Alterations in the masticatory system in patients with amyotrophic lateral sclerosis and its management with an oral appliance

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DOCTORAL THESIS

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ALTERATIONS IN THE MASTICATORY SYSTEM IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS AND ITS MANAGEMENT WITH AN ORAL APPLIANCE

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“Remember to look up at the stars and not down at your feet. Try to make sense of what you see and wonder about what makes the universe exist. Be curious. And however difficult life may seem, there is always something you can do and succeed at. It matters that you don't just give up.”

Stephen Hawking

(1942-2018)

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for their support, and finally my boyfriend for his advice and for being by my side in the hard times. They are the most important people in my world and I dedicate this thesis to them.

INDEX

ABBREVIATIONS

ALS: Amyotrophic Lateral Sclerosis

DC/TMD: Diagnostic Criteria for Temporomandibular Disorders

EDX: Electrodiagnostic

EMG: Electromyography

EP: Electrophysiological

FALS: Familial Amyotrophic Lateral Sclerosis

JFLS: Jaw Functional Limitation Scale

JFLS-8: 8-item Jaw Functional Limitation Scale

LMN: Lower Motor Neurons

MN: Motor Neurons

MND: Motor Neuron Disease

NGT: Nasogastric Tube Feeding

NIV: Non-Invasive Ventilation

PEG: Percutaneous Endoscopic Gastrostomy

PRG: Percutaneous Radiological insertion of Gastrostomy

TMD: Temporomandibular Disorder

TMJ: Temporomandibular Joint

UMN: Upper Motor Neurons

SALS: Sporadic Amyotrophic Lateral Sclerosis

ABSTRACT

Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by progressive degeneration of the lower (LMN) and upper motor neurons (UMN) in the spinal cord and brain, causing muscle atrophy, muscle weakness, and spasticity. Clinical characteristics of the disease are variable and depend on whether the site of onset is spinal, bulbar, or respiratory. ALS with bulbar dysfunction affects the motor neurons responsible for controlling the muscles in the jaw, face, soft palate, pharynx, larynx and tongue.

Aims: With the present thesis we aimed to investigate the alterations and functional limitations of the masticatory system in patients with ALS. It comprises three articles: the first (Study I) aimed to determine the effect of ALS on aspects of masticatory function, including mandibular range of motion, bite force, and prevalence of temporomandibular disorders (TMD). The second one (Study II) aimed to determine the effect of bulbar involvement on functional limitations in the masticatory system in patients with ALS. The third one (Study III) aimed to determine the degree of satisfaction in patients with ALS after treatment with an oral appliance to manage oral self-biting or symptoms related to TMDs.

Methods: The first two studies assessed a total of 153 ALS patients and 23 control subjects. In study I, clinical characteristics including site of onset, medication, type of feeding, and use of non-invasive ventilation (NIV) were recorded. The Diagnostic Criteria for Temporomandibular Disorders protocol (DC/TMD) and a specific questionnaire to assess aspects of masticatory dysfunction and frequency of self-injury of the oral mucosa were applied to all participants. Maximum mandibular range of motion, maximum bite force, and maximum finger-thumb grip force were determined. In study II, all participants answered using the 8- item Jaw Functional Limitation Scale (JFLS- 8). Patients with ALS were grouped by neurologic examination as follows: non-bulbar ALS, bulbar UMN-predominant ALS; bulbar LMN-predominant ALS; and bulbar balanced (UMN + LMN) ALS. Jaw limitation between the different groups was compared. Study III included eleven patients with ALS who sought oral treatment

because of oral self-biting or TMD-related symptoms. A custom complete-coverage acrylic resin device was fabricated and fitted to each participant. A follow-up visit was planned for 3 months after the placement of the oral appliance, at which point the patients would rate the degree of improvement or worsening of the chief complaint and their degree of satisfaction with the treatment.

Results: Study I showed that maximum unassisted and assisted mouth opening, protrusion, left laterotrusion, and finger-thumb grip force were significantly reduced in both spinal- and bulbar-onset patients compared to the control group; however, bite force was reduced only in bulbar-onset patients. ALS patients with tube feeding had the greatest reduction in maximum bite force and mandibular opening. There was no relationship between TMD and ALS. Oral self-injury due to biting was more frequent in the ALS group than in the control group and in the bulbar-onset group compared to the spinal- and respiratory-onset groups. Of the ALS patients in the study, 10% sought dental treatment related to the condition. Thus, in study II, patients with non-bulbar ALS had similar mandibular limitations to healthy participants. Only patients with balanced UMN and LMN bulbar manifestations reported greater difficulties in chewing soft food or in jaw mobility compared to the non-bulbar ALS group. Patients with bulbar involvement also had greater difficulties in chewing tough food or chicken and in swallowing and talking compared to the non-bulbar group, regardless of whether UMN or LMN predominant. No significant differences were found between the groups in smiling and yawning difficulties. Participants in study III reported a mean of 61% improvement of the chief complaint and a mean of 84% satisfaction with the treatment. The mean rate of compliance was 62% of the recommended time and only a few adverse effects were reported.

Conclusions:

Patients with ALS showed a reduction in finger-thumb grip force that was twice as great as the reduction in bite force. The maximum range of mandibular movement was also reduced, especially in bulbar-onset patients. ALS patients did not have a higher prevalence of TMD, but did have more traumatic mucosal injury than controls. Bulbar involvement in patients with ALS is associated with functional limitation of the

masticatory system. However, balanced bulbar UMN and LMN involvement is associated with the worst impairments, affecting soft food chewing and opening the jaw widely. Patients with ALS were highly satisfied with the use of an oral appliance to manage oral self-biting or TMD-related symptoms. Adherence to this treatment was high and no major adverse effects were observed. The dentist should be an integral part of the multidisciplinary team to manage ALS patients.

INTRODUCTION

1. INTRODUCTION

1.1 Definition of the disease

Motor neurons (MN) are nerve cells located in the brain and spinal cord, which transmit electrical signals to muscles for the generation of movement.[1] Messages from MN in the motor cortex, called upper motor neurons (UMN), are transmitted to MN in the brain stem and spinal cord, called lower motor neurons (LMN), and from them to particular muscles.[2] (Figure 1)

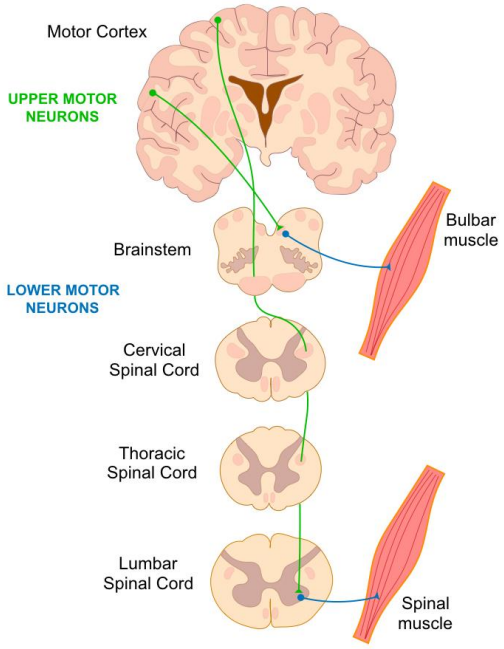

Figure 1. Outline of the motor system.

The term motor neuron disease (MND) refers to various entities that result in progressive degeneration of MN, and the effects of this damage depend on the type of nerve affected.[3] When UMN degenerate, their impulses cannot reach the LMN, and when LMN degenerate, they cannot deliver the neural message to the muscles they supply.[2] Symptoms of UMN include muscle weakness, overactive reflexes, and spasticity. Symptoms of LMN include muscle twitching, weakness, attenuated reflexes, cramps and wasting.[4]

Amyotrophic Lateral Sclerosis (ALS), first described by Jean-Martin Charcot in the 1870s, is a progressive neurodegenerative disorder characterized by degeneration of both UMN and LMN of the central nervous system.[5] ALS, also known as "Lou Gehrig's disease" after the famous baseball player who suffered the disorder, is the most common MND.[6]

The selective degeneration of the neurons that control muscle movement leads to progressive atrophy of skeletal muscles.[7] The term *Amyotrophic* refers to the thinning

and wasting of the muscles, and *lateral* refers to the location of the nerve cells that deteriorate in the spinal cord. When these nerve cells degenerate and die, they leave a scar in the spinal cord that is referred to as *sclerosis.*[8] With the progressive impairment of voluntary muscle action, patients in the later stages of the disease may become totally paralyzed. Many patients die of respiratory failure within a few years of the onset of the first symptoms.[9]

1.2 Epidemiology and molecular genetics

Incidence rates for ALS are approximately 1.4 and 2.1 per 100,000 person/year in Catalonia and in Europe respectively.[10, 11] There is a predominance of men among ALS cases (ratio about 1·5:1). [12, 13] Incidence rates generally increase with age in both men and woman, rising after the age of 40 years and reaching a peak at 70-74 for men and at 65-69 years for women.[14] Median survival ranges from months to years, but averages 19 months from the time of diagnosis and 30 months from symptom onset. Only 5-10% of the patients survive beyond 10 years. [5, 10] Age is a strong prognostic factor in ALS, with decreasing survival time correlating with increasing age of symptom onset.[15]

The explanation for the increased incidence and prevalence of ALS in geographic foci such as the island of Guam in the Western Pacific, parts of the Kii Peninsula of Japan, and Western Papua New Guinea remains enigmatic. Although the prevalence remains high in Guam compared to typical European and North American populations, it has fallen over the last half century.[16, 17]

There are two forms of ALS. The more common form (90-95%) is sporadic ALS (SALS), which has no obvious genetically inherited component. The remaining 5–10% of the cases are termed familial-type ALS (FALS) due to their associated genetic dominant inheritance factor.[14] In about 60–70% of patients with FALS, mutations in different genes can be identified, of which *C9orf72* (40%), *SOD1* (20%), *TARBDP (5%) and FUS* (5%) are the most common.[18, 19]

1.3 Clinical presentations

MN are divided into UMN, in the motor cortex, and LMN, in the brain stem and spinal cord, which innervate skeletal muscle. UMN failure results in muscle spasticity, hyperreflexia and slight weakness. Loss of LMN causes spontaneous muscle twitching (fasciculations), cramps, marked weakness and muscle atrophy.[5]

Classic MND tends to be focal in onset, and affects a particular group of muscles first. Around 25% of patients present with bulbar onset disease around 70% spinal/limb onset and 5% initial respiratory involvement.[18]

In the bulbar form, MN in the part of the brain stem called the medulla oblongata (formerly called the "bulb") start to die first. Patients with bulbar onset present initial symptoms in the bulbar musculature, the oropharyngeal muscles involved with speech, chewing and swallowing.[20] These patients have a worse prognosis than those with spinal onset, with a mean survival of two years and long-term (>10 years) survival of only 3%.[21] Bulbar involvement may be LMN (bulbar palsy), UMN (pseudobulbar palsy), or both. Bulbar palsy is associated with facial weakness and poverty of palatal movement with wasting, weakness, and fasciculation of the tongue. Pseudobulbar palsy is characterised by emotional lability (also known as pathological laughing or crying), brisk jaw jerk, and dysarthria.[22] Dysarthria and dysphagia are the most common bulbar symptoms in ALS. Studies have reported dysarthria in 93%, dysphagia in 86% and tongue fasciculations in 64% of patients with ALS who have bulbar symptoms, and almost all patients have bulbar involvement at later stages of the disease.[23]

Approximately two thirds of patients with typical ALS have the spinal form of the disease, and present symptoms related to focal muscle weakness, which may start either distally or proximally in the upper or lower limbs.[24] In the upper limbs early symptoms are most commonly due to asymmetrical distal weakness, causing patients to drop objects or have difficulty manipulating them with one hand, such as turning keys, writing, and opening bottles. In the lower limbs early symptoms include foot drop, a sensation of heaviness of one or both legs, or a tendency to trip over.[25] In terms

of presentation, UMN disturbance involving the limbs leads to spasticity, weakness, and brisk deep tendon reflexes, while LMN limb features include fasciculations, wasting, and weakness.[18]

The least common pattern of onset is when the respiratory muscles are affected first. These patients present respiratory failure or forms of nocturnal hypoventilation such as dyspnoea and orthopnoea, disturbed sleep, morning headaches, excessive daytime somnolence, anorexia, decrease of concentration and irritability or mood changes. [24, 25]

Most patients with ALS have mild cognitive impairment with subtle executive deficits, and 5% have a clinical subtype of frontotemporal lobar degeneration called frontotemporal dementia. Cognitive decline in ALS is characterised by personality change, irritability, obsessions, poor insight, and pervasive deficits in frontal executive tests.[26]

1.4 Diagnosis

The onset and early progression of ALS is frequently insidious. During the diagnostic evaluation, the patient commonly consults a variety of specialists, and even neurologists may not recognize ALS early in its course.[27] Up to 43% of patients with ALS may be misdiagnosed early in the evaluation.[28] Total diagnostic time, defined as the time from symptom onset to confirmed diagnosis, has been reported to range from eight to 15 months in ALS.[29]

Signs suggestive of combined UMN and LMN impairment that cannot be explained by any other disease process, together with progression compatible with a neurodegenerative process, are invariably suggestive of ALS.[24]

1.4.1 Diagnostic tests

Although researchers are looking for biomarkers that allow precise, prompt diagnosis of ALS, at the present time there is no single laboratory test that is 100% reliable, particularly in the early stages of the condition when its signs and symptoms are limited to a single body region.[30] The combination of suggestive clinical signs with negative laboratory tests and imaging studies for other pathologies supports the diagnosis, although disease progression is a prerequisite.[31]

1.4.1.1 Laboratory testing

Laboratory testing of blood, urine, and sometimes cerebrospinal fluid is performed during the evaluation of MND to search for any potentially treatable metabolic abnormality. Among the most common laboratory tests used are the ones for vitamin B12 levels (to rule out subacute combined degeneration), parathyroid hormone levels (to rule out hyperparathyroidism) and serum protein electrophoresis with immunofixation (to rule out multiple myeloma or monoclonal gammopathy of undetermined significance).[32]

1.4.1.2 Electrodiagnostic studies

Electrodiagnostic (EDX) examination has long been known to play an important role in the evaluation of patients with suspected ALS. Lambert was the first researcher to formally establish the role of EDX studies in the assessment of patients with ALS, emphasizing the importance of fibrillation and fasciculation potentials and motor unit potentials which present reduced numbers and increased duration and amplitude.[33]

The electromyography (EMG) findings in ALS combine features of acute denervation (fibrillation and positive sharp waves), chronic denervation and reinnervation (large amplitude, long duration, complex motor unit action potentials). The electromyographic abnormalities noted in muscles of patients with ALS are not

pathognomonic for the disease but may be a sign of ALS when similar abnormalities are observed in many muscles in the proximal and distal limbs.[34]

In patients with suspected MND, clinicians should perform a thorough EDX evaluation, including peripheral nerve conduction studies and needle EMG both to exclude treatable disease and to gather evidence towards a diagnosis of ALS.[35]

1.4.1.3 Genetic testing

Clinical tests for ALS-linked genes are available, including C9orf72, SOD1, FUS and TARDBP, variants of which are found in over 50% of FALS patients. Clinical DNA test options are expected to increase as new ALS genes are identified.[19]

Genetic testing for symptomatic ALS patients should be requested by a neurologist willing to take responsibility for interpreting and communicating the results and their relevance to the tested subject. Since at least 5–10% of apparently SALS patients carry a mutation in known ALS genes, with more likely to be identified in the future, genetic testing should also be discussed with all other ALS patients, emphasising the major uncertainties involved and its still weak clinical significance.[36]

1.4.1.4 Neuroimaging studies

Routine magnetic resonance imaging (MRI) of the brain and spinal cord remains the most useful neuroimaging technique in ALS, especially for the differential diagnostic work up.[37] No neuroimaging tests are required to support the diagnosis of ALS, but they should be used to rule out treatable structural lesions that mimic ALS by producing varying degrees of UMN and LMN signs.[24]

1.4.2 Diagnostic criteria

In 1994, the World Federation of Neurology developed a set of diagnostic criteria to standardise the diagnosis of ALS, known as the El Escorial criteria, based on the presence and distribution of UMN and LMN signs.[38] The El Escorial criteria for the

diagnosis of ALS have been widely accepted, but there was a feeling that they should be revised in order to increase their sensitivity; in 1998 they were refined further at the Airline House Meeting, to aid the diagnosis and classification of patients for research studies and drug trials.[39]

Diagnosis on the basis of these criteria requires a history of progressive weakness spreading within a region or to other regions, such as bulbar regions (affecting speech and swallowing), cervical regions (affecting the upper limbs), thoracic regions (affecting the chest wall and abdominal muscles) or lumbar regions (affecting the lower limbs), with evidence of the involvement of LMN (through the presence of specific symptoms or evidence of denervation on EMG) and UMN (through the presence of specific symptoms and brisk deep tendon reflexes).[40] The revised El Escorial criteria classify patients into four levels of diagnostic probability: clinically definite, clinically probable, clinically probable-laboratory supported (a category not present in the original El Escorial criteria) and clinically possible ALS (Table 1).[39]

In clinical trials, the revised El Escorial criteria are used predominantly to aid in diagnosing and classifying patients for research studies and drug trials, but they have also been criticized for their lack of sensitivity.[41] A consensus meeting held at Awaji-shima in late 2006 resolved these issues by establishing the equivalence of clinical and EMG data for detecting chronic neurogenic change, and thus integrating EMG and clinical neurophysiological data into a single diagnostic algorithm.[42] By accepting neurogenic EMG abnormality as equivalent to clinical abnormality, the Awaji-shima criteria allow an earlier classification of a currently strong limb as abnormal than the use of EMG or clinical criteria alone. This renders the clinically probable laboratory-supported ALS category redundant, as all categories can now use laboratory support in the diagnosis (Table 2).[43] The Awaji algorithm was devised to increase the importance of fasciculation potentials in the diagnosis of ALS and is particularly helpful in the early diagnosis of the disease, since it is more sensitive but does not sacrifice specificity.[44]

Diagnostic category	Features
Clinically definite ALS	Clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least 2 spinal regions or the presence of LMN and UMN signs in 3 spinal regions.
Clinically probable ALS	Clinical or electrophysiological evidence by LMN and UMN signs in at least 2 regions with some UMN signs necessarily rostral to the LMN signs.
Clinically possible ALS	Clinical or electrophysiological signs of UMN and LMN dysfunction are found in only 1 region or UMN signs are found alone in 2 regions or LMN signs are found rostral to UMN signs.

