AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Magnetic Oculomotor Prosthetics for Acquired Nystagmus

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Purpose: Acquired nystagmus, a highly symptomatic consequence of damage to the substrates of oculomotor control, often is resistant to pharmacotherapy. Although heterogeneous in its neural cause, its expression is unified at the effector—the eye muscles themselves—where physical damping of the oscillation offers an alternative approach. Because direct surgical fixation would immobilize the globe, action at a distance is required to damp the oscillation at the point of fixation, allowing unhindered gaze shifts at other times. Implementing this idea magnetically, herein we describe the successful implantation of a novel magnetic oculomotor prosthesis in a patient.

Design: Case report of a pilot, experimental intervention.

Participant: A 49-year-old man with longstanding, medication-resistant, upbeat nystagmus resulting from a paraneoplastic syndrome caused by stage 2A, grade I, nodular sclerosing Hodgkin's lymphoma.

Methods: We designed a 2-part, titanium-encased, rare-earth magnet oculomotor prosthesis, powered to damp nystagmus without interfering with the larger forces involved in saccades. Its damping effects were confirmed when applied externally. We proceeded to implant the device in the patient, comparing visual functions and high-resolution oculography before and after implantation and monitoring the patient for more than 4 years after surgery.

Main Outcome Measures: We recorded Snellen visual acuity before and after intervention, as well as the amplitude, drift velocity, frequency, and intensity of the nystagmus in each eye.

Results: The patient reported a clinically significant improvement of 1 line of Snellen acuity (from 6/9 bilaterally to 6/6 on the left and 6/5−2 on the right), reflecting an objectively measured reduction in the amplitude, drift velocity, frequency, and intensity of the nystagmus. These improvements were maintained throughout a follow-up of 4 years and enabled him to return to paid employment.

Conclusions: This work opens a new field of implantable therapeutic devices—oculomotor prosthetics—designed to modify eye movements dynamically by physical means in cases where a purely neural approach is ineffective. Applied to acquired nystagmus refractory to all other interventions, it is shown successfully to damp pathologic eye oscillations while allowing normal saccadic shifts of gaze. *Ophthalmology 2017;■:1−9 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Supplemental material available at www.aaojournal.org.

An estimated 0.24% of the population has persistent nystagmus, an abnormal rhythmic oscillation of the eyes typically of neural origin.[1] When acquired later in life, nystagmus often is associated with oscillopsia, a distressing perception of constant movement of the visual scene that is both intrinsically disabling and a cause of reduced visual acuity.[2] The impact of nystagmus on life is substantial, and visual functioning scores typically are lower than those for better-known visual impairments such as age-related macular degeneration.[3] Although many drugs have been evaluated, no generally effective pharmacologic treatment exists.[4] Given the heterogeneity of the underlying physiologic dysfunction, no single agent conceivably could target what is likely to be a complex multiplicity of potential neural loci, and thus the historical wide individual variability in the response to pharmacotherapy is likely to continue.

Although nystagmus has many different origins within the central nervous system, all converge on a single target: the extraocular muscles that move the globe itself. Therefore, an intervention that attenuates the action of oculomotor muscles could offer an effective treatment for nystagmus, regardless of the cause. Unfortunately, although strabismus surgery may sometimes improve the location of the point of gaze where the nystagmus is less pronounced—known as a *null point*—complete immobilization of the eyes generally is unhelpful because it blocks any ability to shift gaze; this type of intervention generally is restricted only to cases of third-nerve palsy with very large angle deviations refractory to other surgical approaches.[5]

The ideal solution is to attenuate the oscillation of the eyes when the patient is fixating a target, while still permitting saccadic movements necessary to refixate. Because saccadic forces are substantially greater than the

http://dx.doi.org/10.1016/j.ophtha.2017.05.028
ISSN 0161-6420/17

forces generating the pathologic drift that triggers each nystagmic jerk,[6] it follows that an intermediate force could damp nystagmus without preventing saccades. Crucially, such force needs to be delivered remotely, without direct physical contact that otherwise would lead to postoperative fibrosis and loss of ocular motility. Currently, the only practical means of achieving action at a distance is magnetic, permanent, rare earth magnets having sufficient magnetic flux density while remaining of implantable size.

We therefore conceived a permanent magnetic implant with a pair of interacting elements: an orbital part fixed to the orbital wall and an ocular part tethered to an extraocular muscle. The implant location is determined by the plane of the dominant drift component of the nystagmus—the orbital floor for vertical nystagmus and the lateral wall for horizontal—with the ocular part sited within the Tenon's sheath of the relevant muscle, thereby maintaining a mobile tissue boundary between the 2 elements. The magnetic force thus damps ocular oscillation, while leaving a full range of movement and essentially normal saccadic gaze shifts. Herein we describe the design, implantation, and evaluation of a prototype device in 1 patient with highly symptomatic, treatment-resistant upbeat nystagmus and report the clinical observations, including those from a more than 4-year follow-up period after surgery.

