OBSERVATION

Pendular Nystagmus in Patients With Peroxisomal Assembly Disorder

Adriana A. Kori, MD; Nathaniel H. Robin, MD; Jonathan B. Jacobs, MEng; Daniel M. Erchul, MS; Osama O. Zaidat, MD; Bernd F. Remler, MD; Lea Averbuch-Heller, MD; Louis F. Dell'Osso, PhD; R. John Leigh, MD; Arthur B. Zinn, MD, PhD

Background: Pendular nystagmus commonly occurs in congenital and acquired disorders of myelin.

Objective: To characterize the nystagmus in 3 siblings with an infantile form of an autosomal recessive peroxisomal assembly disorder causing leukodystrophy.

Design: We examined visual function and measured eye movements using infrared oculography. We noted changes in eye speed and frequency before and after the administration of gabapentin to 1 patient.

Results: All 3 siblings showed optic atrophy and pendular nystagmus that was predominantly horizontal, at a frequency of 3 to 6 Hz, with phase shifts of 45° to 80° between the oscillations of each eye. Gabapentin administered to 1 child caused a modest improvement of vision and the reduction of the velocity and frequency of oscillations in the eye with worse nystagmus.

Conclusion: The pendular nystagmus in these patients was due to their leukodystrophy and may have a similar pathogenesis to the oscillations seen in other disorders affecting central myelin.

Arch Neurol. 1998;55:554-558

From the Departments of Neurology (Drs Kori, Zaidat, Remler, Averbuch-Heller, Dell'Osso, and Leigh), Biomedical Engineering (Messrs Jacobs and Erchul and Drs Dell'Osso and Leigh), and Genetics (Drs Robin and Zinn); the Center for Human Genetics (Drs Robin and Zinn), University Hospitals of Cleveland; and Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, Ohio.

SPONTANEOUS oscillations of the eyes in infants are usually diagnosed as idiopathic congenital nystagmus, but may also be associated with visual loss or hereditary neurological disorders.[1] We evaluated the eye movements of 3 siblings with optic atrophy, developmental delay, spastic quadriparesis, and severe demyelination of the subcortical areas and brainstem. Detailed biochemical studies showed that these siblings had multiple deficiencies of peroxisomal function, thereby establishing the diagnosis of neonatal adrenoleukodystrophy (NALD).[2-5] Neonatal adrenoleukodystrophy, an autosomal recessive disorder, is part of the recently recognized group of disorders known as the peroxisomal assembly deficiencies. Each of these siblings had pendular nystagmus. This is the first time that the nature of these oscillations has been characterized.

REPORT OF CASES

CASE 1

A 14-year-old Arabic boy was the product of a normal pregnancy and delivery from parents who were first cousins. He was able to sit by 8 months of age and crawl by 1 year, but he never walked independently. He stopped crawling at 3½ years of age and could no longer sit independently at age 6. His language development was initially normal but deteriorated by age 4. His father described "jumping eye movements" that developed by age 2 but apparently disappeared 6 months later. He was given the diagnosis of NALD at age 14 years, when he was found to have increased plasma concentrations of very-long-chain fatty acids, phytanic acid, and pipecolic acid; increased concentrations of very-long-chain fatty acids in cultured skin fibroblasts; and mildly deficient plasmalogen biosynthesis and abnormal catalase distribution in cultured skin fibroblasts (**Table 1**). (Similar laboratory findings were observed for patients 2 and 3.) His neurological examination at age 14 years showed that he had no speech output, except for some mumbling. His pupils were equal and reacted symmetrically to light. Ophthalmoscopic examination showed bilateral optic atrophy. He had a full range of eye movements, and nystagmus was not clinically evident. He had severe spastic quadriparesis and areflexia. Magnetic resonance imaging of his head showed dif-

