Acute Bilateral Ophthalmoplegias

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Introduction

Bilateral ophthalmoplegia is that condition of weakness or paralysis involving one or more ocular muscles in each eye. Its sudden appearance due to an acute ocular myopathy is indeed unusual. Swash reported a single patient with acute necrotizing orbital myositis and carcinomatosis neuromyopathy.[1] The more common bilateral ocular muscle diseases, such as dysthyroid exophthalmopathy, orbital myositis, and progressive external ophthalmoplegia, develop insidiously and are restricted to the orbit.

In general, acute bilateral ophthalmoplegias afford a unique differential diagnosis of disorders affecting infranuclear and supranuclear pathways for the control of eye movements (Table). They present more abruptly than the myopathies and seriously jeopardize respiratory and/or neurologic function. Among these acute bilateral ophthalmoplegias are disorders which diffusely affect neuromuscular junctions or the nerves to ocular muscles (Table, Parts I and II). Occasionally these diseases are troublesome to diagnose because additional neurologic signs are sparse. In these instances progressive bulbar and respiratory weakness may develop unexpectedly. Familiarity with their differential diagnosis allows for timely therapeutic intervention. This discussion focuses on recognition of this group of acute bilateral ophthalmoplegias and their treatment.

Those disorders (Table, Parts III and IV) which involve only the intracranial portions of the nerves to ocular muscles or their brain stem origins have either distinctive patterns of ophthalmoplegia or are attended by telltale neurologic findings. These disorders are more easily identified and require less deliberation.

I. Disorders Affecting Neuromuscular Junctions

Botulism is the linchpin to the differential diagnosis of acute bilateral ophthalmoplegia because this disease primarily affects ocular and bulbar muscles. Furthermore it is both an individual and public health emergency, making its detection doubly necessary.

Although its epidemic occurrence is well known to physicians, several facets of the disease are less well recognized. Sporadic outbreaks frequently occur. Onset of symptoms appears up to eight days after ingestion of spoiled food.[2] Wound botulism which presents in the same manner as food-borne botulism was once thought rare, but is now more frequently diagnosed.[3,4] Available neurophysiologic techniques assist in its recognition; however, the presence of botulin is only confirmed by a biologic assay. Therefore diagnosis rests heavily upon clinical suspicion.

The following patient presentation typifies the disease.

A 42-year-old fish meal plant employee vomited and complained of pain in his throat while eating homemade vegetable soup. Shortly thereafter his vision was blurred. The following day he came to the Medical College of Virginia Hospitals because of dysphagia, diplopia, and hoarseness. He was not in any distress. Vital signs were normal. There was mild ptosis of each eyelid. His pupils were dilated to 8 mm and did not react to light or accommodation (Figure). Near card assessment of visual acuity was 20/100 in each eye. Moderate abduction and mild

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downgaze paresis of external ocular muscles was present. Schirmer's I test showed deficient tear formation in each eye. Facial muscles were mildly weak bilaterally, the mouth was dry, and the gag reflex was slightly impaired. Motor, sensory, and reflex examinations of the limbs were normal.

Diagnostic studies began in the emergency room with a Tensilon test which was twice negative. A lumbar puncture yielded cerebrospinal fluid (CSF) under normal pressure which contained sugar of 71 mg%, protein of 28 mg%, and three RBC's. Routine laboratory data were normal. A clinical diagnosis of botulism was made, and serum was sent to the Center for Disease Control (CDC) in Atlanta, Ga. Bivalent (A,B) and trivalent (A,B,E) antitoxin prepared from horse serum was administered. Following a mild urticarial reaction, antitoxin therapy was discontinued. Weakness soon progressed to involve respiratory more than extremity muscles. Vital capacity dropped to 1100 cc. Tracheostomy was performed. Neurophysiologic tests were consistent with a diagnosis of mild botulism. Muscle potentials in the face were low in amplitude and short in duration, and rapid repetitive nerve stimulation (30 Hz) produced an incremental increase in muscle potentials recorded over the thenar eminence. Mouse-toxin neutralization tests performed by the CDC were positive for type B *Clostridium botulinum* toxin. Injection of the patient's serum killed all the mice not protected with antitoxin B. Although the most frequent cause of sporadic botulism occurs with home-processed foods, the source of this patient's exposure was not located. His family had eaten the same vegetable soup with him on two occasions and cultures of the soup did not grow *C botulinum*.

