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Beneficial effects of 3,4-diaminopyridine on positioning downbeat nystagmus in a circumscribed uvulo-nodular lesion

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Sirs: Central *positioning* downbeat nystagmus (pDBN) presents with transient nystagmus in supine or the head hanging position in the absence of DBN in the head erect position. In contrast to central *positional* downbeat nystagmus, pDBN requires rapid head positioning manoeuvres to be elicited. The pathomechanism and therapy of central pDBN is not yet known and circumscribed lesions are missing so far [1, 2]. We examined the effect of 3,4-diaminopyridine (DAP) [3, 4] on the oculomotor behavior of a patient with pDBN.

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The 43-year old man had a 4 years history of gait unsteadiness. Cranial MRI and histology revealed a multi-nodular dysembroplastic neuroepithelial tumor. Immediately after partial neurosurgical removal he suffered from head positioning vertigo and vertical oscillopsia on bending the head rapidly into the supine or head hanging position. Neurological examination revealed mild gait ataxia and impaired downward smooth pursuit eye movements. Rapid but not slow head positioning manoeuvres into the head hanging position elicited a typical DBN which increased within a few seconds and lasted for about 30 s. Eye movements were recorded with the Eyelink II system [3], electro-oculography and the scleral search coil system. Vertical vestibulo-ocular reflex (VOR) was tested by rapid head pulses. Visually guided saccades were examined with targets presented on lateral gaze; smooth pursuit eye movements at 0.2 and 0.3 (±16°). Vestibular turntable stimulation and the VOR tilt suppression were analyzed [5]. Eye movements were recorded prior and up to 90 minutes after DAP ingestion (20 mg). The patient gave informed written consent. The protocol was approved by the local ethics committee. Statistical differences were significant for $p < 0.05$. There was no nystagmus on lateral gaze with the head erect. When the head was rapidly turned back into the head hanging position there was profound downbeat nystagmus, which increased on lateral and downward gaze (Fig. 1A). Slow phase velocity (SPV) of pDBN was linear and revealed a crescendo/decrescendo time course (Fig. 1B) with a maximal peak SPV of 72°/s. Downward but not upward smooth pursuit was impaired (Fig. 1C, D; grey). Horizontal pursuit, saccades, subjective visual vertical and responses to caloric irrigation were normal. Vertical (up: 0.93 ± 0.4; down: 0.93 ± 0.6) and horizontal VOR gain was normal. Prolonged head shaking elicited a perverted nystagmus [6]. Time constants of postrotatory nystagmus were severely prolonged and dumping of the postrotatory vestibular time constant by head tilts was virtually abolished (without: 20.5 s, with head tilt: 22.3 s).

Following DAP ingestion downward smooth pursuit (gain: 0.63 ± 0.13 to 0.77 ± 0.1; $p < 0.001$; Fig. 1C, D; dark) and peak SPV of pDBN (72°/s–56°/s; $p < 0.001$; Fig. 1B) significantly improved by on average 22% and 21%, respectively. Before surgery, T2-weighted cranial MR images showed multilocular lesions in the nodulus, ventral uvula, and immediately adjacent to the fourth ventricle (Fig. 1E–H). The lesions did not affect the flocculus, paraflocculus, posterior vermis (Fig. 1G) and the vestibular nuclei.

Several lines of evidence indicate that pDBN was caused by the uvulo-nodular lesion: (1) the prolongation of postrotatory nystagmus [7], (2) the abolished tilt suppression of the postrotatory vestibular nystagmus by pitching the head forward [7], (3) perverted headshaking nystagmus [6] and (4) the fact that pDBN appeared immediately after the uvulo-nodular tumor resection. Importantly, there was exclusively pDBN suggesting inappropriate velocity storage mechanisms of vertical angular VOR signals. For the first time we describe small but beneficial effects of DAP on pDBN. DAP reduced pDBN and downward pursuit to a similar extent suggesting a common pathomechanism. Deficient downward smooth pursuit has recently been