METHODS

After obtaining informed consent from the patients' father, we recorded horizontal movements of each eye using infrared oculography. Patients 2 and 3 were able to see the test targets (light-emitting diodes presented at a viewing distance of 1.3 m in a dark room), but calibration was approximate because no "foveation periods" were present (see below). Eye-movement signals were digitized at 200 or 400 Hz. Digitized eye-position signals were differentiated, and saccades were removed interactively, using a criteria of 40°/s. These "desaccaded" records of nystagmus velocity (typical array size >2000 points) were then converted to eye speed (by taking absolute values of the arrays), and the mean value was computed. We performed a fast Fourier transform on the eye-velocity data to determine the predominant frequency of oscillations. We also made qualitative estimates of the conjugacy, relative speed, and gain of saccades.

Table 1. Biochemical Findings in Patient 1

Biochemical Findings*	Patient 1	Controls
Plasma		
Very-long-chain fatty acids, μg/mL		
C26:0	2.67	0.33±0.18
C26:1	0.81	0.29±0.19
C24/C22	1.90	0.84±0.08
C26/C22	0.32	0.01±0.01
Phytanic acid, μg/mL	46	<3
Pipecolic acid, μmol/L	144	1.9±0.9
Cultured fibroblasts		
Very-long-chain fatty acids, μg/mg protein		
C22:0	0.62	0.90±0.40
C26:0	0.36	0.07±0.04
C26:1	0.28	0.09±0.07
C26/C22	0.58	0.08±0.03
Plasmalogen synthesis†	1.01	1.65±0.66
Catalase, % cytosolic	45.5	<10

**These studies were done in the Peroxisomal Diseases Laboratory, Kennedy Krieger Laboratory, Baltimore, Md. Control data are given as mean±SD.*

†Expressed as the ratio of the rate of microsomal steps of plasmalogen synthesis to that of peroxisomal steps of plasmalogen synthesis.

fuse demyelination subcortically (**Figure 1**) and in the brainstem.

CASE 2

The 11-year-old brother of patient 1 had an unremarkable birth and early development. He walked at 16 months, but his gait was reported as always being abnormally wide-based and waddling. He stopped walking at age 6 years. At age 2 years, tremor of his hands developed. His intellectual development was mildly impaired. He has passed the fourth grade and is fluent in both English and Arabic. Nystagmus was first noted at age 1½ years, but his

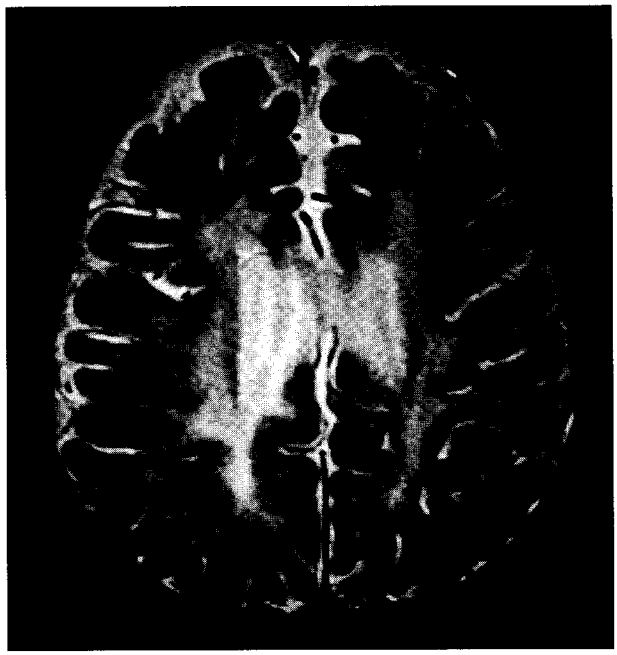

Figure 1. *Magnetic resonance imaging scan of patient 1 (echo time, 80 milliseconds; repetition time, 2200 milliseconds) shows an abnormal, diffuse increase of signal from subcortical and periventricular white matter.*

