Eye movements in amyotrophic lateral sclerosis and its mimics: a review with illustrative cases

Colette Donaghy, Matthew J Thurtell, Erik P Pioro, J Mark Gibson, R John Leigh

ABSTRACT
Abnormal eye movements are increasingly recognised in patients with amyotrophic lateral sclerosis (ALS) and, when they occur, may provide insights into the pattern and pathogenesis of the disease process. In patients with disorders that mimic ALS, abnormal eye movements may point to the correct diagnosis. In both of these circumstances, systematic examination of eye movements and interpretation of the findings with reference to modern concepts of their neural substrate will aid diagnosis and suggest pathogenesis. Here, key points with illustrative case histories and eye movement records are highlighted.

INTRODUCTION
Classical teaching is that eye movements are spared in amyotrophic lateral sclerosis (ALS), except in those patients whose lives are prolonged by artificial ventilation. Over the past 20 years, however, a number of reports have indicated that patients with ALS may show a range of eye movement disorders similar to those encountered in other degenerative and hereditary neurological diseases. These reports raise several questions. Do abnormal eye movements provide any insights into the pathogenesis of the disease process in those patients who show them? Which diagnoses should the clinician consider when confronted with an apparent ALS patient who has abnormal eye movements? Can eye movement abnormalities provide clues to accurate diagnosis of disorders that mimic ALS? What eye movement abnormalities are consistent with a diagnosis of ALS? Much is now known about the neurobiology of eye movements, making them widely used as diagnostic and research tools. Salient features of the properties and neural substrate of the functional classes of eye movement are summarised in table 1 of the supplementary material (available online only) and in figure 1 as a background to this review; the reader is referred to current texts for more details.

Is there a progressive supranuclear palsy variant of ALS?
Supranuclear gaze palsies with slow saccades have been reported in ALS patients, often in association with cognitive impairment or bulbar onset disease. Averbuch-Heller et al reported slow vertical saccades in two ALS patients with bulbar symptoms; post mortem examination in one demonstrated neuronal cell loss in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the midbrain brains of ALS patients and showed slower reflexive saccades compared with age matched controls. It is therefore likely that slow saccades in ALS patients are indicative of brainstem pathology.

Disturbance of visually guided (‘reflexive’) saccades in ALS
The peak velocity of saccades is a function of their amplitude; large saccades in humans may exceed 500°/s. The pulse of innervation driving the eye muscles is generated by burst neurons in the brainstem reticular formation (figure 1B). The paramedian pontine reticular formation houses burst neurons for horizontal saccades whereas the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the midbrain houses burst neurons for vertical and torsional saccades (figure 1B). Between saccades, burst neurons are inhibited by omnipause neurons in the nucleus raphe interpositus in the pons. Prior to the onset of a saccade, omnipause neurons cease discharging, allowing the burst neurons to fire. Current views are that lesions of either the burst or omnipause neurons could cause slowed saccades.

SACCADe ABNORMALITIES IN ALS
A saccade is a rapid eye movement that brings the image of an object of interest onto the fovea, for clearest vision. Several types of saccade can be tested at the bedside and measured in the laboratory, including visually guided saccades, memory guided saccades and antisaccades; we will discuss abnormalities of each of these, in turn.
as well as slow vertical and horizontal saccades with supranuclear gaze palsy. Neuropathological findings included corticospinal tract degeneration and loss of anterior horn motor neurons. TDP-43 positive inclusions were found in anterior horn cells, motor cortex, midbrain, hypoglossal nucleus, globus pallidus, caudate, putamen, hippocampus and substantia nigra.

