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Neuropathy in Navajo children: Clinical and epidemiologic features

Article abstract—We describe a rare and apparently unique neuropathic syndrome among Navajo children living on the Navajo Reservation. Clinical features include sensorimotor neuropathy, corneal ulcerations, acral mutilation, poor weight gain, short stature, sexual infantilism, serious systemic infections, and liver derangement including Reye's syndrome-like episodes. Progressive CNS white matter lesions were diagnosed through magnetic resonance imaging. We identified 20 definite and 4 probable cases occurring between 1959 and 1986. Mean age at the time of 1st recognized symptom was 13 months (range, 1 month to 4 years 6 months). Ten individuals have died; 6 of the deaths occurred before 5 years of age. The incidence of this syndrome on the western Navajo reservation is 5 times higher than that on the eastern reservation (38 compared with 7 cases per 100,000 births). Although the etiology is unknown, this syndrome is consistent with an inborn error of metabolism, inherited in an autosomal recessive manner.

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R. Singleton, MD; S.D. Helgerson, MD; R.D. Snyder, MD; P.J. O'Conner, MD; S. Nelson, BS; S.D. Johnsen, MD; and J.E. Allanson, MD

In 1976, Appenzeller et al[1] described 4 Navajo children with an apparently unique sensorimotor neuropathy manifested by weakness, hypotonia, areflexia, loss of sensation in extremities, acral mutilation, corneal ulceration, and painless fractures. Sural nerve biopsies showed nearly total absence of myelinated fibers, with degeneration and regeneration of unmyelinated fibers. The biopsies did not suggest a demyelinating process. Sural nerve biopsy on a 10-month-old child with this condition showed axonal degenerative neuropathy on light and electron microscopy.[2] This syndrome was referred to as Navajo neuropathy.

After the initial report, the authors identified additional features in the original 4 patients and 11 new patients with clinically similar presentations. These features included poor weight gain, short stature, sexual infantilism, serious systemic infections, and liver derangement. Liver derangement was characterized by fulminant hepatic failure, Reye-like syndrome, or indolent progression to cirrhosis. Unexplained episodes of hypoglycemia with metabolic acidosis occurred in some patients during acute illnesses. Magnetic resonance imaging (MRI) findings of focal white matter abnormalities in the brain broadened the definition of the syndrome to include progressive CNS involvement.[2]

To determine the incidence and geographic distribution of this syndrome on the Navajo Reservation and to describe the characteristics of the cases, we established an epidemiologic surveillance system in January 1988 to identify cases occurring since 1960. The results of the surveillance are the subject of this paper.

Background. The Navajo Reservation encompasses an area of 25,000 square miles in northeast Arizona, extending into Utah and New Mexico. The Navajo Nation has experienced rapid growth, from a population decimated to 8,000 in 1868 to the current reservation population of 181,000 (based on estimates extrapolated from the 1980 Census).

The western half of the reservation, including the communities of Tuba City, Chinle, Kayenta, and Winslow, contains 40% of the population. The eastern reservation, encompassing the larger communities of Gallup, Shiprock, and Crownpoint, contains 60% of the population. Because of the close proximity of the eastern reservation to major communities outside the reservation, the Navajos in the eastern reservation had earlier contact with western culture. The earliest government agencies, trading centers, schools, and roads were in the eastern reservation. The western reservation has remained remote with restricted access until the past 15 to 20 years (figure 1).[3]

Case reports. Patient 1. A healthy boy twin experienced a febrile illness with hepatomegaly and coagulopathy at 10 months of age. At 3 years of age he developed meningism, clonic jerks, and metabolic acidosis. CSF was sterile, with 51 neutrophils and 50 lymphocytes per mm^3, and protein of 263 mg/dl. Subsequently, he lost weight and developed progressive weakness.

On physical examination at 7 years of age, his weight and height were below the 3rd percentile. Positive physical findings included bilateral corneal scars, pectus carinatum, hepatomegaly, partial resorption of distal digits, and bilateral cryptorchidism. Neurologic examination was remarkable for uniformly diminished muscle bulk, decreased strength more distally than proximally, flexion contractures of the hands, bilateral foot drop, diminished deep tendon reflexes, and decreased sensation to pinprick in distal extremities.

