Experimental internuclear ophthalmoplegia

RONALD M. BURDE, RALPH A. W. LEHMAN, G. ROPER-HALL, JOHN BROOKS, AND JOHN L. KELTNER

From the Department of Ophthalmology and from the Departments of Neurology and Neurological Surgery, Washington University School of Medicine, St. Louis, Missouri, USA

SUMMARY A midline experimental lesion separating the medial longitudinal fasciculi at and below the level of the abducens nuclei without damaging either fasciculus at the level of the nuclei has produced defects of ocular motility resembling those of clinical internuclear ophthalmoplegia. Electromyographic recordings during lateral gaze demonstrate: (1) lack of inhibition of the lateral rectus muscle in the adducting eye, (2) delayed inhibition of the medial rectus muscle in the abducting eye, and (3) occasional evidence of excitation of the medial rectus muscle of the abducting eye probably associated with pupillary constriction. The presumed physiologic mechanisms involved in conjugate gaze movements are discussed in the light of the experimental findings.

Internuclear ophthalmoplegia (INO) is the dissociation of ocular movements during horizontal versions, consisting of an underacting medial rectus muscle (in the adducting eye), often accompanied by abducting nystagmus of the fellow eye. The presence of this movement disorder is considered to be pathognomonic of a lesion in the medial longitudinal fasciculus (MLF) in the brainstem. The pathophysiologic mechanism by which the dissociated nystagmus of the abducting eye is produced has remained elusive. Stroud et al. (1973, 1974) proposed that asymmetric convergence is used to drive the weak medial rectus muscle, which secondarily produces the abducting nystagmus on the uninvolved side. More recently, Pola and Robinson (1976) have postulated that a lesion of one MLF would interrupt both ipsilateral excitatory and contralateral inhibitory fibres to the respective medial rectus subnuclei of the third cranial nerve. This postulate would fit well with clinical findings previously reported by Loeffler et al. (1966). In contrast to Stroud et al. these authors believe that the nystagmus of the abducting eye after a contralateral MLF lesion is due to loss of inhibition of the medial rectus activity of that eye. A third hypothesis attributes the nystagmus to interruption of nerve fibre pathways passing to the abducens nucleus of the abducting eye (Carpenter and Strominger, 1965).

The purpose of this study was to produce an experimental model of inter-nuclear ophthalmoplegia in the primate without damaging the parapontine gaze centres or their subservient ocular motor nuclei. The animals were studied by electromyography in order to gain an understanding of the underlying pathophysiology of INO.

Methods

Four male and one female rhesus monkeys of weights ranging from 9.5 to 12.5 lb (4.3 to 5.7 kg) underwent suboccipital craniectomy under barbiturate anaesthesia. In each case the cerebellar vermis overlying the caudal portion of the fourth ventricle was split in the midline to a depth of approximately 1.5 cm. Under magnification the two cerebellar hemispheres were held apart in this region, and a midline cut was made in the floor of the fourth ventricle with a fine knife.

A week or more after surgery the animals were studied in a primate chair with and without head restraint. Motion pictures, 8 and 16 mm, were made of the extraocular movements of all animals. Time projection comparisons were made to estimate the speed of movement in all animals. In addition all animals were re-studied during electromyography, at which time simultaneous recordings were made from 2 to 4 of the horizontal rectus muscles.

The following ocular motor functions were studied...
Figs. 1 and 2. The EMG records are developed from the 6-channel recordings in pairs and then appropriately matched in order to assure accurate timing. Voltages have been adjusted in order to obtain similarity of records for qualitative comparison. These records reflect time moving from right to left.

The following findings are demonstrated with saccadic movement to the left (Fig. 1): (1) Failure of inhibition of the right lateral rectus muscle (RLR); (2) delayed inhibition of the left medial rectus (LMR) muscle; and (3) a suggestion of delay to peak discharge in the right medial rectus muscle.