Although the inclusions were found in the midbrain, the authors did not mention involvement of the riMLF. PSP is known to be a tauopathy, and is defined pathologically by an accumulation of tau protein and neurofilament threads in the pallidum, subthalamic nucleus, red nucleus, substantia nigra, pontine tegmentum, striatum, oculomotor nucleus, medulla and dentate nucleus.16 Although not proven, it is likely that the supranuclear vertical gaze palsy of PSP arises due to involvement of burst neurons in the riMLF.16 TDP-43 has recently been found to be a major component of the ubiquinated inclusions characteristic of frontotemporal lobar dementia (FTLD) and sporadic ALS,19 and so one might ask why, with such differing pathologies, there are clinical similarities in the ocular motor phenotypes of PSP and ALS? Firstly, neurodegenerative disorders associated with extrapyramidal disease can be seen in association with both tau and alpha-synuclein pathology, highlighting that one phenotype does not necessarily indicate a particular pathology. Secondly, with the discovery of TDP-43 as the major disease protein in ALS, we now have a clearer idea about the extent of pathology in ALS. In a neuropathological study of TDP-43 in 31 ALS patients, Geser et al found that the basal ganglia and substantia nigra were the regions most frequently involved outside of the motor system; the midbrain andpons, which house the burst neurons for saccades, are also involved in about 50% of cases.22

We propose that slow saccades can be part of the clinical profile of bulbar onset ALS and that they indicate involvement of the brainstem reticular formation that houses the neural machinery for generating saccades (figure 1B). In a proportion of such cases, the pathology may be extensive enough to produce supranuclear gaze palsy, with or without extrapyramidal features, thus presenting as a PSP variant of ALS. Unpublished work by one of the authors (CD) comparing eye movements in eight patients with PSP and 14 patients with bulbar onset ALS found that there were many similarities, with both having slowed reflexive saccades and an increased frequency of saccadic

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**Figure 1**

(A) Probable location of cortical areas important for eye movements in human brain. See text for discussion. Adapted from Leigh and Zee. MST, medial superior temporal visual area; MT, middle temporal visual area (in humans, may form a contiguous area with MST). (B) A sagittal section of the monkey brainstem showing structures important in the control of vertical and horizontal gaze. Excitatory burst neurons (EBN) for vertical saccades lie in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). The interstitial nucleus of Cajal contributes to vertical gaze holding and also houses some inhibitory burst neurons for vertical saccades. The shaded areas indicate the paramedian pontine reticular formation (PPRF), which houses EBN for horizontal saccades, and medullary reticular formation (Med RF), which houses (inhibitory burst neurons) for horizontal saccades. The asterisk indicates the location of omnipause neurons. III, oculomotor nucleus; IV, trochlear nucleus; VI, abducens nucleus; CG, central grey; cranial nerve (CN) III, rootlets of the oculomotor nerve; CN VI, rootlets of the abducens nerve; CN VII, genu of the facial nerve; h, habenular complex; mb, mammillary body; MRF, mesencephalic reticular formation; N IV, trochlear nerve; ND, nucleus of Darkschewitsch; NPH, nucleus prepositus hypoglossi; NRTP, nucleus reticularis tegmenti pontis; PC, posterior commissure; TR, tractus retroflexus. The arrow refers to the Horsley–Clarke plane of section. Courtesy of Jean Buttner-Ennever.
intrusions (SIs) during attempted fixation although the abnormalities were more marked in the PSP group. Clinicians should therefore be aware of the potential for misdiagnosis due to overlap between the clinical and eye movement abnormalities in these conditions.

Disturbance of volitional saccades in ALS

Although the clinical examination of eye movements may be normal in ALS, laboratory evaluation of the cognitive control of saccades, especially testing of memory guided saccades and antisaccades, has provided important insights. Memory guided saccades are made towards a visual target that has been flashed at a peripheral location some time (typically several seconds) previously. Antisaccades are made to the imagined mirror image of a visually presented target; for example, when a target is flashed at a location 10° to the left of centre, the subject is required to generate a saccade to an imagined location 10° to the right of centre. Both ‘short term’ memory guided saccades (where the remembered target was shown seconds before) and antisaccades are abnormal in ALS patients. ALS patients make accurate memory guided saccades but with increased latency (reaction time).12 In the antisaccade task, ALS patients generate saccades that are both inaccurate and made at increased latency.5 12 One study separated antisaccade errors into type 1 (subject looks incorrectly towards the target and does not self-correct) and type 2 (subject looks incorrectly towards the target but self-corrects) and found that only type 1 errors were increased in ALS patients.5 Furthermore, a positive correlation was found between type 1 errors and both the Stroop test (a neuropsychological test of attention and frontal lobe function) and the Amyotrophic Lateral Sclerosis Functional Rating Scale-revised, including its bulbar subscore.