Table 1. El Escorial revised criteria.

Making the diagnosis has major implications for determining patients' eligibility to participate in clinical trials. On the basis of the El Escorial criteria, patients with clinical signs of UMN and LMN degeneration in at least two body regions were included in clinical trials;[38] the revised El Escorial criteria allowed the inclusion in clinical trials of patients with clinical signs of UMN and LMN degeneration in at least two body regions, or signs of UMN degeneration in at least one body region, but with electrophysiological (EP) signs of LMN degeneration.[39] Finally, the application of the Awaji algorithm allowed the inclusion in clinical trials of patients with clinical signs of UMN degeneration in at least two body regions and clinical or EP signs of LMN degeneration also in at least two body regions.[42]

Diagnostic category	Features
Clinically definite ALS	Clinical evidence of UMN and LMN signs in bulbar and at least two spinal (lumbosacral, thoracic, or cervical) regions or UMN and LMN signs in three spinal regions
Clinically probable ALS	Clinical evidence of UMN and LMN signs in at least two regions (bulbar or spinal) with some UMN signs rostral to the LMN signs
Clinically probable laboratory-supported ALS	Clinical evidence of UMN and LMN signs in one body region or of UMN signs in one region and electromyography findings of LMN involvement in at least two body regions
Clinically possible ALS	Clinical evidence of UMN and LMN signs in only the bulbar or only one spinal region or UMN signs in two or more regions or LMN signs rostral to upper motor neuron signs

Table 2. Diagnostic classification: Awaji-Shima Consensus recommendations and the Revised El Escorial Criteria.

1.5 Management of ALS patients

Although the condition is incurable, many of the symptoms arising during the course of the disease are treatable and all efforts should made to improve quality of life and help to maintain the patient's autonomy for as long as possible. The management of ALS should be focused on a combination of neuroprotective medication, multidisciplinary clinical treatment and respiratory support.[5, 9]

1.5.1 Medical treatment

Even though multiple randomised placebo-controlled clinical trials have been performed, no therapy has been shown to offer a substantial clinical benefit for patients with ALS. Riluzole (Rilutek®) was approved by the Food and Drug Administrations (FDA) in 1995 as the first drug treatment for the disease after two clinical trials had shown that it slowed diseased progression.[45, 46] Its exact mechanism in ALS is unknown, but the excess of glutamate may be associated with neurodegeneration and the drug inhibits presynaptic glutamate release.[47] Riluzole prolongs median survival by two to three months in patients with probable and definite ALS and symptoms lasting less than five years, forced vital capacity greater than 60%, and age below 75 years.[48]

1.5.2 Multidisciplinary approach

Optimum care for patients with ALS is provided within a multidisciplinary environment since patients managed in a specialised clinic have better quality of life, possibly due to the more effective use of resources.[18] Most large centres currently use a multidisciplinary approach to care, and some data suggest that patients cared for at multidisciplinary clinics survive longer.[49] Multidisciplinary care models have been shown to be predictors of survival, reducing the risk of death by 45% at 5 years.[18]

The multidisciplinary team should comprise, or have easy access to, the following specialists: a consultant in neurology, a pulmonologist, a gastroenterologist, a rehabilitation medicine physician, a social counsellor, an occupational therapist, a speech therapist, a specialised nurse, a physical therapist, a dietician, a psychologist, a palliative care physician and a dentist.[50]

The rationale of this care approach is that ALS patients should be followed up closely throughout the course of their disease in order to detect impediments in motor function, nutrition or respiration.[51]

1.5.2.1 Physical management

The main goal of physical therapy is to maintain the patient's independence with regard to functional mobility and activities of daily living. It attempts to avoid the joint contractures and stiffness that increase the disability of the patient.[51, 52] Moderate regular physical activity has a mild temporary positive effect on motor deficit and disability, fatigue, and health-related quality of life of patients with ALS.[53]

Many ALS patients experience spasticity, which may cause them to feel stiff or tight, limit voluntary movement, and reduce coordination and function.[52] Current clinical practice in treating spasticity varies somewhat between different clinicians and centers, but most would probably consider the use of an anti-spasticity drug with a programme of regular muscle stretching.[54] A daily range of motion, particularly for weakened muscles, is important for maintaining joint mobility and preventing contractures.[55]

Occupational therapy practitioners are uniquely qualified to help people with ALS to make wise choices regarding equipment and environmental modifications and thus remain as safe and independent as possible in their activities of daily living. Naturally, the practitioners' advice should bear in mind the disease progression.[55]

1.5.2.2 Nutritional therapy

Malnutrition is a significant negative prognostic indicator for survival in ALS.[56] The symptoms and progression of ALS can affect a patient's nutrition and hydration in two ways. First, upper extremity weakness limits the patient's skills so that cutting food and feeding can be difficult; secondly, the onset of dysphagia impairs swallowing.[57]

Initial management of dysphagia in patients with ALS is based on dietary counselling, modification of food and fluid consistency, prescription of high protein and calorie supplements and education of the patient and carers in feeding and swallowing techniques such as supraglottic swallowing and postural changes.[50]

Monitoring weight at each clinical visit is a simple and useful measure, and enteral feeding should be considered after a loss in baseline weight of more than 10%.[58] Enteral feeding consists of percutaneous endoscopic gastrostomy (PEG), percutaneous radiological insertion of gastrostomy (PRG) or nasogastric tube feeding (NGT).[57] PEG is the standard procedure and is widely available, but as mild sedation is needed for its placement it is not recommended in patients with a forced vital capacity of less than 50%.[59] In cases in which PEG is technically risky or impossible, PRG represents a reliable alternative because it does not require sedation.[50] When gastrostomy is contraindicated, NGT represents a reliable alternative, but is not as effective as PEG or PRG; the placement of a NGT can lead to problems, as tubes may fall out or migrate, causing aspiration or nasal discomfort.[60] For this reason, NGT is an adequate short-term option to maintain nutrition over a period of several days, weeks or months, if tubes are removed and replaced regularly.[57]

1.5.2.3 Respiratory management

The high prevalence of respiratory muscle weakness is consistently found in the current literature on ALS.[61] Symptoms of respiratory muscle weakness include dyspnoea, orthopnoea, sleep fragmentation, poor cough, difficulty clearing respiratory secretions, morning headaches and daytime fatigue.[5]

The diagnosis and management of respiratory insufficiency is critical because most deaths from ALS are due to respiratory failure; a decline in respiratory function is an important negative prognostic indicator.[62] Care of respiratory impairment in patients with ALS includes the use of airway clearance techniques, mechanically assisted cough and invasive or non-invasive ventilation (NIV).[63] The choice of ventilation will depend on the symptoms of hypoventilation and upper airway obstruction, bronchial secretions and factors such as availability, cost, patient preference and type of care.[50] Current evidence would suggest that patients with a vital capacity of 50%, a sniff nasal inspiratory pressure (SNIP) of 40 cm H_2O, and/or clinical evidence of respiratory decline should be offered NIV.[64] This treatment improves both quality of life and survival in patients with ALS who can tolerate its use.[65]

As weakness progresses, NIV may be insufficient to control symptoms and patients may ultimately need invasive ventilation with a tracheostomy to maintain adequate air exchange and control of the upper airway, although the decision to undergo tracheostomy and invasive ventilation is very personal; both the family and patient require extensive training.[66]

1.6 Alterations in the stomatognathic system

Dysarthria and dysphagia are the most common clinical problems detected in patients with ALS, and are observed as initial symptoms in 30% of patients with bulbar onset. Almost all patients develop speech and swallowing problems in the later stages of the disease, even in those with spinal onset of symptoms.[23]

Bulbar UMN dysfunction results in spastic dysarthria, brisk jaw jerk and emotional lability.[22] Bulbar LMN dysfunction can be identified by tongue wasting, weakness and fasciculations, flaccid dysarthria and dysphagia.[18]

Patients with bulbar involvement present significantly reduced strength and speed of movement in the orofacial structures.[67] Findings may include weakness of the facial muscles, palate, or tongue.[68] However, measures of muscle strength have revealed nonuniform patterns of muscle weakness in orofacial muscles in patients with ALS.[69]

1.6.1 Dysarthria

The term “dysarthria” comprises a group of speech disorders deriving from disturbances in muscular control due to the impairment of any of the basic motor processes involved in the execution of speech.[70] The underlying pathology of dysarthria in ALS disease is paresis of the musculature of the face, tongue, lips, palate, pharynx and larynx.[23]

Neurological disease affecting different structures can lead to different forms of dysarthria: spastic dysarthria (UMN), flaccid dysarthria (LMN), and mixed dysarthria

(both UMN and LMN).[71] The prototypical motor speech disorder in ALS is progressive spastic-flaccid dysarthria.[72] In addition to dysarthric features, the voice may sound hypernasal, breathy, strained, or harsh.[68]

1.6.2 Dysphagia

Dysphagia refers to any neurological deglutition disorder in the oral, pharyngeal, and esophageal phases of swallowing.[73] Dysphagia in ALS patients is due to weakness or spasticity of muscles innervated by the trigeminal, facial, hypoglossal, glossopharyngeal or vagal nerves.[74]

Among the disabling problems associated with dysphagia are the collection of secretions in the oropharynx, which may result in drooling (sialorrhea), episodes of choking and immovable deep throat thick secretions, with a danger of aspiration of these secretions into the lungs and a high risk of infection.[75] It is estimated that 50% of ALS patients suffer from sialorrhea.[66]

1.6.3 Weakness of bulbar muscles

Patients with ALS manifest varying degrees of weakness and deficits of rapid force generation in the tongue, lip, and jaw muscles, regardless of the initial ALS symptoms, muscle sites involved, or time post onset.[69] Bulbar muscle weakness is usually more pronounced in the muscles of the tongue than in the muscles of the lips and jaw.[76]

ALS eventually weakens the muscles of mastication, and swallowing can significantly increase the risk of choking, aspiration, and malnutrition. This in turn may require hospitalisation or the placement of a gastronomy tube, and in general reduces quality of life.[23, 77]

The most frequent early physical findings of bulbar ALS are often associated with the tongue muscles.[78] In addition to weakness, the tongues of patients with ALS can be

both spastic and flaccid, with atrophy and fasciculations, which are noted with the tongue at rest.[79]

The loss of tone and strength in the muscles that control lip closure is often associated with drooping lips and drooling. Furthermore, the inability to keep the lips closed increases the tendency to breathe through the mouth, leading to thickening of oral secretions.[23]

Few symptoms are noted in the early stages of the weakening of the muscles of mastication. In advanced bulbar ALS, the weakness of these muscles causes the jaw to be pulled downward by gravity, leaving the mouth open. The airflow pattern changed from nasal breathing to oral with the resulting problems of dry lips, dry mouth, and tenacious oral secretions.[78]

1.6.4 Jaw quivering and clenching

Some ALS patients develop jaw quivering or clenching due to UMN degeneration. These symptoms are often precipitated by pain, anxiety or cold.[80] Examination of the cranial nerves shows the jaw jerk may be brisk, especially in bulbar-onset disease.[9] A mild tap on the chin when the jaw is slightly open may evoke clonus in patients with ALS, due to the spasticity of their jaw muscles.[81]

The prolonged tonic contraction of the jaw muscles restricting mouth opening may be associated with pain, malnutrition and poor oral hygiene. Trismus due to masseter muscle spasticity has been reported during the follow-up of ALS patients with bulbar involvement, and it has also been reported as an isolated first symptom.[82]

1.7 The role of the dentist in ALS

The management of patients with ALS is mainly palliative and requires a multidisciplinary approach; therefore, the management of oral conditions and the clinical assessment of bulbar symptoms form an important part of these palliative

measures.[83] For this reason, dentists are key members of the ALS multidisciplinary team and it is important that they understand the disease and its effects.[50]

Oral hygiene maintenance, access to dental care, ambulation and chair transference are all potential problems for those affected with MND. Patients with ALS may have difficulty maintaining good oral health due to bulbar and upper limb involvement.[84]

Some treatments have been reported to alleviate bulbar symptoms of dysarthria, dysphagia and traumatic biting.[84] Various prosthetic appliances have been described for managing the dysarthria associated with ALS. Palatal lift prosthesis may improve palatopharyngeal insufficiency and reduce hypernasality, and palatal augmentation prosthesis may improve articulation by lowering the palate.[85, 86]

Sialorrhea or drooling can cause a range of physical and psychosocial complications in patients with ALS. Its management includes injection of Botox into the parotid glands to inhibit salivary secretion.[87] However, a case of recurrent temporomandibular joint (TMJ) dislocation two months after parotid Botox injections was reported in which the patient complained of a sudden inability to close her mouth and pain in her jaws.[88] Another patient was reported with an isolated trismus, reflecting early UMN involvement, specifically as the first manifestation of ALS.[82] An acrylic prosthesis has also been described for the management of chronic drooling, which provides an adequate seal against loss of saliva and fluids.[89]

The dental literature in MND is limited, with only a few case reports and single case series. No clinical studies with large samples have been performed to assess the alterations and functional limitations of the masticatory system in patients with ALS, and dentists lack information on the management of the alterations in the masticatory system due to bulbar involvement in these patients.


OBJECTIVES

2. OBJECTIVES

The main objectives of this doctoral thesis were:

- To determine the effect of ALS on aspects of masticatory function, including mandibular range of motion, bite force, and prevalence of temporomandibular disorders (TMDs).
- To determine the effect of bulbar involvement on functional limitations in the masticatory system in patients with ALS.
- To determine the degree of satisfaction in patients with ALS after treatment with an oral appliance to manage oral self-biting or symptoms related to TMDs.

The study objectives include:

- To assess the relationship between ALS and the prevalence of traumatic mucosal lesions caused by oral self-injury.
- To explore potential differences between bulbar- and spinal-onset patients.
- To compare the functional limitation of the masticatory system between patients with ALS and pseudobulbar palsy (UMN involvement) and patients with ALS and bulbar palsy (LMN involvement).
- To assess the degree of improvement in the chief complaint, and the change in the quality of life due to changes in the chief complaint.
- To explore other aspects of the treatment including compliance, side effects, and technical failures.


HYPOTHESIS

3. HYPOTHESIS

In view of the theoretical framework, the following hypotheses were suggested:

- Patients with ALS have lower bite force, a reduced mandibular range of motion, a higher prevalence of TMD, and a higher incidence of traumatic mucosal ulcers due to self-injury than healthy subjects.
- Bulbar involvement causes functional limitations of the masticatory system in patients with ALS.
- Patients with ALS are satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMDs.


PUBLICATIONS

4. PUBLICATIONS

4.1 Study I: Alterations in the Masticatory System in Patients with Amyotrophic Lateral Sclerosis.

Riera-Punet N, Martinez-Gomis J, Paipa A, Povedano M, Peraire M. Alterations in the Masticatory System in Patients with Amyotrophic Lateral Sclerosis. J Oral Facial Pan Headache. Winter 2018;32:84–90.

doi: 10.11607/ofph.1882.

ABSTRACT

Aims

To determine the effect of amyotrophic lateral sclerosis (ALS) on aspects of masticatory function and to assess the relationship between ALS and the prevalence of traumatic mucosal lesions caused by oral self-injury.

Methods

A total of 153 ALS patients and 23 control subjects participated in this cross- sectional study. Clinical characteristics including site of onset, medication, type of feeding, and use of noninvasive mechanical ventilation were recorded. The Diagnostic Criteria for Temporomandibular Disorders protocol (DC/TMD) and a specific questionnaire to assess aspects of masticatory dysfunction and frequency of self-injury of the oral mucosa were applied to all participants. Maximum mandibular range of motion, maximum bite force, and maximum finger- thumb grip force were determined and tested with Mann Whitney, Kruskal-Wallis, or chi-square tests. $P < .05$ was considered significant.

Results

Maximum unassisted and assisted mouth opening, protrusion, left laterotrusion, and finger-thumb grip force were significantly reduced in both spinal (n=102) and bulbar (n=40) onset patients compared to the control group; however, bite force was only reduced in bulbar-onset patients. ALS patients with tube feeding only (n=16) had the greatest reduction in maximum bite force and mandibular opening. There was no relationship between TMD and ALS. Oral self-injury due to biting was more frequent in the ALS group (29.9 %) than in the control group (8.7 %) and in the bulbar-onset (55.0 %) compared to the spinal- (20.8 %) or respiratory-onset (18.2 %) groups. Of the ALS patients in the study, 10% sought dental treatment related to the condition.