The following findings are demonstrated with saccadic movement to the right (Fig. 2): (1) Failure of inhibition of the left lateral rectus muscle (LLR); (2) delayed inhibition of the right medial rectus (RMR) muscle; and (3) a suggestion of delay to peak discharge in the left medial rectus muscle.

(RLR—right lateral rectus; RMR—right medial rectus; LMR—left medial rectus; LLR—left lateral rectus.)
Experimental internuclear ophthalmoplegia

The animals were killed under deep barbiturate anaesthesia by intracardial perfusion with 3000 ml of 10% formalin in saline. The perfusion was accomplished by means of a Mayo roller pump adjusted to deliver 200–400 ml/minute. The brains were removed and stored in 10% formalin for a minimum period of three months and the brainstem imbedded in paraffin. Transverse 50 μm serial sections were made from the inferior olivary nuclei to the level of the third nerve nucleus. Every tenth section was stained with either Weigert's or Bodine's stain. Additional sections were stained and studied as deemed necessary.

Results

Clinically four of the five animals showed bilateral INO, which was relatively symmetrical but present only in far lateral gaze. Three of the four animals with INO had normal saccadic movements within the range they normally moved their eyes. Other neurological functions were normal except that one of these animals had ptosis and a slightly enlarged pupil on the left side. All vertical eye movements, both saccadic and following, as well as convergence movements, were normal.

Smooth horizontal following movements were present with dissociation occurring only in far lateral gaze. Adduction became deficient, and the abducting eye displayed a slow abducting movement followed by a slow, but faster, abducting movement for 1 or 2 beats. The speed of this abducting movement was slower than that of a normal saccadic movement (less than 400°/s). Only 2 of the 4 affected animals responded to optokinetic stimuli consistently, and the response resulted in an exaggeration of the dissociated movements. Cold caloric stimulus induced dissociation of the fast phase movements in all 4 animals. One animal with ptosis and mydriasis could not generate saccades to the left.

It is of particular interest that 2 of 4 animals with INO demonstrated an asymmetrical pupillary constriction during the abducting phase of nystagmus in the abducting eye. This constriction was greater in the abducting eye. During the abducting phase a corresponding asymmetrical pupillary dilatation took place.

Electromyographic recordings consistently demonstrated the following abnormalities: (1) Delayed inhibition of the medial rectus muscle of the abducting eye in all four of the animals with INO (Figs. 1 and 2); (2) failure of inhibition of the lateral rectus muscle of the abducting eye in 3 of the 4 animals (Figs. 1 and 2); and (3) occasional intermittent excitation of the medial rectus muscle of the abducting eye.

Fig. 3  Co-firing of the left medial rectus muscle during saccadic (see arrow) movement to the left (RLR—right lateral rectus; RMR—right medial rectus; LMR—left medial rectus; LLR—left lateral rectus)

in almost all of the cases: (1) Spontaneous gaze (i.e., the presence or absence of nystagmus, strabismus, skew deviation, conjugate gaze weakness or deviation); (2) horizontal and vertical saccades; (3) following movements; (4) convergence; (5) horizontal and vertical optokinetic nystagmus; (6) oculocephalic reflexes, and (7) cold water caloric testing (30°C).

A special canaliculus extension earpiece of Teflon tubing (1 mm internal diameter) was threaded into the external auditory canal of each animal to ensure adequate caloric stimulus delivery. 15 ml of water was then flushed into the external ear in approximately 15 seconds.
eye, associated with observable abducting nystagmus was seen in all four animals (Figs. 3 and 4). These findings were absent in the remaining animal.

In three of the animals with INO histological studies for the most part showed a clean vertical separation of the two longitudinal fasciculi from the inferior olive to just rostral to the sixth nerve nucleus (Fig. 5). The cut tended to extend deeper at the most caudal end of the lesion, becoming more superficial and fading rostrally. Damage to the MLF was limited to its most medial border, and in two of these cases there was no MLF damage visible from just caudal to the level of the abducens nuclei up to the rostral end of the lesion (Fig. 6).

