

## Clinical Findings in Isolated Bulbar Amyotrophic Lateral Sclerosis

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### ABSTRACT

**Background.** Isolated bulbar amyotrophic lateral sclerosis (IBALS) is a regional variant of amyotrophic lateral sclerosis (ALS) with weakness restricted to the bulbar muscles for at least 2 years, and slower progression than generalized ALS. Bulbar-onset generalized ALS, by contrast, typically has a more rapid progression than limb-onset ALS.

**Objective.** To characterize patients with IBALS and compare them to patients with isolated bulbar disease at presentation who progress to generalized ALS.

**Methods:** We performed a retrospective chart review of patients seen in our ALS specialty clinic at the University of Kansas Medical Center between 2001-2011.

**Results.** Of 543 patients seen in the ALS clinic, 150 presented with bulbar symptoms at disease onset: 28 (18.7%) had bulbar signs and no evidence of extremity involvement on exam or electrodiagnostic testing at their initial visit; and 14 (9.3%) had weakness restricted to the bulbar muscles after 2 years of follow up (IBALS). IBALS patients were 57.1% male, with a mean age of symptom onset of 60.8 years (range 39-77 years). The mean disease duration was 3.1 years (range of 2-8 years), with 50% mortality at a mean follow up of 3.5 years. Minimal denervation changes were seen in at least one limb in 6 subjects (42.9%). Other clinical features included: 4 subjects (28.6%) had cognitive impairment, 4 (28.6%) had pseudo-bulbar affect, and 5 subjects (35.7%) had impaired eye movements on smooth pursuit.

**Conclusions.** Isolated bulbar ALS IBALS is an identifiable restricted regional ALS pattern if there is no clinical limb weakness 2 years after symptom onset. It may have a slower progression from typical ALS. The biologic factors that account for the IBALS restricted pattern are unknown.

**Keywords:** *Amyotrophic Lateral Sclerosis, ALS, isolated, bulbar.*

### Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects motor neurons in the brain and spinal cord. The median survival in typical ALS is between 2-3 years from symptom onset, and 16-19 months from diagnosis.<sup>1,2</sup> Patients with bulbar onset have poorer prognoses, with shorter median survival compared to limb onset.<sup>1,3</sup> Several restricted regional phenotypes have been described with a slower disease course and better prognosis. These include brachial amyotrophic diplegia (BAD) and leg amyotrophic diplegia (LAD), with longer overall survival times between 3-11 years.<sup>4-7</sup>

Bulbar onset ALS represents a third of all ALS cases. Patients are typically older at onset, with a higher prevalence of frontotemporal dementia.<sup>8</sup> Despite this, the bulbar onset ALS population is very heterogeneous, with some patients having disease which stays restricted to the bulbar region for many years. A better understanding of which patients stay with restricted disease could be important for prognosis and when planning clinical trials.

Here we performed a retrospective chart review to identify and characterize ALS patients with isolated bulbar involvement after 2 years of follow up (IBALS).

### Methods

We performed a retrospective chart review of all patients seen in our specialty ALS clinic at the University of Kansas Medical Center between 2001 to 2011. Patients were categorized by their initial symptom at presentation. Bulbar onset patients were further broken down into whether their disease was isolated to the bulbar region at the initial clinic visit, by the following criteria:

- 1) Presence of progressive bulbar symptoms (difficulty swallowing, or difficulty with speech);
- 2) Either bulbar upper motor neuron signs on exam (slow spastic speech, brisk jaw jerk, jaw clonus), or lower motor neuron signs (nasal speech, tongue fasciculation, atrophy);
- 3) An MRI of the brain without lesions that may cause bulbar dysfunction;
- 4) And no evidence for limb weakness on exam.

The following data was abstracted for analysis: age, gender, disease duration, survival, motor neuron signs, bulbar symptoms, extremity signs and symptoms, electromyography, use of percutaneous gastrostomy (PEG) or BiPAP.

## Results

A total of 543 patients were seen in the ALS clinic between 2001-2011. Just under a third of patients presented with bulbar symptoms (150, or 27.6%), and out of these 28 (18.7%) had isolated bulbar symptoms at initial presentation. Fourteen out of 28 (50%) patients had disease confined to bulbar muscles after  $\geq 2$  years of follow up. The age of onset of IBALS without progression to limbs involvement was 64.1 years (39-77) with a male to female ratio of 1.3/1. Four out of 14 (28.5%) of IBALS had cognitive impairment, 5/14 (35.5%) of IBALS had impaired smooth pursuit and 4/14 (28.5%) had pseudobulbar affect. Eight patients out of 14 (57%) had denervation signs on EMG at least in one limb. All 14 IBALS had dysarthria and dysphagia symptoms. Five out of 14 (35.7%) were on BiPAP and 10/14 (71.4%) had PEG tube inserted. Creatinine Kinase was normal in all patients and there was no family history of motor neuron disease in all patients with IBALS. The clinical features of these 14 patients with IBALS are presented in the Table.

