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LETTER TO THE EDITORS

Transition from downbeat to upbeat nystagmus caused by 4-aminopyridine

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Dear Sirs,

Since 2003, aminopyridines have been used to treat downbeat nystagmus (DBN) [1] and more recently to treat episodic ataxia type 2 (EA2) [2] and cerebellar gait disorders [3]. Therefore, aminopyridines have become a treatment option as symptomatic therapy for different cerebellar disorders (for ref. see [4]). Here we report on a case of idiopathic DBN that exhibited a transition from persistent DBN to transient upbeat nystagmus (UBN) during medication with sustained-release 4-aminopyridine (fampridine, Fampyra^{TM}).

A 68-year-old woman presented in with permanent dizziness, unsteadiness of gait, spontaneous vertical oscillopsia and blurred vision. The symptoms started about 1 year prior to examination at our center. Neurological examination revealed a DBN during fixation, which increased on lateral gaze. In addition, a gaze-evoked nystagmus, saccadic smooth pursuit particularly in downward direction, reduced optokinetic nystagmus and impaired visual fixation suppression of the vestibulo ocular reflex (VOR) were found. Thus, a DBN syndrome was diagnosed. The patient had no family history of neurodegenerative disease. Brain MRI showed supratentorial microangiopathic lesions and no cerebellar atrophy or infratentorial lesions. Blood chemistry was normal. As in most cases [5], the etiology remained unclear.

Eye movements were measured in an upright position by a 30-second eye movement recording carried out with 3-D video-oculography (EyeSeeCam$^{®}$) according to prior work (Resolution = 0.02°, Accuracy = 0.6°, Sampling rate = 120 Hz, Range ±20° in horizontal and vertical direction) [6]. Data were analyzed off-line using Matlab version R2011b (The Mathworks, Natick, MA, USA) to analyse the slow-phase velocity (SPV) of DBN. Slow-phase velocity of DBN was evaluated in primary position with fixed straight position of head in a frame at three different times (before medication, 180 min after the first administration and after 2 weeks of treatment). Tests were performed in darkness. Due to the dependence of DBN of daytime [7], all tests were performed until noon. Patients were seated upright while recording in the following order: (1) calibration primary position and 8.5° right, left, up and down, (2) gaze straight ahead with fixation. Targets were video-projected at eye level onto a wall with white projector screen paint located 180 cm in front of the patient [6].

After giving her written consent, the patient was treated with a test dose of fampridine, the sustained-release of 4-aminopyridine (Fampyra^{TM}) 10 mg orally. Then she was treated for a period of 2 weeks with 10 mg twice daily.

Before treatment, she exhibited a linear vertical nystagmus with a slow upward phase velocity (SPV ± SD) during fixation straight ahead of 1.04°/s ± 0.60. One hundred and eighty minutes after ingestion of the first dose of 10 mg of Fampyra^{TM} she had a transition from a DBN to an UBN with a mean SPV of −1.40°/s ± 0.70 (Fig 1). After the first administration the patient already did not notice any symptoms. After a treatment period of 2 weeks with Fampyra^{TM} 10 mg twice daily, the patient had no nystagmus at all in the video-oculography and no subjective symptoms, i.e., she responded very well to this treatment.

Downbeat nystagmus is the most frequent form of acquired persisting fixation nystagmus [8, 9]. It is most often caused by bilaterally impaired function of the

