Recovery of Peripheral Versus Central Nerves Identified by Saccadic Velocity After Abducens Neuropathy

JAMES A. SHARPE, KYLEN MCREEILS, AND AGNES M.F. WONG

Division of Neurology and Department of Ophthalmology and Vision Sciences, University Health Network, University of Toronto, Toronto, Ontario, Canada

ABSTRACT: The abducens is the motor nerve with the most substantial course, both within and outside the brain and it innervates only one muscle. Sixth nerve palsy affords an opportunity to compare recovery after central versus peripheral nerve damage by assessing the dynamics of abduction. Horizontal saccade peak velocities and durations in 14 patients with unilateral peripheral sixth nerve palsies (5 acute, 9 chronic) are compared with those in 5 patients with central sixth nerve palsies (2 acute, 3 chronic) and with those in 10 normal subjects. Acutely, abducting saccades in the paretic eye were slow in both central and peripheral palsies, as anticipated from weakness of the lateral rectus muscle. In chronic central palsies, abducting saccadic velocities remained reduced, but in chronic peripheral palsies, they increased to normal within the limited range of excursion. The chronically damaged peripheral nerve behaves like a high-pass filter in transmitting phasic velocity commands, whereas tonic position commands remain defective, accounting for limited abduction but normal velocities within the range of duction. In chronic central (fascicular) palsies, saccade velocities remain reduced. Impaired conduction from damage to central myelin or axons is more persistent in central palsies, consistent with limited regeneration within the brain. Recording of saccade velocities may aid the distinction of fascicular from peripheral palsies. Saccade speed is repaired in peripheral palsies, probably by remyelination, and perhaps also by central monocular adaptation of innervation selectively to the paretic eye in order to drive both eyes rapidly and simultaneously to a target in the paretic field of motion.

KEYWORDS: saccades; sixth nerve palsy; abducens nerve; repair; regeneration; adaptation; saccade velocity; saccade duration; Hering’s law

INTRODUCTION

The abducens is the motor nerve with the most substantial course both within and outside the brain, where it is vulnerable to damage. Comparison of recovery after central versus peripheral nerve palsy provides an opportunity to investigate differ-
ences in repair properties between the central and peripheral nervous systems. The abducens nerve innervates only one muscle, the lateral rectus, so the amount of recovery can be quantified readily by assessing the dynamic properties of that muscle alone.

Abducens nerve palsy lowers saccade amplitude and velocity in the direction of action of the paretic lateral rectus muscle. We investigated patients with unilateral sixth nerve palsy and assessed the saccades of both the paretic and nonparetic eyes during monocular viewing with each eye. We studied idiopathic peripheral palsy versus central (fascicular) palsy of structural cause and compared the effects of the two sites of damage and the duration of the palsy on the speed of saccades.

METHODS AND SUBJECTS

Among the 19 patients with unilateral sixth nerve palsy, 14 patients had idiopathic, presumed ischemic, peripheral palsy (mean age 63 ± 10 years, range 46 to 77, median 64; nine were men). All 14 had normal MR or CT imaging. Four patients had identifiable ischemic risk factors (hypertension or diabetes mellitus). Symptom durations ranged from three weeks to 96 months (mean duration 21 months). Patients with diplopia of less than one month duration were classified as having acute palsy; all others were designated as chronic. Five patients with peripheral palsy were tested acutely (within one month of symptom onset). Serial eye-movement recordings were performed on these five patients with acute peripheral palsy, first at presentation and then at two months after symptom onset.

Five patients had central (fascicular) lesions identified on MR imaging. Two had cavernomas and three had demyelinating lesions from multiple sclerosis, involving the abducens nerve fascicle in the pons, but sparing the abducens nucleus. They had no other ocular motor abnormalities. Their mean age was 52 ± 18 years (range 30 to 75 years, median 56; two were men). The duration of symptoms ranged from one week to 132 months (mean duration 38 months). Two patients were tested acutely (within one month of symptom onset). Serial recordings were performed on these two patients at presentation and at two months after symptom onset.