Methods

Patient

The patient, a right-handed man in full-time employment as a driver of commercial heavy goods vehicles, was referred to the neuro-ophthalmology clinic at 49 years of age for progressive unsteadiness, slurred speech, vertigo, and variable diplopia evolving over 2 years. At presentation, there was upbeat nystagmus on lateral gaze, but not in the primary position, and broken pursuit. Horizontal diplopia was present just for distance causing a concomitant distance right esotropia of 8 prism diopters (PD) base out. His Snellen visual acuity was 6/5+3 in the right eye and 6/5−3 in the left. Other than mild dysarthria, the rest of the neurologic examination was unremarkable.

Routine investigations revealed a mediastinal mass subsequently identified as stage 2A, grade I, nodular sclerosing Hodgkin's lymphoma, for which he received 3 courses of standard doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy and involved field radiotherapy of 35 Gy in 20 fractions, leaving him in sustained, complete remission. There were otherwise no biochemical, hematologic, serologic, or cerebrospinal fluid abnormalities. Magnetic resonance imaging of the brain showed only mild cerebellar atrophy.

Despite successful tumor treatment, his symptoms progressed to include distressing oscillopsia. Repeat examination now showed nystagmus in the primary gaze with no null point, and his visual acuity had dropped to 6/9 bilaterally. The angle of squint increased and stabilized at 30/35 PD base out, near and distance. Ocular motility revealed mild lateral gaze defects (−0.5) in both eyes, −0.5 right inferior rectus underaction, and an A pattern. This symptomatic progression contributed to his loss of employment.

A diagnosis of paraneoplastic cerebellar syndrome was made. There was no response to corticosteroid immunomodulation or to a course of intravenous immunoglobulins. The clinical picture remained static until the present intervention, 7 years after the original diagnosis.

In the intervening years, many pharmacologic agents for symptomatic treatment of the nystagmus were tried without success, including benzodiazepines, carbamazepine, valproate, levetiracetam, gabapentin, acetazolamide, phenytoin, memantine, baclofen, 3-4 diaminopyridine, and 4-aminopyridine.

Faced with symptoms he found profoundly debilitating, the patient asked us to consider novel experimental approaches. This led us to recollect an informal report from a Brazilian ophthalmologist, Harley Bicas, about the successful use of implantable magnets in nystagmus (theoretically elaborated by him after our intervention was concluded[7]). The patient's request prompted the research project described in this study. Informed consent was obtained following procedures approved by an ethics committee with specific expertise in handling device studies (London-Dulwich NRES Committee). All research adhered to the tenets of the Declaration of Helsinki.

Implant Design

We designed a 2-part rare-earth magnetic implant consisting of a small cylindrical ocular part designed to be sutured to an extraocular muscle near its insertion and within the tendinous sheath and a larger cylindrical orbital part designed to be fixed to the orbital wall. The thickness of the orbital magnet was conceived to be variable, guided by the external testing of prototypes of the same diameter, but of different lengths, externally before implantation (see below). The ocular magnet was designed to be made of sintered samarium−cobalt material, and the orbital magnet was designed to be made of sintered neodymium−iron−boron, with the magnetic axis in both being aligned to the cylindrical axis. The ocular magnet was a cylinder 3 mm in diameter and 1 mm in length, and the orbital magnet was a cylinder 3.73 mm in diameter and 2 mm in length. Because permanent magnetic materials are biologically reactive, each part was encased in grade 2 titanium, with laser welded joints, and the titanium cases included small flanges to facilitate suturing (for the ocular part) or gluing (for the orbital part). The final design was custom manufactured by Magnet Sales & Service Ltd (Swindon, United Kingdom). Note that the magnetic materials exhibit sufficient temperature stability to allow standard sterilization techniques to be applied.

Extraoperative Procedures

Oculometrics. The capacity to maintain fixation at cardinal positions of the gaze was assessed with the aid of high-resolution video-based eye tracking. A single, white, square-shaped stimulus subtending 0.5° of visual angle was displayed on a black background on a 21-inch cathode ray tube monitor (1024 × 768 pixels; refresh rate, 140 Hz) at a viewing distance of 60 cm. Eye position was monitored at 1000 Hz (EyeLink 1000; SR Research, Ottawa, Canada). Both pupil and corneal reflections were used (dual tracking mode), and eye position calibration was performed using EyeLink's standard 9-point calibration screen.

The patient followed the fixation stimulus sequentially to each of 9 positions on the screen in a randomized predetermined order while keeping his head fixed with the aid of a chinrest and headrest. Each fixation point was maintained for 30 seconds. The 9 positions fell on an invisible regular rectilinear grid subtending 30° of visual angle in each dimension. He was encouraged to maintain fixation as accurately as he could. No optical correction was used. Data for each eye were acquired during both binocular and monocular viewing; binocular data are reported as closest to real-life experience. Both the raw position data with respect to time and saccades