

Oculomotor Dysfunction in Amyotrophic Lateral Sclerosis

A Comprehensive Review

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Although traditionally regarded as spared, a range of oculomotor dysfunction has been recorded in patients with amyotrophic lateral sclerosis (ALS). Most frequent is ophthalmoparesis, particularly in patients with prolonged survival; however, pursuit, nystagmus, and saccadic impairments have also been reported. The apparent resistance to pathologic involvement of oculomotor (and sphincter) control pathways in most patients with ALS has prompted comparative study to establish the key pathways that underlie motor neuronal vulnerability, with the hope of generating novel therapeutic strategies. Developments in the assessment of oculomotor function, including portable eye-tracking devices, have revealed more subtle impairments in ALS in relation to phenotype, which can now be better understood through parallel elucidation of the normal cerebral oculomotor control network. Given the clinicopathologic overlap between ALS and some types of frontotemporal dementia, the study of oculomotor function has particular value in probing the variable but consistent cognitive impairment seen in ALS and that reflects frontotemporal extramotor cerebral abnormalities. By transcending the requirement to write or speak, loss of which precludes standard neuropsychological testing in some patients with advanced ALS, cognitive tests performed using only oculomotor functions offer additional potential, allowing the study of patients much later in their disease course. The study of oculomotor dysfunction holds significant promise as an additional source of much needed prognostic, monitoring, and mechanistic biomarkers for ALS. *Arch Neurol.* 2011;68(7):857-861

Eye movements are traditionally regarded as spared from involvement in most cases of amyotrophic lateral sclerosis (ALS), despite progressive weakness of limb, respiratory, and bulbar musculature. The central diagnostic criterion for ALS (as the most common form of motor neuron disease) is the combined degeneration of upper motor neurons of the corticospinal tract and lower motor neurons in brainstem nuclei and spinal anterior horns. It has been long established, however, that ALS is a neurodegenerative disorder of a third compartment comprising widespread areas of the extramotor brain. Neuroimaging and neuropsychological studies¹⁻³ have demonstrated particular involvement of frontal, es-

pecially dorsolateral prefrontal, regions. Although the exact nature and cause of the observed variability in the region of onset and spread of abnormality in ALS remain uncertain, the recognition of clinicopathologic overlap with frontotemporal dementia (FTD) clearly points to more widespread central nervous system involvement. Frank dementia affects only a small minority of patients with ALS, but the true extent of diffuse central nervous system involvement in ALS may be masked because life-span is so drastically reduced as a result of respiratory failure. Recognition of this confounding factor challenges simplistic concepts of intellectual sparing in ALS, and it is estimated that up to half of patients with ALS may have detectable cognitive impairment on rigorous neuropsychological testing.⁴ Oculomotor function, sphincter con-

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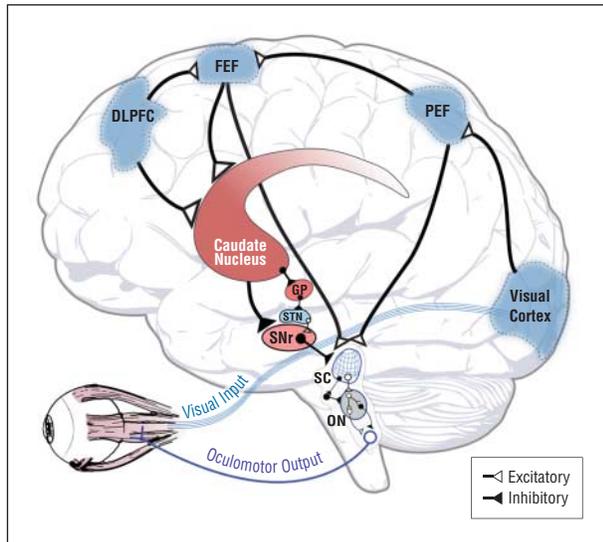


Figure. Saccadic eye movements are supported by a distributed network of cortical and subcortical regions. Saccades are initiated by direct signals sent from the frontal or parietal eye fields (FEFs or PEFs) to the superior colliculus (SC), which drives the oculomotor network (ON) in the brainstem. An indirect “gating” circuit arising from the FEFs and dorsolateral prefrontal cortex (DLPFC) projects via the basal ganglia (caudate nucleus, globus pallidus [GP], and subthalamic nucleus [STN]) to the substantia nigra pars reticulata (SNr). The SNr inhibits the SC, preventing saccade generation. To switch off this inhibition, when the FEFs and other frontal structures are activated before a saccade, the caudate nucleus is activated, which, in turn, inhibits the SNr via an inhibitory pathway.