The patient's course was marked by a moderately severe aspiration pneumonia. He responded within one week to antibiotics and frequent suctioning. Four weeks after admission, he was discharged with mild hoarseness. Recovery was, otherwise, complete.

A pattern of weakness descending from bulbar regions to respiratory and extremity muscles characterizes botulism. Ideally the diagnosis is made before this descending paralysis occurs so that the option to use mechanical ventilation and antitoxin therapy is available. In the early stage of diagnosis several additional findings are helpful. A history of ingestion of putrid or home-processed food, exposure to epidemic botulism, or a recent outdoor wound or extremity surgery is important. To be kept in mind is that botulin is the most potent toxin known to man and that ingestion of one spoiled bean is reported to have led to death.[5]

Acute Bilateral Ophthalmoplegias

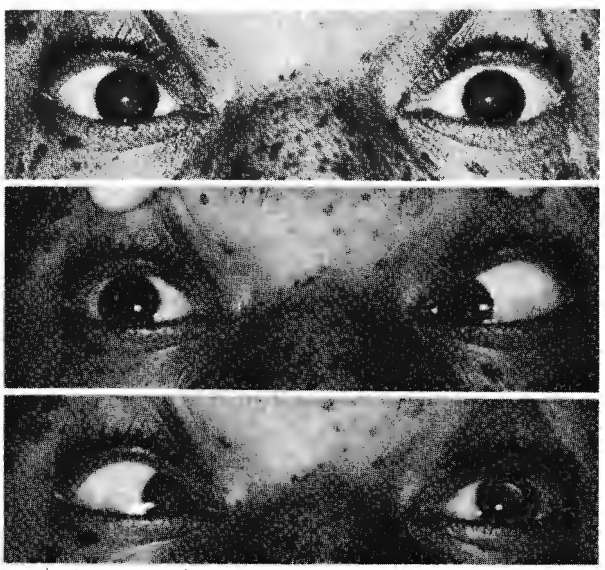
I. Disorders affecting neuromuscular junctions
   1. Botulism
   2. Myasthenia gravis

II. Disorders of ocular nerves
   1. Acute idiopathic polyneuropathy
   2. Diphtheria

III. Disorders within the meninges
   1. Infection
   2. Aneurysm
   3. Trauma

IV. Disorders of the brain stem
   1. Wernicke encephalopathy
   2. Multiple sclerosis
   3. Poliomyelitis
   4. Infarction
   5. Hemorrhage
   6. Trauma

Since botulin interferes with the release of acetylcholine from the distal nerve terminals of skeletal and smooth muscles, signs and symptoms referable to parasympathetic blockade are helpful. Dry eyes and dry mouth occur due to secretomotor inhibition of lacrimal and salivary glands. Blurred vision results from accommodation failure of a weakened ciliary



Fig—Botulism is suggested by the presence of dilated pupils (*top*) which are fixed to light, and accommodation and bilateral abduction paresis (*middle* and *bottom*). Ptotic lids are manually retracted.

muscle. Nonreactive pupillary light responses are caused by paralysis of the pupillary sphincter muscle. The involvement of the pupil coupled with acute bulbar and extraocular muscle weakness makes a diagnosis of botulism almost certain. However, pupillary paralysis occurs infrequently and is not to be depended upon for the diagnosis.

Once the diagnosis of botulism is suspected, specimens from serum and gastric contents are obtained for analysis and typing by mouse-toxin neutralization tests. Six pathogenic toxins have been identified (A, B, C, D, E, F).[6] Food suspected of contamination and stools from the patient are cultured for *C botulinum*. Recent use of stool cultures have shown botulism poisoning to cause a floppy infant syndrome.[7] An indication of botulism is obtained by standard neurophysiologic techniques. In severe cases size and duration of motor units are reduced and low-rate repetitive nerve stimulation (3 Hz) causes decremental muscle potentials, but at high rates of stimulation (50 Hz) an incremental response occurs. Mild cases show only the incremental response of muscle potentials at high rates of stimulation.[8] In botulism these phenomena are more likely to be found in the weakened muscles, and in some instances are not present in the early course of the disease.[9] Careful screening by the electromyographer is required for incremental responses caused by artifacts.