Thus ALS patients have increased errors during the antisaccade task, as well as increased latency of antisaccades and ‘short term’ memory guided saccades. How can these findings be explained? Both the frontal eye fields (FEF) and dorsolateral prefrontal cortex (DLPC), shown in figure 1A, contribute to the programming of antisaccades, but in different ways. On the one hand, the right hemisphere DLPC is activated during antisaccades23 and patients with DLPC lesions have an increased percentage of errors in the antisaccade task.18 On the other hand, patients with FEF lesions have a normal percentage of errors on the antisaccade task (a neuropsychological test of attention and frontal lobe function) and the Amyotrophic Lateral Sclerosis Functional Rating Scale-revised, including its bulbar subscore.

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antisaccade type 1 errors and latencies encountered in ALS are
due to involvement of both DLPC and FEF. It is also possible to
propose a hypothesis to account for generation of memory
guided saccades as functional imaging studies suggest that DLPC
contributes to spatial memory for up to about 20 s. In
summary, abnormalities in the cognitive control of saccades in
ALS patients indicate frontal lobe involvement, which fits well
with the ever enlarging literature from neuroimaging and
neuropsychological studies of frontal lobe impairment in
patients with ALS, even in those without clinical evidence of
dementia. Based on neuropsychological studies, up to 50%
of non-demented ALS patients have frontal lobe impairment, although these studies come from ALS clinic based populations and may be biased. Traditionally, it had been thought that 3–5% of ALS patients have an associated FTLD although recent evidence suggests a clinicopathological disease spectrum with overlap between ALS and FTLD.  

SMOOTH PURSUIT ABNORMALITIES IN ALS

Smooth pursuit eye movements evolved to permit foveation of
moving targets. It is possible to measure both the onset and
maintenance of smooth pursuit. The onset of smooth pursuit is
usually measured using step ramp stimuli, in which the target
steps to one side and then moves smoothly in the opposite
direction. Step ramp stimuli aim to position the image of the
moving target close to the fovea of the retina at the time when
the eye first starts to move; thus they allow for the reaction time
to onset of smooth pursuit and promote generation of smooth
pursuit without superimposed saccades. Maintenance of smooth
pursuit is often studied using small visual targets that move in
predictable triangular or sinusoidal waveforms. The mainte-
nance of smooth pursuit is usually expressed as velocity gain,
the ratio of pursuit eye velocity to stimulus velocity. A more
indirect method to assess pursuit gain is to look for catch-up
saccades, which are generated to place the fovea back on target if
pursuit is inadequate. 
   
Using a predictable, triangular stimulus waveform, Donaghy
et al found a reduced velocity gain in 44 ALS patients compared
with controls, as well as a reduced proportion of time spent in
smooth pursuit. An example of impaired smooth pursuit is shown in figure 1B of the supplementary material (available online only). Three further studies using triangular and sinu-
soidal waveforms also found reduced velocity gain in ALS
patients compared with controls. A further study found that
smooth pursuit was impaired and largely replaced by catch-
up saccades in 11 out of 18 ALS patients. In contrast, Shaunak
et al assessed 17 ALS patients with a triangular waveform
stimulus and found that pursuit velocity gain was normal. However, Gizzi et al found reduced smooth pursuit velocity gain
only in ALS patients with parkinsonian features, and concluded
that pursuit was normal in classical sporadic ALS. Thus most,
but not all, studies have reported abnormalities of smooth
pursuit gain in ALS patients. How can these findings be
explained?