trol (subserved by the Onuf nucleus in the sacral cord), and sensory neuronal function, although also superficially spared in ALS, have been similarly observed to be involved in longer-surviving patients. The pervasive nature of the networks that mediate oculomotor function, which lie outside the traditional regions that characterize ALS abnormalities, and the increased sophistication and practicality of eye-tracking equipment make this an attractive tool for the study of various aspects of ALS pathogenesis, particularly because it can be performed in patients unable to communicate.

This review article explores what is known about normal oculomotor control, the nature of oculomotor dysfunction observed in ALS to date and how this might inform our understanding of regional pathologic abnormalities and current concepts of neuronal vulnerability, and the potential of eye tracking to generate biomarkers of extramotor cerebral involvement in ALS.

NORMAL OCULOMOTOR PATHWAYS

Voluntary eye movements are supported by a distributed network of cortical and subcortical regions (**Figure**). Voluntary saccades are initiated by 2 principle cortical areas: the frontal eye fields and parietal eye fields,⁵⁻⁷ which help identify and select targets. Both of these areas contain neurons that fire before a saccade and send projections directly to the superior colliculus, where command signals descend to the brainstem oculomotor network, leading to the initiation of rapidly orienting saccadic eye movements.

The superior colliculus is controlled by high-frequency tonic GABAergic inhibition from the substan-

tia nigra pars reticulata.⁸ Removal of this inhibition (or disinhibition) is necessary for saccadic output and comes from GABAergic inhibitory neurons that project from the caudate nucleus to the substantia nigra pars reticulata.⁹ Although generally silent, many of the inhibitory caudate nucleus neurons exhibit a burst or a train of spikes in relation to saccadic eye movements. This suggests that the saccade-related decrease in firing in substantia nigra pars reticulata neurons is caused by the saccade-related increase in firing of caudate neurons (see the study by Hikosaka et al¹⁰ for a review).

The caudate receives input throughout the cerebral cortex, including a large portion of the association cortices, but the oculomotor region largely receives input from the frontal and supplementary eye fields and the dorsolateral prefrontal cortex.¹¹⁻¹³ Executive saccadic control seems to be performed by the dorsolateral prefrontal cortex through projections to the caudate nucleus and reciprocal connections with the frontal and supplementary eye fields, which affects the generation or suppression of saccades in relation to online task information.

The simultaneous occurrence of excitatory input from cortical eye fields and disinhibition of the superior colliculus is necessary for generating saccadic eye movements. Diseases that disrupt the frontal cortex or caudate nucleus lead to difficulties in initiating voluntary saccades, directional errors, and disinhibited saccade generation for executively controlled eye movements (see the article by Leigh and Kennard¹⁴ for a review).

OCULOMOTOR PATHWAYS AS A CLUE TO NEURONAL VULNERABILITY IN ALS

In the vivid clinical history recounted by Radcliffe and Lockhart Clarke¹⁵ in one of the earliest descriptions of ALS, the (now) familiar list of spared regions was mentioned, namely, cognitive function, sphincter control, sensation, and oculomotor function: “Looking at the clinical facts, it was obvious that there was no material injury in the seat of intelligence. . . . Nor was there anything wrong in relation to urination. . . . There was no pain anywhere . . . Nor was there anything faulty in the action of the special senses.^(p219) . . . The eye was intelligent. . . .”^(p216)

At the beginning of the era of modern molecular biology, such observations held the promise of important clues to understanding pathogenesis.¹⁶ The concept of selective vulnerability has become less tenable with the demonstration of sensory neuronal abnormalities in ALS¹⁷ and the frequent involvement of bladder and bowel functions in some genotypes, such as those homozygous for the D90A superoxide dismutase-1 (*SOD1*) gene.¹⁸ Furthermore, the long-term survival of some patients with ALS as a result of tracheostomy confirmed that oculomotor function is eventually involved,¹⁹ and dementia, commoner than previously thought, may be inevitable given enough time.