SGOT was 105 U/ml (normal, 5 to 40), total bilirubin 0.5 mg/dl, total serum protein 7.2 g/dl with normal electrophoretic pattern, and creatine phosphokinase 90 U/l (normal, 12 to 70). Serum electrolytes, cholesterol, BUN, glucose, T_4, immunoglobulin, and complement were normal. Urine amino acid chromatography, organic acid determination, and heavy metal screen were normal. EMG of the proximal and distal muscles of the upper and lower extremities showed changes compatible with a severe peripheral neuropathy. Motor nerve conduction velocity (NCV) of the right ulnar nerve was 10.5 m/sec with low amplitude response (normal, greater than 50). An EEG was abnormal because of slow nonlocalizing background rhythms. Noncontrast CT of the head was normal. Subcutaneous his-

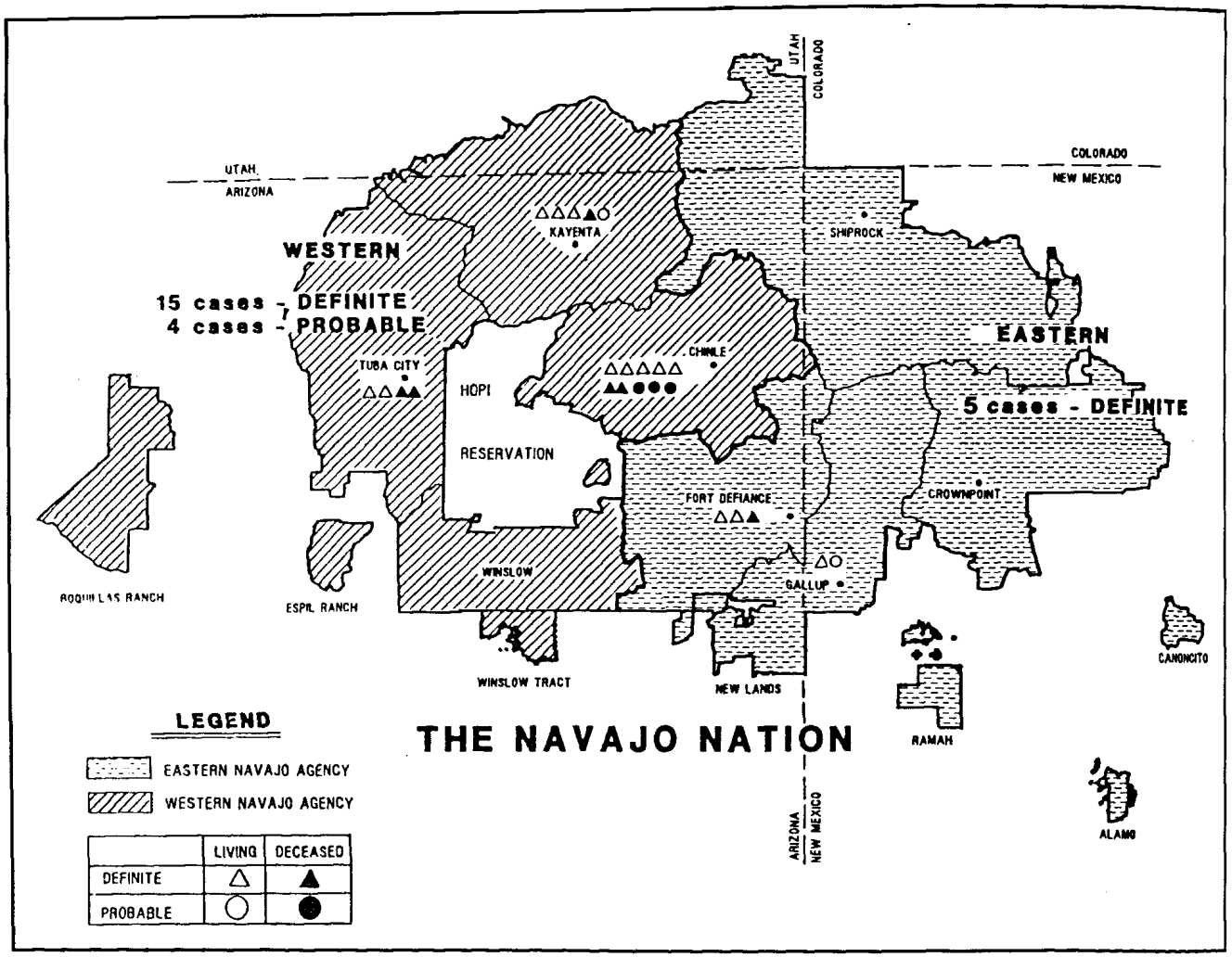

Figure 1. Cases of Navajo neuropathy on the Navajo reservation between 1959-1986.

tamine test revealed no wheal or flare response. Sural nerve biopsy was refused.