Conclusion

The ALS patients in this study had a reduction in finger-thumb grip force that was twice as great as the reduction in bite force. The maximum range of mandibular movement was also reduced, especially in bulbar-onset patients. ALS patients did not have a higher prevalence of TMD, but did have more traumatic mucosal injury than controls. The dentist should be an integral part of the multidisciplinary team to manage ALS patients.

Key words: *amyotrophic lateral sclerosis, craniomandibular disorders, mandibular range of motion, occlusal force, self-biting*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a heterogeneous multisystem progressive neurodegenerative disease that affects the lower and upper motor neurons in the spinal cord and in the brain, and causes muscle atrophy, muscle weakness and spasticity.[1] Risk factors associated with ALS are older age, male sex, and family history.[2] Its incidence rates in Catalonia and Europe are approximately 1.4 and 2.1 per 100,000 people a year, respectively, [3,4] and survival rates vary from months to several years, with median survival time from onset ranging from 24 months in northern Europe to 48 months in central Asia.[5]

The typical clinical characteristics of ALS are variable and depend on whether the site of onset is spinal, bulbar or respiratory. Most patients with ALS have a spinal onset, causing referred weakness and muscle atrophy, fasciculations (reflecting involvement of lower motor neuron), and hyperreflexia and hypertonia (reflecting involvement of upper motor neurons). Weakness starts in bulbar muscles in about 20% of patients, with dysarthria, dysphagia and tongue fasciculations. Bulbar-onset ALS has poorer prognosis due to swallowing difficulties, weight loss, aspiration and respiratory involvement with poorer adaptation to noninvasive ventilation. About 3% to 5% of ALS patients have a respiratory onset, reporting orthopnea or dyspnea and mild or even no spinal or bulbar signs. Up to 10% of patients with ALS have an affected relative and are thus considered to have familial ALS.[6]

The role of the dentist in ALS disease is not yet well defined. For example, one patient with ALS was misdiagnosed as having a temporomandibular disorder (TMD) because she reported a decreased mouth-opening range and pain on palpation of the temporalis muscles.[7] In another clinical case, masseter muscle spasticity was also described as a first symptom of ALS.[8] Recurrent jaw dislocation following botulinum toxin treatment for sialorrhea has also been reported.[9] Several treatments have been described to improve dysarthria in ALS patients, including palatal lift and palatal

augmentation prostheses,[10,11] and a special oral appliance has been devised to decrease drooling in a patient with a Class II malocclusion.[12] In another study, dental treatment with total intravenous (IV) anesthesia in an ALS patient was successful, although the patient had a severe gag reflex and an impaired airway protection reflex.[13] Although oral health status was not affected by ALS in a cohort of 37 Australian patients, [14] the study concluded that the dental profession should be a part of the multidisciplinary team for the management of ALS patients. These patients' oral health could be maintained during the disease period with minimal clinical intervention.[15]

Masticatory function includes a number of features, such as bite force, mandibular mobility, and masticatory performance.[16,17] To the best of the authors' knowledge, no clinical study with a large sample has been performed to assess alterations in the masticatory system in patients with ALS. Information on this topic would help in the preparation of guidelines for dentists regarding the management of ALS patients and may contribute to improving patients' comfort.

The main objective of the present cross-sectional controlled study was to determine the effect of ALS on aspects of masticatory function, including mandibular range of motion, bite force and prevalence of TMD. The study also aimed to assess the relationship between ALS and the prevalence of traumatic mucosal lesions caused by oral self-injury. Additionally, potential differences between bulbar- and spinal-onset patients were explored. The working hypothesis was that patients affected by ALS would have lower bite force, a reduced mandibular range of motion, a higher prevalence of TMD, and a higher incidence of traumatic mucosal ulcers due to self-injury than healthy subjects.

MATERIAL AND METHODS

Participants

Between April 2015 and September 2016, patients diagnosed with ALS according to the revised El Escorial diagnostic criteria[18] and attending the Motor Neuron Disease Unit of the Bellvitge University Hospital were invited to participate in this cross-sectional study. Patients who could not be evaluated because of their clinical condition were excluded.

The control group included 23 participants recruited from families or caregivers of ALS patients and other age- and gender-matched subjects. The nature of the study was explained in full to all the participants, and all signed an informed consent form approved by Bellvitge University Hospital Ethics Committee (Code PR260/15). All experiments were carried out in accordance with the principles of the Helsinki Declaration.

ALS-related characteristics

Patients were routinely evaluated by the ALS unit neurology team. Chronologic variables registered were date of onset, time to diagnosis, and time to evaluation. Demographics on sex, age, and family history were also registered, and a phenotypic classification was performed according to the site of onset (bulbar, spinal, and respiratory). Medication, use of mechanical ventilation, and gastrostomy were also registered (Table 1).

Assessment of TMD

All participants were examined and interviewed by the same trained dental clinician and answered the symptom questionnaire of the Diagnostic Criteria for TMD (DC/TMD) protocol.[19] The clinical examination included the measurement of maximum opening, protrusion, and laterotrusion; palpation and auscultation of the temporomandibular joints (TMJs); and palpation of the masticatory muscles.[19-21] Following the DC/TMD algorithms, all subjects were defined as non-TMD or assigned to one of the four subgroups (myalgia, arthralgia, TMD-related headache, or disc-displacement). Multiple diagnoses were also possible.

Questionnaire

Participants were also assessed by means of a questionnaire about awareness of clenching/grinding, jaw blocking, and presence of cramps in the masticatory muscles (with dichotomous no/yes answers for all three questions). Self-injury to the tongue, lips, or cheeks was also assessed and rated on a 5-point Likert scale (never, yearly, monthly, weekly, daily) and was considered clinically relevant if the participant answered either weekly or daily. Finally, the information from this questionnaire was

used to determine whether participants might be candidates for receiving oral treatment to manage these oral-related problems (no/yes).

Clinical examination

Overbite was measured according to the DC/TMD protocol.[19] Briefly, a horizontal pencil mark was placed on the buccal surface of the right mandibular central incisor in relation to the maxillary antagonist incisor in relation to the maxillary antagonist incisor while the posterior teeth were in the maximum intercuspal position.[22] To measure both maximum unassisted and maximum active mouth opening, the interincisal distance between the maxillary and mandibular reference teeth (the same as the ones used to measure the overbite) was measured after asking the participants to open as wide as they could, even if it was painful. To measure the maximum assisted or maximum passive mouth opening, participants were asked to open as wide as they could, and the operator pushed the mouth open further using moderate pressure. Afterwards, the interincisal distance between the maxillary and mandibular reference teeth (the same as the ones used to measure the overbite) was measured. Right and left laterotrusion were measured taking into account the midline discrepancy, and protrusion was assessed by adding the overjet to correct the amount of movement.[21]

Bite and Grip Measurements

A bite-force transducer (gnathodynamometer) calibrated with loads from 0–1,200 N was used to measure unilateral maximum bite force between the second premolars or the first molars on both sides.[23, 24] Bite force was measured three times with the order changed for each side, and the highest value was selected for analysis. The finger-thumb grip force of each hand was measured in a similar manner using the bite-force transducer.[25]

Statistical Analyses

The normal distribution fit of the data was tested by means of the Kolmogorov–Smirnov test. Comparisons between patient and control groups were performed using Mann Whitney *U* test or chi-square test, as appropriate. Comparisons between bulbar-, spinal-, and respiratory-onset groups and the control group were performed using the

Kruskal-Wallis H test and chi-square test, as appropriate. Spearman rank correlation coefficients were calculated in order to evaluate the bivariate correlations between quantitative parameters. Statistical analysis was performed using the SPSS program (IBM SPSS Statistics, version 23.0.0.2), and P < .05 was considered significant.

RESULTS

This study included 153 patients (median age 64 years; 46% women) and 23 controls (median age 52 years; 56% women). Among the patients with ALS, onset was bulbar in 26%, spinal in 67%, and respiratory in 7% (Table 1). Only 5.2% of these patients had a hereditary component. The median time from symptom onset to exploration was 30.8 months, and the median time since diagnosis was 16.1 months. The medications prescribed were riluzol (77.8%), baclofen (25.5%), amitriptyline (28.1%), and botulinum toxin (9.8%). Almost a third (32%) of the ALS patients received noninvasive ventilation, while 11% needed supplemental tube feeding, 77% had normal eating habits, and 12% had either probe or oral feeding.

Table 1 Characteristics of Patients with Amyotrophic Lateral Sclerosis (ALS)

	ALS onset				
Characteristics	Total (n = 153)	Bulbar (n = 40)	Spinal (n = 102)	Respiratory (n = 11)	*P* value between each onset subgroup*
Sex (% male)	53.6	42.5	54.9	81.8	.06
Median age (y)	64.2	66.1	61.8	70.7	.001
Familiar (%)	5.2	10	3.9	0	.247
Median time elapsed since symptom onset (mo)	30.8	21.6	35.4	32.3	.001
Median time elapsed since ALS diagnosis (mo)	16.1	9.1	20.9	11.6	.003
Riluzol (%)	77.8	77.5	77.5	81.8	.946
Baclofen (%)	25.5	17.5	31.4	0	.031
Amitriptyline (%)	28.1	57.5	18.6	9.1	< .001
Botulinum toxin (%)	9.8	25	4.9	0	.001
Noninvasive ventilation (%)	32	25	27.5	100	< .001
Oral feeding (%)	89.5	72.5	95.1	100	< .001
Tube feeding (%)	22.9	45	14.7	18.2	.001

* Chi-square test or Kruskal-Wallis test were used for statistical analyses.

Participants' perceptions of alterations in the masticatory system are shown in Table 2. Although ALS patients did not report clenching or grinding their teeth or suffering cramps more frequently than controls, they reported more limitations in mouth movement and more sialorrhea, especially those with bulbar onset (P < .001; chi-square). Oral self-injury due to biting was reported more frequently in the ALS group than in the control group (P < .001; chi-square) and by those with bulbar onset more than by those with spinal or respiratory onset (P < .05; chi-square). The most frequently

injured sites were the tongue and cheeks, and 35% of bulbar-onset patients reported self-injury due to biting the cheek daily or weekly. Ten percent of ALS patients were candidates for oral treatment related to their ALS. Among the patients with bulbar onset, 20% sought oral treatment compared with only 7% of spinal onset patients (*P* = .02, chi-square).

Table 2 Comparison Between ALS Patients and Control Group of Participants' Perceptions of Alterations in the Masticatory System

		ALS onset				*P* value:	*P* value:
	Total (n = 153)	Bulbar (n = 40)	Spinal (n = 102)	Respiratory (n = 11)	Control group (n = 23)	Patient vs control group*	Control vs each onset subgroup*
Grinding or clenching (%)	51.0	60.0	51.0	18.2	65.2	.2	.053
Cramps (%)	2.7	2.7	3.0	0	0	.44	.8
Limitations in mouth movement (%)	37.3	70.0	28.4	0	0	< .001	< .001
Sialorrhea (%)	44.4	85.0	31.0	18.2	4.3	< .001	< .001
Total self-injury/oral lesions (%)	29.9	55.0	20.8	18.2	8.7	.03	< .001
Self-injury tongue (%)	13.6	27.5	7.3	18.2	0	.06	.002
Self-injury lip (%)	12.2	15.0	11.5	9.1	4.3	.26	.63
Self-injury cheek (%)	17.0	35.0	11.5	0	4.3	.12	.001
Seeking oral treatment (%)	9.8	20.0	6.9	0	0	.12	.016

*Chi-square test used for statistical analyses.

The proportions of participants with TMD according to DC/TMD subgroup are shown in Table 3. There was no relationship between the diagnosis of any TMD group and ALS (P > .05, chi-square), nor between arthralgia and feeding via gastric tube (P > .05, chi-square). Maximum unassisted and assisted mouth opening, protrusion, and left laterotrusion were significantly reduced in the spinal-onset group compared to the control group (*P* < .05, Mann Whitney) and also in bulbar-group compared to the spinal-onset group (*P* < .05, Mann Whitney). In the bulbar-onset group, 40% had limited unassisted mouth opening (ie, < 40 mm), and both finger-thumb grip force and bite force were significantly reduced in bulbar-onset patients compared to the control group (*P* < .001, Mann Whitney). In spinal-onset patients, only finger-thumb grip force was significantly reduced compared to the bulbar-onset group (*P* < .05, Mann Whitney); however, whereas the scores of bulbar-onset patients for finger-thumb grip and bite forces were nearly 50% of those recorded by control subjects, the scores of spinal-onset patients were 22% (finger force) and 74% (bite force) with respect to normal control scores.

Table 3 Comparison Between ALS Patients and Control Group of Temporomandibular Disorder (TMD) Diagnoses, Mandibular Movements, and Muscular Force

		ALS onset					
	Total (n = 153)	Bulbar (n = 40)	Spinal (n = 102)	Respiratory (n = 11)	Control group (n = 23)	*P* value: Patient vs control group	*P* value: Control vs each onset subgroup*
TMD							
Myalgia (%)	9.2	10.0	8.8	9.1	17.4	.22	.68
Arthralgia (%)	5.9	7.5	5.9	0	0	.23	.49
TMD-related headache (%)	0.7	0	1.0	0	4.3	.12	.44
Disc displacement (%)	25.5	17.5	30.4	9.1	39.1	.17	.12
Mandibular movement							
Median maximum unassisted opening (mm)	44.0	42.5	46.0	43.0	50.0	.001	< .001
Median maximum assisted opening (mm)	46.5	44.5	48.0	46.0	53.0	< .001	< .001
Median difference between assisted and unassisted maximum opening (mm)	2.0	2.5	2.0	2.0	2.0	.59	.23
Limited mouth opening (%)	20.3	40	14.7	0	4.3	.07	< .001
Median maximum right laterotrusion (mm)	6.0	5.0	6.0	8.0	8.0	.02	.005
Median maximum left laterotrusion (mm)	6.0	5.5	6.0	6.0	8.0	< .001	< .001
Median maximum protrusion (mm)	6.0	4.0	7.0	6.0	8.0	.001	< .001
Muscular force							
Median maximum bite force (N)	237	198	256	274	346	< .001	< .001
Median finger-thumb grip force (N)	22.6	41.2	16.7	22.6	75.5	< .001	< .001

*Chi-square test or Kruskal-Wallis test used for statistical analyses.

Comparisons between type of feeding for ALS patients and control subjects for mandibular force and mouth opening, respectively, are shown in Figs 1 and 2. ALS patients with gastrostomy had a significant reduction in maximum bite force and in mandibular opening compared to control subjects. ALS patients with tube feeding only (n=16) had the greatest reduction in maximum bite force and mandibular opening.

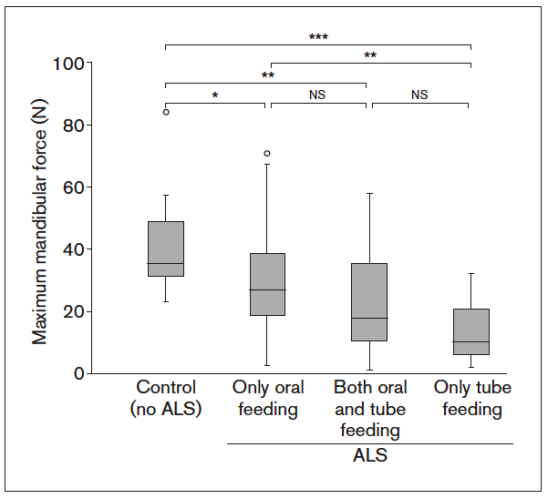

Fig 1 Box plot of maximum bite force comparison between feeding groups. NS = not significant. *$P \leq .05$. **$P \leq .01$. ***$P \leq .001$. Kruskal-Wallis test and pairwise comparisons were used for statistical analyses.

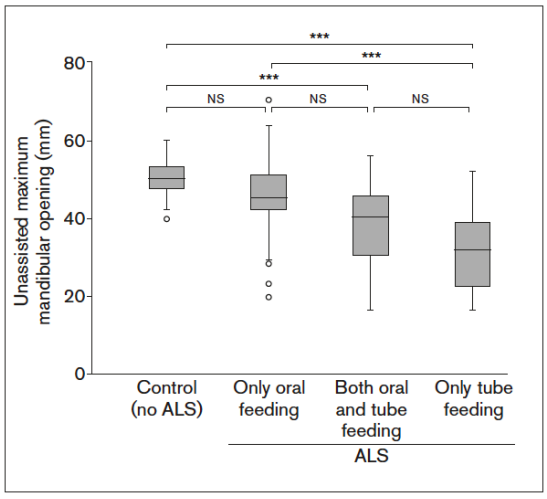

Fig 2 Box plot of maximum unassisted mouth opening comparison between feeding groups. NS = not significant. ***$P \leq .001$. Kruskal-Wallis test and pairwise comparisons were used for statistical analyses.

The Spearman correlation coefficients between variables related to mandibular movement or muscular force are shown in Table 4. All variables related to mandibular movement and bite force were significantly correlated with each other ($P < .01$,

Spearman correlation). Although maximum finger-thumb grip force was correlated with maximum mouth opening, it was not correlated with bite force.