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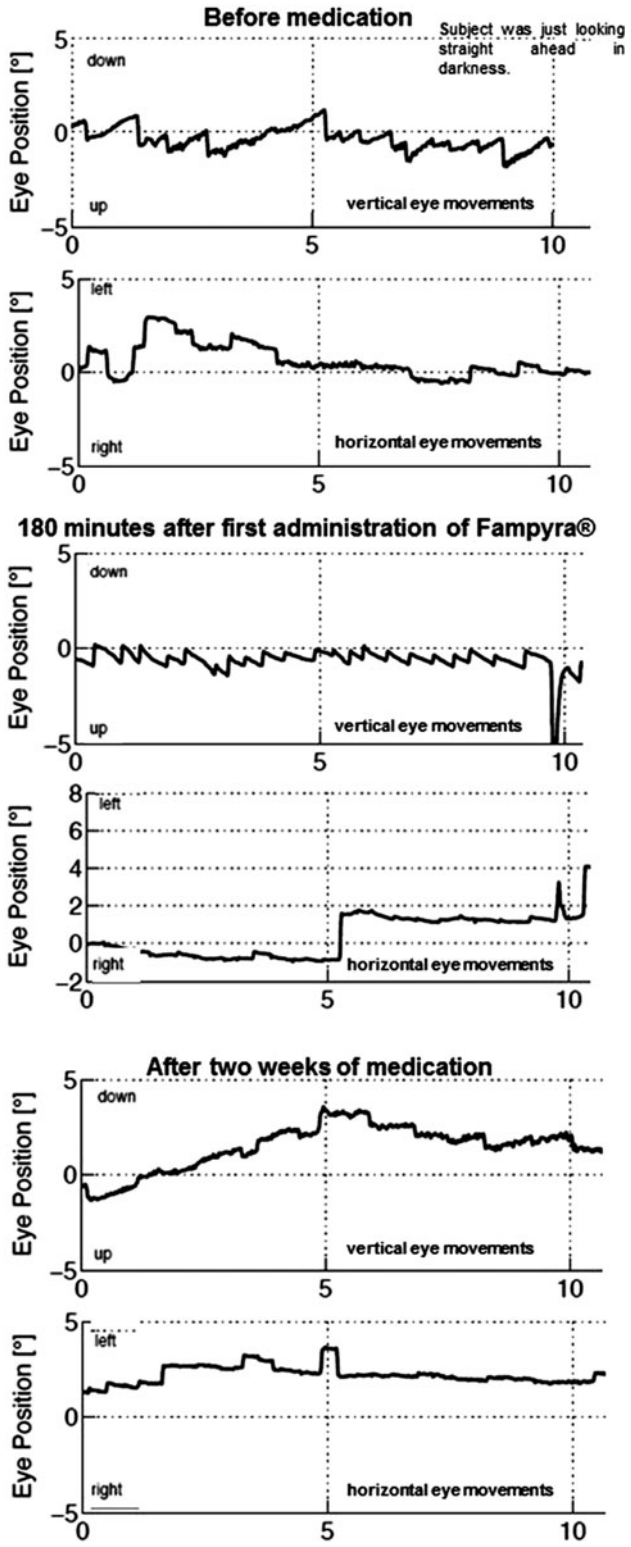

Fig. 1 Vertical and horizontal eye movements at different time spots before medication (*upper trace*), 180 min after ingesting 10 mg Fampyra™ (*middle trace*) and after 2 weeks of treatment (*lower trace*)

flocculus [10]. The causative mechanism of UBN is still a matter of debate and evidently several mechanisms are conceivable [4, 9]. It may have a pathogenesis similar to that of DBN with an underlying imbalance of the vertical VOR [11]. Also a mismatch in the neural coordinate systems of saccade generation and neural velocity-to-position integration due to deficiency of the latter is possible [12]. The UBN usually persists for only a few weeks [13]. In one case it was shown that 4-AP can reduce the intensity of UBN when the subject was fixating a target, and, therefore, most likely by a restoration of fixation suppression of the nystagmus [12].

A report on a case of UBN due to posterior medullary haemorrhage showed that the direction of UBN can change to DBN, suggesting that an underlying central vestibular imbalance caused this transition [14]. Furthermore, a case of Wernicke's enzephalopathy also showed a transition from transient UBN to a permanent DBN over a period of months. The authors advanced the idea that the alteration is caused by the predominant difference in vertical velocity induced by gravity [15].

How can the transition from DBN to UBN in our patient be explained? As mentioned above, several studies showed that DBN can be successfully treated with aminopyridines (for ref. see [4]). Its effect on DBN is most likely caused by an increase of the activity of impaired cerebellar Purkinje cells (PC) [16] and/or the modulation of their resting discharge rate [17]. Both presumably lead to an increased release of GABA [17], thereby augmenting the physiological inhibitory influence on cerebellar nuclei neurons. It is likely that in our patient there was a 4-AP induced transient over-activity of PC which led to increased inhibition of superior vestibular nuclei neurons and the rectus superior muscles, which caused a slow downward drift leading to UBN. A similar mechanism is assumed to be one possible cause of UBN [11].

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Ethical standard This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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