Macroglossia in Amyotrophic Lateral Sclerosis

Heather R. McKee, MD; Edward Escott, MD; Douglas Damm, DDS; Edward Kasarskis, MD, PhD

In amyotrophic lateral sclerosis (ALS), hypoglossal motor neurons degenerate. This is recognized clinically by dysarthria and difficulty manipulating food in the oropharynx to initiate swallowing. Usual findings on examination include tongue atrophy, weakness, fasciculations, pseudobulbar affect in some, and spasticity of jaw musculature.1 In this case report, we describe 2 atypical ALS cases with enlargement of the tongue (macroglossia).

Report of Cases

Case 1

A 54-year-old man developed weakness of both upper extremities in 1997, followed by lower extremity weakness. The diagnosis of ALS was made in 1999 based on history, examination, electromyograph findings, and exclusion of other causes. By this time, his speech was incomprehensible with significant dysphagia, drooling, and a 40-lb weight loss. On examination, his tongue could not protrude beyond the lip margin.

After tracheostomy, he was placed on continuous mechanical ventilation in 2002. Macroglossia fully developed by 2003, although his family did not seek medical attention until August 2006, by which time his tongue protruded 5 to 6 cm (Figure 1A). He was edentulous and was found clenching his jaw, unable to relax to open his mouth. The patient was euthyroid on testing. An excisional biopsy was taken from the anterior dorsum of the tongue.

Case 2

A 41-year-old woman presented with a 1-year history of progressive dysarthria, dysphagia, tongue atrophy, neck extensor weakness, and weakness of jaw closure during a 1-year period. Both required tracheostomy and mechanical ventilation and afterward developed macroglossia. A 3-dimensional–reconstructed sagittal computed tomographic image confirmed tongue protrusion outside the oral cavity with focal compression and showed the transition from the atrophied part of the tongue in the oropharynx to the edematous part outside the mouth. Tongue biopsy demonstrated fatty replacement and fascicles of degenerative muscle.

Results

The clinical features of our patients are summarized in the Table. Figure 1A illustrates patient 1 with fully developed...
Figure 1. Case 1

A. Photograph demonstrates patient 1 when his macroglossia was fully developed. B. The patient’s tongue biopsy demonstrates a cluster of normal-sized striated muscle bundles surrounded by extensive fatty replacement and thin strands of extremely atrophic muscle fibers (arrow; hematoxylin and eosin stain). Original magnification ×40.

Figure 2. Case 2

The rapid progression of macroglossia during a period of 3 months in patient 2 (A-C). D. Reformatted computed tomography (CT) of patient 2 shows her enlarged tongue protruding from her mouth. There is a transition in density from the intraoral part, which is heterogeneously replaced with fat (asterisk) to the exteriorized part distal to the compression (black arrow). A indicates anterior; F, foot; H, head; L, left; R, right.
macroglossia in August 2006. Figure 2A-C document the rapid evolution of macroglossia in patient 2 during 3 months.

**Neuroimaging**
A sagittal reformatted head/neck computed tomography scan shows the enlarged tongue protruding from the mouth (Figure 2D). There is a transition in the density of the tongue from the intraoral part, which is heterogeneously replaced with fat (asterisk), to the exteriorized part distal to the point of compression as it exits the oral cavity (black arrow) due to jaw spasticity. The hyoid bone and the tongue base are elevated (white arrow) and there is marked atrophy of the musculature of the floor of the mouth.

**Pathology**
Both superficial and deep tongue biopsies were performed for patient 1. The deeper specimen illustrated in Figure 1B demonstrates a small cluster of normal-sized striated muscle bundles surrounded by extensive fatty replacement and thin strands of extremely atrophic fibers (arrow).