Although a wealth of experimental work has emerged concerning the sparing of the Onuf nucleus,²⁰ comparatively little has been performed in relation to the apparent resistance of oculomotor nuclei (cranial nerve nuclei III, IV, and VI). An immunohistologic study²¹ of cranial nerve nuclei III and IV in 27 patients with ALS

revealed that approximately one-third of the sporadic cases had morphologic changes similar to those in anterior horns (Bunina bodies, ubiquitin-positive skeinlike inclusions, Lewy body–like inclusions, conglomerate inclusions, and spheroids). This included all 3 patients with ophthalmoplegia but notably also 4 of 5 with dementia, demonstrating that oculomotor dysfunction might also serve as an independent marker of wider cerebral involvement and cognitive impairment in ALS.

The finding of mutations of the *SOD1* gene in approximately 20% of familial cases of ALS led to the development of *SOD1* transgenic mouse models of ALS abnormalities. Oculomotor nucleus involvement was significantly less compared with that of other cranial nerve nuclei and was seen only in animals with very severe disease, again suggesting only a relative resistance to involvement rather than fundamental sparing,²² confirmed in another study that also considered a related model of motor neuronal degeneration.²³

It was observed that oculomotor nuclei III and VI lacked the high concentration of glycinergic and muscarinic cholinergic receptors compared with lower motor neurons in the spinal cord and cranial nerve nuclei VII and XII in patients with ALS.²⁴ The researchers commented that such differences might relate to separate observations that nuclei relating to ocular movements have faster firing rates and lack recurrent collaterals. Differences in connectivity as a clue to vulnerability is a theme also taken up more recently, noting that an evolutionarily more recent and direct corticospinal tract pathway has its origins in the caudal M1 region but has no monosynaptic connections to the motor neuron pools involved in ocular motility or the bladder.²⁵

Excitotoxicity is one of several themes in ALS pathogenesis,²⁶ and one in which intracellular calcium increase may have a key mediating role. Absence of the expression of calcium-binding proteins (calbindin D and parvalbumin) is linked to the population of motor neurons lost early in the disease process, with notably higher expression on oculomotor nuclei and the Onuf nucleus.^{27,28} Moreover, retrovirally induced expression of calbindin D conferred resistance to motor neurons exposed to sera from patients with ALS,²⁹ and neurotransmitter release from motor neuron terminals in response to sera derived from patients with ALS (a calcium-dependent process) was found to occur in spinal but not oculomotor motor neuron terminals.³⁰ Patch-clamp recording has revealed 5 to 6 times the calcium-binding ratio for oculomotor vs spinal or hypoglossal neurons.³¹

Finally, the widespread distribution of the normal saccadic control network beyond the brainstem suggests that oculomotor function may be independently impaired in ALS, despite any relative resistance at the nuclear level, through frontal lobe involvement as part of the spectrum of ALS-FTD. A predominantly dysexecutive syndrome characterizes the cognitive impairment in many patients with ALS,³² although frank FTD is rare, and several studies have highlighted the dorsolateral prefrontal cortex as a particularly vulnerable area, including positron emission tomography^{2,3} and neuropathologic assessment.³³ Although specific neuropathologic study of patients with ALS-FTD in relation to oculomotor path-

ways has not been undertaken to date, we postulate that the dorsolateral prefrontal cortex and frontal eye fields are likely to be involved. A study³⁴ of eye movements that compared those with different forms of frontal lobe degeneration and Alzheimer disease reported that patients with clinical syndromes associated with dorsal frontal lobe damage, which would be expected in ALS, although this group was not tested in this study, had normal visually guided saccades but were impaired in smooth pursuit eye movements and on the antisaccade task.

STUDIES OF OCULOMOTOR DYSFUNCTION IN ALS

A range of oculomotor disorders has been reported in ALS, including ophthalmoplegia, defective pursuit, saccadic impairments, nystagmus, and abnormal Bell phenomenon (listed in the eTable; <http://www.archneurology.com>).

Ophthalmoplegia

Oculomotor dysfunction was described as early as 1925 in a case of ALS said to have occurred with convergent strabismus that progressed to complete ophthalmoplegia.³⁵ An early postmortem case series³⁶ observed abnormal oculomotor nuclei in only 4 of 54 cases of ALS with no clinical ophthalmoparesis. One study³⁷ postulated that the order of impairment of cranial motor functions in ALS might be in the reverse order of their developmental sequence, with the preserved ocular motor function reflecting the fact that this network is relatively old ontogenetically.

