Internuclear ophthalmoplegia (INO) is a sign of exquisite localizing value, often due to either multiple sclerosis or infarction. To demonstrate that unusual causes of INO are more common than the 11% reported in previous series, this review considers a case series of 410 inpatients whom I personally examined during a 33-year period. In this series, the cause of INO was infarction in 157 patients (38%), multiple sclerosis in 139 (34%), and unusual causes in 114 (28%). Unusual causes included trauma (20 cases), tentorial herniation (20 cases), infection (17 cases), tumor (17 cases), iatrogenic injury (12 cases), hemorrhage (13 cases), vasculitis (7 cases), and miscellaneous (8 cases). Internuclear ophthalmoplegia was unilateral in 136 of the infarct cases (87%), 38 of those with multiple sclerosis (27%), and 48 of the unusual cases (42%). Because unusual causes compose more than one quarter of the cases, the differential diagnosis of INO should be tripartite: multiple sclerosis, stroke, and other causes.

**PATIENTS**

I examined all the patients in this study on the wards of the Los Angeles County/University of Southern California Medical Center and Rancho Los Amigos Hospital (rehabilitation) during a 33-year period. I reviewed my notes on all patients, still photographs (n=171), motion pictures (n=39), videotapes (n=35), and selected hospital records and radiographs.

Internuclear ophthalmoplegia was defined as medial rectus limitation or obvious slowing, often accompanied by dissociated nystagmus and preserved convergence, and not better explained on any other basis than medial longitudinal fasciculus injury. Patients with the one-and-a-half syndrome were included, as were those with limited abduction in the same eye or lesser abduction limitation in the opposite eye. Of 435 patients with possible INO, 25—usually those with complex horizontal or fragmentary third nerve eye movement abnormalities—were excluded.

The cause of INO was determined using clinical criteria and appropriate course, laboratory studies of blood and cerebrospinal fluid, and the best contemporary radiologic studies. Multiple sclerosis was diagnosed using Poser or McDonald criteria. Tumors were diagnosed using biopsy find-
ings in 9 cases, were inferred from biopsy findings of an associated metastasis in 4 cases, and were diagnosed using clinical and radiologic criteria in 3 pontine gliomas and 1 AIDS-related lymphoma. Cysticercosis was diagnosed using epidemiologic analysis, imaging studies, and cerebrospinal fluid cysticercal antibody titers, and presence of eosinophilia. Patients with syphilis had cerebrospinal fluid pleocytosis and a positive cerebrospinal fluid VDRL test. Systemic lupus erythematosus was diagnosed using the modified criteria of the American Rheumatological Association.

**RESULTS**

Of 410 cases of INO, 157 (38%) were caused by infarction (from cardiac emboli in 5 cases), 139 (34%) were caused by MS, and 114 (28%) were due to unusual causes (Table). Infarction was considered definite in 133 of 157 patients, and MS was considered definite in 99 of 139 cases. Unilateral INO occurred in 136 infarcts (87%), 38 MS cases (27%), and 48 unusual cases (42%).

Blunt head injury was the cause of INO in 16 patients, a gunshot wound with an occipital-to-quadrigeminal plate...
cistern course in 1 patient, and shock from blood loss in a patient with multiple stab wounds. Two victims of motor vehicle crashes sustained traumatic C5-6 spinal injury, resulting in vertebral artery damage, which led to brainstem infarction after 1- and 2-day intervals. Causes of blunt head trauma were motor vehicle crashes (5 patients), pedestrians hit by cars (4 patients), motorcycle crashes (3 patients), bicycle crashes (2 patients), a fall (1 patient), and a fight (1 patient).

Tenorial herniation\textsuperscript{8,9} was associated with infections in 2 cases. In 1 patient, a blow to the head resulted in decompensation of a chronic subdural empyema associated with intravenous drug use and endocarditis. The other patient had chronic bilateral subdural hematomas after tuberculous meningitis.

Of 6 patients with AIDS, 2 had toxoplasmosis involving the brainstem, 1 had a possible lymphoma (lymphoma was highly likely in another patient with AIDS tailed as a tumor), and 3 had probable viral brainstem encephalitis. Three of 4 patients with cysticercosis had enhancing cysts in the caudal aqueduct, and 1 had a large inflammatory cyst in the fourth ventricle that produced intense brainstem edema. Two patients (without AIDS) had meningoencephalitis with strokes and meningitis due to tuberculosis and an unknown chronic condition in 1 patient each. In 2 patients, infection was an indirect cause: septic shock with brainstem infarction and a diabetic leg infection that progressed to sepsis with meningitis and basal artery occlusion.