Table 4 Spearman Correlation Coefficients Between Variables Related to Maximum Range of Mandibular Movement or Maximum Muscular Force

	unAMO	AMO	RL	LL	Protrusion	Bite force	Finger force
Unassisted mouth opening	1						
Assisted mouth opening	.966**	1					
Right laterotrusion	.278**	.293**	1				
Left laterotrusion	.400**	.431**	.544**	1			
Protrusion	.462**	.466**	.443**	.488**	1		
Bite force	.217**	.218**	.309**	.244**	.362**	1	
Finger-thumb grip force	.260**	.273**	.066	.074	.086	.079	1

**Correlation significant at $P < .01$ level (2-tailed test). unAMO = unassisted mouth opening; AMO = assisted mouth opening; RL = right laterotrusion; LL = left laterotrusion.

DISCUSSION

The results of the present study suggest that approximately 10% of ALS patients are candidates for oral treatment specifically because of their disease. The chief complaint of the majority of these patients was traumatic lesions in the lips, cheeks, or tongue due to self-biting. To the author's knowledge, this is the first large study demonstrating such a high rate of oral self-biting injuries, especially in bulbar-onset patients. Customized oral appliances or acrylic splints and mouthguards have been used in other cases of oral self-injury[26]; however, prospective studies are needed to assess the efficacy, side effects, and technical complications of an oral appliance for managing alterations in the masticatory system in ALS patients. This study supports a multidisciplinary approach to the management of ALS patients, and the dentist should be an integral part of the management team to help treat the negative effects of ALS on the stomatognatic system. [14, 15]

Maximum mandibular movement and bite force were both significantly reduced in ALS patients regardless of type of onset, and both aspects of masticatory function were significantly correlated. Moreover, the greatest reduction was observed in bulbar-onset ALS patients, especially those with tube feeding only. Whereas the relative amount of muscular force reduction in bulbar-onset patients was similar in the finger-thumb grip and in bite force, in spinal-onset patients, the relative reduction was three times higher for the finger force than for the bite force. This result is expected due to the limb muscle weakness that characterizes this type of patient. A reduction in mouth opening

may hinder oral hygiene and also perhaps the efficacy of noninvasive ventilation. Therefore, in order to minimize these complications and before indicating gastric tube feeding, especially in bulbar-onset patients, a physiotherapy program comprising active exercises could be applied to slow down the reduction in mouth opening. The relationship between mouth opening and efficacy of noninvasive ventilation could be the focus of new research in a prospective study.

No differences in TMD prevalence were detected in ALS patients compared to the control group or compared to general or geriatric populations.[27, 28] As ALS patients report arthralgia in joints with weak musculature,[29] they might also be expected to suffer TMJ arthralgia. Some ALS patients did not use the jaw to eat because they were feeding via a gastric tube; however, these patients did not report arthralgia in the TMJ probably because they still used masticatory muscles for functions besides chewing, such as clenching.

The 153 ALS patients who participated in the present study represent approximately 30% of all ALS patients diagnosed in Catalonia, which has a population of some 7,500,000 inhabitants.[3] The clinical characteristics of this patient group were consistent with the results of other studies, such as the distribution of ALS site of onset,[30] the percentage of the hereditary component,[31] the male/female ratio (regardless of the site of onset), the differentiation between bulbar and spinal onset,[5,32] and the time elapsed since the first symptom or the time since diagnosis.[33] Therefore, this sample was highly representative of the population, which is one of the strengths of the present study. The small sample size of the control group and the method of recruitment are considered study limitations; however, although most of the control group came from the families of the patients and were slightly younger, the range of mandibular motion and the prevalence of TMD in the control group were consistent with data from the general population and from elderly subjects reported in other studies.[27,28] Another limitation was the lack of attempt to correlate masticatory system measures with ALS functional rating scale scores.

CONCLUSIONS

The ALS patients in the present study showed reductions in both bite force and finger-thumb grip force. The reduction was twice as large for the finger force than for the bite force. The maximum range of mandibular movement (mouth opening, protrusion, and laterotrusion) was also reduced in the ALS patients, especially in bulbar-onset phenotypes. The prevalence of TMD in the ALS patients was similar to that in the control subjects and consistent with that in general population studies. The ALS patients had more traumatic mucosal injury than controls, especially in the tongue and cheek. The dentist should be an integral part of the multidisciplinary team in order to improve the comfort of ALS patients.

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4.2 Study II: Functional limitation of the masticatory system in patients with bulbar involvement in amyotrophic lateral sclerosis.

Riera-Punet N, Martinez-Gomis J, Willaert E, Povedano M, Peraire M. Functional limitation of the masticatory system in patients with bulbar involvement in amyotrophic lateral sclerosis. J Oral Rehabil. 2018 Mar; 45:204-210.

doi: 10.1111/joor.12597.

ABSTRACT

Amyotrophic lateral sclerosis (ALS) with bulbar dysfunction affects the motor neurons responsible for controlling the muscles in the jaw, face, soft palate, pharynx, larynx, and tongue. This cross-sectional study aimed to determine the functional limitation of the jaw in patients with ALS and bulbar dysfunction who had upper motor neurons (UMN), lower motor neurons (LMN) or balanced involvement. One hundred and fifty-three patients with ALS and 23 controls were included. All participants answered using the 8-item Jaw Functional Limitation Scale (JFLS-8). Patients with ALS were grouped by neurologic examination as follows: non-bulbar ALS, bulbar UMN-predominant ALS; bulbar LMN-predominant ALS; and bulbar balanced (UMN + LMN) ALS. Jaw limitation between the different groups was compared using the Kruskal–Wallis test. Patients with non-bulbar ALS had similar mandibular limitations to healthy participants. Only patients with balanced UMN and LMN bulbar manifestations reported greater difficulties in chewing soft food or in jaw mobility compared to the non-bulbar ALS group. Patients with bulbar involvement also had greater difficulties in chewing tough food or chicken and in swallowing and talking compared to the non-bulbar group, regardless of whether UMN or LMN predominant. No significant differences were found between the groups in smiling and yawning difficulties. Bulbar involvement in patients with ALS is associated with functional limitation of the masticatory system. However, balanced bulbar UMN and LMN involvement is associated with the worst impairments in chewing soft food and in opening the jaw widely.

Keywords:
amyotrophic lateral sclerosis, bulbar involvement, jaw functional limitation, JFLS-8

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease characterized by progressive degeneration of motor neurons in the brain, brainstem, and spinal cord. Affected individuals show significant variation in the locus of disease onset, presentation at diagnosis and rate of progression.[1] Incidence rates for ALS are approximately 1.4 and 2.1 per 100 000 person/year in Catalonia and Europe, respectively.[2,3] Sufferers develop progressive wasting and weakness of limb, bulbar and respiratory muscles, and die on average within 3 years from symptom onset, usually from respiratory failure; however, roughly 10% of patients with ALS survive for ten or more years.[4] The mean age of onset for sporadic ALS ranges from 55 to 65 years, with a median age of onset of 64 years.[5] The diagnosis of ALS is based on the El Escorial and Airlie House Diagnostic Criteria .[6]

Approximately two-thirds of patients with a typical ALS disease pattern develop initial symptoms in the upper or lower extremities (limb or spinal onset), most commonly in distal muscles. The other third of patients have bulbar onset, usually starting with dysarthria, but almost all demonstrate bulbar involvement at later stages. About 5% of patients present with respiratory weakness without significant limb or bulbar symptoms.[7, 8] In patients with bulbar dysfunction, upper motor neurons (UMN) involvement causes supranuclear symptoms that are also commonly referred to as pseudobulbar palsy. The clinical characteristics of pseudobulbar palsy are spasticity and hyperreflexia of the bulbar muscles (ie jaw, face, soft palate, pharynx, larynx and tongue), emotional lability (pathological laughing and crying) and a brisk jaw jerk. Degeneration of lower motor neuron (LMN), with involvement of the cranial nerve nuclei in the medulla oblongata and pons that innervate the bulbar muscles, results in a bulbar palsy with flaccid paresis, muscular atrophy and fasciculations and/or tongue fibrillations.[7, 9]

Oro-facial function is an important contributor to an individual's general health and quality of life. The masticatory system is responsible for complex biopsychosocial functions, where basic functions such as chewing, swallowing, eating and yawning manifest simultaneously with emotional functions such as smiling, laughing, screaming

and kissing. Functional limitation and disability can be measured with generic, disease-specific or organ-specific instruments. The 20-item Jaw Functional Limitation Scale (JFLS-20) is a reliable and valid organ-specific instrument for measuring limitations in mastication, jaw mobility and verbal and emotional expression, together with a global functional limitation score. Global limitation can also be determined with a short version, the JFLS-8. These scales have three subscales that cover mastication, vertical jaw mobility and emotional and verbal expressions. The properties of the JFLS-8 scales are ideal for both research and patient evaluation when assessing global functional limitation of the jaw.[10]

Masticatory function includes phenomena such as bite force, mandibular mobility and masticatory performance[11-13] and has been studied by assessing these phenomena in other neurological diseases.[14-19] However, to the authors' knowledge, functional limitation of the masticatory system has not been assessed in a large sample of patients with ALS. The main objective of this study was to determine the effect of bulbar involvement on functional limitation of the masticatory system in patients with ALS. This study also aimed to compare the functional limitation of the masticatory system between patients with ALS and a pseudobulbar palsy (UMN involvement) and patients with ALS and a bulbar palsy (LMN involvement). The working hypothesis was that bulbar involvement would cause functional limitation of the masticatory system in patients with ALS.

MATERIAL AND METHODS

Participants

In this cross-sectional study, 153 patients diagnosed with ALS according to the revised El Escorial and Airlie House Diagnostic Criteria at the Motor Neuron Disease Unit of the Bellvitge University Hospital were selected. A control group was included that comprised 23 participants recruited from the families or caregivers of patients with ALS and other age- and gender-matched people. All subjects participated in a previous investigation.[20] Patients were excluded if they could not be evaluated because of their clinical condition or sensory deficits. All participants were fully informed and signed an informed consent form approved by Bellvitge University Hospital Ethics Committee

(Code PR260/15), and all experiments were carried out in accordance with the principles of the Helsinki Declaration.

ALS-related Characteristics

Bulbar dysfunction involvement was determined as UMN, LMN or balanced (UMN + LMN) based on neurologic examination by a neurologist, using upper motor signs (ie brisk jaw jerk, tongue spasticity and spastic dysarthria) and lower motor signs (ie tongue wasting, tongue fasciculations and flaccid dysarthria). [21]

Functional Jaw Limitations Scale

Functional limitation of the masticatory system was assessed using the JFLS-8.[10] This scale evaluates eight items: (1) chew tough food, (2) chew chicken (eg prepared in oven), (3) eat soft food requiring no chewing (eg mashed potatoes, apple sauce, pudding, pureed food), (4) open wide enough to drink from a cup, (5) swallow, (6) yawn, (7) talk and (8) smile. The participants rated the level of limitation for each item during last month using a 0-10 numerical rating scale, with 0 corresponding to "no limitation" and 10 corresponding to "maximal limitation". The examiner interviewed each participant orally asking all JFLS items. The patient's caregiver helped answering in case the patient had some difficulties. Questionnaires were filled when the patients were attended by the ALS unit multidisciplinary team for a check-up. The median time elapsed between the first symptom onset and the questionnaire was 31 months, and the median time elapsed between the diagnostic and the questionnaire was 16 months (Table 1).

TABLE 1 Characteristics of healthy and patients with amyotrophic lateral sclerosis

Characteristics	Healthy (n = 23)	ALS Patients (n = 157)				*P*-value between each subgroup[a]
		No Bulbar affectation (n = 47)	Bulbar UMN-predominant (n = 28)	Bulbar LMN-predominant (n = 18)	Balanced bulbar UMN and LMN (n = 60)	
Sex (% of Male)	44	64	36	56	53	NS
Mean age (years)	51	62	62	69	60	<.0005
Median time elapsed since symptom onset (months)		35.4	35.0	33.2	24.4	.015
Median time elapsed since ALS diagnosis (months)		18.8	19	12.5	13.3	.554
Botulinum toxin (%)		2.1	3.6	16.7	16.9	.034
Non-invasive ventilation (%)		36.2	25	55.6	25	.074
Oral feeding (%)		100	92.9	83.3	81.7	.015
Use of tube feeding (%)		6.4	14.3	50	31.7	<.0005

[a]Chi-squared test or Kruskal-Wallis test.

Data analysis

Participants were distributed into 1 of the 5 groups. The control group included 23 healthy participants, and the 153 patients with ALS were grouped as those with non-bulbar ALS, bulbar UMN-predominant ALS, bulbar LMN-predominant ALS, and bulbar balanced ALS (with both UMN and LMN) groups. Items from the same subscale of the JFLS-8 with similar results were averaged, such as the chew tough food and chew chicken items, the swallow and talk items, or the yawn and smile items. The degree of jaw limitation for each subscale and for the eight items was compared between the different groups using the Kruskal–Wallis test with adjustment for pairwise comparisons. All analyses were performed in IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA), and P-values ≤.05 were considered statistically significant.

RESULTS

Participants

This study included 153 patients with ALS (mean age 62 years, SD 12 years; 46% women) and 23 controls (mean age 51 years, SD 12 years; 56% women). Patients with ALS were assigned to one of four groups according to bulbar involvement and their characteristics are summarized in Table 1. In total, 10% of patients with ALS received parotid botulin toxin injections, 32% required non-invasive ventilation, and although 76% had normal eating habits, 11% required supplemental tube feeding and 12% required either probe or oral feeding.

Comparison of the bulbar and non-bulbar groups

Two of the three mastication subscale items of the JFLS-8, chew tough food and chew chicken, were averaged because the results were similar. Although patients in the non-bulbar ALS group were similar to controls on the chewing measures, patients in the bulbar ALS groups had greater difficulties in chewing tough food or chicken compared to those in the non-bulbar group, regardless of the motor neuron affected (Figure 1). However, only patients in the balanced bulbar ALS group reported greater difficulties in chewing soft food compared with the non-bulbar ALS group (Figure 2). Patients in the balanced bulbar ALS group reported greater difficulties in opening their mouths wide enough to drink from a cup compared to those in the non-bulbar group (Figure 3).

Although patients in the non-bulbar ALS group had no significant differences in swallow and talk difficulties compared with the control group, patients in the ALS groups with bulbar involvement had greater swallow and talk difficulties compared with the non-bulbar group regardless of the motor neuron affected (Figure 4). However, there were no significant differences in smiling and yawning difficulties between any of the groups (Figure 5).

Considering all items of the three subscales, patients without bulbar involvement in ALS had similarly low functional jaw difficulties compared to healthy participants. By contrast, patients with bulbar involvement in ALS had greater functional jaw difficulties compared to those without bulbar involvement, regardless of the motor neuron affected (Figure 6).

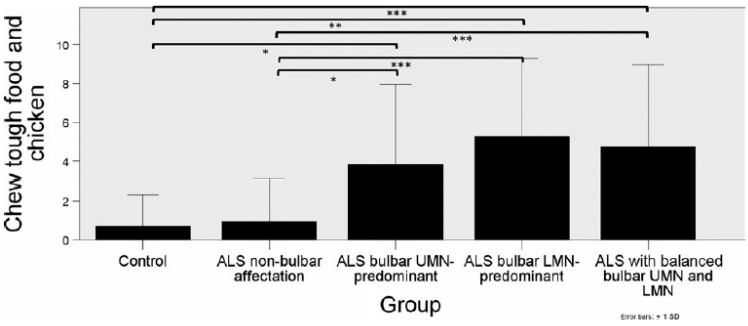

FIGURE 1 Means and standard deviation of limitation score of chewing tough food and chicken. *$P \leq .05$; **$P \leq .01$; ***$P \leq .001$ Kruskal-Wallis test and pairwise comparisons of different groups

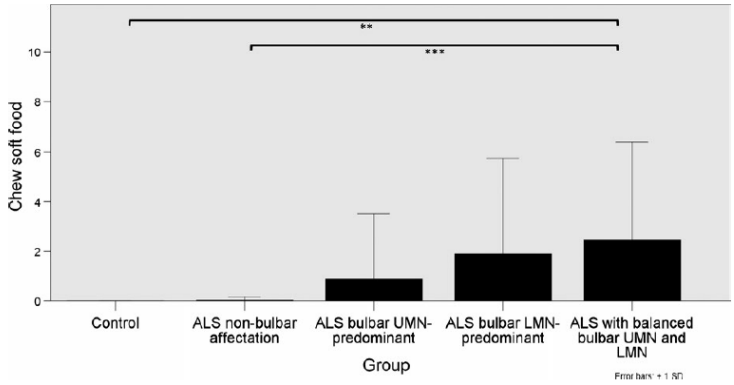

FIGURE 2 Means and standard deviation of limitation score of chewing soft food. **$P \leq .01$; ***$P \leq .001$ Kruskal-Wallis test and pairwise comparisons of different groups

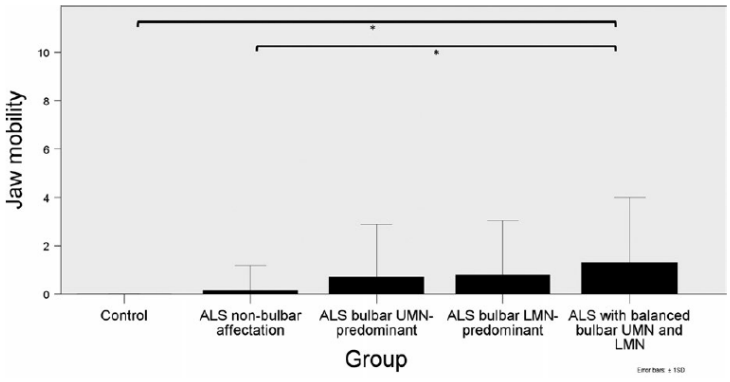

FIGURE 3 Means and standard deviation of limitation score of jaw mobility. *$P \leq .05$ Kruskal-Wallis test and pairwise comparisons of different groups