father thought that it was less pronounced during the 2 months before he was seen by us. A general neurological examination, at age 11 years, showed quadriparesis, with greater involvement of the lower extremities, and areflexia. His speech was dysarthric, and he had titubation of his head and marked dysmetria of his upper limbs. His best near visual acuity was Jaeger 10 +1 in the right eye and Jaeger 5 −1 in the left eye. He was able to identify 2 of 12 of the pseudoisochromatic plates with each eye. He did not have oscillopsia. His pupils were equal and reacted symmetrically to light. An ophthalmoscopic examination showed bilateral optic atrophy. His eye movements were full and in range. There was no overt internuclear ophthalmoparesis. Occasionally saccadic intrusions were observed.

He had a spontaneous, conjugate, horizontal, pendular nystagmus that was increased in the rightward gaze and decreased in the leftward gaze, but unaffected by convergence. Magnetic resonance imaging of his brain showed diffuse demyelination in the subcortical white matter. Areas of increased signal in the T_2-weighted images were also seen at the pontine level, especially in the dorsal paramedian region extending into the medulla. The inferior olives appeared normal. There were no signs of brainstem or cerebellar atrophy.

A regimen of gabapentin, 200 mg 3 times a day, was started, and the patient reported improved vision, more noticeable in the left eye. His visual acuity improved to Jaeger 7 −1 in the right eye and Jaeger 2 +2 in the left eye. By clinical examination, his pendular nystagmus did not appear to have changed.

CASE 3

The patient, the 4½-year-old sister of patients 1 and 2, was the product of a normal pregnancy, labor, and de-

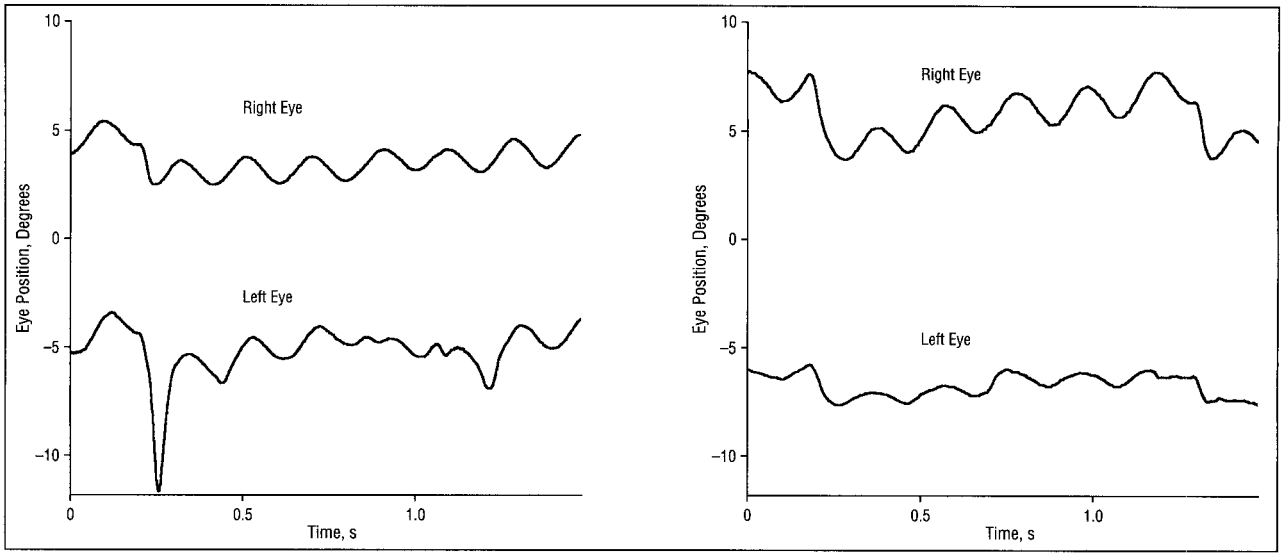

Figure 2. *A representative record of the spontaneous nystagmus shown by patient 2 during attempted fixation of a target straight ahead. The horizontal component of his right and left eyes are shown; records have been offset for clarity of display, and eye positions are relative rather than absolute. Left, The pendular oscillation shows larger and more variable amplitudes in the left than in the right eye. Right, Record showing the effects of gabapentin. The amplitude and frequency of oscillations have decreased in the left eye, but the amplitude has increased slightly in the right eye.*