All patients had an incomitant esotropia with a clinically obvious unilateral abduction deficit. Mean abduction deficit was the same in both lesion-site groups: 80% of normal (range 60 to 95%) in peripheral, and 75% of normal (range 70 to 90%) in central fascicular palsy. Ductions in the fellow eye were normal.

Ten normal subjects served as controls (five men; mean age 49 ± 12 years; median age 55; age range 19 to 69). Investigations followed the tenets of the Declaration of Helsinki and the Ethics Review Board of the University Health Network, and informed consent was obtained from each participant.

Oculography

Participants fixated a red laser spot of 0.25-degree diameter 1 m away from the nasion, which stepped at 3-s intervals 10° right, then back to center, then 10° left, cycling through this pattern 20 times. The study design of 10° target steps assured that testing was within the limited range of abduction, as patients were prospectively entered. Head position was stabilized with an occipital support and monitored by a
search coil taped to the forehead. With the normal eye covered, patients were instructed to follow the laser spot as it stepped among positions. The target sequence was then repeated viewing with the normal eye while the paretic eye was covered.

Eye positions were measured by a three-dimensional magnetic search coil technique, using 6 ft (183 cm) diameter coils field arranged in a cube (CNC Engineering, Seattle, WA). In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, The Netherlands). Eye position data were filtered with a bandwidth of 0 to 90 Hz and digitized at 500 Hz.

Saccade amplitudes, peak velocities, and durations were analyzed for the paretic and nonparetic eyes. In all patients, the peak velocity–amplitude and duration–amplitude relationships in both the paretic and nonparetic eyes did not differ between viewing with the paretic or the nonparetic eye. We report the peak velocity–amplitude and duration–amplitude relationships during paretic eye viewing.

**RESULTS**

*Saccades in Peripheral Abducens Nerve Palsy*

Peak velocity–amplitude and duration–amplitude relationships were correlated with bins of amplitude in the 2-degree ranges (Figs. 1 and 2) because the palsies precluded measuring large-amplitude saccades to determine asymptotic features of the peak velocity–amplitude main sequence. In the acute state, centrifugal abducting saccades in the paretic eye had reduced peak velocities (Fig. 1) and longer durations.

![Figure 1](image-url)

**FIGURE 1.** Group mean peak velocity versus amplitude (in bins) of initial saccades in the paretic eye of 14 patients with idiopathic (presumed ischemic) sixth nerve palsies. Centrifugal abducting saccades from center to 10° abducted position in peripheral palsy were significantly slowed acutely (<1 month of diplopia) but normal in the chronic state.
FIGURE 2. Mean duration versus amplitude (in bins) of initial saccades in the paretic eye. (A) Centrifugal abducting saccades from center to 10° abducted position in peripheral palsy are prolonged acutely but normal in the chronic state (>1 month). (B) Centripetal abducting saccades from 10° adducted position to center in peripheral palsy are normal both acutely and chronically.
FIGURE 2 — continued. (C) In central (fascicular) palsy, centrifugal abducting saccades from center to 10° abducted position are slowed both acutely and chronically. (D) Centripetal abducting saccades from 10° adducted position to center in central (fascicular) palsy are normal.
for any given amplitude (Fig. 2A) when compared with normal controls ($P < .05$; Wilcoxon rank sum test), as anticipated from weakness of the lateral rectus muscle. However, in the chronic state, centrifugal abducting saccadic peak velocities (Fig. 1) and durations (Fig. 2A) in the paretic eye were within the normal range, despite limited abduction in the nine chronic palsies. In the five initially acute palsies tested serially, saccade peak velocities and durations became normal within two months of symptom onset despite persisting limited abduction. Centripetal abducting saccades from $10^\circ$ adducted position to center in the paretic eye had normal peak velocities (Fig. 3A) and durations (Fig. 2B), both in acute and chronic states. Saccade peak velocities and durations in the nonparetic eye were normal in both acute and chronic states.