Smooth pursuit is controlled by cerebro-ponto-cerebellar
pathways; the cortical areas involved include parts of the
temporal and parietal lobes, as well as the FEF. Posterior cortical
areas involved in smooth pursuit project to the cerebellum via
the dorsolateral pontine nuclei whereas the FEF projects via
nucleus reticularis tegmenti pontis. Neurons from the dorsal
vermis and flocculus/paraflocculus of the cerebellum are thought
to project to the ocular motor nuclei of the brainstem via the
cerebellar fastigial nuclei, vestibular nuclei and y-group nuclei of
the brainstem. Smooth pursuit gain is reduced in normal
elderly subjects, as well as in patients with parkinsonian disor-
ders, FTLD, Alzheimer’s disease, cerebellar disorders and meta-
bolic disturbances, such as hepatic encephalopathy. Impaired
smooth pursuit is also due to certain medication or drug
intoxications and is therefore not diagnostically specific. Nonethe-
less, electrophysiological and microstimulation studies of
the pursuit region of the FEF indicate a role for the FEF in the
setting of gain. Thus reduced smooth pursuit velocity gain in
ALS patients could arise from involvement of the frontal lobes
and, more specifically, the FEF.

OCULAR FIXATION ABNORMALITIES IN ALS

Saccadic intrusions
SIs consist of involuntary saccades that disrupt fixation. SIs are
evident on clinical examination, especially during ophthalmos-
copy. Measurements have demonstrated several types of SI,
including square wave jerks, single saccadic pulses, double
saccadic pulses, and monophasic and biphasic square wave jerks,
which are most common. Examples of SIs are shown in figure
1A of the supplementary material (available online only). SIs can
occur in normal subjects. However, saccadic oscillations without
an intersaccadic interval, such as flutter and opsoclonus, do not
occur in healthy subjects.  

Palmowski et al first described fixation abnormalities in seven of eight ALS patients. Shaunak et al noted an increased frequency of square wave jerks in ALS patients compared with controls but they did not measure other SIs. Donaghy et al formally examined fixation in ALS and not only demonstrated an increased SI amplitude in ALS patients compared with controls but also showed a correlation between SI amplitude, verbal fluency and Stroop test scores (measures sensitive to frontal lobe dysfunction). Thus fixation abnormalities may be
due, at least in part, to impairment of the frontal lobes or their
projections to the superior colliculus.

The neural substrate of fixation comprises both cortical and
brainstem components. In the monkey, numerous studies have
demonstrated that FEF is important for suppressing saccades, as
well as initiating them. Functional imaging studies suggest
that the frontal lobes have a role in sustaining steady fixation in
humans, with a positron emission tomography study finding
activation clusters in the FEF and intraparietal sulci bilaterally
when subjects fixated on a central target but not when they
simply kept their eyes open in darkness. In the brainstem,
electrophysiological and pharmacological inactivation studies in
monkey suggest that the rostral pole of the superior colliculus is
important in sustaining steady fixation. The superior colliculus
receives inputs from cortical areas concerned with eye move-
ments; projections from the FEF are both direct and via the basal
ganglia. Other inputs are from the mesencephalic reticular
formation and cerebellar fastigial nucleus. In one monkey,
irrepressible saccades resulted from an infarct involving the
rostral pole of the superior colliculus, adjacent reticular forma-
tion and periaqueductal grey. Pharmacological inactivation of
the mesencephalic reticular formation has produced square wave
erikps in monkeys. Similarly, pharmacological inactivation of the
rostral pole of the superior colliculus in a monkey reduced
suppression of saccades. Square wave jerks are prominent in
PSF and pallidotomy has been found to increase square wave
jerks in patients with Parkinson’s disease, suggesting a role for
the basal ganglia in producing SIs. Square wave jerks have also
been reported in cerebellar disorders, such as in some spinocer-
ebbular ataxias.
In summary, the most consistent abnormality of fixation in ALS is increased SI amplitude.\textsuperscript{5} SIs show the same relationship between amplitude, peak velocity and duration as do voluntary saccades, and are therefore thought to be generated by the same brainstem machinery. While increases in SI amplitude could arise due to dysfunction within these pathways, correlations between SI amplitude and measures of frontal lobe dysfunction suggest that SIs could arise due to involvement of frontal-colllicular pathways.