livery. She walked at age 14 months with an unsteady gait but has never been able to run. She is easily fatigued. She can feed herself, but her hands are described as shaky. She was noted to have nystagmus 6 months before being seen by us. On examination, her arm movements were dysmetric, tone was increased in the lower extremities, and her gait was wide-based with foot-drop and scissoring. She was areflexic. She was able to name colors. Her pupils were equal and reacted symmetrically. Ophthalmoscopy revealed bilateral optic atrophy. Spontaneous pendular nystagmus was noted and was mainly horizontal but occasionally showed vertical and torsional components. The result of her brain magnetic imaging scan was unremarkable.

RESULTS

It was not possible to calibrate the records of this patient's eye movements because of the patient's difficulty in cooperating, but intermittent low-amplitude nystagmus was evident at a frequency of about 3 Hz, with phase shifts between the oscillations of the 2 eyes of up to 180°.

CASE 4

The patient showed a pendular nystagmus (**Figure 2**, left). The frequency of the nystagmus was predominantly at 5.5 Hz in both eyes, sometimes with a superimposed left-beating jerk component. There was a phase shift between the oscillations of the 2 eyes of about 45°. When the patient attempted to fixate on a target straight ahead, the mean (±SD) amplitude of the horizontal component was 1.36° (±0.27°) in the right eye and 2.35° (±1.07) in the left eye. The mean eye speed was 14.5°/s in the right eye and 34.6°/s in the left eye. Covering either eye to prevent fixation affected the amplitude of the nystagmus in the left eye only; when the right eye was covered, the mean amplitude of the left eye nystagmus decreased to 1.5°, and when the left eye was covered, it decreased to 1.35°. The nystagmus in the left eye also was modified with different gaze angles. For example, at 15° of rightward gaze, the mean (±SD) amplitude of oscillations in the left eye was 2.96° (±0.60°) whereas at 15° of leftward gaze, it was 0.7° (±0.1°). Convergence produced a phase shift of 90° and a decrease in the frequency of oscillations to 4.7 Hz but did not substantially change the amplitude and speed of the nystagmus.

In addition to affecting visual acuity, the administration of gabapentin reduced the peak-to-peak amplitude of the nystagmus in the left eye to a mean (±SD) of 0.96° (±0.47°), but in the right eye, the peak-to-peak amplitude increased to 1.99° (±0.47°) (Figure 2, right). The frequency of the oscillations decreased to 4.7 Hz in both eyes, so that the mean speed of the nystagmus was 17.9°/s in the right eye and 10.8°/s in the left eye. The phase shift remained at approximately 45°.

CASE 5

The calibration of eye movement records was not possible because of the patient's lack of cooperation. The records showed a pendular nystagmus in the horizontal plane with frequencies that varied from 5.0 to 6.5 Hz in both eyes. There was usually a phase shift of 90° between the eyes that occasionally increased to about 180°.

COMMENT

This report of 3 siblings with an autosomal recessive peroxisomal disorder and clinical evidence of leukodystrophy expands the number of conditions in which pendular nystagmus has been associated with disorders affecting myelin of the central nervous system (**Table 2**). To interpret the significance of this association, we will first review the nature of the peroxisomal disorders and then

Table 2. Biochemical Findings in Peroxisomal Disorders*

Biochemical Test	Present Report	Assembly Disorder NALD	Single-Enzyme Defect XALD	Single-Enzyme Defect RD
Plasma very-long-chain fatty acid	↑	↑	↑	N
Plasma phytanic acid	↑	↑	N	↑
Urine pipecolic acid	↑	↑	N	N
Plasmalogen synthesis	↓	↓	N	N
Phytanic acid oxidation	ND	↓	N	N
Catalase, % cytosolic	↑	↑	N	N

*NALD indicates neonatal adrenoleukodystrophy; XALD, X-linked adrenoleukodystrophy; RD, Refsum disease; N, normal; ND, not determined; up-pointing arrow, increased levels; and down-pointing arrow, decreased levels.

