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SUPPRESSION OF SACCADIC INTRUSIONS IN HEREDITARY ATAXIA BY MEMANTINE

Spinocerebellar ataxia with saccadic intrusions and neuropathy (SCASI) is an autosomal recessive disorder with linkage to chromosome 1p36.¹ Affected patients are unable to read because of frequent horizontal saccadic intrusions and hypermetria. We report here therapeutic effects of memantine in SCASI and a possible mechanism.

Methods. We studied two brothers with SCASI (ages 54 and 58 years).¹ Both had corrected visual acuity of 20/20, but reading was barely possible because of saccadic intrusions and hypermetria. Ten normal subjects, ages 24 to 65 years, served as controls.² All subjects gave informed consent in accordance with our Institutional Review Board and the Declaration of Helsinki. Eye movements were measured (magnetic search coil technique)³ before and 1 month after increasing memantine to a dose of 20 mg/day. Patients attempted to fixate a target at 1.2 m for 3 minutes in ambient lighting. We also studied saccades and microsaccades, using reported methods for analysis.^{2,4}

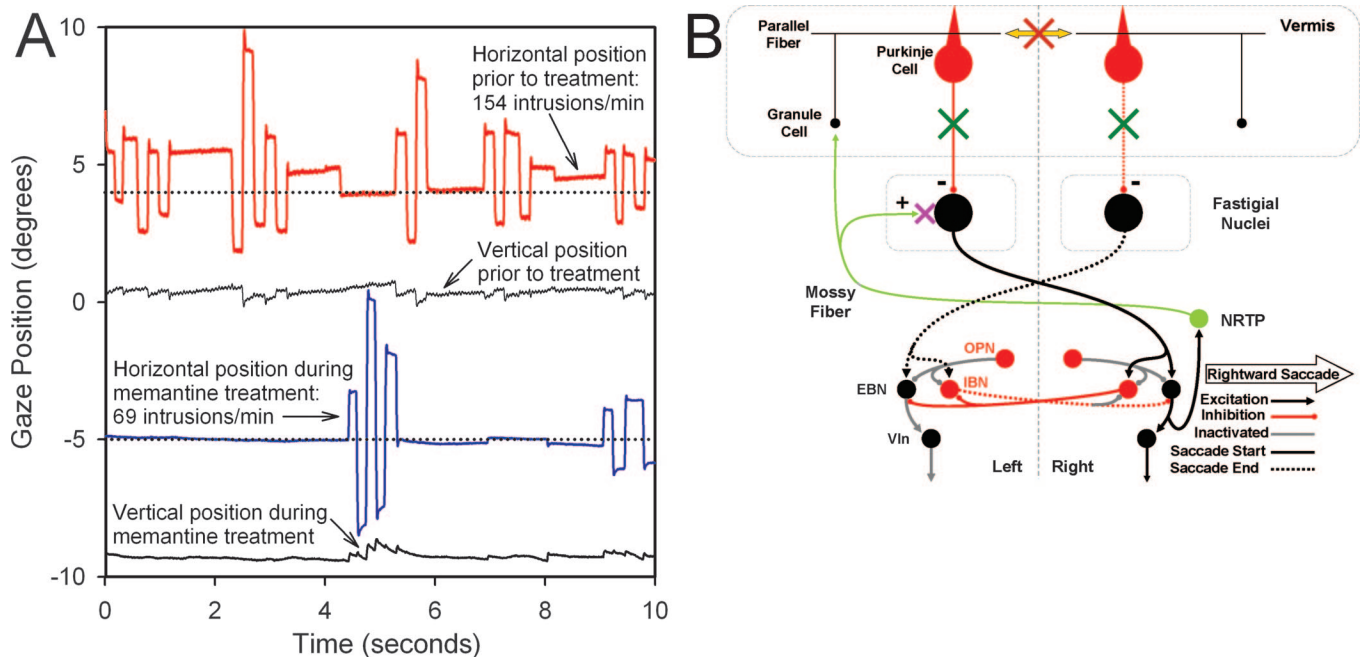
Results. Prior to treatment, both patients with SCASI had similar inability to hold steady fixation because of horizontal macrosaccadic oscillations, more marked in Patient 1 (figure, A; see supplemental data on the *Neurology*[®] Web site at www.neurology.org). Larger saccades were faster than normal.¹ Gain of horizontal saccades was increased in both patients. Treatment with memantine caused sustained improvement in reading in both patients without side effects. Thus, memantine made it possible for Patient 2 to fill out medical insurance forms for the first time. The frequency of saccadic intrusions declined from 154/minute to 69/minute in Patient 1 (figure, A), and from 168/minute to 89/minute in Patient 2; microsaccades were also reduced 22% in Patient 1 and 33% in Patient 2. The size of saccadic intrusions was unchanged in Patient 1 (figure, A) but reduced in Patient 2 ($p < 0.001$). Peak velocity/amplitude relationships remained unchanged in both patients for saccades and microsaccades.