**FIGURE 3.** Centripetal abducting saccades from $10^\circ$ adducted position to center in peripheral (A) and in central (fascicular) palsy (B) had normal peak velocities in both acute and chronic palsies.
Saccades in Central Abducens Nerve Palsy

Centrifugal abducting saccades in the paretic eye had reduced peak velocities (Fig. 4) and had longer durations (Fig. 2C) for any given amplitude, both in the acute and chronic states, when compared with normal controls ($P < .05$; Wilcoxon rank sum test). Persistent slowing of abducting saccades was recorded in all five chronic palsies (including the two cases of acute central palsies that were recorded within one month of onset of diplopia and later at two months after onset). Centripetal abducting saccades from the $10^\circ$ adducted position to center in the paretic eye had normal peak velocities (Fig. 3B) and durations (Fig. 2D), both in acute and chronic states. Saccade peak velocities and durations in the nonparetic eye were normal in both acute and chronic states.

**DISCUSSION**

Information about saccadic dynamics in paralytic strabismus is sparse. The effects of duration and lesion site of abducens nerve palsy on saccade dynamics had not been systematically investigated and the potential for recovery or adaptation had not been assessed. We measured the effects of idiopathic (presumed ischemic) peripheral palsy, and central fascicular palsy on the peak velocity and duration of saccades, and assessed changes over time. Abducting saccades are hypometric and slow in the paretic eye in lateral rectus palsy. In the present investigation, abducting saccades in the paretic eye had amplitudes appropriate to the $\pm 10^\circ$ target steps, because our patients had mild to moderate palsies with full ductions within the tested range. Acutely, centrifugal abducting saccades in the paretic orbital hemirange of duction (from center to an abducted position) in the paretic eye were slow in both...
Central and peripheral palsy, as anticipated from weakness of the lateral rectus muscle. In the chronic state, centrifugal abducting saccadic peak velocities remained reduced and durations remain prolonged in the paretic eye in central palsy, but they became normal in peripheral palsy.

Centripetal abducting saccades (from an adducted position to center) in the paretic eye were normal in amplitude, peak velocity, and duration in both central and peripheral palsy, whether acute or chronic. The two horizontal rectus muscles in each eye contribute reciprocally to horizontal eye movements. Abducting movements require an increase in force of the lateral rectus and a decrease in force of the medial rectus. The amount by which the force of the agonist increases and the antagonist decreases depends on the initial position of the eye in the orbit.8 Most of the force for centrifugal abducting movements (starting from the orbital midposition to the adducted hemirange) comes from contraction of the agonist lateral rectus muscle. However, when abducting movements are centripetal (starting in the adducted hemirange toward orbital midposition), most of the force for abduction comes from relaxation of the antagonist medial rectus muscle.8 Thus, in sixth nerve palsy, abduction is little affected when the eye starts from an adducted (nasal) position, as most of the change in force is contributed by relaxation of the normal antagonist, that is, the medial rectus. When the movement begins from orbital midposition, however, the change in force comes mainly from contraction of the agonist, that is, the paretic lateral rectus, and hence saccades in the paretic orbital hemirange of duction are abnormal. Our finding that abducting saccades in the paretic orbital hemirange (from center to an abducted position) in the paretic eye are slow, while abducting saccades from an adducted position to center in the paretic eye are normal can be explained by the relative contribution of the agonist and antagonist muscles in different orbital positions.8

Paralytic strabismus may be accompanied by contracture (shortening and increased stiffness) in the nonparetic antagonist muscle,9–12 while the paretic muscle lengthens in response to a change in orbital position of the globe. Contracture of the nonparetic antagonist is associated with a decrease in the number of sarcomeres, whereas lengthening of the paretic muscle is accompanied by an increase in sarcomeres.13 The persistent reduction in centrifugal abducting saccadic velocities found in our patients with chronic central palsy is unlikely to be the result of contracture of the medial rectus (antagonist) muscle because the function of the medial rectus would not be expected to differ between peripheral and central palsy of the same duration, but it did. Also, contracture of the medial rectus might be expected to cause slowing of centripetal abducting saccades (from adducted hemirange to orbital midposition) and adducting saccades in the paretic eye; however, those velocities were normal.