**Nystagmus**

A second cause for disruption of steady fixation is nystagmus, which is a repetitive to and fro movement of the eyes that is initiated by a slow phase. It occurs when there is a disturbance within any of the mechanisms that have evolved to hold gaze steady (see supplementary table 1, available online only).\textsuperscript{18} One such mechanism is the vestibulo-ocular reflex, which generates eye movements that compensate for head movements, and another is the gaze holding mechanism, which holds the eyes in an eccentric position against the elastic restoring forces of the orbital tissues and depends on a neural network (the ‘neural integrator’) within the brainstem and cerebellum. Lastly, pathology affecting the afferent visual system, from the eye to the posterior cortex and its pontine-cerebellar projections, can also cause nystagmus. In this case, nystagmus can result from an impaired ability to correct for retinal image drift or disruption of the visual inputs that allow eye movement calibration according to visual demands. Nystagmus is rarely reported in ALS although there are two reported cases of ALS, confirmed post mortem, with nystagmus.\textsuperscript{30} One of these had gaze evoked nystagmus followed later by supranuclear palsy of horizontal gaze and upgaze, while the other had gaze evoked nystagmus with a normal range of eye movements. Gaze evoked nystagmus often occurs with brainstem or cerebellar disease\textsuperscript{18} although the ensuing supranuclear gaze paresis in the first patient suggests involvement of the midbrain and pons. Post mortem examination in one of the patients revealed two small carcinoid tumours in the terminal ileum, raising the question of whether the nystagmus could have been a feature of a paraneoplastic syndrome rather than the patient’s ALS.

Thakore et al described three patients with downbeat nystagmus (figure 1A, see supplementary material available online only) and a predominantly lower motor neuron syndrome, with wrist and finger extensor weakness and evidence of anterior horn cell disease.\textsuperscript{31} Cerebellar atrophy was noted on imaging in one patient, who had initially presented with balance and gait difficulties. It is possible that these patients had a distinct syndrome although their electrophysiology was consistent with ALS. In summary, nystagmus is not a common finding in ALS; when it occurs, it may present an opportunity to investigate the pathophysiology of the disorder but could also suggest an ALS mimic (discussed in the last section).

**OPHTHALMOPLEGIA**

Case reports of ALS patients with external ophthalmoplegia are uncommon and mainly concern patients whose life has been prolonged by long term ventilation.\textsuperscript{1} In some reports, involvement of the ocular motor nuclei has been noted on post mortem examination.\textsuperscript{32} Kaminski et al reviewed the evidence for sparing of ocular motor neurons in ALS.\textsuperscript{32a} When comparing ocular motor with spinal motor neurons, there are differences in glutamate neurotransmitter activity, calcium binding protein, androgen receptor expression and their dependence on trophic factors. However, no single theory satisfactorily explains why ocular motor neurons are relatively spared in ALS. It is possible that patients who develop external ophthalmoplegia represent the extreme end of the disease spectrum where the process has extended to involve the ocular motor nuclei of the brainstem.

**SUMMARY OF EYE MOVEMENT ABNORMALITIES IN ALS**

Much like the continuum of cognitive disturbance proposed in the ALS literature,\textsuperscript{28} eye movement abnormalities probably form a spectrum, with normal eye movements at one end of the spectrum and supranuclear gaze palsies and, rarely, ophthalmoplegia at the other. Many patients with sporadic ALS have increased latency of antisaccades, with increased antisaccade errors, reduced smooth pursuit velocity gain and increased saccadic intrusion amplitude. Current evidence suggests that these abnormalities arise due to frontal lobe involvement. In those patients with advanced or bulbar onset disease, however, it is likely that more extensive pathological changes in the brainstem give rise to slowed saccades with or without supranuclear gaze palsy. In these instances, ocular motor abnormalities may mimic those of PSP, with more marked involvement of vertical saccades and relative sparing of horizontal saccades. Many of these ALS patients have other ocular motor signs suggestive of SI, increased antisaccade errors and decreased smooth pursuit gain.\textsuperscript{6} 8 12 14 Nonetheless, with the advent of sensitive molecular pathological markers, such as TDP-43, future clincopathological studies are likely to identify the neural substrate of atypical eye movement and clinical findings in ALS and, in doing so, further our understanding of the clinical spectrum of this disorder.