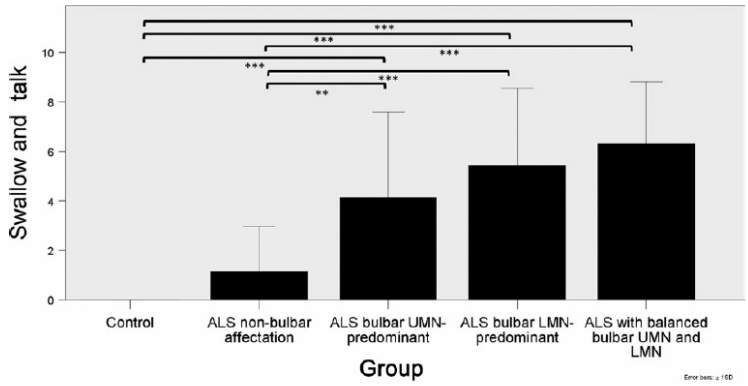

FIGURE 4 Means and standard deviation of limitation score of swallowing and talking. **$P \leq .01$; ***$P \leq .001$ Kruskal-Wallis test and pairwise comparisons of different groups

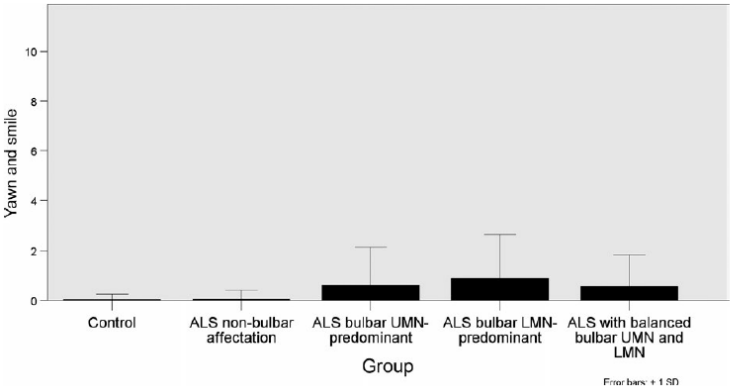

FIGURE 5 Means and standard deviation of limitation score of yawning and smiling. $P > .05$ Kruskal-Wallis test and pairwise comparisons of different groups

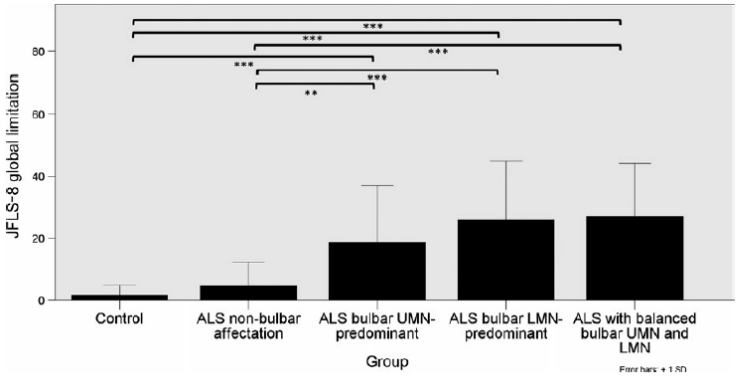

FIGURE 6 Means and standard deviation of JFLS-8 global limitation score. **$P \leq .01$; ***$P \leq .001$ Kruskal-Wallis test and pairwise comparisons of different groups

DISCUSSION

The results of this study indicate that bulbar involvement was significantly associated with perceived functional limitation of the masticatory system in patients with ALS. In the bulbar group, the greatest impairment was seen in those with balanced UMN and LMN diseases, as evidenced primarily by difficulties in chewing soft food and opening the jaw widely, as well as difficulties in chewing tough food and chicken, swallowing and talking.

When patients have been grouped by symptom type at onset, aspects of masticatory function, like bite force and range of jaw mobility, were objectively shown to be reduced in bulbar-onset groups compared with spinal or respiratory onset groups.[20] Moreover, the bulbar-onset group showed more severe oro-facial impairment than the spinal-onset group assessed with the Nordic Oro-facial Test-Screening.[21] Results of the present study suggest that masticatory function is also affected when the involvement of the bulbar region occurs during the evolution of the disease. This is consistent with the fact that the bulbar target damages neurons responsible for controlling facial, masticatory, pharyngeal and laryngeal muscles. There are differences in neurological symptoms between UMN and LMN involvement.[8] Emotional lability, nasal speech, nasal regurgitation, excessive saliva, slow tongue and brisk jaw jerk and facial reflexes are characteristics of UMN. Slurred speech, difficulty in swallowing, excessive saliva, small and fasciculating tongue are characteristics for LMN.[8] The difficulties in masticatory function are related to upper motor neuron signs as tongue spasticity or to lower motor neuron signs as tongue atrophy. Despite the neurological differences between patients with upper or lower motor neuron involvement, no differences in mastication, jaw mobility or verbal and emotional expression were observed. However, when both motor neurons were affected, there was a greater degree of functional limitation in these measures.

Although the jaw mobility is reduced in balanced bulbar UMN and LMN ALS, yawning was not affected in this study. It is known that excessive yawning occurs in a substantial number of patients with ALS specially in those with a bulbar onset.[8, 22] Probably this could be related to the inhibition of normal control mechanisms of emotions, which

would mean that neurological paths controlling voluntary mandibular opening and yawning are different. However, to date, no physiological significance has been associated with yawning, and the neural pathways underlying it are not known.[23] Moreover, even though patients with bulbar symptoms experience facial weakness affecting the lower half of the face, no patient in this study reported difficulty smiling.

Amyotrophic lateral sclerosis (ALS) is a low-prevalent disease, and therefore, it should not be considered as a first-line differential diagnosis in patients with temporomandibular disorders. Nevertheless, as most of bulbar-onset patients reported the first symptoms in the oro-facial region, dentists should keep in mind this possibility in those situations in which, in a patient with apparent symptoms of temporomandibular disorders, there are incongruous signs or symptoms.[24] These signs and symptoms may include difficulty in mastication, speech or swallowing due to an impairment in tongue control or a weakness in masticatory muscles, and difficulty in mandibular mobility not attributable to muscular or articular pain or disc displacement.[7,8]

Mandibular mobility and/or bite force are also reduced in patients with other neuromuscular diseases, including spinal muscular atrophy, [14-16] bulbar myasthenia gravis [17,18] and Duchenne muscular dystrophy.[19] A reduced ability to open the mouth may hinder oral hygiene and perhaps even the efficacy of non-invasive ventilation. To minimise these complications, especially in patients with bulbar onset, an effective physiotherapy programme of active exercises is needed to slow the rate of reduction in mouth opening.[19] The physiotherapy programme could consist on moderate-load and moderate-intensity resistance and stretching exercise programme to improve mandibular mobility.[25] Moreover, the dentist could also manage ALS patients to avoid traumatic lesions in the lips, cheeks or tongue due to self-biting.[20] Recommendations for dental care in patients with ALS also include a regular oral maintenance care to maintain oral health and avoid dental disease, as well as counselling for dietary modifications.[26] Symptoms of dysphagia may occur at any time in the act of swallowing. Patients may report failure to chew or intolerance to texture in the oral preparatory phase and pocketing of food in the oral phase.[27] Recommendations to

improve or mitigate swallowing function include compensatory manoeuvres, behavioural strategies, sensory tricks and dietary modifications such as mechanically altered food, thickened liquids, soft diet or liquidize food.[26] Consequently, dentists should also be included in the multidisciplinary team to improve the quality of life of patients with ALS.

The sample of this study was representative to the population of Catalonia, corresponding to 30% of the approximate 451 patients with ALS diagnosed among the 7 500 000 inhabitants.[2] However, the small sample size and recruitment method for the control group are potential limitations. Nevertheless, the prevalence of TMD and the range of mandibular motion in the control group were comparable to those reported in other studies.[28,29]

In conclusion, bulbar involvement in patients with ALS is associated with functional limitation of the masticatory system. However, balanced bulbar UMN and LMN involvement is associated with the worst impairments, affecting soft food chewing and opening the jaw widely.

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4.3 Study III: Satisfaction of patients with amyotrophic lateral sclerosis with an oral appliance for managing oral self-biting injuries and alterations in their masticatory system: A case-series study.

Riera-Punet N, Martinez-Gomis J, Zamora Olave C, Willaert E, Peraire M. Satisfaction of patients with amyotrophic lateral sclerosis with an oral appliance for managing oral self-biting injuries and alterations in their masticatory system: A case-series study. J Prosthet Dent. 2018 Nov 30.

doi: 10.1016/j.prosdent.2018.06.010

ABSTRACT

Statement of problem. About 10% of patients with amyotrophic lateral sclerosis (ALS) are candidates for oral treatment specifically because of traumatic injuries in the lips, cheeks, or tongue due to self-biting. However, patients with ALS have a prevalence of TMD similar to that in the general population.

Purpose. The purpose of this case series study was to determine the degree of satisfaction of patients with ALS with an oral appliance for managing oral self-biting lesions or symptoms related to temporomandibular disorders (TMDs). This study also assessed the degree of improvement of the chief complaint and the compliance with and adverse effects of this treatment.

Material and methods. Eleven patients with ALS who sought oral treatment because of oral self-biting or TMD-related symptoms were included. A custom complete-coverage acrylic resin device was fabricated and fitted to each participant. A follow-up visit was planned for 3 months after the placement of the oral appliance, at which point the patients would rate the degree of improvement or worsening of the chief complaint and their degree of satisfaction with the treatment. A 1-sample *t* test was used to assess whether the degree of improvement of the chief complaint was significant.

Results. Participants reported a mean of 61% (95%CI; 38% to 84%) improvement of the chief complaint and a mean of 84% (95%CI 72% to 97%) satisfaction with the treatment. The mean rate of compliance was 62% (95%CI 40% to 84%) of the recommended time and only a few adverse effects were reported.

Conclusions. Patients with ALS were highly satisfied with the use of an oral appliance to manage oral self-biting or TMD-related symptoms. Adherence to this treatment was high and no major adverse effects were observed.

CLINICAL IMPLICATIONS

Patients with amyotrophic lateral sclerosis referred for oral self-biting or TMD symptoms can be managed efficiently by means of an acrylic resin device.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive muscular paralysis reflecting the degeneration of motor neurons in the primary motor cortex, corticospinal tract, brainstem, and spinal cord.[1] Its incidence rate is approximately 1.4 and 2.1 per 100 000 persons/year in Catalonia and Europe respectively.[2,3] Since ALS is rapidly progressive in nature, life expectancy is 3 to 5 years after diagnosis, although approximately 10% of patients with ALS survive for 10 or more years.[4] The typical clinical characteristics of ALS are variable and depend on whether the site of onset is spinal, bulbar, or respiratory. Most patients with ALS have a spinal onset, referring with weakness, muscle atrophy, and fasciculations due to lower motor neuron involvement and hyperreflexia and hypertonia due to upper motor neuron involvement. In about 20% of patients, weakness starts in the bulbar muscles, with dysarthria, dysphagia, and tongue fasciculations. Bulbar onset ALS has a poorer prognosis because of swallowing difficulties, weight loss, aspiration, and respiratory involvement, with poorer adaptation to noninvasive ventilation. About 3% to 5% of patients have a respiratory onset, referring with orthopnoea or dyspnoea and mild or even absent spinal or bulbar signs.[1]

About 10% of patients with ALS are candidates for oral treatment specifically because of their disease. The chief complaint may include traumatic injuries to the lips, cheeks, or tongue due to self-biting in the case of bulbar involvement.[5] However, patients with ALS have a prevalence of temporomandibular disorder (TMD) similar to that of the general population. Almost 50% report grinding and clenching, and 9% may be diagnosed with myalgia.[5] Furthermore, bulbar involvement is associated with the perception of functional limitation of the masticatory system, especially when masticating tough food or chicken or when swallowing or talking.[6]

The dentist should be part of a multidisciplinary team for the management of patients with ALS.[5-9] The treatment options available to the dentist include the use of a palatal lift and/or palatal augmentation prosthesis to improve dysarthria, as described in several patients with ALS.[10] Other types of oral appliances have been reported in clinical reports to assist with noninvasive ventilation or to control drooling.[11,12]

However, the authors are unaware of a study that considered how to manage traumatic injuries to the lips, cheeks, or tongue because of self-biting in patients with ALS. Customized oral appliances, acrylic resin devices, or mouthguards have been used in other patients with oral self-injury.[13-28] For example, an acrylic resin device with a labial bumper for displacing the lower lip forward was effective in preventing traumatic lesions in the lip due to self-biting in an adult with severe neurological impairment.[13] Oral appliances are also recommended for the treatment of TMDs.[29-34]

The purpose of the present study was to determine the degree of satisfaction in patients with ALS after treatment with an oral appliance to manage oral self-biting or symptoms related to TMDs. This study also assessed the degree of improvement in the chief complaint, the change in the quality of life due to changes in the chief complaint, and other aspects of the treatment including compliance, side effects, and technical failures. The research hypothesis was that patients with ALS are satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMDs.

MATERIAL AND METHODS

Nineteen adult patients diagnosed with ALS according to the revised El Escorial diagnostic criteria and who were referred with alterations of the masticatory system were invited to participate in this prospective case series.[35] All patients were attending the Motor Neuron Disease Unit of the Bellvitge University Hospital between September 2015 and July 2016 and had participated in previous studies.[5,6] Patients who could not be treated with an orofacial device because of the advanced stage of their disease, those with severe periodontal disease, or those without a sufficient number of teeth to hold an oral appliance were excluded. The nature of the study was explained in full to all participants, and all signed an informed consent form approved by the Bellvitge University Hospital Ethics Committee (Code PR259/15). All experiments were carried out in accordance with the principles of the Helsinki Declaration.

One dental clinician (N.R-P.) recorded chronologic variables including the time elapsed since symptom onset and since the ALS diagnosis. Demographics such as sex, age, and a

phenotypic classification according to the site of onset were recorded. Medication, use of mechanical ventilation, and gastrostomy were also recorded (Table 1).

Table 1. Clinical characteristics of patients with amyotrophic lateral sclerosis according to the chief complaint

	Chief complaint	
	TMDs (n=7)	**Self-biting (n=12)**
Sex (% of Male)	43	17
Median age (years)	61.8	61.7
Bulbar-onset ALS type (%)	43	58
Bulbar Involvement (%)	71.4	100
Median time elapsed since symptom onset (months)	27.2	24
Median time elapsed since ALS diagnosis (months)	18.7	13.2
Botulinum toxin (%)	14	25
Non invasive ventilation (%)	0	33
Oral feeding (%)	100	58
Use of tube feeding (%)	14	50
Median number of missing teeth	7	5.5

ALS, Amyotrophic lateral sclerosis; TMDs, temporomandibular disorders.

All participants were examined by the same dental clinician (N.R-P.) and answered the symptom questionnaire of the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) protocol.[36] The clinical examination included the measurement of maximum opening, protrusion, and laterotrusion; palpation and auscultation of the temporomandibular joints (TMJs); and palpation of the masticatory muscles.[36-38] Participants were also assessed by means of a questionnaire about awareness of clenching/grinding and self-biting of the tongue, lips, or cheeks with dichotomous no/yes answers. Patients were asked about the chief complaint because most had been referred with more than one. They were assigned to the TMDs or self-biting group accordingly. The most frequent complaints were lower lip self-biting, grinding/clenching, and masticatory muscle pain (Fig. 1).

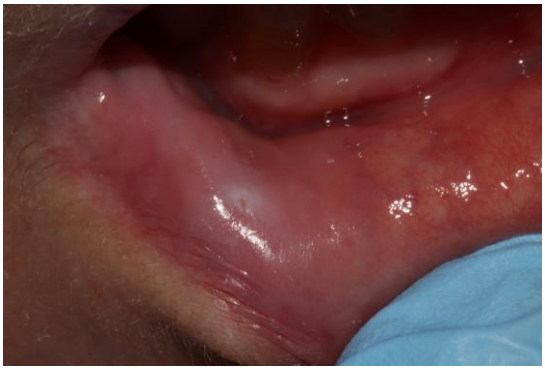

Figure 1. Lower lip self-biting lesion in patient with amyotrophic lateral sclerosis.

The oral appliance was a custom complete-coverage acrylic resin occlusal device with a flat occlusal surface in contact with all antagonistic teeth at habitual closure and providing anterior guidance in lateral and protrusive movements (Fig. 2).[29,32] It was placed on the maxillary or mandibular arch depending on the chief complaint and on the dental conditions (Table 2). Alginate impressions of the maxillary and mandibular arches were used to make gypsum casts. Among the 19 participants, difficulties making the impression were encountered in 5 individuals, mainly because these patients were not able to open their mouth wide enough or keep it sufficiently open while the impression material was setting (Table 2). If the chief complaint was self-biting the lower lip or cheeks, the acrylic resin device could include a buccal bumper to move the lower lip forward (Fig. 2). If the chief complaint was self-biting the tongue, the acrylic resin device could include a lingual bumper to move the tongue backward. All oral appliances were fabricated by the same dental technician and fitted and adjusted by the same dental clinician (N.R-P.). The patients were instructed to use the oral appliance every night during sleep and/or during the day at times they considered helpful.

