

## **Ophthalmoplegia in Young Onset Amyotrophic Lateral Sclerosis: A Case Report and Review of Literature**

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### **Abstract**

**Accumulated evidence has revealed that oculomotor system is not immune to ALS. With advances in eye movement tracking techniques, changes has been picked up in ALS which points to an involvement of the oculomotor system both at the nuclear and supranuclear level. Most of the cases previously described have shown a tendency for clinical oculomotor abnormalities to be associated with bulbar predominant form of the disease and has been reported late into the clinical course. In this case report we describe a thirty four year old lady with definite ALS with marked supranuclear gaze palsy within five months of symptoms onset. She had a rapidly progressive course and eleven months into the illness developed bulbar and respiratory muscle weakness. Through a detailed review of literature we also attempt to postulate the site of lesion and the pathological process in our patient.**

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### **Introduction**

Over the last few years, the accumulated clinical evidence have shown that the oculomotor system, which along with sensory and sphincter functions, previously thought to be untouched in amyotrophic lateral sclerosis (ALS), is not immune to its relentlessly progressive degenerating march. Oculomotor system involvement was traditionally considered as an atypical feature of ALS which is revealed only by unnaturally long term survival of patients on ventilator. However, there are several instances where asymptomatic clinical signs of supranuclear gaze pathway were reported relatively early in the disease process [1-4]. There is no consensus on the site of lesion or the pathology for oculomotor dysfunction in ALS. As it shares a common ground with atypical parkinsonian diseases, it is still undecided whether to lump this combination as part of this pathological spectrum or to split into a separate entity [2].

Most of the cases previously described have shown a tendency for clinical oculomotor abnormalities to be associated with bulbar predominant form of the disease and has been reported fairly late into the clinical course. Here we report a case of a patient with young onset ALS who had marked involvement of supranuclear gaze system very early in the disease course. Through a detailed review of literature we also attempt to postulate the site of lesion

and the pathological process in our patient. The study was done in accordance with Helsinki declaration 1975.

### **Case Report**

Our patient, a 34-year-old lady, primary school teacher, with no comorbidities other than mild intermittent asthma, presented with subacute onset rapidly progressive symptoms over the preceding five months. Initially she noted weakness of right hand muscles which progressed to difficulty in flexion of right wrist over the next month. In another two months, she developed right lower limb stiffness and weakness with frequent tripping and dragging of that limb. One month later, she noted dysarthria with slow deliberate and effortful speech, without any change in volume or nasal quality. Her family also noted that she had episodes of emotional incontinence which were congruous to the situation. In the last month, she developed grip weakness with left hand. Patient had also noted guttering of both hands and thinning of forearms with frequent muscle twitching of muscles over arms, forearms and thighs. Sensory and bladder symptoms were notable by their absence and nor was there any cognitive decline. At the time of presentation, she had no difficulty with swallowing or respiration. The disease had become significantly disabling over the preceding one month so that she was no longer working and required assistance for the activities of daily living though she was ambulant without support.

At admission, she had spastic dysarthria, with bifacial weakness and tongue fasciculations. Her motor examination revealed moderate spasticity in right upper limb and both lower limbs. There was marked wasting in intrinsic muscles of both hands, more prominent over right hand and of bilateral forearm and right thigh with diffuse fasciculations. Except for weakness of intrinsic hand muscles as well as that of long flexors of hand as evidenced by grip weakness, she had preserved motor power on formal testing, though on functional testing she had difficulty in getting up off the floor. Her deep tendon reflexes including jaw jerk were exaggerated. Her sensory system was completely spared.

The most remarkable finding was noted in the ocular examination. The patient had significant restriction of all extraocular movements. Testing of saccades showed a decreased saccadic velocity as well as range which were impaired more for the vertical rather than horizontal gaze, with normal saccadic latency (video). There was also loss of smooth pursuit movements in the same directions with restricted range of movements. The vestibulo-ocular reflex (VOR) was normal in the horizontal and vertical directions (video) and optokinetic nystagmus was impaired for corrective saccades bilaterally in all directions pointing to a predominant supranuclear involvement of gaze mechanisms.

Thus, our patient had an asymmetric pure motor syndrome with clinical signs of simultaneous upper and lower motor neuron involvement in cranial, cervical and lumbar segments consistent with the diagnosis of clinically definite ALS with coexistent supranuclear horizontal and vertical gaze restriction. She did not have any features of parkinsonism, cerebellar dysfunction or cognitive impairment.