Therapy begins with gastric lavage, cathartics, and enemas. Purgation of the gastrointestinal track is now recommended since stool cultures of *C botulinum* have preceded detection of botulin in the serum. Administration of antitoxin involves risk of adverse reaction, particularly serum sickness, which is comparable to that for tetanus antitoxin.[6] Therefore, use of antitoxin is weighed against the rapidity of development and degree of respiratory failure. Moreover, antitoxin therapy has not resulted in a major decline in mortality rates. Guanidine hydrochloride enhances the release of acetylcholine from the nerve terminal and is used to reverse the neuromuscular blockade of botulism. It is helpful in reducing extraocular and limb weakness but unfortunately is least effective in reversing paralysis of respiratory muscles.[9] It also tends to depress the bone marrow.

In myasthenia gravis 40% of the patients have diplopia and ptosis either alone or accompanied by bulbar or extremity weakness.[10] The pattern of ocular muscle involvement is variable. Diagnosis of myasthenia gravis is often suggested by the observation of fatigue in extraocular muscles upon requesting the patient to maintain upgaze. In this position palpebral and elevator muscles of the eye gradually weaken. Another distinctive ocular sign in myasthenia gravis is the lid twitch phenomenon described by Cogan.[11] Rapid shift of the eyes from a downward position to quick upgaze results in a brief contraction or twitch of the levator palpebral muscle before it weakens and returns to its ptotic position. Claims of pupillary involvement in myasthenia gravis are poorly documented and unexpected since this is a disease of striated muscle.

Ordinarily the urgency of a diagnosis in myasthenia gravis does not occur because of its typically insidious onset. However, an acute fulminating form of ocular and bulbar weakness with early respiratory muscle involvement has been described.[10] In either instance the diagnosis of myasthenia gravis is usually made by intravenous injection of edrophonium chloride (Tensilon). Caution in the interpretation of this test in relation to the differential diagnosis of acute ophthalmoplegias is warranted by the report of Cherington,[12] who described improved muscle strength and resolution of ptosis following intravenous Tensilon in two patients with proven botulism. Clinically these patients also demonstrated fatigability, but neither responded to sustained amounts of anticholinesterase medication. In those unusual instances in which diagnosis of myasthenia gravis is not clearly established by intravenous Tensilon, repetitive nerve stimulation is recommended. A decremental response of muscle potentials is found with slow and rapid sequential stimulation of the nerve. Control of acute muscle weakness is usually gained by anticholinesterase medication. Steroids and possibly thymectomy are useful in later stages.

II. Disorders of Ocular Nerves

In patients with acute idiopathic polyneuropathy (Landry-Guillain-Barré syndrome), involvement of ocular nerves occurs in less than one quarter of the cases while bulbar and facial weakness are found in over one half the patients in large series.[13,14] Pupils are usually but not invariably spared. Ordinarily, ocular muscle weakness follows extremity weakness. This ascending paralysis in acute idiopathic polyneuropathy constitutes a major distinction with the descending paralysis that occurs in botulism. Acute idiopathic polyneuropathy is also suggested by the presence of sensory loss and early disappearance

of deep tendon reflexes. Laboratory evidence favoring acute idiopathic polyneuropathy is obtained by finding elevated protein in the CSF with no more than a mild pleocytosis and detection of slowed motor nerve conduction velocities. These tests are not always abnormal in the early course of this disease.

Recognition of an ophthalmoplegia due to acute idiopathic polyneuropathy is not always simple. Although others before him had described such a condition, Fisher in 1956 drew attention to a more restricted form of acute idiopathic polyneuropathy.[15] He described an acute polycranial neuritis manifested by an ophthalmoplegia with only generalized areflexia and ataxia. CSF protein was elevated. Others have since described this acute bilateral ophthalmoplegia and pointed out that subsequent weakness of the extremities does occur.[16] Pupils are usually spared, which has led to disputes regarding the central vs peripheral nature of acute polycranial neuritis. Success with prednisone therapy has not been shown, but its use is worthy of consideration early in the course of the disease.