Of 12 patients with iatrogenic injury, 7 involved neurosurgery and 5 involved vascular mishaps (2 angiography and each tumor embolization, carotid endarterectomy, and cardiac catheterization). The 8 miscellaneous cases consisted of 2 patients each with hydrocephalus (1 with Chiari malformation) and probable Wernicke syndrome and 1 each congenital with fixed brainstem atrophy, carbamazepine overdose, cerebellar hemorrhagic infarct with pontine compression, and spinocerebellar atrophy with pigmentary retinopathy.

By comparison, during the period of this study, convincing pseudo-INO was seen in 27 (15%) of 182 patients with myasthenia, in 2 patients with Guillain-Barré syndrome, and in 1 of 38 patients with Fisher syndrome. A single patient with abetalipoproteinemia had typical internuclear ophthalmoplegia with weakness and nystagmus of the medial rectus muscles. An INO pattern on caloric testing was seen occasionally in comatose patients.

**COMMENT**

Foville’s landmark 1859 study of pontine gaze palsy identified the sixth nerve nucleus as a gaze center, introduced the concept of yoked eye muscles, and postulated a crossed pathway connecting the pons and midbrain to coordinate horizontal gaze.\textsuperscript{10} Although illustrated in Stilling’s atlas of 1846, the posterior (medial) longitudinal fasciculus was not identified as the connecting gaze pathway until 1873.\textsuperscript{11}

Clinical recognition of INO lagged far behind the anatomy and theory of horizontal eye movements. By 1910, 4 clearly recognizable cases of INO and 4 cases of the one-and-a-half syndrome had been published.\textsuperscript{21(p478)} In 1921, the year that Lhermitte named INO,\textsuperscript{12} Gordon Holmes\textsuperscript{13(p247)} wrote that he had seen only 2 dissociated medial rectus palsies in his career. Spiller,\textsuperscript{1} in describing the first clinicopathologic case in 1924, accepted only 8 reported cases of INO. Internuclear ophthalmoplegia continued to be reported as “partial third nerve palsies” or “supranuclear third nerve palsies” for another quarter century.\textsuperscript{14} In 1950, Cogan and colleagues\textsuperscript{15} found fewer than 10 cases of unilateral INO in the literature, and in 1957, at least half of “all 20 reported cases of NO” had horizontal gaze palsies with preserved convergence.\textsuperscript{16} Finally, however, Cogan’s appreciation of the distinctive features and relatively common incidence of INO established the diagnosis and allowed him to accumulate approximately 200 personal cases by 1970.\textsuperscript{2}

Although 4 series\textsuperscript{2-5} of approximately 400 combined cases of INO (Table 1) contain only 2 cases due to trauma, at least 32 case reports of traumatic INO have been published.\textsuperscript{1,3,11,17} AIDS\textsuperscript{18} has replaced tuberculosis\textsuperscript{16} and syphilis\textsuperscript{19} as an infectious cause of brainstem disease. Cysticercosis, the most common infection on our neurology ward, is a rare cause of INO, as are cryptococcus,\textsuperscript{2} herpes zoster, aspergillus, borrelia, listeria, Whipple disease, and prion disease.\textsuperscript{17} Systemic lupus erythematous\textsuperscript{9,20} and Sjogren syndrome\textsuperscript{21} are the principal vasculitic causes of INO. Temporal arteritis was first reported to cause INO as late as 1989, but at least 5 cases, and several cases of periarteritis, have now been published.

Drug overdose from a variety of medicines causes INO in the absence of structural lesions of the medial longitudinal fasciculus.\textsuperscript{17(p561-569)} Single cases of hyperparathyroidism,\textsuperscript{22} a great imitator of posterior fossa disease; Fabry disease,\textsuperscript{23} known to cause lacunar infarcts; and hexosaminidase deficiency\textsuperscript{24} have been reported with INO.

Although myasthenia is the usual cause of pseudo-INO, a review of 243 cases of Fisher syndrome found 15 cases of apparent NO.\textsuperscript{24} Preferential weakness of the medial rectus muscle with generalized ophthalmoplegia may occur in progressive supranuclear palsy,\textsuperscript{25} but improvement with vestibular stimulation suggests pseudo-INO. Similarly, localization of the INO pattern with spinocerebellar atrophies and reverse dissociated nystagmus in abetalipoproteinemia is uncertain. Selective medial rectus limitation on caloric testing in comatose patients can represent a stage of general anesthesia and may reflect the depth of coma rather than a focal medial longitudinal fasciculus lesion.

In summary, unusual causes of INO are responsible for more than a quarter of inpatient cases and merit serious consideration in differential diagnosis.

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