The gain of visually guided saccades was reduced only for leftward saccades in Patient 2.

Discussion. Memantine halved the frequency of saccadic intrusions in two patients with a form of spinocerebellar ataxia, but only decreased their size in Patient 2. Memantine, an uncompetitive NMDA receptor channel blocking drug, is reported to improve vision in several forms of nystagmus.³ However, the neurobiology of saccades differs from mechanisms responsible for nystagmus.^{3,5} Saccades are generated by premotor burst neurons—excitatory (EBN) and inhibitory (IBN)—which lie in the reticular formation of the brainstem; they fire intensely during saccades, but are silent at other times. Burst neurons receive glycinergic inhibition from omnidirectional pause neurons (OPN) that lie in the midline pons. Starting a saccade requires the cessation of the OPN. Once started, a saccade can stop either because OPN restarts and inhibits the premotor burst neurons, or because the caudal part of the ipsilateral cerebellar fastigial nucleus fires the brainstem's contralateral IBN and chokes off the drive to the motor neurons.⁶

Hypermetria in our patients with SCASI could be due to late arrival of a stop signal on parallel fibers of the dorsal vermis, and thence to the ipsilateral fastigial nucleus.¹ Consequently, once started, saccades overshoot the target. However, this mechanism does not explain how oscillations can start during fixation. Our desire to search the visual field continually gives rise to potential eye movements, which are normally suppressed by the frontal eye fields in favor of fixating the object of interest.³ However, the fixation command is not so strong that it can suppress saccades induced by electrical stimulation of superior colliculus or cerebellar vermis.³ We assume that when signals related to potential saccades arrive randomly on the mossy fibers, the output of the deep cerebellar nuclei is suppressed by inhibition from the cerebellar cortex (figure, B), so that there is little or no output from the cerebellum to disturb fixation. In our patients, we propose that disease affecting the cerebellar cortex reduces the

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(A) Fixation of stationary target (dotted line) before and during memantine treatment; traces are offset to aid clarity. (B) Schematic of cerebellar and brainstem circuitry showing our hypothesis (only major pathways active during rightward saccades are shown). Bilateral input on mossy fibers (green) goes to the granule cells in cortex and, through collaterals, to the fastigial neurons. Input is relayed from granule cells to Purkinje cells via parallel fibers. The Purkinje cells inhibit the fastigial neurons, normally canceling out the excitatory drive from the mossy fibers. The main role of the vermis is to set the timing (indicated by the gold arrow) between the contralateral fastigial nucleus (which fires early to accelerate the saccade) and the ipsilateral fastigial nucleus (which fires late to choke off the saccade drive).⁶ In SCASI, cortical circuits may be affected so that the transfer across the midline is slowed (red X) and the inhibition of the fastigial cells is reduced (green X). These effects make saccades abnormally fast (uninhibited drive through contralateral fastigial nucleus) and hypermetric (late choke signal). We hypothesize that memantine (pink X) inhibits NMDA receptors receiving mossy fiber input on fastigial neurons and reduces the probability that an input will cross the reduced threshold. This reduces the frequency of saccadic intrusions without affecting their amplitude. Vin = abducens motor neuron; N RTP = nucleus reticularis tegmenti pontis.

inhibition on the deep nuclei. When the potential saccade signals arrive on the mossy fiber collaterals, the deep nuclei generate a substantial output and cause a saccade.