**EYE MOVEMENT ABNORMALITIES IN ALS MIMICS**

The syndromes that most commonly mimic ALS—benign fasciculation syndrome, cervical spondylitic myelopathy, multifocal motor neuropathy and inclusion body myositis—are not known to cause eye movement abnormalities. However, a range of other motor neuron disorders can produce an ALS-like picture, with associated eye movement abnormalities (table 1). Palsies of the oculomotor (III), trochlear (IV) and abducens (VI) cranial nerves should suggest disease in the subarachnoid space, cavernous sinuses, orbit or posterior nasopharynx. Rare hereditary progressive bulbar syndromes, such as Brown–Vialletto–Van Laere\textsuperscript{34} and Fazio–Londe\textsuperscript{33} syndromes, can also produce cranial nerve III, IV and VI palsies. Although hearing loss is suggestive of these syndromes, it is unknown if vestibular dysfunction occurs in affected patients.

Parkinsonian syndromes, especially PSP, may present like ALS, with prominent bulbar dysfunction and decreased mobility. PSP patients are known to have a distinctive eye movement disorder: slowing of vertical saccades, along with increased frequency of saccadic intrusions (square wave jerks).\textsuperscript{18} However, the potential for diagnostic difficulty exists when taking into consideration the case reports describing slow saccades with or without supranuclear gaze palsy in ALS patients with or without a bulbar onset.\textsuperscript{3} 10 15

Kennedy’s disease (KD), also known as spinal bulbar muscular atrophy, is an X linked degenerative condition of lower motor neurons causing late onset muscular atrophy, with fasciculations of the face and tongue. KD can mimic ALS, but differs from sporadic ALS with absence of pyramidal involvement and a slowly progressive course. Unpublished work by one of the authors (CD) has found normal fixation, saccades and smooth pursuit in four patients with KD. Reflexive saccades, however, were found to be slowed in one KD patient we have studied (see figure 2 in the supplementary material, available online only).\textsuperscript{39}
Bulbar myasthenia gravis (MG) can occasionally be mistaken for ALS. MG can present with fluctuating ptosis, reduced range of eye movements that does not conform to specific ocular motor nerves or even complete ophthalmoplegia. Finding a reduced range of eye movement with preservation of small, fast saccades (‘quiver movements’) is highly suggestive of MG.\textsuperscript{10} Although rare, late onset Tay–Sachs’s disease, a lysosomal storage disorder due to inactivity of the enzyme hexosaminidase A, can also mimic ALS, but typically gives rise to interrupted or multi-step saccades, which have not been reported to occur in ALS.\textsuperscript{10} The spinocerebellar ataxias (SCAs) are a constantly enlarging group of inherited multisystem disorders that can present with cerebellar, pyramidal and extrapyramidal dysfunctions. SCA-5 (Machado–Joseph disease) can present with an ALS-like picture and therefore should be considered in the differential diagnosis of ALS. While approximately 56% of SCA-5 patients have ophthalmoplegia, other ocular motor findings, such as saccadic hypermetria and gaze evoked nystagmus, are suggestive of cerebellar disease.\textsuperscript{9} SCA-3 is also known to cause reduced gain of the vestibulo-ocular reflex.\textsuperscript{10}

**CONCLUSIONS**

We can now challenge the widely held view that eye movements are normal in ALS. As we have shown, a range of eye movement abnormalities can occur in ALS and have provided insights into the distribution and nature of the disease process. Eye movements have the potential to help identify ALS mimics in patients who are misdiagnosed due to the inherent difficulty in diagnosing ALS. Eye movements, which are easy to record and for which a neural substrate is well established, provide us with a powerful behavioural tool to investigate the workings of the brain in ALS. Measurement of eye movement abnormalities in future longitudinal studies seems likely to provide further insights into the nature of this stubborn and malignant disease.