Table 3. Causes of Pendular Nystagmus

- Visual loss (including unilateral disease of the optic nerve)
- Disorders affecting CNS* myelin
  - Multiple sclerosis
  - Toluene abuse
  - Pelizaeus-Merzbacher disease
  - Cockayne syndrome
  - Peroxisomal assembly disorders
- Oculopalatal myoclonus
- Acute brainstem stroke
- Whipple disease
- Spinocerebellar degenerations
- Congenital nystagmus

*CNS indicates central nervous system.

discuss how congenital or acquired disorders involving myelin could lead to such ocular oscillations.

SPECTRUM OF PEROXISOMAL DISORDERS

The peroxisomal disorders are a clinically diverse group of genetic diseases.[2-5] This clinical diversity reflects the metabolic diversity of the enzymes contained in peroxisomes and the complex mechanisms required for the biosynthesis and importation of these enzymes into a peroxisome. The peroxisomal disorders are classified into 2 groups according to their morphologic appearance and the number of peroxisomal enzymes affected: peroxisomal assembly defects and single-enzyme defects. The peroxisomal assembly disorders are characterized by absent or reduced numbers of peroxisomes and multiple enzyme deficiencies and are caused by defects in the importation of peroxisomal proteins from the cytosol into the peroxisomal matrix. This group of disorders comprises 5 clinically defined disorders, including Zellweger syndrome, NALD, and infantile Refsum disease. Zellweger syndrome, the most severe disorder in the spectrum, is characterized by a prenatal onset, craniofacial dysmorphism, cataracts, retinopathy, hepatocellular disease, renal cysts, adrenal hypoplasia, chondrodysplasia punctata, profound hypotonia, a neuronal migration defect, severe psychomotor retardation, and leukodystrophy; death usually occurs in the first year of life. Patients with NALD and those with infantile Refsum disease have a similar but milder clinical course; they do not have renal malformations or chondrodysplasia punctata, and they may survive into childhood or, rarely, adulthood. When a patient has evidence of leukodystrophy, the diagnosis of NALD is made.[4] Detailed genetic studies, including complementation analysis, have shown that the peroxisomal assembly disorders are genetically heterogenous, ie, the same phenotype may be caused by mutations of different loci. Conversely, mutations of a specific locus may produce different phenotypes. Complementation studies using direct gene transfer are currently under way to define the molecular basis of this complicated genotype-phenotype relationship.

The single-enzyme disorders are characterized by a normal number of peroxisomes and deficiency of a single enzyme. This group of disorders is composed of 10 clinically and biochemically defined entities. X-linked adrenoleukodystrophy (ALD) and Refsum disease are the best known of these disorders. X-linked ALD generally has its onset in childhood and presents as a severe, progressive neurodegenerative process. It may also occur as a neurodegenerative disorder in adolescence or adulthood or as adrenomyeloneuropathy or isolated adrenal insufficiency. All forms of X-linked ALD are caused by mutations affecting the same gene, which encodes for a protein required for the transport of very-long-chain fatty acids across the peroxisomal membrane.

The diagnosis of NALD was established for our patients by demonstrating multiple enzyme deficiencies and an abnormal intracellular distribution of peroxisomal enzymes in combination with evidence of leukodystrophy on magnetic resonance imaging. In addition, the studies done with cultured skin fibroblasts showed incomplete deficiencies, consistent with the relatively mild phenotype of our patients. From a practical perspective, these findings demonstrate the benefit of performing a battery of peroxisomal function tests rather than simply measuring the concentration of plasma very-long-chain fatty acids, as is commonly done when a peroxisomal disorder is suspected. This battery of tests readily distinguishes NALD (and other assembly disorders) from X-linked ALD (Table 2); if the results of more than 1 measurement are abnormal, a disorder of peroxisomal assembly is present.