At 14 years of age, secondary sexual characteristics were absent. No distal motor or sensory evoked responses were obtained in median, ulnar, or peroneal nerves. Growth hormone therapy failed to produce an increase in linear growth rate. At 15 years of age he developed hematemesis and anemia from unsuspected esophageal varices. Liver biopsy revealed macronodular cirrhosis with fatty changes and scarring. Anti-smooth muscle antibody, anti-RNP antibody, anti-mitochondrial antibody, hepatitis A antibody, and hepatitis B antigen were negative. Carnitine levels were normal. Cranial MRI revealed multiple focal periventricular and subcortical white matter lesions on T_2-weighted images; the spinal cord was atrophic except for preservation of the conus.

A girl twin with peripheral neuropathy, corneal opacities, failure to thrive, and acral mutilation expired at 4 years of age from end-stage liver failure. Family history is otherwise noncontributory.

Patient 2. A newborn boy had persistent neonatal jaundice with hepatomegaly at 2 months of age. His total bilirubin was 5.0 mg/dl, with a direct bilirubin of 3.6 mg/dl and SGOT of 170 U/ml. Hepatitis A antibody was negative, alpha$_1$-antitrypsin was normal, and liver ultrasound showed no intrahepatic duct obstruction. Liver biopsy revealed chronic aggressive hepatitis with portal fibrosis. Hepatomegaly resolved, but liver enzymes remained mildly elevated.

He had 6 hospitalizations for acute gastroenteritis or pneumonia, frequently with associated metabolic acidosis. At 15 months of age, failure to thrive, delayed motor milestones, and generalized muscle weakness were noted. Physical examination was remarkable for weight and height below the 3rd percentile, hypotonia, decreased muscle bulk, and areflexia. EMG, EEG, leukocyte stimulation test, thyroid studies, ceruloplasmin, and urine amino acid screen were normal. NCV of the peroneal nerve was normal. Creatine phosphokinase was 158 U/l.

Progressive weakness prompted reevaluation at 6 years of age. Physical examination revealed a cachectic boy with corneal opacities and chronic ulcerations on knees and ankles. Positive findings included diminished muscle strength in all extremities, flexion contractures of the hands, bilateral foot drop, and decreased sensation in distal extremities. No distal evoked responses were obtained in median and peroneal nerves. Sural nerve biopsy showed severe loss of myelinated fibers. A muscle biopsy revealed marked loss of all fibers with some group atrophy. Histochemical staining showed poor fiber type differentiation. Muscle carnitine level was normal.

His neurologic status has remained stable. He has 2 brothers, 1 living and 1 deceased, who meet criteria for definite Navajo neuropathy. A 3rd brother died at 6 months of age with disseminated varicella. One female cousin meets criteria for probable Navajo neuropathy, and another female cousin is a definite case of Navajo neuropathy.

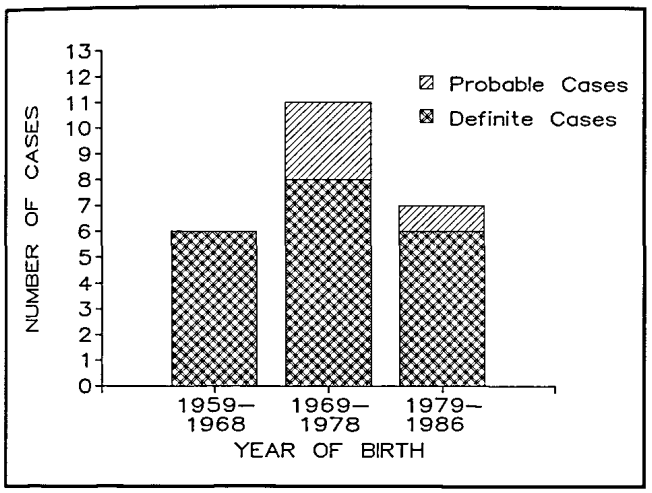

Figure 2. Number of cases of Navajo neuropathy occurring on the Navajo reservation by year of birth, 1959-1986.