Discussion

While the lesions certainly did not interrupt all of the nerve fibres concerned with any of the eye movements studied, the disturbed movements observed are a clue to the role of the nerve fibres in the damaged area.

In two of the animals that developed INO after a midline dorsal ponto-medullary lesion, the MLFs were uninjured throughout their course in the pons. The only lesions of the midline were in the medial portion of the MLFs in the medulla. Since all the pathologically documented clinical, as well as experimentally produced, cases of INO had lesions above the medullary level, these lower lesions are presumed not to be responsible for the abnormalities of ocular movement observed in our animals. It appears that a single midline lesion at and about the level of the abducens nuclei separating both MLFs, but not involving either one, can produce bilateral INO. This INO is assumed to be due to the interruption of fibres crossing from one side of the brainstem to the other as originally postulated by Cogan et al. (1950) and as demonstrated anatomically after MLF lesions producing INO in monkeys by Carpenter and McMasters (1963), as well as Carpenter and Strominger (1965).

If the interruption of fibres crossing the midline produces INO, then some of these fibres should...
Experimental internuclear ophthalmoplegia

control ocular adduction. That such a crossed pathway exists was demonstrated in monkeys by Bender and Weinstein (1944). The nuclei of origin of these fibres has been placed in the vestibular nuclei (McMasters et al., 1966; Carpenter and Strominger, 1965) and in the reticular formation (Szentagothai, 1961). These fibres cross to the contralateral MLF at the level of the abducens nuclei (McMasters et al., 1966; Carpenter and McMasters, 1963) so that lesions of the MLF above this region produce an ipsilateral weakness of adduction.

The remaining component of INO, abducting nystagmus, has been the subject of varied explanations. These include the interruption of doubly-crossed excitatory pathways to the medial rectus subnucleus (Pola and Robinson, 1976), loss of excitatory input to the contralateral abducens nucleus (Carpenter and McMasters, 1963; Carpenter and Strominger, 1965), and the utilisation of convergence movements in an attempt to compensate for the weakness of adduction (Stroud et al., 1973, 1974). The results of our study lend support to two of these explanations.

Pola and Robinson (1976) postulated that each parapontine reticular formation (PPRF) sends its excitatory and inhibitory fibres into the contralateral MLF and up to both medial rectus subnuclei (Fig. 7). The excitatory fibres were thought to remain on the contralateral side to enter the subnucleus of that side, whereas the inhibitory fibres were presumed to recross the midline to enter the medial rectus subnucleus on the original side of origin. They suggested that during gaze to one side the excitatory and inhibitory commands originating from PPRF on that side are augmented by decreased activity of the opposing contralateral PPRF. In addition they mention that during lateral gaze there are also excitatory and inhibitory signals sent to the motor neurons of each sixth nerve nucleus.

The electromyographic (EMG) findings in INO of Loeffler et al. (1966) are difficult to relate to the relatively clean experimental situation. All of their patients had diffuse brainstem disease. Three had evidence of involvement of the area around the third nerve nucleus, and two had failure of conjugate gaze to one side in addition to other signs. In one case that had neither rostral nor caudal involvement they demonstrated a failure of complete inhibition of the ipsilateral medial rectus muscle on conjugate gaze. This muscle also failed to develop appropriate burst activity on attempted contralateral gaze. Electromyographic recordings of our animals with INO

---

**Fig. 5** Bodine stain of obliquely cut section of the brainstem demonstrating a superficial lesion extending ventrally from the fourth ventricle. There is some damage to the left medial longitudinal fasciculus (×10)

**Fig. 6** Bodine stain of obliquely cut section of the pons demonstrating a lesion extending into the pontine tegmentum with a fibrous ingrowth from the fourth ventricle. The brainstem structures are remarkably intact (×10)
Assume a conjugate movement to the left is programmed. Two pools of neurons are activated in the left parapontine reticular formation: (1) An excitatory pool sending axons to the left abducens nucleus (VI) and to the contralateral medial rectus subnucleus of the oculomotor nucleus (III) via the MLF; and (2) an inhibitory pool sending axons to the contralateral abducens nucleus in a relatively ventral pontine decussation and to the ipsilateral medial rectus subnucleus via the contralateral MLF involving a double decussation.