RELATIONSHIP BETWEEN PEROXISOMAL ASSEMBLY DISORDERS AND PENDULAR NYSTAGMUS

A factor common to disorders that have been previously reported in association with pendular nystagmus (**Table 3**) and the peroxisomal disorder that afflicted our patients is the involvement of central myelin. Furthermore, the visual system is commonly involved in disorders of central myelin, including the peroxisomal disorders. For example, Zellweger syndrome is characterized by pigmentary retinopathy and NALD by optic atrophy, whereas visual involvement in X-linked ALD is less severe, with most patients having normal visual acuity.[6-8] Unlike with X-linked ALD, disorders of peroxisome assembly may show neuronal lipidosis.[9] Nystagmus has been

previously noted in NALD, but it was neither characterized nor recorded.[10,11] Our 3 patients' nystagmus was pendular in waveform, with predominant frequencies of 3.0, 5.5, and up to 6.5 Hz; these characteristics are similar to the forms of pendular nystagmus reported with other disorders of myelin, such as multiple sclerosis.[1,12] A correlation was noted between the severity of visual acuity loss and the amplitude of nystagmus in patients with multiple sclerosis, which led to the hypothesis that delays in visual transmission may be responsible for these ocular oscillations.[13] This hypothesis, however, was tested, and findings indicated that delays in the control of eye movements by vision are not the root cause of such nystagmus; it was suggested that these oscillations occur when feedback loops between the brainstem and cerebellum go awry.[12] Furthermore, disorders that do not affect vision, such as oculopalatal tremor following brainstem stroke, may lead to pendular nystagmus.[1] In such disorders, the frequency of oscillation tends to be lower (1-2 Hz) than in our patients or in patients with other demyelinating diseases. These disorders may reflect the interruption of visual inputs that reach the cerebellum via the inferior olive and are important for optimal eye movements. Magnetic resonance imaging of the brain of patient 2 showed an area of demyelination in the paramedian dorsal pons and medulla. This is similar to the location of demyelinative lesions in patients with acquired pendular nystagmus,[14] and it has been suggested that cell groups of the paramedian tracts,[15] which project to the cerebellar flocculus, may be involved. Lesions within these brainstem-cerebellar feedback circuits might lead to instability and produce pendular nystagmus.[12] Autopsy findings have shown that cerebellar degeneration is particularly severe in patients with NALD,[11] with marked gliosis and demyelination of the cerebellar white matter and atrophy of the granular layer, along with Purkinje cell loss and Bergmann gliosis.

In adults, acquired pendular nystagmus may be reduced or abolished by the use of gabapentin.[16] The mechanism of action of gabapentin in pendular nystagmus remains uncertain, although γ-aminobutyric acid is known to be important in brainstem and cerebellar circuits concerned with holding the gaze steady.[17,18] In patient 2, the administration of gabapentin decreased the amplitude and frequency of oscillations in the left eye, with a corresponding improvement in visual acuity. There was a small increase in the amplitude of oscillations in the right eye, however. These findings suggest that the pendular oscillations in our patients—like those shown by other disorders affecting central myelin—probably reflect common involvement in brainstem-cerebellar circuits important for holding the gaze steady.

Accepted for publication August 25, 1997.

This work was supported in part by US Public Health Service grant EY06717, the Office of Research and Development, Medical Research Service, Department of Veterans Affairs, Washington, DC; the Evenor Armington Fund, Cleveland, Ohio (Dr Leigh); and Genetic Services grant (525/D), Ohio Department of Health, Columbus (Dr Zinn).