Methods. For the purpose of epidemiologic surveillance, a "case" was defined as a Navajo who experienced the onset of the following signs and symptoms before age 10 years with no alternative diagnosis: (1) sensory neuropathy demonstrated by physical examination, acral mutilation, or sural nerve biopsy; (2) motor neuropathy demonstrated by physical examination, denervation on EMG, or delayed motor nerve conduction velocity; (3) corneal ulceration and/or scarring; (4) liver derangement defined as seronegative hepatitis, chronic active hepatitis, fulminant liver failure, Reye's syndrome-like episode or cirrhosis; and (5) at least 1 documented metabolic or infectious derangement, including short stature (height below the 5th percentile), inadequate weight gain (weight below the 5th percentile), delayed puberty (no secondary sexual characteristics by 14 years), or systemic infections (at least 1 episode of sepsis, meningitis, disseminated viral infection, pyelonephritis, or pneumonia requiring hospitalization). A case was considered definite if 4 of the 5 criteria were met, and probable if at least 2 of the criteria were met.

We ascertained cases by passive surveillance of health providers on the Navajo Reservation using a case reporting form distributed to all Navajo area practitioners in February 1988. In addition, 2 of us (R.S. and S.N.) reviewed all 1965 to 1988 inpatient medical records in Navajo IHS hospitals for which the discharge diagnosis was corneal ulcer (ICD-9 code 370.00-07) or corneal scar (371.00-05). We also reviewed medical records of 15 previously identified cases, 9 newly identified cases, and selected family members.

Demographic, environmental, and family histories were obtained from families of definite cases through home visits conducted by 1 of us (S.N.) following approval from the Navajo Area Health Advisory Committee, Navajo Health Foundation, and the Navajo Area Indian Health Service Research Committee. Standard descriptive statistical techniques were used. Data from the Navajo Area Vital Statistics Reports were used to calculate incidence rates.

Results. *Epidemiologic investigation.* Epidemiologic surveillance resulted in identification of 9 previously unidentified cases: 6 definite and 3 probable cases. In all, we identified 20 definite cases and 4 probable cases. The average annual incidence of definite and probable cases on the Navajo Reservation from 1972 to 1986 was 20 cases/100,000 births. The incidence in the western half of the reservation was 38 cases/100,000 births, compared with 7 cases/100,000 in the eastern reservation (odds ratio, 5.3; CI, 1.4 to 24.0) (figure 1). These 24 cases were from 13 Navajo families; 6 families had more than 1 affected sibling. Extensive family histories have revealed common ancestors in at least 3 of the 13 families. No common environmental factors (ie, water source, heavy metal exposure, toxin exposure, family occupation) have been discovered in families of definite cases.

Table. Proportion of Navajo neuropathy cases with selected symptoms, 1959 to 1986

Symptom	Percent with symptom: Definite cases (N=20)	Probable cases (N=4)
Weakness	100	75
Weight 5th percentile	90	75
Corneal ulcers/scars	85	0
Systemic infections	80	100
Sensory loss	80	25
Liver derangements	70	75
Delayed puberty*	60	0
Acral mutilation	40	0

* Based on 10 definite and no probable cases who were of pubertal age.

All probable cases were siblings of definite cases and had highly suggestive histories; however, insufficient medical information was available to fully classify them. Definite cases were born from 1959 to 1986; 10 (50%) births occurred between 1969 and 1979, and 5 (25%) occurred after 1979 (figure 2).

Clinical investigation. The patients' mean age at 1st recognized symptom was 13 months (range, 1 month to 4 years 6 months). Among the 20 definite cases, 6 (28%) presented with a serious systemic infection, 5 (24%) with inadequate weight gain, 5 (24%) with liver derangements, and 4 (20%) with corneal ulcerations.

The most common clinical finding was weakness, which was documented in all the definite cases; 16 (80%) of definite cases had sensory deficits on physical exam, and 8 (40%) had evidence of acral mutilation. Corneal lesions were identified in 17 (85%) of definite cases, and 18 (90%) had inadequate weight gain. Among 10 patients over 14 years of age, 6 (60%) had delayed puberty. Serious systemic infections occurred in 16 (80%) of the definite cases (including 3 episodes of meningitis and 8 episodes of culture-positive sepsis), and liver derangement was identified in 14 (70%) (table).