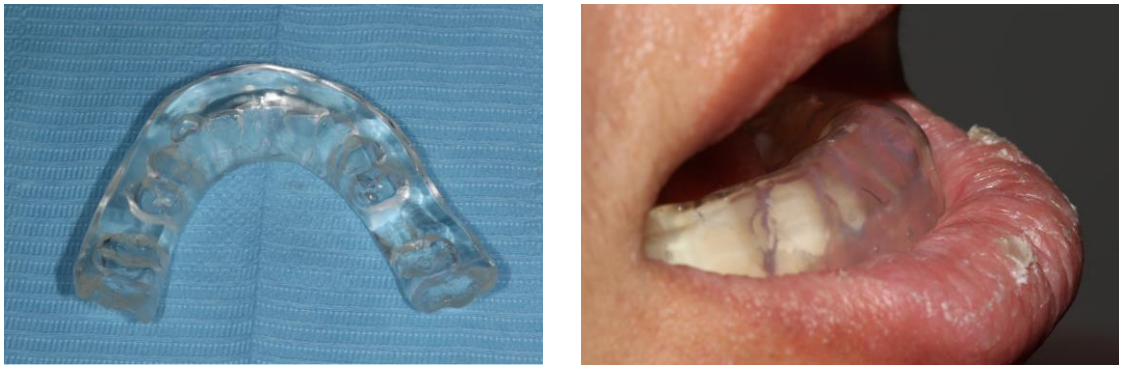

Figure 2. A, Mandibular acrylic resin occlusal device with buccal bumper. B, Device inserted in participant with lip biting.

Table 2. Characteristics of the oral appliance and degree of difficulty when taking impressions according to the chief complaint

	Chief complaint	
	TMDs (n=7)	**Self-biting (n=12)**
Maxillary oral appliance (%)	29	0
Mandibular oral appliance (%)	71	100
Presence of buccal bumper (%)	14	67
Presence of lingual bumper (%)	0	17
Difficulty taking impressions (%)	14	33

TMDs, temporomandibular disorders.

During treatment, patients with technical complications involving the oral appliance and/or adverse effects involving the masticatory system were seen by the same dental clinician (N.R-P.). The number of additional dental visits, the reason for each extra visit, and the number of oral appliance repairs in the dental laboratory were recorded.

The follow-up visit was planned for 3 months after the patient had worn the oral appliance normally. This follow-up consisted of a questionnaire to assess compliance as the percentage of time the oral appliance was used with respect to the recommended time and the adverse effects reported by the patients. This questionnaire also assessed the degree of improvement or worsening of the chief complaint after 3 months of oral appliance treatment by means of a visual analog scale (VAS), for which the patient made a mark on a 10-cm line anchored by “extreme worsening” (-100%) or “completely improved” (+100%) at either end and “no change” in the center of the line (0%).[39] The change in quality of life because of changes in the chief complaint after 3 months of treatment was assessed using a similar VAS. Finally, patients also rated their degree of satisfaction with treatment using a VAS anchored by “extremely dissatisfied” (0%) or “completely satisfied” (+100%) at either end.

The outcome variables were the degree of improvement of the chief complaint, the change in quality of life because of changes in the chief complaint, and the degree of satisfaction with the treatment. The degree of improvement of the chief complaint and

the change in quality of life because of changes in the chief complaint were assessed using a 1-sample *t* test. The degree of satisfaction with the treatment was expressed as a mean (95% confidence interval) (α=.05).

RESULTS

Among the 19 treated participants, 8 were excluded because they did not attend the 3-month evaluation (7 from the self-biting group and 1 from the TMD group). Of these 8 participants, 4 did not attend the evaluation because their disease had worsened, 1 because the individual considered the oral appliance no longer necessary, 1 because she had developed hypersalivation and had stopped using the oral appliance, and 2 because they preferred not to attend the clinic, even though the treatment had apparently improved the chief complaint. Therefore, 11 participants were included in the study and performed their evaluation a mean of 4.4 months after being fitted with the oral appliance.

The participants reported a mean of 61.2% (95%CI 38% to 84.4%) improvement in the chief complaint (*P*<.001, 2-tailed 1-sample *t* test) and a mean of 84.3% (95%CI 72% to 96.6%) satisfaction with the treatment. Because of changes in the chief complaint, quality of life improved by a mean of 58.6% (95%CI 23.5% to 93.7%) (*P*=.004, 2-tailed 1-sample *t* test). Of the 11 participants, only 1 reported a reduction in quality of life because the chief complaint had not improved (Table 3).

Table 3. Treatment success perceived by the patients according to the chief complaint

	Chief complaint	
	TMDs (n=6)	**Self-biting (n=5)**
Mean (95%CI) improvement of the chief complaint (-100 to 100)	56.8 (16.4 to 97.2)	66.4 (25.7 to 100)
Mean (95%CI) satisfaction with treatment (0 to 100)	83.8 (62.0 to 100)	85.0 (64.5 to 100)
Mean (95%CI) improvement in QoL (-100 to 100)	55.8 (0 to 100)	62.0 (25.4 to 98.7)

CI, Confidence interval; TMDs, temporomandibular disorders; QoL; Quality of life.

Of the participants who attended the 3-month evaluation, 5 had needed at least 1 extra visit because of technical complications with the oral appliance, 3 of them for adjustment and 2 for loosening. Only 1 oral appliance needed to be repaired at a dental laboratory because of lack of retention. The mean rate of compliance was 62.3% (95%CI 40.3% to 84.2%) of the recommended time. The main reason for not having used the oral appliance 100% of the recommended time was discomfort, as reported by 4 participants (36%). Only 3 participants reported no side effects at the evaluation, and the most reported side effect was excessive salivation, affecting 64% of the participants (Table 4). The participant who reported worsening of the chief complaint and had stopped using the oral appliance reported all types of side effects (Table 4).

Table 4. Number of patients (percentage) who reported side effects related to the use of the oral appliance at the 3-months check-up according to the chief complaint

	Chief complaint	
	TMDs (n=6)	**Self-biting (n=5)**
Excessive salivation	3 (50%)	4 (80%)
Dry mouth	1 (17%)	0 (0%)
Tooth discomfort or pain	2 (33%)	1 (20%)
Mucosal irritation	1 (17%)	0 (0%)
Muscular discomfort	1 (17%)	0 (0%)
TMJ discomfort or pain	1 (17%)	0 (0%)
TMJ sounds	1 (17%)	0 (0%)
Bite change	2 (33%)	0 (0%)
Other	1 (17%)	0 (0%)
At least 1 side effect	4 (67%)	4 (80%)

TMDs, temporomandibular disorders; TMJ, temporomandibular joint.

DISCUSSION

The results of this study suggest that patients with ALS are satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMDs, and therefore, the hypothesis was not rejected. The effectiveness of this treatment can be demonstrated by a mean of 61% improvement of the chief complaint, implying improved quality of life, and by a mean of 84% degree of satisfaction with the

treatment. Furthermore, compliance was high, and few and nonrelevant side effects or technical complications were detected.

The effectiveness of an oral appliance in preventing self-biting has also been reported in other neurological diseases but not in ALS and only in case reports.[13,14,17-24] However, the authors are unaware of previous prospective case series studies that evaluated effectiveness in patients with ALS. In some individuals, the increased vertical dimension produced by the oral appliance was sufficient to avoid oral self-biting because the lips, tongue, or cheeks did not invade the interocclusal space. In others, a bumper was needed to separate the lower lip from the teeth because the increased vertical dimension was not sufficient to stop the soft tissues encroaching on the interocclusal region. Before fabricating the oral appliance, the dentist should explore the placement of the tissues being traumatized in several mouth opening increments, from the intercuspal position to the resting position, to determine the required increase in vertical dimension increase and whether a bumper is required in the oral appliance.

The degree of patient satisfaction with the acrylic resin device and the compliance rate of participants with ALS were similar to those reported in those without ALS but with TMD symptoms.[29] Oral appliance therapy is a common approach to manage patients with TMDs. Although the mechanism of action of this approach remains unclear, multiple effects may be present, including allowing an orthopedically comfortable jaw position, reducing masticatory muscle activity and joint loading, and increasing patients' awareness and ability to reduce bad oral habits.[30-34] Therefore, patients with ALS with the chief complaint of clenching/grinding and/or muscular pain can be managed using an acrylic resin occlusal device.

The most common complication encountered in these patients during treatment was difficulty in making impressions due to the evolution of their disease. A poor impression can compromise the quality of the cast and therefore the acrylic resin device. Only one impression of one arch without the antagonist and/or the anterior region of this arch can be made in those who cannot be fed orally and when the dental occlusion has lost its normal function.[13] Intraoral scanning could be an alternative to

traditional impression procedure in cases where patients are not able to keep their mouth sufficiently open while the impression material was setting.[40] Another option could be a removable lip-bumper fabricated at the chairside without making an impression.[17] Similarly, custom mouthguards have been described as an option for the treatment of self-inflicted oral trauma.[16,25] A self-modeled mouthguard was reported to protect against cheek biting in a patient under orthodontic treatment,[26] although the self-modeled mouthguard is worn on the maxillary arch and this could be inconvenient.

Although the prevalence of ALS is low and the percentage of patients with ALS who require an oral appliance treatment is only about 10%, this disease is highly disabling; patients will appreciate any help that improves their quality of life. The use of an oral appliance permits daily oral care, its maintenance is straightforward, it can be placed and removed easily by the patient or the caregiver, it can be repaired or modified, and treatment can be conducted by a general dentist. Using an oral appliance can help the patient avoid the more extreme solution of extraction of all teeth.[27,28]

Side effects were generally the same as those reported in other studies of oral appliances.[29,37,41] However, excessive salivation could exacerbate the problem of drooling, which is common in ALS. Moreover, sialorrhoea itself is already common in ALS and can be treated with amitriptyline, oral or transdermal hyoscine, or sublingual atropine drops.[7]

This study has several limitations. First, no control group was used, and a cause-and-effect relationship between the improvement of the chief complaint and the use of an oral appliance should be assumed with caution. The present findings encourage further studies with appropriate controls to demonstrate the effectiveness of the oral appliance in patients with ALS. Moreover, the initial sample size and the high proportion of drop-outs could reduce the validity of these results. The fact that patients with ALS may have difficulty travelling from their homes to the clinic, mainly because of the evolution of their disease, could make it difficult to monitor treatment for longer periods. In the 4 patients excluded because of worsening of the disease, it is not known whether the acrylic resin device was effective or not. This suggests that patients with

ALS should use the acrylic resin device in the first phase of their disease and not wait until their condition deteriorates, at which point compliance might decline. An early diagnosis and appropriate dental approach are indispensable to avoid severe injuries to the oral mucosa.[26]

CONCLUSIONS

Within the limitation of this case-series clinical study, the following conclusions were drawn:

1. Patients with ALS were highly satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMDs because of the improvement in the chief complaint, which increased their quality of life.
2. Compliance regarding the use of an oral appliance was high, and few side effects and technical failures were observed.

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DISCUSSION

5. DISCUSSION

The results of the first two studies in this thesis indicate that patients with ALS have functional alterations in the masticatory system. Maximum mandibular movement and bite force were both significantly reduced in ALS patients, especially in the bulbar-onset group. Bulbar involvement with balanced UMN and LMN presented a significant association with the perceived limitation of jaw mobility and chewing soft food.

In our first study we found that the reduction of muscular force in patients with ALS was similar for finger-thumb grip and bite force in bulbar-onset patients. However, in spinal-onset patients, the relative reduction was three times higher for finger force than for bite force. This may be due to the limb muscle weakness that characterizes spinal-onset patients. Bite force is significantly reduced in bulbar-onset patients, especially those with tube feeding only. However, a recent study found no differences between patients with ALS and healthy individuals regarding maximal bite force.[90] Furthermore, it has been reported that the jaw closing muscles maintained normal strength in the presence of tongue and lip weakness in patients with ALS.[69] These discrepancies may be related to the differences in sample size and clinical characteristics of the population studied. De Paul et al. included 10 participants with mildly impaired early ALS, and Gonçalves et al. selected 15 subjects from 70 who were in an early stage of the disease without severe muscle impairment. In contrast, the current study included 150 ALS subjects with a median time from symptom onset to exploration of 30.8 months, of whom 40 had bulbar-onset and 106 had bulbar involvement.

Several authors have reported mouth-opening limitation as the first symptom of ALS.[82, 91] The results of our first study showed limited mouth opening, especially in the bulbar-onset group, in accordance with previous reports.[18, 91] While the maximum mouth opening of healthy people is typically 45-55mm, a recent study reported a restricted mouth opening in ALS patients with a mean distance of 13.7 mm.[92] In our study, ALS patients with tube feeding only had the greatest reduction in mandibular opening. Moreover, in our second study, bulbar patients with balanced UMN and LMN

involvement reported greater difficulties in opening their mouths wide enough to drink from a cup than those in the non-bulbar group. A reduction in mouth opening may hinder oral hygiene and possibly also the efficacy of NIV. Therefore, in order to minimize these complications and before indicating gastric tube feeding, especially in patients with bulbar onset, a physiotherapy program comprising active exercises could be applied to slow down the reduction in mouth opening. This programme could consist of moderate-load and moderate-intensity resistance and stretching exercise programmes to improve mandibular mobility, although further studies are needed to develop specific exercise guidelines.[93, 94] Some authors suggest that mouth-opening exercises are effective for increasing the range of motion of the TMJ and for stretching the masticatory muscles; however, the frequency, load and duration of the exercises must be customized to individual patients.[92] The relationship between the degree of mouth opening and the efficacy of NIV could be the focus of research in a prospective study.

Even though aspects of masticatory function like bite force and jaw mobility were objectively shown to be reduced in bulbar-onset patients, especially in those with tube feeding only, these aspects are also affected when the bulbar region becomes involved during the evolution of the disease, as reported in previous studies.[20, 95, 96, 97] This is evidenced by the fact that the bulbar target damages neurons responsible for controlling facial, masticatory, pharyngeal and laryngeal muscles. Moreover, the greater reduction in maximum bite force and mandibular movement of patients fed entirely via gastrostomy is probably due to the advanced stage of their disease. Additionally, the reduction in bite force and jaw mobility suggests that ALS patients may present an objective reduction in masticatory performance.[98, 99] Accordingly, the results in the second study showed that patients with bulbar involvement perceived more chewing difficulties, particularly those with UMN and LMN impairment, compared to those without bulbar involvement.

It has previously been reported that bulbar-onset patients showed more severe orofacial impairment than the spinal-onset group.[100] In accordance with this idea, the results of our second study demonstrate that bulbar involvement in patients with ALS is

associated with functional limitation of the masticatory system in a large proportion of patients. We determined the functional limitation of the masticatory system using the 8-item Jaw Functional Limitation Scale, since the properties of this organ-specific instrument are ideal for assessing the global functional limitation of the jaw.[101] Interestingly, despite the neurological differences between ALS patients with bulbar UMN or LMN involvement, we found no differences in mastication, jaw mobility or verbal and emotional expression. However, the greatest impairment in the bulbar group was seen in patients with bulbar dysfunction and balanced UMN and LMN diseases, as evidenced primarily by difficulties in chewing soft food and opening the jaw wide, as well as difficulties in chewing tough food, swallowing and talking.

It is known that excessive yawning occurs in a substantial number of patients with ALS, especially in those with bulbar onset.[9, 102] There is a report of a patient with ALS who could not open his jaw fully on command, but could open his mouth fully when yawning.[103] Accordingly, in the second study, although jaw mobility was reduced in balanced bulbar UMN and LMN ALS, yawning was not affected. This may be related to the inhibition of normal control mechanisms of emotions, which would mean that the neurological paths controlling voluntary mandibular opening and yawning are different. However, to date, no physiological significance has been attributed with yawning, and the neural pathways underlying it are not known.[104]

The 153 patients with ALS who participated in the first and second studies represent approximately 30% of all ALS patients diagnosed in Catalonia, which has a population of some 7,500,000 inhabitants.[10, 11] Forty-six per cent were women, median age was 64 years, and the site of onset was bulbar in 26% of cases, spinal in 67%, and respiratory in 7%; only 5% of these patients had a hereditary component. These clinical characteristics reflect the true disease distribution and site of onset in this disease, as shown in other population-based studies with ALS patients.[18, 105, 106, 107, 108] The median time from symptom onset to diagnosis was 16 months and to our examination was 31 months, similar to epidemiological data reported in other studies.[5, 14, 29] Regarding symptoms arising during the course of the disease, the literature stresses that the management of ALS should be focused on a combination of neuroprotective

medication, multidisciplinary clinical care and respiratory support.[109] The medications prescribed to our participants were riluzol (78%), baclofen (26%), amitriptyline (28%), and botulinum toxin (10%). Furthermore, 32% of these patients received NIV, and although 76% had normal eating habits, 11% required supplemental tube feeding and 12% required either probe or oral feeding. Therefore, this sample was highly representative of the population; this is one of the strengths of this thesis.

The results of the first study suggested that approximately 10% of ALS patients are candidates for oral treatment specifically because of their disease, particularly patients with bulbar onset. The majority of our participants reported traumatic lesions in the lips, cheeks, or tongue as their chief complaint, and 35% of bulbar-onset patients reported self-injury due to biting the cheek daily or weekly. This may be the first large study demonstrating such a high rate of oral self-biting injuries, especially in bulbar-onset patients.