Nerve conduction and electromyographic studies further confirmed the presence of diffuse anterior horn cell involvement with preserved sensory nerve potentials and evidence for active denervation and reinnervation from all four segments.

She was extensively evaluated for a secondary etiology in view of her young age of presentation and atypical oculomotor findings. Metabolic evaluation and MRI brain and spinal cord were normal.

On follow up after 6 months, the patient had developed significant progression with bulbar weakness with choking spells and respiratory involvement in the form of orthopnea. No features of parkinsonism or cerebellar dysfunction were noted at follow up.

## **Discussion**

In cases of ALS, it was thought that extraocular eye movement involvement is not commonly seen except in rare instances where the patient survives late into the disease course [5]. With advances in monitoring techniques, subtle changes in eye movement tracking

has been picked up in ALS which points to an early but definite involvement of the oculomotor system both at the nuclear and supranuclear level.

The most intriguing feature in our patient is that ocular involvement set in as early as five months into clinical onset and was well established at presentation. The clinical findings of preserved VOR and normal saccadic range would point to the supranuclear gaze pathways as sites of involvement.

The phylogenetically older oculomotor system has extensive ramifications from frontal and parietal cortices and subcortical structures including caudate and basal ganglia to brainstem tracts and nuclei [6]. The relative sparing of the ALS 'touch' on the oculomotor nuclei has been documented pathologically. A recent autopsy study sampling extra ocular muscles from patients succumbing to ALS revealed that compared to limb muscles, the extraocular muscles were remarkably spared though there was evidence of involvement with hypertrophic and atrophic fibers, increased connective tissue, and areas with fatty replacement [7]. This sparing has been proposed due to various reasons such as the relative abundance of calbindin and parvalbumin which effectively detoxifies the calcium excito-toxicity of ALS, differential concentrations of GABA and glycine in oculomotor nuclei and faster firing rates of these neuron which lack of collateral innervations [8].

Over the years, a host of supranuclear ocular abnormalities ranging from saccadic and pursuit abnormalities to ocular fixation errors and contrast vision deficits have been described in ALS with the aid of newer techniques including electrooculograms and ocular tracking devices [9]. The summary of a detailed review of the literature on oculomotor involvement in ALS is provided in Table 1.

There are two pathways through the affection of which ocular movement abnormalities can manifest in ALS. One is the involvement of cortico-oculomotor pathway and the loss of neurons in and around ocular motor nuclei in the midbrain and pons. The degenerative process in ALS affecting the pyramidal neurons in the dorsolateral frontal cortex leads to the abnormalities noted in saccadic generation especially in antisaccade and memory guided saccade generation [9,10]. Pathologically described cases also showed ubiquitin positive intracytoplasmic inclusions in the posterior commissure, rostral interstitial nucleus of medial longitudinal fasciculus (riMLF) and interstitial nucleus of Cajal in patients of ALS with vertical gaze palsy shedding further evidence in this regard [11]. In fact a few of the studies noted slow saccades as a part of the clinical profile of bulbar onset ALS which indicates the involvement of the brainstem reticular formation that houses the neural machinery for generating saccades. In the autopsy series by Okamoto, changes similar to that occurring in the anterior horn cells in ALS (namely