Ten deaths occurred among the 24 identified cases. Seven of these deaths were among definite cases. The causes of death were complications of liver failure (3), respiratory failure (2), and unknown (2). Age at death for definite cases ranged from 3 years 1 month to 25 years 2 months (mean, 9.9 years; median, 4 years). Three of the 4 probable cases have died, with age of death ranging from 6 months to 3 years. All these deaths were secondary to complications of liver failure. Six of the 10 deaths were before 5 years of age, and 4 of these

early deaths resulted from liver failure. The oldest living case is a 27-year-old woman.

Laboratory investigation. Twelve of 13 sural nerve biopsies obtained from 13 of the definite cases showed severe loss of myelinated fibers with degeneration and regeneration of nonmyelinated axons. The normal study was performed at 6 months of age on the sibling of a definite case who was neurologically normal at the time of biopsy but developed signs of peripheral neuropathy at age 12 months.

Diagnoses on 8 liver biopsy specimens obtained from 8 individuals included: resolving hepatitis (1), chronic active hepatitis (4), and cirrhosis (3). One of these was a postmortem biopsy after death from fulminant liver failure which revealed fatty degeneration with early cirrhosis. Liver serologies for hepatitis B on all patients with liver derangement have been negative.

MRIs were abnormal in 5 of 7 patients studied, showing white matter abnormalities in the cerebral hemispheres and cerebellum on T_2-weighted images, and thinning of the spinal cord. Two patients with serial imaging showed progressive white matter abnormalities. Although MRI abnormalities appear common, suggesting an associated encephalomyelopathy, this was not known when the surveillance criteria were developed, and MRI was not included in those criteria.

Toxicology screening, including testing for copper, lead, arsenic, cadmium, thalium, and mercury were normal in several patients. Analysis of serum very-long-chain fatty acids has shown normal levels. Subcutaneous histamine testing elicited a normal wheal and flare in 2 of 3 patients tested.

Discussion. Navajo neuropathy may be a unique syndrome characterized by progressive motor and sensory neuropathy with corneal scarring, metabolic derangement, and MRI evidence of encephalomyelopathy. The involvement of more than 1 individual in a sibship with normal parents, and the relatively small gene pool of the Navajo people suggest that this may be a genetic condition transmitted in an autosomal recessive manner. The apparent predominance of this disorder in the western half of the Navajo Reservation may reflect the relative lack of mobility of the Navajos in the western reservation. Traditionally, endogamy within one's clan or linked clans is not accepted in Navajo society; however, marriages to blood relatives do occur because of the small population base and limited migration.[3] Severe combined immune deficiency syndrome, a rare autosomal recessive disorder with incidence estimated at 1:1,000,000, occurs in the western half of the reservation with a calculated incidence of 1 in 2,000 live births (Sheila Gahagan, MD, Navajo Area IHS Pediatric Consultant, personal communication).

The etiology of this disorder is unknown. The pattern of nerve fiber loss resembles that of hereditary sensory neuropathy type II.[4] However, the severe motor disorder, corneal ulcerations, metabolic derangement, leukoencephalopathy, and degeneration of myelinated fibers in our patients suggest that this syndrome is a distinct entity. The pattern of sensory loss is similar to hereditary sensory neuropathy with neurotrophic keratitis and acromutilation found in a Kashmiri family,[5] but motor function is normal in the Kashmiri patients and sural nerve biopsies show a selective reduction in small myelinated nerve fibers. The encephalitis and leukoencephalopathy syndromes among native Indians in northern Quebec show minor similarities to Navajo neuropathy in white matter lesions and immunologic abnormalities predisposing children to recurrent infection, but otherwise appear to be unrelated.[6,7] Navajo neuropathy patients have some features of peroxisomal disorders (hypotonia, hepatomegaly, failure to thrive)[8] but lack the characteristic facies, ocular abnormalities, and dementia. The familial pattern coupled with clinical findings of white matter disease, Reye's syndrome-like episodes, multisystem involvement, and recurrent metabolic acidosis suggest that an inborn error of oxidative metabolism may be responsible for Navajo neuropathy.[9] A slow virus might also be an etiologic agent.

Treatment at this time is preventive and supportive. Families of a diagnosed patient are counselled regarding the possibility of autosomal-recessive inheritance. Medical intervention is aimed at preventing contractures, corneal scarring, and acral mutilation, and assisting ambulation and supporting nutrition. Growth hormone and vitamin A therapy have not proven to be efficacious.

