrain, omnipause, olivary, and cerebellar neurons (Pirker et al., 2000). Different subunit composition and GABA availability at synaptic and extra-synaptic GABA receptors might