Recovery in Peripheral Abducens Nerve Palsy

The study of abducens nerve palsy provides a unique opportunity to investigate the different repair properties of the central and peripheral nervous systems. Central myelin, consisting of membrane layers of oligodendrocytes and maintained by their cell bodies, extends for a few millimeters distal to the emergence of the nerve from the brain.14 The rest of the peripheral abducens nerve is ensheathed in peripheral myelin, which consists of layers of Schwann cell membranes and is maintained by
their somata. The central (fascicular) portion of the nerve is surrounded by a glial environment that is generally inhospitable to neural recovery, whereas the peripheral nerve should have the capacity for recovery. In addition, because the abducens nerve only innervates one muscle, the lateral rectus, the degree of recovery can be quantified readily by assessing the dynamic properties of that muscle alone by the speed of the paretic eye during abduction.

By comparing saccade peak velocities and durations in central fascicular versus peripheral idiopathic abducens nerve palsy, we found that in peripheral palsy, abducted saccadic peak velocity and duration for the tested range of excursion (10°) becomes normal, despite persistent esotropia and limitation of abduction. In contrast, there was no improvement in saccadic peak velocity or duration in chronic central fascicular palsy. Our findings are concordant with the capacity for recovery of peripheral nerves, as exemplified here by function of the abducens nerve after it exits from the brain stem, and also concordant with the limited capacity for recovery of central nerves, as measured by function of the abducens nerve after damage to its fascicle.

The time course for recovery of peripheral palsy in our patients is consistent with demyelinating damage, or neurapraxia consisting of local conduction block with no distal Wallerian degeneration.\textsuperscript{15,16} If the myelin sheath is disrupted, recovery depends on remyelination, which has a time course of many days or weeks. In axonotmesis or second-degree injury, the axons are disrupted. Wallerian degeneration occurs, in which the distal axon and myelin undergo degradation and the proximal neuron soma undergoes chromatolysis. Regeneration occurs by the outgrowth of multiple axonal sprouts proximal to the site of lesion, and by growth of axons at a rate of 1 to 2 mm a day.\textsuperscript{17}

Histopathological correlation of peripheral ocular motor nerve palsy is sparse.\textsuperscript{18–21} In diabetic third nerve palsy\textsuperscript{18–20} the lesion is ischemic and primarily demyelinating, with a paucity of Wallerian degeneration distally, and an absence of chromatolysis in neuronal cell bodies in the oculomotor nucleus. These findings are compatible with the rapid and complete recovery of ocular motor nerve palsy commonly seen in diabetes mellitus.

No histopathological study of diabetic, hypertensive, or idiopathic sixth nerve palsy is available. In cats, axotomy of the abducens nerve is followed by structural and functional recovery in about three months.\textsuperscript{21} We found that abducting saccadic peak velocity and duration became normal within two months in patients with idiopathic (presumed ischemic) peripheral palsy. Although the range of abduction remained limited in the peripheral sixth nerve palsies we studied, in contrast to the typical complete recovery of abduction after presumed ischemic palsies, the time course of recovery of saccade speed and duration to normal in these patients suggests that their palsies resulted from a primarily demyelinating event, rather than from axonal disruption.

Recovery of Saccadic Velocity in Peripheral Abducens Nerve Palsy

In our patients with central palsy, both acute and chronic abducting saccades were slow and of longer duration. In contrast, in our patients with peripheral palsy, abducting saccadic peak velocity and duration became normal, in the face of persistent esotropia.
The partially recovered peripheral nerve appears to act as a high-pass filter, allowing the transmission of high firing rates during the pulse of innervation, such that the resulting saccades are of normal peak velocity and duration. In contrast, the partially recovered nerve may be unable to transmit low-frequency tonic signals (the step of saccadic innervation), resulting in an abnormal tonic position (i.e., esotropia) and the limited abduction of the paretic eye, evident in each of our patients in the acute (<1 month) and chronic states.

A cellular correlate of disparity between the repair of saccade speed and the persistence of defective ranges of abduction may be the selective nature of the nerve fibers damaged or the tempo of their regeneration and remyelination. Although all ocular motoneurons participate in saccadic and slow eye movements, and in the tonic discharges that maintain eye positions, some may be specialized in function. Large motoneurons within the abducens nucleus innervate singly innervated twitch muscle fibers, whereas smaller motoneurons around its periphery innervate multiply innervated nontwitch muscle fibers. The high-pass filter response of the damaged peripheral abducens nerve to saccadic velocity commands, as described earlier, might be explained either by damage predominantly to nerve fibers from nontwitch motoneurons just outside the abducens nucleus, or by better repair of nerve fibers from twitch motoneurons within the nucleus.