**Table 1.** Summary of group characteristics and test scores.

Author	Objective	No: of patients(age)	Ocular involvement	Onset of ocular signs	Other associated	Autopsy	Remarks
Harvey 1979(13)	Case report	1	Complete external ophthalmoplegia with absent VOR	NA	-	Neuronal loss and gliosis of 3rd, 4th, 6th CN nuclei Degeneration in SN and demyelination in integral capsule	First case report
Jacobs 1981(14)	Oculomotor abnormalities in ALS	11 (out of 18 patients)	Defective pursuit, saccadic deficits in 3	NA	-		
Leveille 1982(15)	subclinical involvement of the ocular motor system in ALS	4 out of 10 patients with MND(38-76years)	Decreased pursuit gains and saccadic velocity	NA	-	-	All 4 had rapidly progressive disease; bulbar predominant
Kushner 1984(16)	Case report	2	Nystagmus, upgaze restriction, absent convergence, limited abduction	NA	-	Central chromatolysis in SN, reticular formation of pons and midbrain, rare involvement of 3rd N nuclei	Longer survival may make subgroup of ALS patients develop atypical clinical and neuropathological features
Mizutani 1992(5)	Case report	2(43years, 51years)	Slow saccades which progressed to Complete external ophthalmoplegia with absent VOR	20months, 8 years	-	Brainstem nuclear degenerations as well as multisystem involvement	Only those patients with parkinsonian features had gaze abnormality
Gizzi 1992(17)	Oculomotor abnormality in MND, case control	5(out of 34 patients)	Impaired saccades and pursuits	NA	Five of these patients had pronounced parkinsonism		
Okuda 1992(3)	Case report	2(48years, 52 years)	Slow saccades, vertical gaze restriction, square wave jerks	18months, 12 months	Dementia and behavioural changes	Degeneration of SN, 3rd nerve nuclei normal	-
Shaunak 1992(10)	Ocular motor abnormality in ALS, case control	17	Abnormalities in antisaccade and remembered saccades; not in reflexive saccade	NA	-	-	Concluded as related to prefrontal dysfunction
Ohki 1994(18)	Quantitative analysis of ocular movements in ALS	9	Markedly reduced saccadic velocity (4), abnormal pursuit, OKN and visual suppression(one each)	NA	-	-	Found more patients with bulbar signs
Palmowski 1995(4)	Early subclinical oculomotor involvement in ALS	Follow-up study of 9	8 had either clinical or EOG abnormalities during follow-up	NA	-	-	Longitudinal study
Averbuch-Heller 1998(11)	Case report	Two (54years, 50years)	Slow vertical saccades	3 years in both	-	Cell loss in riMLF and SN	Eyelid opening apraxia in one patient

Vaphaides 2002(19)	Case report	1(46years)	Slow vertical & horizontal saccades	NA	Dementia	UB positive inclusions, Bunina bodies in Hypoglossal nuclei	-
Donaghy 2010(2)	Saccade and pursuit differences between bulbar- and spinal-onset MND, comparison with healthy control	and 30 spinal-onset patients (mean age 60)	Abnormality in reflexive and antisaccades in bulbar onset MND	NA	-	-	Smooth pursuit velocity gain and time spend in pursuit more in MND
Kasahata 2011(20)	Case report	One, 67years	Slow saccades	2years	-	-	Possible coexisting oculomotor apraxia
Beaufils 2012(1)	Case report	1(71years)	Severe vertical gaze restriction, eyelid apraxia	11months	Executive dysfunction	-	-
Current study	Case report	1(34 years)	Severe slowing of saccade and pursuit with preserved VOR	5months	None	-	Young onset ALS, early ocular involvement

NA- Not Available; SN- Substantia Nigra; riMLF- rostral interstitial Medial Longitudinal Fasciculus, UB- Ubiquitin, VOR- Vestibule Ocular Reflex, MND- Motor Neuron Disease

Bunina bodies, ubiquitin-positive skein-like inclusions, Lewy body-like inclusions, conglomerate inclusions and spheroids) were observed in the oculomotor nuclei as well [12]. However, the authors noted that the degree of pathological involvement is less than that necessary for development of ophthalmoplegia in the majority of ALS patients.

There are other differentials for motor neuron disease like presentation with supranuclear gaze palsy including late onset Tay-Sachs disease, Machado-Joseph disease and Parkinsonism-Dementia complex of Guam which could be confidently excluded in our case [13-17]. The remarkably young age of onset points to a possibility of familial ALS, however a genetic testing for the known mutations could not be done in our patient. A detailed charting of the pedigree tree across three generations failed to show any consanguinity or a family history compatible with this illness.

It could perhaps be argued that since her symptoms started only five months earlier and since she had significant extraocular involvement at presentation, our case may point towards a variant of motor neuron disease which could even have started with supranuclear palsy [18]. Though their pathological substrate differs widely, with the unifying theme of supranuclear gaze palsy in both, a PSP variant of ALS could also be tempered [11].

Our case provides a few new interesting extensions to the existing literature. This patient is, to our knowledge, the youngest reported case of ALS with ophthalmoparesis to date. Moreover, it is quite notable that our patient had well established supranuclear gaze palsy within five

months of clinical onset [19]. Hitherto reported cases in literature tends to associate ophthalmoplegia with bulbar onset variant of motor neuron disease while in our patient the clinical presentation was classical of ALS and though had bulbar involvement at presentation, was noted relatively late in the disease course. Hence supranuclear ophthalmoparesis in ALS, though uncommon, should be recognized as a part of the degenerative spectrum of ALS [20]. The possibility of an entity with supranuclear oculomotor degeneration as the onset needs to be entertained.

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