Abnormal Pursuit

Defective pursuit movements have been commonly described in ALS, although the pursuit system becomes progressively more inefficient with advancing age, with increasing discrepancies between target and eye velocities leading to more frequent catch-up saccades in older individuals.³⁸ In a study³⁹ of 18 patients using electrooculography, 11 were found to have defective pursuit movements, correcting for the age effect, with the conclusion that the selective pursuit defect in ALS was probably due to nonnuclear involvement (supratentorial or infratentorial) of extrapyramidal or corticobulbar components of the oculomotor system.

Saccadic Impairments

Slowing of saccades, especially vertical saccades, has been a widely reported abnormality, with 1 study⁴⁰ suggesting that ALS with early such involvement represented a distinct clinicopathologic entity. Slow vertical saccades were noted to be common in ALS-FTD,⁴¹ and another study⁴² suggested that oculomotor dysfunction (including saccadic impairment) in ALS might reflect the incidence of secondary abnormalities, such as parkinsonism. Patients with ALS have been shown to have significantly elevated error rates (distractability) and latency in the antisaccade and memory-guided (remem-

bered) saccade paradigms but no abnormality of reflexive saccades (the most widely used but least sensitive saccadic paradigm).⁴³

With the advent of sophisticated equipment, such as eye trackers, detailed examination of saccades and their abnormalities in various disease processes has been made easier. In a large study⁴⁴ of 44 patients with ALS and 50 controls, the saccadic intrusion amplitude was found to be greater in patients than in controls and, in particular, in patients with spinal onset. Saccadic intrusion amplitude in patients also correlated with neuropsychological measures sensitive to lesions of the frontal lobes. The authors postulated that progressive deterioration in saccadic intrusion amplitude could be a quantifiable objective marker of disease progression. In a later study,⁴⁵ the slowing of reflexive saccades in bulbar-onset compared with limb-onset patients was specifically noted.

Nystagmus

An early case report⁴⁶ described horizontal gaze-evoked nystagmus in 1 case and rotatory horizontal gaze-evoked nystagmus in another. In another case with rotatory nystagmus and primary position nystagmus, with reversal of direction of the slow phase, the researchers concluded that it could be due to dysfunction of vestibulo-cerebellar connections with an intact peripheral vestibular apparatus.⁴⁷

Bell Phenomenon

Other less frequently reported oculomotor abnormalities include an abnormal Bell phenomenon, the physiologic upward rotation of the globe in response to attempted eyelid closure. A study⁴⁸ reported that this reflex (Bell phenomenon) was altered in 15 of 24 patients with ALS. All the patients had preserved oculocephalic reflexes, with the conclusion that the lesions were supranuclear as a result of corticogeniculate tract involvement. These oculomotor alterations were not directly related to the type of ALS at onset of the illness or to its duration. However, they were correlated with the relative degree of the clinical bilateral pyramidal tract signs at the supraspinal level.

FUTURE DIRECTIONS

Studies of eye movement abnormalities can provide insight into multiple aspects of cerebral abnormalities in ALS and have potential as easily derived, quantitative biomarkers of extramotor disease progression in particular. With patients with ALS generally surviving longer, a potential challenge of eye-tracking experiments will be separating late involvement of abnormalities at the nuclear level from impairment as a result of cortical involvement. This may be possible through the development of more sophisticated eye-tracking tasks, with cognitive testing elements embedded, a major advantage being that such testing does not exclude patients with ALS and loss of useful speech or the ability to write.

Cortical hyperexcitability may be a key event in the symptomatic onset of ALS.⁴⁹ It is not yet clear where the

balance of loss of inhibitory function vs excitotoxicity mediated by glutamatergic effects lies, but calcium may be an important mediator.⁵⁰ Further comparative studies of oculomotor vs spinal motor neurons in relation to emerging calcium-dependent mechanisms may provide novel strategies for therapeutic intervention.

Finally, the finding of genes with a common theme of aberrant RNA processing (*TDP-43* and *FUS*) that have more direct relevance to sporadic familial cases of ALS will result in new transgenic models becoming available for further study of the nature of oculomotor nuclei resistance.

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