Since NMDA receptors are present at mossy fiber synapses on cerebellar nuclei,⁷ this could be a site where memantine exerts its glutamate-antagonist effect (figure, B). Thus, the level of inhibition from cerebellar cortex could set a threshold below which random signals arriving at the fastigial nuclei on mossy fibers cannot elicit a saccade. We hypothesize that the effect of memantine is to reduce mossy fiber inputs below that threshold. This mechanism is involved in triggering the saccade, and would not necessarily affect their amplitude or speed. Further studies are required to confirm our findings, test our model, and explore other possible effects of memantine on the saccadic system.

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INTERNAL JUGULAR VEIN VALVE INSUFFICIENCY IN COUGH SYNCOPE

A 53-year-old man with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea was admitted to the hospital for the evaluation of recurrent syncopal episodes induced by paroxysmal cough. Loss of consciousness was brief, and preceded by the sensation of “fullness in the head.” Syncope was provoked also by prolonged expiration during spirometry, which revealed severe bronchial obstruction. However, oxygen saturation on room air and blood gases were within normal limits. To reproduce reported symptoms, the Valsalva maneuver (VM) was performed with the patient in the supine position with noninvasive, continuous blood pressure monitoring (Finapres, Ohmeda) and finger pulse oximetry. This resulted in a brief loss of consciousness, although no desaturation, decrease in blood pressure, or bradycardia was noted. Transthoracic echocardiography revealed normal left and right ventricular function, mild tricuspid insufficiency, and no evidence of pulmonary hypertension. There was no right-to-left shunt detected on the bubble-contrast study. Neurologic assessment, MRI of the brain, and EEG were unremarkable. Duplex-Doppler examination of extracranial carotid and vertebral arteries showed no stenosis. However, evaluation of the internal jugular veins (IJVs) with the use of color Doppler revealed right internal jugular valve insufficiency with flow reversal during inspiration (figure A, first two arrows). During the straining phase of VM, valve insufficiency became severe, and complete flow reversal in right IJV was demonstrated (figure A, third arrow). The reversal of flow in the right innominate vein was also demonstrated when assessed from the right suprasternal window with 2.5-MHz cardiac probe (figure B). Evaluation of the left IJV did not reveal valvular insufficiency.

Discussion. Pathogenesis of cough syncope is unclear and probably multifactorial. It typically occurs in middle-age, overweight men with COPD.¹ Various mechanisms have been postulated, in-

cluding those decreasing arterial blood pressure (ABP) or increasing intracranial pressure (ICP) (according to the relation $CPP = ABP - ICP$, where CPP is cerebral perfusion pressure). Recent studies have demonstrated that many cough syncope patients exhibit prolonged hypotension in response to VM or cough.^{2,3} Potential mechanisms of cough-induced hypotension include decreased cardiac output secondary to reflex-mediated vasodilation or bradycardia, or impaired venous return. Coexistence of significant cerebral atherosclerosis may facilitate the occurrence of syncope under these circumstances.

The possible role of transiently increased ICP in the pathomechanism of cough syncope is supported by the results of transcranial Doppler (TCD) and ABP monitoring during cough-induced loss of consciousness. In one study, cessation of forward flow in middle cerebral artery and even diastolic flow reversal during cough syncope was demonstrated.⁴ At that time, no hypotension, bradycardia, or hypoxia was present, and TCD evaluation at baseline was normal. In another study, invasive assessment of IJV pressure was performed in cough syncope patients.⁵ During cough, IJV pressure equalized ABP in patients with cough syncope, but not in a healthy volunteer. These observations suggest that cough-induced syncope may result from transiently increased ICP due to abnormally high IJV pressure that is transmitted from the thoracic cavity.

The association between cough syncope and COPD is not satisfactorily explained. It was proposed that patients with chronic bronchial obstruction are able to generate higher intrathoracic and, in consequence, higher IJV pressure. However, the low incidence of cough syncope, disproportionate to the high number of patients with COPD exacerbations and cough, suggests that additional factors are involved. One of them may be the functional status of IJV valves. These valves are located just above the termination of both the right and the left IJV and are competent in the majority of healthy individuals.⁶ Their physiologic role is to prevent cephalad venous

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