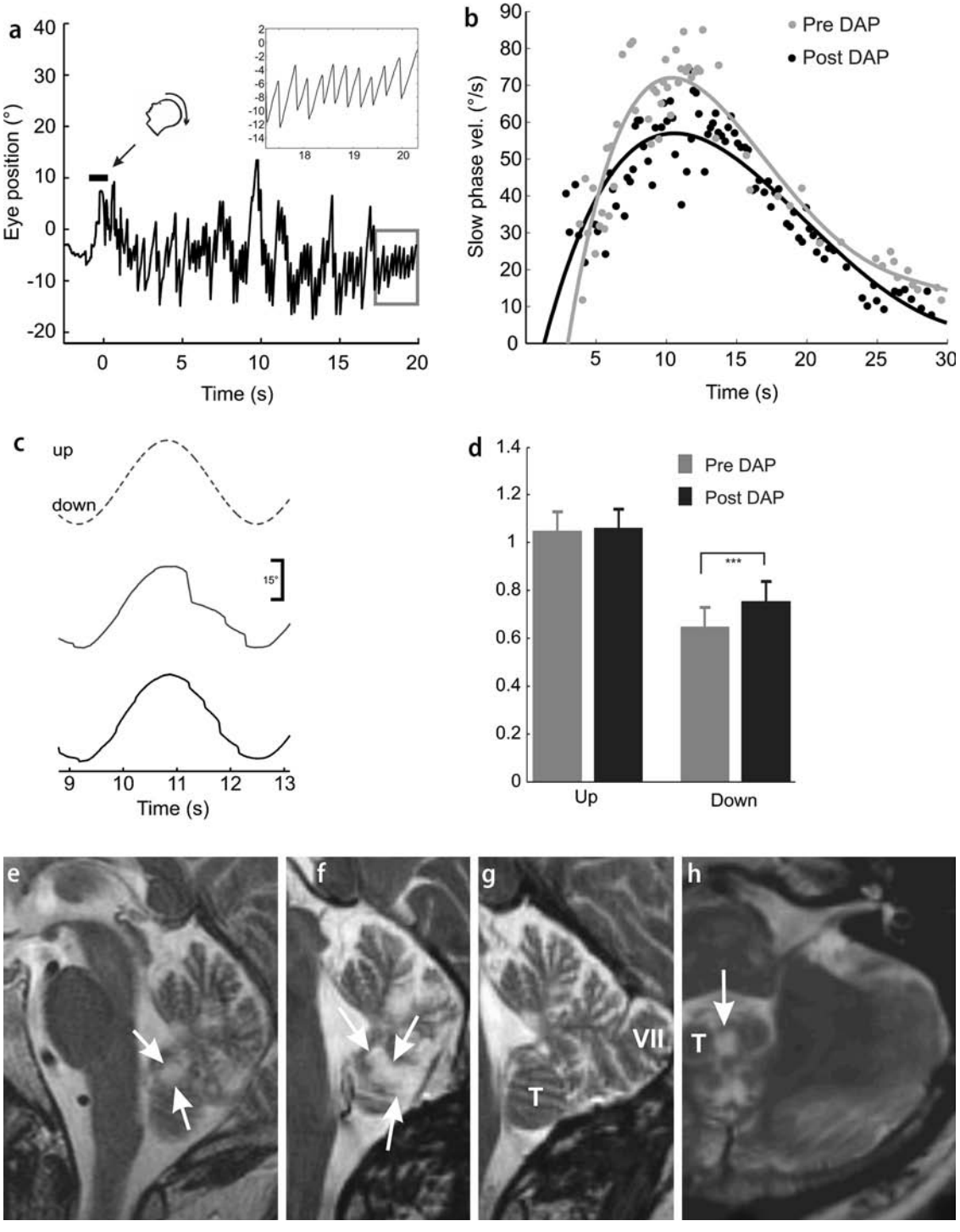

Fig. 1 Eliciting manouvre for pDBN (**A, B**): Vertical eye position is shown on lateral gaze over time before and after rapid backward movements of the head in the head hanging position. In contrast to the head erect position, there is severe pDBN with a linear SPV (magnified view in the window). (**B**: Peak SPV of pDBN before (grey) and 45 min after (black) DAP ingestion (stimulus: dashed line). Downward smooth pursuit before (grey; top trace=stimulus) and after (black) medication is shown with original recordings (**C**) and (**D**) median + 25% quartil (*** = $p < 0.001$). T2-weighted sagittal (**E-G**) and transversal (**H**) images of the patient's cerebellum before (**E**) and after (**F-H**) the operation. A tumor lesion comprises the ventral uvula and nodulus (arrows, **E**, **H**). After the tumor resection there is a longitudinal signal intensity (arrows, **F**) reflecting the surgical canal towards the nodular lesion. The tumor and the transsection did not affect the tonsils (**T**) and the posterior vermis (lobulus VII, arrows, **G**)

suggested to cause DBN [8]. However, pursuit gain is increased with uvula lesions [9] indicating other mechanisms. Nodulus and uvula control the angular VOR [10] and participate in the velocity storage mechanisms during rapid head tilts. We propose that pDBN is related to impaired vestibulo-cerebellar inhibition of the brainstem velocity storage or its inputs from the vertical VOR signals. DAP may partially restore this deficient uvulo-nodular inhibition, e.g. by reducing an asymmetric charge of the velocity storage.

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