Effect of 3,4-diaminopyridine on the gravity dependence of oculardrift in downbeat nystagmus

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The pathomechanism of downbeat nystagmus (DBN) remains controversial but each mechanism has to account for 1) its gaze-evoked vertical centripetal component which increases on down and lateral gaze, and 2) the vertical bias component of the upward slow phase velocity (SPV) in gaze straight ahead. The vertical velocity bias of DBN has a gravity-dependent component which leads to maximal drift velocity when patients lie in prone position and minimal in supine position. Recently, 3,4-diaminopyridine (3,4-DAP) has been shown to be effective in reducing DBN in patients with their heads upright. However, DBN of several of those patients showed only small changes. One reason might be that gravity-dependent mechanisms were not considered.

Patients and methods. A 63-year-old woman had a 4-year history of vertical oscillopsia, diplopia, blurred vision, and postural instability. Symptoms increased on downward gaze and considerably more when she bent her head forward. Clinically she showed DBN. In the head forward bending position there was a marked increase of DBN. Except for the tendency to fall backward, the neurologic examination was unremarkable. MRI, CSF, and blood screening were normal. Electronystagmography was normal except for mildly impaired horizontal smooth pursuit. DBN was superimposed on downward vertical smooth pursuit (gain: 0.54 at 0.3 Hz), upward pursuit was only slightly impaired (gain: 0.79). Saccades, subjective visual vertical, and funduscopy were normal.

After the patient gave written consent DBN was recorded using the video-based Eyelink II system (SR Research, Toronto, Canada). Head-fixed LEDs attached to the headband of the Eye-link system were presented in front of the patient at a fixed distance (0.6 m) in gaze straight ahead and ± 10° up and down. Horizontal targets were presented at 40°. The head position was monitored by an inclinometer. The following five pitch positions of the head relative to the upright position were examined: head upright (0°), bending backward by 45° (−45°) and 90° (−90°), bending forward by 45° (+45°) and 90° (+90°). Eye position calibration was performed in vivo. Each eye movement channel was recorded with a sampling rate of 500 Hz and filtered using a Gaussian filter (50 Hz).

Recordings of DBN were performed 15, 45, and 90 minutes after 20 mg 3,4-DAP ingestion (university hospital pharmacy). Nystagmus was detected semiautomatically, using a velocity criterion of 30°/second. Negative SPV indicates upbeat, positive downbeating nystagmus.

Results. Prior to 3,4-DAP ingestion, the SPV of DBN was small, ranging from 0.8 ± 0.3°/second in gaze straight ahead to 3.7 ± 0.93°/second on lateral gaze. SPV of ocular drift varied as a function of head position (figure, A), e.g., SPV in gaze straight ahead increased from 0.8 ± 0.3°/second in the upright head position to 12.6 ± 1.1°/second in the +45° head position (anteflexion), and on lateral gaze from 3.7 ± 0.9°/second to 23.6 ± 1.7°/second (figure, B). In the −90° (“supine”) head position, DBN changed into an upbeat nystagmus (UBN) of −8.43 ± 2.8°/second in gaze straight ahead. There were three main effects after 3,4-DAP ingestion.

First, SPV of DBN was hardly changed in the upright head position, either with gaze straight ahead (see figure, A) or in the lateral gaze position (see figure, B). Second, in the +90° (“prone”) head position SPV of DBN was reduced from 11.1 ± 1.3°/second to 3.2 ± 1.3°/second (>70%) (see figure, A). In lateral gaze, in the +45° head position 15 minutes after ingestion, SPV was reduced from 23.6 ± 1.7°/second to 14.8 ± 2.8°/second (see figure, B). Third, SPV of UBN increased in the −90° head (“supine”) position 90 minutes after ingestion from −8.4 ± 2.8°/second to −14.1 ± 1.3°/second in gaze straight ahead (see figure, A), whereas it did not change in lateral gaze. These effects on positional DBN started after 15 minutes and lasted for at least 1 hour (see figure, B).

In the +45° and +90° head position the patient noticed a strong improvement of blurred vision and oscillopsia disappeared. Thirty minutes after ingestion visual acuity was improved from 20/60 to 20/30. About 60 minutes after ingestion she noticed peri-oral and digital paresthesia for 10 minutes.