Mean duration of disease among the IBALS was 3.1 years (2-8 years) while the mean duration of the illness among isolated bulbar onset ALS with progression to limbs before 2 years was 2.2 years (1-5 years). Among the 14 patients with bulbar onset and progression to limb weakness,

50% of the progression occurred in the first year after the onset.

Seven out of 14 (50%) of IBALS were on Riluzole and eight out of 14 (57%) of bulbar onset ALS who progressed to limb involvement were on Riluzole.

## Discussion

We and others have previously identified regional phenotypic variants of motor neuron disease that progress slower than typical ALS.<sup>4-6</sup> The arm restricted variant has been labeled brachial amyotrophic diplegia (BAD) or flail arm syndrome. The leg restricted variant is called leg amyotrophic diplegia (LAD) or flail leg syndrome. We now report a bulbar restricted phenotype isolated bulbar ALS (IBALS).

IBALS has a longer survival than typical bulbar onset ALS with a mean duration of 3 years. We termed this phenotype as isolated bulbar ALS (IBALS). We found mean age of onset of 64 years old which is slightly younger than the classic bulbar onset ALS age of onset (68 years) and slightly more male involvement (Male: female, 1.3: 1) than the classic bulbar onset (Male: female; 0.98:1). Long survival (>101 months) has been reported to occur in 10% of ALS, with spinal ALS being the predominant subgroup (92%), while bulbar onset represents 8% of the long survival subgroup.<sup>8,9</sup>

**Table.** IBALS disease characteristics. Abbreviations: A, arm; L, leg; EMG, Electromyography; abn, abnormality; Fibs/PSW, fibrillation potentials / positive sharp waves.

Patient number	Bulbar symptoms	Extremity weakness	Extremity UMN signs	Extremity LMN signs	EMG tongue (Fibs/PSW) any EMG abn	EMG A/L (Fibs/PSW)	Disease duration in years
1.	Yes	NO	NO	NO	NO	NO	3
2.	Yes	NO	NO	Yes (A)	Yes	Yes	4
3.	Yes	NO	Yes (A,L)	Yes (A)	NO	Yes	8
4.	Yes	NO	Yes (A)	NO	NO	Yes	3
5.	Yes	NO	NO	NO	NO	NO	2
6.	Yes	NO	Yes (A,L)	NO	Yes	NO	2
7.	Yes	NO	NO	NO	Yes	NO	3
8.	Yes	NO	Yes (L)	NO	NO	Yes	1
9.	Yes	NO	Yes (L)	NO	Yes	Yes	3
10.	Yes	NO	Yes (A,L)	NO	Yes	Yes	3
11.	Yes	NO	Yes (A)	NO	Yes	NO	2
12.	Yes	NO	Yes (A,L)	NO	Yes	NO	3
13.	Yes	NO	Yes (L)	NO	Yes	Yes	2
14.	Yes	NO	Yes (A,L)	NO	NO	Yes	2

Our data suggests that IBALS represent 2.5 % (14/543) of ALS.

Prior study showed that PEG tube insertion is associated with a poor prognosis (8% among long survivors),<sup>9</sup> however our data shows that 71% of IBALS were on PEG tubes. Similarly, 34% of IBALS were on BiPAP while prior studies showed that none of the long survivors have been on BiPAP.<sup>9</sup>

The somewhat arbitrary timeline for “restricted” motor neuron disease pattern is two years without clinical progression into another region. We used this 2-year time period for BAD and LAD and we used it again for IBALS. However, half of our patients had minimal EMG changes in one limb in addition. It should be emphasized that placing a patient in a restricted regional variant group such as IBALS, BAD, or LAD does not imply they do not have progressive disease that will eventually go to other regions. Instead, these restricted phenotypes imply a somewhat longer disease duration and slower progression. In addition, these restricted patterns should raise the question of what are the biologic factors that determine if a patient has a typical ALS or one of these slower phenotypes. If we can get some understanding of the factors that may be responsible for slower progression of the disease process through the nervous system, we might be able to develop more effective therapies to slow motor neuron disease progression.

Our data suggests that there might be an underlying, yet to be determined, pathological mechanism that might determine the prognosis beyond the restricted initial involvement of bulbar and respiratory muscles.

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