The results of our third study suggest that patients with ALS are satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMDs because of the improvement achieved in their chief complaint and the resulting increase in their quality of life. The degree of patient satisfaction with the acrylic resin device and the compliance rate of participants with ALS were similar to those reported in those without ALS but with TMD symptoms.[110] The effectiveness of this treatment is demonstrated by a mean improvement of 61% in the chief complaint, indicating increased quality of life, and by a mean degree of satisfaction with the treatment of 84%. It should be noted that compliance was high and that few side effects or technical complications were detected, none of which were relevant. Therefore, dentists should manage ALS patients with customized oral appliances to prevent self-biting, as reported in several clinical cases suffering other neurological diseases.[111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126]

Among the 19 participants treated in this study, eight were excluded because they did not attend the 3-month evaluation. Of these, four did not attend this evaluation because their disease had worsened, and it is not known whether the acrylic resin

device was effective or not. The fact that patients with ALS may have difficulty travelling from their homes to the clinic, mainly because of the evolution of their disease, may have hindered the monitoring of treatment for longer periods. In any case, the results suggest that patients with ALS should use the acrylic resin device in the first phase of their disease and not wait until their condition deteriorates, at which point compliance may decline. Prompt diagnosis and an appropriate dental approach are indispensable to avoid severe injuries to the oral mucosa.[121]

Although the prevalence of ALS is low and the percentage of patients with ALS who require an oral appliance treatment was only around 10% in our study, this disease is highly disabling and patients appreciate any help that improves their quality of life. The use of an oral appliance permits daily oral care; its maintenance is straightforward, it can be placed and removed easily by the patient or the caregiver, it can be repaired or modified, and treatment can be conducted by a general dentist. Furthermore, using an oral appliance can help the patient avoid the more extreme solution of extraction of all teeth.[119, 124]

In some participants who complained of self-biting in the third study, the increased vertical dimension produced by the oral appliance was sufficient to prevent it because the lips, tongue, or cheeks did not invade the interocclusal space. In others patients, a bumper was needed to separate the lower lip from the teeth because the increased vertical dimension was not sufficient to stop the soft tissues encroaching on the interocclusal region. Before creating the oral appliance, the dentist should explore the placement of the tissues that are traumatised in several mouth opening increments, from the intercuspal position to the resting position, so as to determine the increase required in the vertical dimension and also whether a bumper is needed in the oral appliance.

Symptoms in the orofacial region have been reported to be the first to appear in ALS, and may mimic those that are frequently seen in, and thus mistaken for, TMD.[91, 127] These signs and symptoms may include difficulty in mastication, speech or swallowing due to an impairment in tongue control or a weakness in masticatory muscles, and a

difficulty in mandibular mobility that is not attributable to muscular or articular pain or disc displacement.[9, 23] Importantly, dentists should consider TMD as a potential early form of presentation of ALS, and should carry out an exhaustive examination to establish a differential diagnosis between the two conditions.

Further, as ALS patients report arthralgia in joints with weak musculature, they might also be expected to suffer TMJ arthralgia.[128] A case of recurrent TMJ dislocation has also been reported in a patient with ALS after parotid botulinum toxin injections performed to reduce the production of saliva.[88] However, in our first study no differences in TMD prevalence were detected in ALS patients compared to the control group or to general or geriatric populations.[129, 130] We suppose that, even though some ALS patients did not use their jaw to eat because they were feeding via a gastric tube, they did not report arthralgia in the TMJ probably because they were still using their masticatory muscles for functions besides chewing. Although several authors have suggested the development of jaw quivering or clenching due to spasticity in patients with ALS,[66, 109] in our first study ALS patients did not report clenching or grinding their teeth or suffering cramps more frequently than the control group. The results of our third study suggest that oral appliances are effective for managing symptoms related to TMD. The mechanism of action of splint therapy for the management of TMD remains unclear; there may be multiple effects, including allowing an orthopedically comfortable jaw position, reducing masticatory muscle activity and joint loading, and increasing patients' awareness and ability to reduce bad oral habits.[131, 132, 133, 134, 135] Therefore, oral appliance therapy is a common approach to manage patients with TMD. Consequently, patients with ALS whose chief complaints are clenching/grinding and/or muscular pain can be managed using an acrylic resin occlusal device in the same way as patients who do not have ALS but present TMD symptoms.

The problem most commonly encountered during oral appliance treatment is the difficulty in making impressions due to the evolution of their disease. A poor impression can compromise the quality of the cast and therefore the acrylic resin device. Only one impression of one arch without the antagonist and/or the anterior region of this arch can be made in patients who cannot be fed orally and when the

dental occlusion has lost its normal function.[115] Intraoral scanning may be an alternative to traditional impression procedures in patients who are not able to keep their mouth open sufficiently while the impression material is setting.[136] Another option is a removable lip-bumper made at the chairside without making an impression.[111] Custom mouthguards have been proposed as options for the treatment of self-inflicted oral trauma.[113, 114, 116, 117, 118, 122, 125, 126] Other authors reported a self-modeled mouthguard to protect against cheek biting in a patient under orthodontic treatment,[121] although this mouthguard is worn on the maxillary arch and may be inconvenient. However, the dentist must check the parameters of each patient in order to apply the most suitable technique for their clinical conditions.

With regard to side effects of the use of the oral appliance at the 3-month check-up, the results of the third study showed few differences with respect to those reported in other studies of oral appliances.[110, 137, 138] The most frequently reported side effect was excessive salivation, affecting 64% of the participants. However, excessive salivation may exacerbate the problem of drooling, which is already common in ALS: it can be treated with amitriptyline, oral or transdermal hyoscine, or sublingual atropine drops.[63] Few technical complications were associated with the oral appliance. Of the participants who attended the 3-month evaluation, five needed at least one extra visit due of technical complications, three of them for adjustment and two for loosening. Only one oral appliance needed to be repaired at a dental laboratory due to the lack of retention.

This thesis presents a number of limitations. The first is the small sample size of the control group and the method of recruitment in the first two studies; however, although most of the control group came from the families of the patients and were slightly younger, the range of mandibular motion and the prevalence of TMD were consistent with data from the general population and from elderly subjects reported in other studies.[129, 130] A second limitation was the lack of any attempt to correlate masticatory system measures with ALS functional rating scale scores. The third study had also a number of limitations. First, no control group was used, and caution should be exercised before assuming a cause-and-effect relationship between the

improvement of the chief complaint and the use of an oral appliance. The present findings encourage further studies with appropriate controls to demonstrate the effectiveness of the oral appliance in patients with ALS. Finally, the initial sample size and the high proportion of dropouts may restrict the validity of these results.

Despite these limitations, the results of this thesis support a multidisciplinary approach to the management of ALS patients. Dentists should be an integral part of the management team to help treat the negative effects of ALS on the stomatognathic system.[84, 100] Dental professionals are not habitually included in teams for monitoring orofacial functions and oral health of patients with ALS, which probably explains the scarcity of the information available in the literature on the different aspects of orofacial dysfunction and oral health maintenance care in these patients. Since most dental professionals are unfamiliar with ALS, patients with this condition may not be given treatment at numerous dental offices. This situation draws attention to the need for more professional education and more attention to medically compromised dental patients.[139] Recommendations for dental care in patients with ALS also include regular oral maintenance care to maintain oral health and to avoid dental disease, as well as counselling with regard to dietary modifications.[83] Moreover, dentists may also be able to train ALS patients to avoid traumatic lesions in the lips, cheeks or tongue due to self-biting.

CONCLUSIONS

6. CONCLUSIONS

The following conclusions were drawn from the studies that make up this thesis:

1. Patients with ALS showed reductions in both bite force and finger-thumb grip force. The reduction was twice as large for the finger force.
2. The maximum range of mandibular movement (mouth opening, protrusion, and laterotrusion) was reduced in ALS patients, especially in bulbar-onset phenotypes.
3. The prevalence of TMD in ALS patients was similar to that in the control subjects and in general population studies.
4. ALS patients had more traumatic mucosal injury than controls, especially in the tongue and cheek.
5. Bulbar involvement in patients with ALS is associated with functional limitation of the masticatory system.
6. Balanced bulbar UMN and LMN involvement is associated with the worst impairments, affecting soft food chewing and the ability to open the jaw wide.
7. Patients with ALS were highly satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMD; it improved their chief complaint and thus increased their quality of life.
8. Compliance with the use of an oral appliance was high, and few side effects and technical failures were observed.
9. The dentist should be an integral part of the multidisciplinary team in order to improve the comfort of ALS patients.


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APPENDIX

STUDY I

Alterations in the masticatory system in patients with Amyotrophic Lateral Sclerosis

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ORIGINAL PUBLICATION

Alterations in the Masticatory System in Patients with Amyotrophic Lateral Sclerosis

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Aims: To determine the effect of amyotrophic lateral sclerosis (ALS) on aspects of masticatory function and to assess the relationship between ALS and the prevalence of traumatic mucosal lesions caused by oral self-injury. **Methods:** A total of 153 ALS patients and 23 control subjects participated in this cross-sectional study. Clinical characteristics including site of onset, medication, type of feeding, and use of noninvasive mechanical ventilation were recorded. The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) protocol and a specific questionnaire to assess aspects of masticatory dysfunction and frequency of self-injury of the oral mucosa were applied to all participants. Maximum mandibular range of motion, maximum bite force, and maximum finger-thumb grip force were determined and tested with Mann Whitney, Kruskal-Wallis, or chi-square tests. $P < .05$ was considered significant. **Results:** Maximum unassisted and assisted mouth opening, protrusion, left laterotrusion, and finger-thumb grip force were significantly reduced in both spinal- (n = 102) and bulbar-onset (n = 40) patients compared to the control group; however, bite force was reduced only in bulbar-onset patients. ALS patients with tube feeding (n = 16) had the greatest reduction in maximum bite force and mandibular opening. There was no relationship between TMD and ALS. Oral self-injury due to biting was more frequent in the ALS group (29.9%) than in the control group (8.7%) and in the bulbar-onset group (55.0%) compared to the spinal- (20.8%) and respiratory-onset (18.2%) groups. Of the ALS patients in the study, 10% sought dental treatment related to the condition. **Conclusion:** The ALS patients in this study had a reduction in finger-thumb grip force that was twice as great as the reduction in bite force. The maximum range of mandibular movement was also reduced, especially in bulbar-onset patients. ALS patients did not have a higher prevalence of TMD but did have more traumatic mucosal injury than controls. The dentist should be an integral part of the multidisciplinary team to manage ALS patients.
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Keywords: *amyotrophic lateral sclerosis, craniomandibular disorders, mandibular range of motion, occlusal force, self-biting*

Amyotrophic lateral sclerosis (ALS) is a heterogenous, multisystem, progressive neurodegenerative disease that affects the lower and upper motor neurons in the spinal cord, brainstem, and brain, causing muscle atrophy, muscle weakness, and spasticity.[1] Risk factors associated with ALS are older age, male sex, and family history.[2] Its incidence rates in Catalonia and Europe are approximately 1.4 and 2.1 per 100,000 people a year, respectively,[3,4] and survival rates vary from months to several years, with median survival time from onset ranging from 24 months in northern Europe to 48 months in central Asia.[5]

The typical clinical characteristics of ALS are variable and depend on whether the site of onset is spinal, bulbar, or respiratory. Most patients with ALS have a spinal onset, causing referred weakness and muscle atrophy, fasciculations (reflecting involvement of lower motor neurons), and hyperreflexia and hypertonia (reflecting involvement of upper motor neurons). Weakness starts in bulbar muscles in about 20% of patients, with dysarthria, dysphagia, and tongue fasciculations. Bulbar-onset ALS has a poorer prognosis due to swallowing difficulties, weight loss, aspiration, and respiratory involvement, with poorer

Table 1 Characteristics of Patients with Amyotrophic Lateral Sclerosis (ALS)

Characteristics	Total (n = 153)	ALS onset			*P* value between each onset subgroup*
		Bulbar (n = 40)	Spinal (n = 102)	Respiratory (n = 11)	
Sex (% male)	53.6	42.5	54.9	81.8	.06
Median age (y)	64.2	66.1	61.8	70.7	.001
Familiar (%)	5.2	10	3.9	0	.247
Median time elapsed since symptom onset (mo)	30.8	21.6	35.4	32.3	.001
Median time elapsed since ALS diagnosis (mo)	16.1	9.1	20.9	11.6	.003
Riluzol (%)	77.8	77.5	77.5	81.8	.946
Baclofen (%)	25.5	17.5	31.4	0	.031
Amitriptyline (%)	28.1	57.5	18.6	9.1	< .001
Botulinum toxin (%)	9.8	25	4.9	0	.001
Noninvasive ventilation (%)	32	25	27.5	100	< .001
Oral feeding (%)	89.5	72.5	95.1	100	< .001
Tube feeding (%)	22.9	45	14.7	18.2	.001

*Chi-square test or Kruskal-Wallis test were used for statistical analyses.

adaptation to noninvasive ventilation. About 3% to 5% of ALS patients have a respiratory onset, reporting orthopnea or dyspnea and mild or even no spinal or bulbar signs. Up to 10% of patients with ALS have an affected relative and are thus considered to have familial ALS.[6]

The role of the dentist in ALS disease is not yet well defined. For example, one patient with ALS was misdiagnosed as having a temporomandibular disorder (TMD) because she reported a decreased mouth-opening range and pain on palpation of the temporalis muscles.[7] In another clinical case, masseter muscle spasticity was also described as a first symptom of ALS.[8] Recurrent jaw dislocation following botulinum toxin treatment for sialorrhea has also been reported.[9] Several treatments have been described to improve dysarthria in ALS patients, including palatal lift and palatal augmentation prostheses,[10,11] and a special oral appliance has been devised to decrease drooling in a patient with a Class II malocclusion.[12] In another study, dental treatment with total intravenous (IV) anesthesia in an ALS patient was successful, although the patient had a severe gag reflex and an impaired airway protection reflex.[13] Although oral health status was not affected by ALS in a cohort of 37 Australian patients,[14] the study concluded that the dental profession should be a part of the multidisciplinary team for the management of ALS patients. These patients' oral health could be maintained during the disease period with minimal clinical intervention.[15]

Masticatory function includes a number of features, such as bite force, mandibular mobility, and masticatory performance.[16,17] To the best of the authors' knowledge, no clinical study with a large sample has been performed to assess alterations in the masticatory system in patients with ALS. Information on this topic would help in the preparation of guidelines for dentists regarding the management of ALS patients and may contribute to improving patients' comfort.

The main aim of the present cross-sectional controlled study was to determine the effect of ALS on aspects of masticatory function, including mandibular range of motion, bite force, and prevalence of TMD. The study also aimed to assess the relationship between ALS and the prevalence of traumatic mucosal lesions caused by oral self-injury. Additionally, potential differences between bulbar- and spinal-onset patients were explored. The working hypothesis was that patients affected by ALS would have lower bite force, a reduced mandibular range of motion, a higher prevalence of TMD, and a higher incidence of traumatic mucosal ulcers due to self-injury than healthy subjects.

Materials and Methods

Participants

Between April 2015 and September 2016, patients diagnosed with ALS according to the revised El Escorial diagnostic criteria[18] and attending the Motor Neuron Disease Unit of the Bellvitge University Hospital were invited to participate in this cross-sectional study. Patients who could not be evaluated because of their clinical condition were excluded. The control group included 23 participants recruited from families or caregivers of ALS patients and other age- and gender-matched subjects. The nature of the study was explained in full to all the participants, and all signed an informed consent form approved by Bellvitge University Hospital Ethics Committee (Code PR260/15). All experiments were carried out in accordance with the principles of the Helsinki Declaration.

ALS-Related Characteristics

Patients were routinely evaluated by the ALS unit neurology team. Chronologic variables registered were date of onset, time to diagnosis, and time to evaluation. Demographics on sex, age, and family

history were also registered, and a phenotypic classification was performed according to the site of onset (bulbar, spinal, or respiratory). Medication, use of mechanical ventilation, and gastrostomy were also registered (Table 1).

Assessment of TMD

All participants were examined and interviewed by the same trained dental clinician and answered the symptoms questionnaire of the Diagnostic Criteria for TMD (DC/TMD) protocol.[19] The clinical examination included the measurement of maximum opening, protrusion, and laterotrusion; palpation and auscultation of the temporomandibular joints (TMJs); and palpation of the masticatory muscles.[19–21] Following the DC/TMD algorithms, all subjects were defined as non-TMD or assigned to one of the four subgroups (myalgia, arthralgia, TMD-related headache, or disc displacement). Multiple diagnoses were possible.

Questionnaire

Participants were also assessed by means of a questionnaire about awareness of clenching/grinding, jaw blocking, and presence of cramps in the masticatory muscles (with dichotomous no/yes answers for all three questions). Self-injury to the tongue, lips, or cheeks was also assessed and rated on a 5-point Likert scale (never, yearly, monthly, weekly, or daily) and was considered clinically relevant if the participant answered either weekly or daily. Finally, the information from this questionnaire was used to determine whether participants might be candidates for receiving oral treatment to manage these oral-related problems (no/yes).