Disease surveillance continues on the Navajo reservation, with an additional search for cases among Native Americans in surrounding geographic areas and from all United States IHS sites. Surveillance of known cases includes probing for common geographic, environmental, and demographic factors. No similar disorder has been described among other Athabaskan tribes; however, 1 of us (R.D.S.) has recently identified 2 siblings of Spanish-American descent residing in an adjacent state who have symptoms indistinguishable from those of Navajo neuropathy. These siblings were the subject of a previous report which did not recognize the potential relationship to Navajo neuropathy.[10] There is a history of intermarriage between Spanish-Americans and Navajos, and at least 2 of the 13 families described above have Spanish ancestry.

We request that physicians aware of other patients with signs and symptoms that meet the case definition described in this article contact the corresponding author of this report (R.D.S.).

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Superior oblique myokymia associated with a posterior fossa tumor: Oculographic correlation with an idiopathic case

Article abstract— Superior oblique myokymia (SOM) was the only neurologic sign in a patient with an astrocytoma involving the midbrain tectum. Oculography showed monocular bursts of tonic and phasic intorsion and depression and miniature oscillations identical to those of idiopathic SOM. SOM stopped after tumor resection.

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Superior oblique myokymia (SOM) is an uncommon eye movement disorder, causing episodic torsional and vertical diplopia and monocular oscillopsia, and is attributed to intermittent spontaneous contraction of 1 superior oblique muscle.[1] The disorder is usually "benign"[1,2] in that symptoms often remit spontaneously or are controlled with carbamazepine. SOM occurs in otherwise healthy individuals and has never been reported as the initial manifestation of an intracranial mass lesion. We report 2 cases of SOM, 1 associated with a posterior fossa tumor, the other idiopathic, and the results of oculography of their dyskinesia.

Case reports. Patient 1. A 33-year-old fireman had a 3-year history of brief episodes of vertical diplopia and oscillopsia which occurred many times daily and stopped with occlusion of the right eye. He had no other symptoms. Neurologic examination showed only intermittent tonic intorsion and depression of the right eye with small torsional-vertical oscillations that were obvious with funduscopy or slit-lamp examination. Between episodes, ocular motility was normal.

Carbamazepine, 200 mg TID, relieved his symptoms. Cranial CT revealed a large, contrast-enhancing mass centered in the rostral cerebellar vermis, with midbrain tectal compression and obstructive hydrocephalus (figure 1). The mass was partially resected; pathologic examination revealed a cerebellar astrocytoma without malignant features. Following surgery, carbamazepine was stopped; the patient remained free of visual symptoms over follow-up of 10 months.

Patient 2. A 49-year-old businessman had 1 year of episodic torsional oscillopsia "as if rocking on a boat" and torsional-vertical diplopia, with a quivering sensation in the right orbit. Slit-lamp and funduscopic examination showed intermittent tonic intorsion and depression of the right eye with fine torsional-vertical oscillations; examination was otherwise normal. Neither carbamazepine nor phenytoin alleviated his symptoms. Contrast-enhanced cranial CT was normal.

Methods. We recorded eye movements in each patient using a magnetic search coil method with a coil designed to record torsional, vertical, and horizontal movements.[3] System bandwidth was 0 to 400 Hz. Paper recordings were made with a rectilinear ink jet polygraph. Minimum amplitude resolution was about 0.1° in each plane. Each patient had simultaneous binocular recordings. Neither patient was taking medication during the period of testing.

Results. Both patients had similar oculographic findings. Abnormal spontaneous eye movements were frequent; initial movements from primary position always intorted and depressed the right eye (figures 2 and 3). The largest amplitude movements of SOM were tonic deviations that began as step changes in eye velocity with decelerating trajectories; peak velocities were less than 20°/sec. Following the deviation, the eye remained tonically intorted and depressed for variable periods, then returned toward primary position with a slow drift lasting 2 to 3 seconds (figure 3) or with a quicker, decreasing velocity drift (figures 2 and 3). Periods of tonic eye deviation were irregular, typically occurring every 5 to 20 seconds and lasting 2 to 5 seconds. Torsional and vertical movements were synchronous and had similar waveforms, but the amplitudes of torsional movements were about twice those of vertical move-