Published in final edited form as:

Neurology. 2008 March 4; 70(10): 810–812. doi:10.1212/01.wnl.0000286952.01476.eb.

SUPPRESSION OF SACCADIC INTRUSIONS IN HEREDITARY ATAXIA BY MEMANTINE

A. Serra, MD, K. Liao, MS, S. Martinez-Conde, PhD, L.M. Optican, PhD, and R.J. Leigh, MD
From the Veterans Affairs Medical Center (A.S., K.L., R.J.L.), Case Western Reserve University, Cleveland, OH; Institute of Clinical Neurology (A.S.), University of Sassari, Italy; Department of Neurobiology (S.M.-C.), Barrow Neurological Institute, Phoenix, AZ; and Laboratory of Sensorimotor Research (L.M.O.), National Eye Institute, NIH, DHHS, Bethesda, MD.

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.

Address correspondence and reprint requests to Dr. R. John Leigh, Department of Neurology, University Hospitals, 11100 Euclid Avenue, Cleveland, OH 44106-5040; rjl4@po.cwru.edu.

Disclosure: The authors report no conflicts of interest.

Supplementary data at www.neurology.org

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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Jorge Otero-Millan for assistance with data analysis.

Supported by NIH grant EY06717, the Office of Research and Development, Medical Research Service, Department of Veterans Affairs, the Evenor Armington Fund, OASI Institute for Research and Care (IRCCS) on Mental Retardation and Brain Aging, Troina, Italy, and the Barrow Neurological Foundation.

References

1. Swartz BE, Bsepavola IN, Burmeister M, et al. Pathogenesis of clinical signs in recessive cerebellar ataxia with saccadic intrusions and sensorimotor neuropathy (SCASI). *Ann Neurol* 2003;54:824–828. [PubMed: 14681893]

2. Kumar AN, Han YH, Liao K, et al. Evaluating large saccades in patients with brain-stem or cerebellar disorders. *Ann NY Acad Sci* 2005;1039:404–416. [PubMed: 15826993]
3. Leigh, RJ.; Zee, DS. *The Neurology of Eye Movements (Book/DVD)*. Vol. 4. New York: Oxford University Press; 2006.
4. Engbert R, Kliegl R. Microsaccades uncover the orientation of covert attention. *Vision Res* 2003;43:1035–1045. [PubMed: 12676246]
5. Ramat S, Leigh RJ, Zee DS, et al. What clinical disorders tell us about the neural control of saccadic eye movements. *Brain* 2006;130:10–35. [PubMed: 17121745]
6. Quaia C, Lefevre P, Optican LM. Model of the control of saccades by superior colliculus and cerebellum. *J Neurophysiol* 1999;82:999–1018. [PubMed: 10444693]
7. Pugh JR, Raman IM. Potentiation of mossy fiber EP-SCs in the cerebellar nuclei by NMDA receptor activation followed by postinhibitory rebound current. *Neuron* 2006;51:5–7. [PubMed: 16815325]

Figure. Fixation of stationary target before and during memantine treatment and schematic of cerebellar and brainstem circuitry

(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). Furthermore, reduced inhibition from the Purkinje cells allows any mossy fiber signal larger than the reduced threshold to initiate an intrusive saccade. 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; NRT = nucleus reticularis tegmenti pontis.