Mention of diphtheria today as a cause of ophthalmoplegia is nearly a historical matter. Weakened ocular muscles occur in diphtheria due to a toxic motor neuropathy. Cases are reported in which a mild nasopharyngitis went undetected before the paralytic stage appeared. Recognition is further complicated by the tendency of the exudative membrane of diphtheria to clear off the larynx before paralysis develops. Usually the palate and ciliary muscles are the first to be affected.[17] Paralysis of ocular motor muscles generally follows dysphagia and loss of accommodation within several days to several weeks. Paralysis of respiratory and extremity muscles also follows palate or ciliary muscle weakness. Respiratory failure leads to death if the systemic polyneuropathy is severe. If the patient survives the toxic phase, all involved nerves usually recover in several months.

III. Disorders Within the Meninges

Infection of the leptomeninges, especially tuberculous meningitis, is known to disrupt nerves to ocular muscles bilaterally. Onset is sometimes sudden and the course fulminant. Fever, stiff neck, and typical CSF findings lead directly to the diagnosis. Neurosyphilis with CSF pleocytosis, elevated protein, and positive serology is another frequent cause of meningeal ocular palsies. Abrupt expansion or rupture of a posterior fossa aneurysm is reported to cause bilateral sixth nerve palsies.[18] Bilateral third and fourth nerve palsies[19] are described in closed head injuries and are thought to occur through injury of the nonfixed portion of the nerve in its meningeal compartment. Bilateral sixth nerve palsies due to trauma are usually associated with basilar skull fractures. Delayed onset of ocular muscle palsies is described with fractures of the clivus,[20] presumably from hemorrhage beneath the dura.

IV. Disorders of the Brain Stem

Structural alterations in infranuclear and/or supranuclear regions of the brain stem, which control eye movements, cause acute ophthalmoplegias. Supranuclear deficits include gaze palsies and internuclear ophthalmoplegia (INO) or combinations of both, which are recognized by their distinct pattern of involvement of ocular muscles. Paralysis of conjugate horizontal gaze with consequential contralateral deviation of the eyes occurs with a lesion in the ipsilateral pontine paramedian reticular formation.[21] Paralysis of adduction with abduction nystagmus is an INO and indicates a lesion in the medial longitudinal fasciculus (MLF).[22] Distinction of an INO from an infranuclear medial rectus palsy is evident by the preservation of adduction during convergence. Ipsilateral gaze and adduction paralysis was termed by Fisher the "one and a half" syndrome because of the coexistence of a unilateral pontine gaze center and MLF lesion.[23]

Bilateral involvement of the fasciculi or nuclei of oculomotor nerves is uncommon and is usually attended by additional neurologic findings. Altered consciousness and ataxia with ocular palsies are caused by thiamine deficiency in alcoholic patients with Wernicke encephalopathy. Neuronal degeneration, capillary proliferation, and hemorrhages are diffusely found in periventricular regions of the brain stem including nuclear and fascicular portions of ocular nerves. Similiar infranuclear lesions with long tract deficits occur in white matter regions involved with the demyelinating plaques of multiple sclerosis. Both Wernicke encephalopathy and multiple sclerosis also cause supranuclear oculomotor palsies. Murray and Walsh described infranuclear ocular muscle palsies in several patients with poliomyelitis.[24] Isolated bilateral nuclear or fascicular lesions are described only with infarction of third nerve fasciculi and are indeed rare.

Acute supranuclear gaze palsies in this discussion include unilateral or bilateral horizontal gaze palsy, the "one and a half" syndrome, and bilateral

INO. Contralateral pyramidal tract signs and facial paresis due to a lesion within the pons often accompany an ipsilateral horizontal gaze palsy. Acute upgaze palsy due to a lesion in the pretectal region[25] or sudden downgaze palsy[26] from disruption of the paramedian prerubral field occur rarely. In both horizontal and vertical gaze palsies of abrupt onset, additional neurologic deficits are the rule. They are most frequently caused by infarction, hemorrhage, and trauma. The one supranuclear disorder frequently not associated with contiguous neurologic signs is bilateral INO. In such instances bilateral INO strongly suggests multiple sclerosis.[21]

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