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**Contributors** All authors were involved in writing the manuscript. In addition, CD performed the literature search, MJT and RJL recorded eye movements for the patients highlighted in the case reports and assembled the figures, and EP identified patients for the case studies.

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**REFERENCES**


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**Table 1** Amyotrophic lateral sclerosis and its mimics, categorised according to eye movement findings

<table>
<thead>
<tr>
<th>Eye movement findings</th>
<th>ALS or its mimic</th>
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<tr>
<td>No known abnormality</td>
<td>Benign fasciculation syndrome</td>
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<td></td>
<td>Cervical spondylitic myelopathy</td>
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<td>Inclusion body myositis</td>
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<td>Multifocal motor neuropathy</td>
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<td></td>
<td>2. Neuromuscular junction disease: MG</td>
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<td></td>
<td>3. Restrictive ophthalmopathy: Thyroid associated (Graves’s) orbitopathy/hyperthyroidism</td>
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<td></td>
<td>5. Unspecified restricted vertical and horizontal ocular motility: lead</td>
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<td></td>
<td>6. Chronic progressive external ophthalmoplegia due to mitochondrial myopathy</td>
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<tr>
<td>Vestibular–ocular reflex:</td>
<td>SCA-3 (Machado–Joseph disease)</td>
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<tr>
<td>Reduced gain</td>
<td>Guamanian ALS</td>
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<tr>
<td>Ocular fixation</td>
<td></td>
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<tr>
<td>1. Saccadic intrusions</td>
<td></td>
</tr>
<tr>
<td>(a) Increased frequency</td>
<td>PSP, MSA</td>
</tr>
<tr>
<td>(b) Increased amplitude</td>
<td>ALS, PSP</td>
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<tr>
<td>2. Unspecified nystagmus</td>
<td>Polio</td>
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<tr>
<td>3. Downbeat nystagmus</td>
<td>MSA</td>
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<tr>
<td>4. Periodic alternating and centripetal nystagmus</td>
<td>CJD</td>
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<tr>
<td>Saccades</td>
<td></td>
</tr>
<tr>
<td>1. Slow reflexive saccades</td>
<td>PSP, MSA, CJD, ALS, Kennedy’s disease</td>
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<tr>
<td>2. Increased antisaccade errors</td>
<td>ALS, frontal lobe pathology coexistent with cervical/lumbar root disease</td>
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<tr>
<td>3. Increased antisaccade latency</td>
<td>ALS, frontal lobe pathology coexistent with cervical/lumbar root disease</td>
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<tr>
<td>4. Increased latency of remembered saccades</td>
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<td>5. Increased reflexive saccade latency</td>
<td>PSP</td>
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<tr>
<td>Saccadic dysmetria</td>
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<tr>
<td>1. Hypometria</td>
<td>PSP, MSA, MG</td>
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<td>2. Hypometria due to premature termination</td>
<td>LOTS</td>
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<tr>
<td>3. Hypermetria</td>
<td>SCA-3 (Machado–Joseph disease)</td>
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<td>4. Hyperfast, dysmetria</td>
<td>MG</td>
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<td>Smooth pursuit</td>
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<tr>
<td>1. Reduced velocity gain</td>
<td>ALS</td>
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<tr>
<td>2. Broken by saccades</td>
<td>ALS, HSP (SPG30 mutation), HIV infection</td>
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<tr>
<td>Multisystem</td>
<td>Guamanian ALS</td>
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</table>

*Most particularly noted in vertical saccades.

ALS, amyotrophic lateral sclerosis; CBGD, corticobasal ganglionic degeneration; CJD, Creutzfeldt–Jakob Disease; HSP, hereditary spastic paraplegia; LOTS, late onset Tay–Sachs’s disease; MG, myasthenia gravis; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; SCA, spinocerebellar ataxia.