Central (Fascicular) Abducens Nerve Palsy

Damage to the fascicle of the nerve in the pons was determined by MR imaging. Sparing of the abducens nucleus was assured both by imaging and by normal speeds of adduction in the nonparetic eye (field of action of the contralateral yoked medial rectus muscle). In addition to lateral rectus motoneurons, the abducens nucleus contains internuclear neurons that excite medial rectus motoneurons of the opposite eye.

The central nervous system is a hostile molecular and cellular milieu for neural regeneration. We found that abducting saccadic velocity remained reduced in patients with central palsy from cavernomas or multiple sclerosis. Although multiple sclerosis is generally considered to be an inflammatory demyelinating disease with relative axonal sparing, axonal damage, including loss, transection, or disturbed axonal transport, occurs early in the disease and during lesion development. The absence of recovery of saccade speed and range in our patients with central fascicular palsy indicates limited regeneration of damaged axons and myelin in the glial environment of the brain.

Possible Role of Monocular Adaptation

We found that in chronic peripheral palsy, velocities of abducting saccades in the paretic eye became normal, without a conjugate increase in adducting saccadic velocity in the nonparetic eye (i.e., field of action of the contralateral yoked medial rectus muscle). These findings may be due to partial recovery of the peripheral nerve, as discussed earlier. Alternatively, they may represent a monocular readjustment of innervation selectively to the paretic eye. Hering suggested that the brain controls gaze by two systems, one for conjugate movements and the other for vergence. If common and conjugate premotor signals were sent to motoneurons to both eyes, abducting saccadic velocity in the yoked antagonist of the nonparetic eye would be in-
creased as well. For example, in the case of a left lateral rectus weakness from a left sixth nerve palsy, any adaptive increase in innervation to the left lateral rectus would be accompanied by increased innervation to the right medial rectus, in accord with Hering’s “law.” However, this was not the case; yoked adduction of the fellow eye had a normal velocity–amplitude relationship. Monocular adaptation of saccades to sixth nerve palsy would be consistent with evidence of monocular adaptation of the vestibulo-ocular reflex in sixth, fourth, or third nerve palsy.33–36

An anatomical and physiological prenuclear substrate for possible monocular adjustments of saccade speed in response to peripheral nerve palsy is found in presaccadic burst neurons of the caudal paramedian pontine reticular formation (PPRF). The great majority (about 80%) of short-lead burst neurons in the caudal PPRF of monkeys, which was once thought to encode conjugate velocity commands for horizontal saccades, actually encodes monocular movements of either abduction or adduction.37 This behavior is contrary to Hering’s law. Whether the present results indicate partial recovery, monocular adaptation, or both, the recovery of saccadic speed in chronic peripheral palsy allows both eyes to reach targets in the paretic hemifield of motion rapidly and simultaneously.

Clinical Implications

Idiopathic abducens nerve palsy in patients over 50 years of age is usually presumed to be caused by microvascular ischemia, occurring with greater frequency in patients with diabetes mellitus or hypertension.38,39 Because most such patients recover within three months,40 they may not require imaging of the brain or skull base at the time of initial presentation, provided that the sixth nerve palsy is an isolated neurological finding.39 However, if there is no improvement within three months, imaging studies are indicated. Normal MR imaging in our peripheral cases indicated an idiopathic (presumed ischemic) origin of palsy. Assessment of abducting saccadic velocity may be an adjunct to imaging in distinguishing between a central and peripheral cause of abducens nerve palsy. Study of palsies having comparable severity after partial structural damage to the peripheral nerve will be needed to determine whether their saccadic dynamics differ from those in idiopathic (presumed ischemic) palsies or from central palsies, as investigated here. Normal saccadic velocity over a month after onset of palsy may indicate a peripheral demyelinating or ischemic cause. Conversely, reduced saccadic velocity after a month may signify a central lesion.

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REFERENCES