Concomitantly, appropriate pools are inhibited (or excited) in the opposite parapontine gaze centre leading to a further relative facilitation of the agonist and disfacilitation of the antagonist muscle groups involved in the movement (Adapted from Pola and Robinson, 1976).

Consequently, we have no evidence to support the hypothesis (Carpenter and McMasters, 1963; Carpenter and Strominger, 1965) that loss of input to the abducens nucleus of the abducting eye is responsible for the abducting nystagmus. The lack of normal inhibition of the lateral rectus of the adducting eye may have resulted from interruption of either of two sources of nerve fibres to the abducens nucleus: fibres crossing the midline at the level of the abducens nuclei (Carpenter and McMasters, 1963; McMasters et al., 1966) or fibres ascending from the vestibular nuclei in the MLF. However, these latter fibres do not enter the MLF until they ascend to the level of the abducens nuclei (McMasters et al., 1966), and consequently, injuries to the MLF...
Experimental internuclear ophthalmoplegia

below this level would not be expected to affect ocular motor activity. The animal with INO which did not display the inhibition of the adducting lateral rectus had an extremely superficial lesion at the level of the abducens nucleus, suggesting that the fibres involved cross somewhat ventrally.

The occasional intermittent burst of EMG activity in the antagonist medial rectus of the abducting eye was always associated with nystagmus of that eye. This burst was seen only in the two animals that demonstrated pupillary constriction with the adducting movement. Unfortunately pupillary constriction and this electromyographic pattern were never studied simultaneously. However, the EMG recordings do suggest that with each burst of activity in the antagonist medial rectus there is an accompanying increase in the firing of the opposite medial rectus (Figs. 3 and 4). If such an increase in activity of both medial recti were associated with the observed pupillary constriction, this would indicate activation of asymmetric convergence as suggested by Stroud et al. (1973, 1974). The electromyographic pattern, here represented by burst activity, is compatible with the activity previously reported in asymmetric convergence by Miller (1959).

Though the dissociated nystagmus seen in our animals was most easily induced by cold caloric stimulation, pupillary changes were only noted in two animals and were associated with abducting nystagmus. This was unlike patterns of pupillary constriction and dilatation seen by DeSantis and Gernandt (1971), who observed an initial marked pupillary dilatation to vestibular stimulation (air jet directed at the utricle) with superimposed rapid minor constrictions of random frequency.

Our experiments suggest that it is possible to produce a deficit in extraocular movements having the characteristics of clinical bilateral inter-nuclear ophthalmoplegia without damage to the medial longitudinal fasciculi. The symmetry of the induced ocular motor dysfunction makes precise statements about eye velocity impossible with the comparative frame technique we have used previously (Burde et al., 1975). In spite of this our observations lend supportive evidence to the schema of Pola and Robinson (1976) which postulates the existence of doubly decussating inhibitory fibre pathways in conjugate gaze movements and to their explanation of the abducting nystagmus of INO (Fig. 7). However, our finding of co-firing of the contralateral medial rectus, as well as the association of the adducting phase of nystagmus with pupillary constriction, is also consistent with the proposal of Stroud et al. (1973, 1974) that an asymmetric convergence mechanism is responsible for the abducting nystagmus.

References


NOTE: Dr Ralph A. W. Lehman is now at the Department of Neurosurgery, University of Colorado, Denver, Colorado. Dr John L. Keltner is now at the Department of Ophthalmology, University of California, Davis.
Experimental internuclear ophthalmoplegia.

R. M. Burde, R. A. Lehman, G. Roper-Hall, J. Brooks and J. L. Keltner

doi: 10.1136/bjo.61.3.233

Updated information and services can be found at:
http://bjo.bmj.com/content/61/3/233

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/