Hugo Moser, MD, and Ann Moser provided the biochemical analysis.

Reprints: Arthur B. Zinn, MD, PhD, Center for Human Genetics, University Hospitals of Cleveland, 11100 Euclid Ave, Cleveland, OH 44106.

REFERENCES

1. Leigh RJ, Zee DS. *The Neurology of Eye Movements.* 2nd ed. Philadelphia, Pa: FA Davis Co Publishers; 1991:chap 10.
2. Moser AB, Rasmussen M, Naidu S, et al. Phenotype of patients with peroxisomal disorders subdivided into sixteen complementation groups. *J Pediatr.* 1995; 127:13-22.
3. Lazarow PB, Moser HW. Disorders of peroxisomal biogenesis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease.* 7th ed. New York, NY: McGraw-Hill Book Co; 1994:2287-2324.
4. Moser HW, Moser AB. Peroxisomal disorders: overview. *Ann N Y Acad Sci.* 1996; 804:427-441.
5. Wanders RJA, Barth PG, Schutgens RBH, Heymans HSA. Peroxisomal disorders: post- and prenatal diagnosis based on a new classification with flowcharts. *Int Pediatr.* 1996;11:203-214.
6. Glasgow BJ, Brown HH, Hannah JB, Foos RY. Ocular pathologic findings in neonatal adrenoleukodystrophy. *Ophthalmology.* 1987;94:1054-1060.
7. Folz SJ, Trobe JD. The peroxisome and the eye. *Surv Ophthalmol.* 1991;35:353-368.
8. Kaplan PW, Kruse B, Tusa RJ, Shankroff J, Rignani JE, Moser HW. Visual system abnormalities in adrenomyeloneuropathy. *Ann Neurol.* 1995;37:550-553.
9. Powers JM, Tummons RC, Moser AB, Moser HW, Huff DS, Kelley RI. Neuronal lipidosis and neuroaxonal dystrophy in cerebro-hepato-renal (Zellweger) syndrome. *Acta Neuropathol.* 1987;73:333-343.
10. Benke PJ, Reyes PF, Parker JC. New form of adrenoleukodystrophy. *Hum Genet.* 1981;58:204-208.
11. Kelley RI, Datta NS, Dobyns WB, et al. Neonatal adrenoleukodystrophy: new cases, biochemical studies, and differentiation from Zellweger and related peroxisomal polydystrophy syndromes. *Am J Med Genet.* 1986;23:869-901.
12. Averbuch-Heller L, Zivotofsky AZ, Das VE, DiScenna AO, Leigh RJ. Investigations of the pathogenesis of acquired pendular nystagmus. *Brain.* 1995;118: 369-378.
13. Barton JJS, Cox TA. Acquired pendular nystagmus in multiple sclerosis: clinical observations and the role of optic neuropathy. *J Neurol Neurosurg Psychiatry.* 1993;56:262-267.
14. Lopez LI, Bronstein AM, Gresty MA, Du Boulay EPG, Rudge P. Clinical and MRI correlates in 27 patients with acquired pendular nystagmus. *Brain.* 1996;119: 465-472.
15. Büttner-Ennever JA, Horn AKE, Schmidtke K. Cell groups of the medial longitudinal fasciculus and paramedian tracts. *Rev Neurol (Paris).* 1989;145:533-539.
16. Averbuch-Heller L, Tusa RJ, Fuhry L, et al. A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. *Ann Neurol.* 1997; 41:818-825.
17. Straube A, Kurzan R, Büttner U. Differential effects of bicuculline and muscimol microinjections into the vestibular nuclei on simian eye movements. *Exp Brain Res.* 1991;86:347-358.
18. Mettens P, Godaux E, Cheron G, Galiana HL. Effect of muscimol microinjections into the prepositus hypoglossi and medial vestibular nuclei on cat eye movements. *J Neurophysiol.* 1994;72:785-802.

Printed and Published in the United States of America