Discussion. We show that 3,4-DAP exerts a distinct influence on the gravity-dependent component of the vertical velocity bias of DBN. This effect might account for why some DBN patients did not benefit from the therapy. The spontaneous upward drift in DBN may be due to a vestibular tone imbalance, an upward shift of the eyes' null position for vertical gaze holding, or an asymmetry of vertical smooth pursuit signals. The reduction of DBN in the prone pitch position after 3,4-DAP ingestion seems to occur at the cost of increasing UBN, i.e., the velocity bias is shifted in a downward direction. However, the curve relating SPV to head position (see figure, A) was not shifted since differences of DBN in gaze straight ahead between baseline and 3,4-DAP were only found for prone and supine head positions. This indicates specific but asymmetric effects of 3,4-DAP on the gravity-dependent component but only minor effects on the gravity-independent bias. 3,4-DAP seems to reduce DBN by influencing the vestibulocerebellar inhibition, not only of anterior semicircular canal afferents but also of the physiologically overactive otolith-ocular reflex in an asymmetric way.

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Received March 18, 2004. Accepted in final form May 27, 2004.

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References


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Hallucinations during methylphenidate therapy

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Methylphenidate (MPH) is the medication of choice for attention deficit hyperactivity disorder (ADHD), administered to millions of children with minimal side effects. The appearance of hallucinations at therapeutic doses of MPH has rarely been reported. We describe three children with ADHD, who were treated with low doses of MPH and developed complex visual and haptic hallucinations. The causal role of MPH in the development of hallucinations was based on their appearance after ingestion of the drug, resolving after its withdrawal, and the absence of psychiatric comorbidity that could explain such phenomena. In one patient, the hallucinations reappeared after an inadvertent rechallenge.

Case reports. Case 1. A 7-year-old adopted boy with ADHD and oppositional defiant disorder was treated with MPH, 0.3 mg/kg (7.5 mg), once daily. After 1 year of treatment, he reported seeing and feeling snakes crawling on and around him starting ~1 hour after drug ingestion. The teaching staff assumed an emotional problem and used psychological interventions to free him of these behaviors. When these proved ineffective and to rule out drug-induced hallucinations, placebo was substituted for MPH with immediate cessation of hallucinations. Pemoline was begun, and no psychiatric symptoms reappeared during a follow-up period of >2 years.

Case 2. A 12-year-old boy with cerebral palsy, low normal intelligence, and ADHD, combined subtype, was treated with MPH, 0.3 mg/kg (10 mg), once daily with marked improvement in attention and hyperactivity. One morning, he was observed crawling on the floor complaining that roaches were surrounding him. This phenomenon appeared 2 hours after ingesting MPH, continuing for almost 2 hours, and disappeared without any specific intervention. MPH was withdrawn, and there was no recurrence. However, deterioration in school performance was so dramatic that rechallenge with MPH was attempted at his previous dose. Immediate recurrence of hallucinations necessitated stopping MPH. Three-year follow-up evaluation has been uneventful.

Case 3. A 7.5-year-old boy with normal intelligence was diagnosed with ADHD and mild learning disabilities. He had been treated successfully with 0.25 mg/kg MPH once daily (7.5 mg). Several months later, he became distressed, claiming that mosquitoes and other crawling creatures were in his bedroom and on him. He refused to sleep in his bed and would not enter his room. After several days, MPH was stopped, the visual and haptic sensations ceased, and within a week he returned to sleep in his room. During a follow-up period of 2 years, there was no recurrence of the hallucinations.

Discussion. We describe three patients who developed haptic and visual hallucinations at low therapeutic doses of MPH. Rechallenge in Case 2 elicited hallucinations, and administration of placebo resulted in their cessation. The hallucinations appeared several hours after ingesting MPH. In Patient 2, the hallucinations began shortly after beginning use of MPH, but the other two had received MPH for longer periods. All hallucinatory phenomena resolved promptly after MPH was discontinued.

A previous report of MPH-induced visual and haptic hallucinations in two children is similar to ours; one, after several years of treatment, became fearful and had seen horses and horseshoes, whereas the other saw mosquitoes and other bugs on his face, accompanied by an itching sensation. Rechallenge caused reappearance of the hallucinations, and after MPH cessation, the hallucinations disappeared. In a previous case report of a patient who had been treated with OROS MPH (Concerta, McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, PA), the hallucinations reappeared after an inadvertent rechallenge in August (2 of 2) 2004 NEUROLOGY 63 753