**Discussion**

The typical appearance of the tongue in ALS has been described on magnetic resonance imaging as decreased in size, posteriorly displaced toward the root of the tongue in the floor of the mouth, and having a more rectangular appearance with replacement of muscle with connective tissue and fat. In this case series, the tongue was enlarged and protuberant. Part of the mechanism of macroglossia in our patients is tongue pseudohypertrophy due to denervation atrophy with fatty replacement. However, the distinct contrast in tissue densities between the anterior and posterior parts of the tongue (Figure 2D) implicates an additional mechanism(s) to develop macroglossia, possibly venous and/or lymphatic obstruction due to compression. Arterial occlusion was unlikely because the exteriorized tongue was viable and necrosis was not observed on biopsy. Both patients had neck extensor weakness and continuous mechanical ventilation via tracheostomy.

Mastaglia and Walton reported true muscle hypertrophy associated with denervation and postulated that stretching of muscle fibers and functional overload are important factors in its development. These factors may initiate the structural abnormalities in fibers that are still innervated, which may explain a number of secondary changes such as fiber hypertrophy and regenerative activity. Magnetic resonance imaging of enlarged muscle delineates 2 distinct types: one with normal muscle signal intensity, representing true hypertrophy (as just described) and the other with increased fat and atrophic muscle, representing pseudohypertrophy. Our patients are more representative of the latter form (Figure 1B). The biopsy and imaging document fatty replacement of muscle, or pseudohypertrophy, and desmin staining confirms the presence of atrophic muscle fibers. It is well-known that muscle hypertrophy occurs in Duchenne muscular dystrophy, which has been attributed to deposition of fat and connective tissue, giving rise to the term pseudohypertrophic muscular paralysis. In particular, macroglossia has been described in other neuromuscular diseases including muscular dystrophies and myasthenia gravis.

Other case series report tongue pseudohypertrophy occurring after hypoglossal nerve injury. Kataoka and Ueno reported a case of focal muscle hypertrophy of the hemitongue, which was explained by denervation and reinnervation leading to increasing frequencies of motor unit firing from the injured hypoglossal nerve and adjacent motor fibers. This suggests that continuous, spontaneous electrical activity of muscle could cause a true hypertrophy. Kiran et al reported a case of Hoffman syndrome, a rare form of hypothyroid myopathy, with proximal weakness and pseudohypertrophy of muscles, thought to be secondary to accumulation of glycosaminoglycans.

We are unaware of previous reports of macroglossia in ALS/motor neuron disease. Given the paucity of case material, we speculated this must be an extremely rare complication. It is apparent through imaging and pathology that our patients initially experienced typical neurogenic muscle atrophy, followed later by pseudohypertrophy of the tongue. Other contributing factors may include neck extensor weakness, 24-hour ventilatory support via tracheostomy, tongue trauma at the dental margin secondary to jaw spasticity, and possible venous and/or lymphatic obstruction. We postulated the following pathophysiological steps to account for macroglossia in ALS: (1) bulbar involvement with neurogenic muscle atrophy of the tongue and subsequent fatty replacement; (2) weakness of neck extensor muscles; (3) facial muscle weakness, especially of the orbicularis oris; (4) gravity-assisted escape of the tongue outside of the oral cavity; (5) compression of the tongue at the dental margin due to spasticity of jaw muscles; and (6) distal enlargement (pseudohypertrophy) of the exteriorized tongue due to venous and/or lymphatic obstruction. Although both our patients received continuous mechanical ventilation via tracheostomy, it is unclear whether this factor plays a role in the development of macroglossia in ALS.

**Table. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient/Sex/Age, y</th>
<th>Site Onset</th>
<th>Time to Tracheostomy, y</th>
<th>Time From Tracheostomy to Fully Developed Macroglossia, mo</th>
<th>Time to Death After Tracheostomy, y</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/Male/64</td>
<td>Extremity</td>
<td>4</td>
<td>12</td>
<td>5</td>
<td>Hypertension, hypothyroidism, diabetes mellitus, chronic respiratory failure</td>
</tr>
<tr>
<td>2/Female/41</td>
<td>Bulbar</td>
<td>1</td>
<td>8</td>
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REFERENCES