Clinical Examination

Overbite was measured according to the DC/TMD protocol.[19] Briefly, a horizontal pencil mark was placed on the buccal surface of the right mandibular central incisor in relation to the maxillary antagonist incisor while the posterior teeth were in the maximum intercuspal position.[22] To measure both maximum unassisted and maximum active mouth opening, the interincisal distance between the maxillary and mandibular reference teeth (the same as the ones used to measure the overbite) was measured after asking the participants to open as wide as they could, even if it was painful. To measure the maximum assisted or maximum passive mouth opening, participants were asked to open as wide as they could, and the operator pushed the mouth open further using moderate pressure. Afterwards, the interincisal distance between the maxillary and mandibular reference teeth (the same as the ones used to measure the overbite) was measured. Right and left laterotrusion were measured by taking into account the midline discrepancy, and protrusion was assessed by adding the overjet to correct the amount of movement.[21]

Bite and Grip Force Measurements

A bite-force transducer (gnathodynamometer) calibrated with loads from 0 to 1,200 N was used to measure unilateral maximum bite force between the second premolars or the first molars on both sides.[23,24] Bite force was measured three times with the order changed for each side, and the highest value was selected for analysis. The finger-thumb grip force of each hand was measured in a similar manner using the bite-force transducer.[25]

Statistical Analyses

The normal distribution fit of the data was tested by means of the Kolmogorov-Smirnov test. Comparisons between patient and control groups were performed using Mann-Whitney *U* test or chi-square test, as appropriate. Comparisons between bulbar-, spinal-, and respiratory-onset groups and the control group were performed using Kruskal-Wallis H test and chi-square test, as appropriate. Spearman rank correlation coefficients were calculated in order to evaluate the bivariate correlations between quantitative parameters. Statistical analysis was performed using the SPSS program (IBM SPSS Statistics, version 23.0.0.2), and $P < .05$ was considered significant.

Results

This study included 153 patients (median age 64 years; 46% women) and 23 controls (median age 52 years; 56% women). Among the patients with ALS, onset was bulbar in 26%, spinal in 67%, and respiratory in 7% (Table 1). Only 5.2% of these patients had a hereditary component. The median time from symptom onset to exploration was 30.8 months, and the median time since diagnosis was 16.1 months. The medications prescribed were riluzol (77.8%), baclofen (25.5%), amitriptyline (28.1%), and botulinum toxin (9.8%). Almost a third (32%) of the ALS patients received noninvasive ventilation, while 11% needed supplemental tube feeding, 77% had normal eating habits, and 12% had either probe or oral feeding.

Participants' perceptions of alterations in the masticatory system are shown in Table 2. Although ALS patients did not report clenching or grinding their teeth or suffering cramps more frequently than controls, they reported more limitations in mouth movement and more sialorrhea, especially those with bulbar onset ($P < .001$; chi-square). Oral self-injury due to biting was reported more frequently in the ALS group than in the control group ($P < .001$; chi-square) and by those with bulbar onset more than those with spinal

Table 2 Comparison Between ALS Patients and Control Group of Participants' Perceptions of Alterations in the Masticatory System

		ALS onset					
	Total (n = 153)	Bulbar (n = 40)	Spinal (n = 102)	Respiratory (n = 11)	Control group (n = 23)	*P* value: Patient vs control group*	*P* value: Control vs each onset subgroup*
Grinding or clenching (%)	51.0	60.0	51.0	18.2	65.2	.2	.053
Cramps (%)	2.7	2.7	3.0	0	0	.44	.8
Limitations in mouth movement (%)	37.3	70.0	28.4	0	0	< .001	< .001
Sialorrhea (%)	44.4	85.0	31.0	18.2	4.3	< .001	< .001
Total self-injury/oral lesions (%)	29.9	55.0	20.8	18.2	8.7	.03	< .001
Self-injury tongue (%)	13.6	27.5	7.3	18.2	0	.06	.002
Self-injury lip (%)	12.2	15.0	11.5	9.1	4.3	.26	.63
Self-injury cheek (%)	17.0	35.0	11.5	0	4.3	.12	.001
Seeking oral treatment (%)	9.8	20.0	6.9	0	0	.12	.016

*Chi-square test used for statistical analyses.

Table 3 Comparison Between ALS Patients and Control Group of Temporomandibular Disorder (TMD) Diagnoses, Mandibular Movements, and Muscular Force

		ALS onset					
	Total (n = 153)	Bulbar (n = 40)	Spinal (n = 102)	Respiratory (n = 11)	Control group (n = 23)	*P* value: Patient vs control group	*P* value: Control vs each onset subgroup*
TMD							
Myalgia (%)	9.2	10.0	8.8	9.1	17.4	.22	.68
Arthralgia (%)	5.9	7.5	5.9	0	0	.23	.49
TMD-related headache (%)	0.7	0	1.0	0	4.3	.12	.44
Disc displacement (%)	25.5	17.5	30.4	9.1	39.1	.17	.12
Mandibular movement							
Median maximum unassisted opening (mm)	44.0	42.5	46.0	43.0	50.0	.001	< .001
Median maximum assisted opening (mm)	46.5	44.5	48.0	46.0	53.0	< .001	< .001
Median difference between assisted and unassisted maximum opening (mm)	2.0	2.5	2.0	2.0	2.0	.59	.23
Limited mouth opening (%)	20.3	40	14.7	0	4.3	.07	< .001
Median maximum right laterotrusion (mm)	6.0	5.0	6.0	8.0	8.0	.02	.005
Median maximum left laterotrusion (mm)	6.0	5.5	6.0	6.0	8.0	< .001	< .001
Median maximum protrusion (mm)	6.0	4.0	7.0	6.0	8.0	.001	< .001
Muscular force							
Median maximum bite force (N)	237	198	256	274	346	< .001	< .001
Median finger-thumb grip force (N)	22.6	41.2	16.7	22.6	75.5	< .001	< .001

*Chi-square test or Kruskal-Wallis test used for statistical analyses.

or respiratory onset ($P < .05$; chi-square). The most frequently injured sites were the tongue and cheeks, and 35% of bulbar-onset patients reported self-injury due to biting the cheek daily or weekly. Ten percent of ALS patients were candidates for oral treatment related to their ALS. Among the patients with bulbar onset, 20% sought oral treatment, compared with only 6.9% of spinal-onset patients ($P = .02$, chi-square).

The proportions of participants with TMD according to DC/TMD subgroup are shown in Table 3. There was no relationship between the diagnosis of any TMD group and ALS ($P > .05$, chi-square), nor between arthralgia and feeding via gastric tube ($P > .05$, chi-square). Maximum unassisted and assisted mouth opening, protrusion, and left laterotrusion were significantly reduced in the spinal-onset group compared to the control group ($P < .05$, Mann-Whitney) and also in the bulbar-onset group compared to the spinal-onset group ($P < .05$, Mann Whitney). In the bulbar-onset group, 40% had limited unassisted mouth opening (ie, < 40 mm), and both finger-thumb grip and bite force were significantly reduced in bulbar-onset patients compared to the control group ($P < .001$, Mann Whitney). In spinal-onset patients, only finger-thumb grip force was significantly reduced compared to the bulbar-onset group ($P < .05$, Mann Whitney); however, whereas the scores of bulbar-onset patients for finger-thumb grip and bite forces were nearly 50% of those recorded by control subjects, the scores of spinal-onset patients were 22% (finger force) and 74% (bite force) with respect to normal control scores.

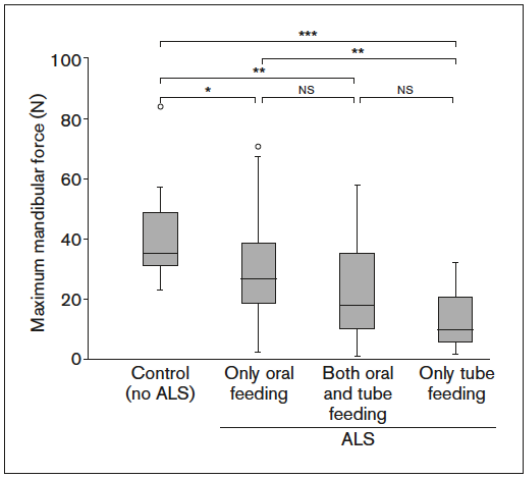

Fig 1 Box plot of maximum bite force comparison between feeding groups. NS = not significant. *$P \leq .05$. **$P \leq .01$. ***$P \leq .001$. Kruskal-Wallis test and pairwise comparisons were used for statistical analyses.

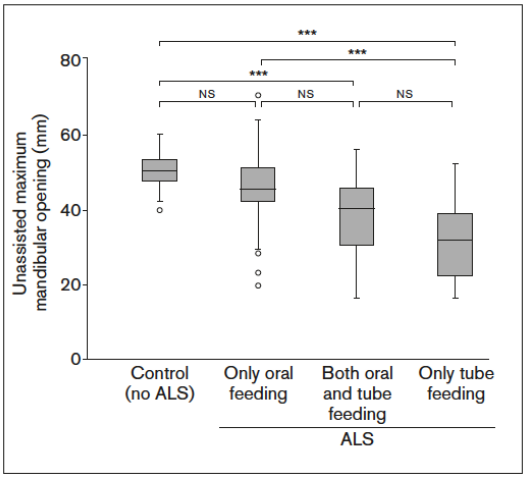

Fig 2 Box plot of maximum unassisted mouth opening comparison between feeding groups. NS = not significant. ***$P \leq .001$. Kruskal-Wallis test and pairwise comparisons were used for statistical analyses.

Table 4 Spearman Correlation Coefficients Between Variables Related to Maximum Range of Mandibular Movement or Maximum Muscular Force

	unAMO	AMO	RL	LL	Protrusion	Bite force	Finger force
Unassisted mouth opening	1						
Assisted mouth opening	.966**	1					
Right laterotrusion	.278**	.293**	1				
Left laterotrusion	.400**	.431**	.544**	1			
Protrusion	.462**	.466**	.443**	.488**	1		
Bite force	.217**	.218**	.309**	.244**	.362**	1	
Finger-thumb grip force	.260**	.273**	.066	.074	.086	.079	1

**Correlation significant at $P < .01$ level (2-tailed test). unAMO = unassisted mouth opening; AMO = assisted mouth opening; RL = right laterotrusion; LL = left laterotrusion.

Comparisons between type of feeding for ALS patients and control subjects for mandibular force and mouth opening, respectively, are shown in Figs 1 and 2. ALS patients with gastrostomy had a significant reduction in maximum bite force and in mandibular opening compared to control subjects. ALS patients with tube feeding only (n = 16) had the greatest reduction in maximum bite force and mandibular opening.

The Spearman correlation coefficients between variables related to mandibular movement or muscular force are shown in Table 4. All variables related to mandibular movement and bite force were significantly correlated with each other ($P < .01$, Spearman correlation). Although maximum finger-thumb grip force was correlated with maximum mouth opening, it was not correlated with bite force.

Discussion

The results of the present study suggest that approximately 10% of ALS patients are candidates for oral treatment specifically because of their disease. The chief complaint of the majority of these patients was traumatic lesions in the lips, cheeks, or tongue due to self-biting. To the authors' knowledge, this is the first large study demonstrating such a high rate of oral self-biting injuries, especially in bulbar-onset patients. Customized oral appliances or acrylic splints and mouthguards have been used in other cases of oral self-injury[26]; however, prospective studies are needed to assess the efficacy, side effects, and technical complications of an oral appliance for managing alterations in the masticatory system in ALS patients. This study supports a multidisciplinary approach to

the management of ALS patients, and the dentist should be an integral part of the management team to help treat the negative effects of ALS on the stomatognathic system.[14,15]

Maximum mandibular movement and bite force were both significantly reduced in ALS patients regardless of type of onset, and both aspects of masticatory function were significantly correlated. Moreover, the greatest reduction was observed in bulbar-onset ALS patients, especially those with tube feeding only. Whereas the relative amount of muscular force reduction in bulbar-onset patients was similar for finger-thumb grip and bite force, in spinal-onset patients, the relative reduction was three times higher for finger force than for bite force. This result is expected due to the limb muscle weakness that characterizes this type of patient. A reduction in mouth opening may hinder oral hygiene and also perhaps the efficacy of noninvasive ventilation. Therefore, in order to minimize these complications and before indicating gastric tube feeding, especially in bulbar-onset patients, a physiotherapy program comprising active exercises could be applied to slow down the reduction in mouth opening. The relationship between mouth opening and efficacy of noninvasive ventilation could be the focus of new research in a prospective study.

No differences in TMD prevalence were detected in ALS patients compared to the control group or compared to general or geriatric populations.[27,28] As ALS patients report arthralgia in joints with weak musculature,[29] they might also be expected to suffer TMJ arthralgia. Some ALS patients did not use the jaw to eat because they were feeding via a gastric tube; however, these patients did not report arthralgia in the TMJ probably because they still used masticatory muscles for functions besides chewing, such as clenching.

The 153 ALS patients who participated in the present study represent approximately 30% of all ALS patients diagnosed in Catalonia, which has a population of some 7,500,000 inhabitants.[3] The clinical characteristics of this patient group were consistent with the results of other studies, such as the distribution of ALS site of onset,[30] the percentage of the hereditary component,[31] the male/female ratio (regardless of the site of onset), the differentiation between bulbar and spinal onset,[5,32] and the time elapsed since the first symptom or the time since diagnosis.[33] Therefore, this sample was highly representative of the population, which is one of the strengths of the present study. The small sample size of the control group and the method of recruitment are considered study limitations; however, although most of the control group came from the families of the patients and were slightly younger, the range of mandibular motion and the prevalence of TMD in the control group were consistent with data from the general population and from elderly subjects reported in other studies.[27,28] Another limitation was the lack of attempt to correlate masticatory system measures with ALS functional rating scale scores.

Conclusions

The ALS patients in the present study showed reductions in both bite force and finger-thumb grip force. The reduction was twice as large for the finger force than for the bite force. The maximum range of mandibular movement (mouth opening, protrusion, and laterotrusion) was also reduced in the ALS patients, especially in bulbar-onset phenotypes. The prevalence of TMD in the ALS patients was similar to that in the control subjects and consistent with that in general population studies. The ALS patients had more traumatic mucosal injury than controls, especially in the tongue and cheek. The dentist should be an integral part of the multidisciplinary team in order to improve the comfort of ALS patients.

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STUDY II

Functional limitation of the masticatory system in patients with bulbar involvement in amyotrophic lateral sclerosis

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ORIGINAL ARTICLE

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Functional limitation of the masticatory system in patients with bulbar involvement in amyotrophic lateral sclerosis

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Summary

Amyotrophic lateral sclerosis (ALS) with bulbar dysfunction affects the motor neurons responsible for controlling the muscles in the jaw, face, soft palate, pharynx, larynx and tongue. This cross-sectional study aimed to determine the functional limitation of the jaw in patients with ALS and bulbar dysfunction who had upper motor neuron (UMN), lower motor neuron (LMN) or balanced involvement. One hundred and fifty-three patients with ALS and 23 controls were included. All participants answered using the 8-item Jaw Functional Limitation Scale (JFLS-8). Patients with ALS were grouped by neurologic examination as follows: non-bulbar ALS, bulbar UMN-predominant ALS; bulbar LMN-predominant ALS; and bulbar balanced (UMN + LMN) ALS. Jaw limitation between the different groups was compared using the Kruskal-Wallis test. Patients with non-bulbar ALS had similar mandibular limitations to healthy participants. Only patients with balanced UMN and LMN bulbar manifestations reported greater difficulties in chewing soft food or in jaw mobility compared to the non-bulbar ALS group. Patients with bulbar involvement also had greater difficulties in chewing tough food or chicken and in swallowing and talking compared to the non-bulbar group, regardless of whether UMN or LMN predominant. No significant differences were found between the groups in smiling and yawning difficulties. Bulbar involvement in patients with ALS is associated with functional limitation of the masticatory system. However, balanced bulbar UMN and LMN involvement is associated with the worst impairments in chewing soft food and in opening the jaw widely.

KEYWORDS
amyotrophic lateral sclerosis, bulbar involvement, jaw functional limitation, JFLS-8

1 | INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease characterised by progressive degeneration of motor neurons in the brain, brainstem and spinal cord. Affected individuals show significant variation in the locus of disease onset, presentation at diagnosis and rate of progression.[1] Incidence rates for ALS are approximately 1.4 and 2.1 per 100 000 person/year in Catalonia and Europe, respectively.[2,3] Sufferers develop progressive wasting and weakness of limb, bulbar and respiratory muscles and die on average within 3 years from symptom onset, usually from respiratory failure; however, roughly 10% of patients with ALS survive for ten or more years.[4] The mean age of onset for sporadic ALS ranges from 55 to 65 years, with a median age of onset of 64 years.[5] The diagnosis of ALS is based on the El Escorial and Airlie House Diagnostic Criteria.[6]

Approximately two-thirds of patients with a typical ALS disease pattern develop initial symptoms in the upper or lower extremities (limb or spinal onset), most commonly in distal muscles. The other third of patients have bulbar onset, usually starting with dysarthria,

but almost all demonstrate bulbar involvement at later stages. About 5% of patients present with respiratory weakness without significant limb or bulbar symptoms.[7,8] In patients with bulbar dysfunction, upper motor neuron (UMN) involvement causes supranuclear symptoms that are also commonly referred to as pseudobulbar palsy. The clinical characteristics of pseudobulbar palsy are spasticity and hyperreflexia of the bulbar muscles (ie jaw, face, soft palate, pharynx, larynx and tongue), emotional lability (pathological laughing and crying) and a brisk jaw jerk. Degeneration of lower motor neuron (LMN), with involvement of the cranial nerve nuclei in the medulla oblongata and pons that innervate the bulbar muscles, results in a bulbar palsy with flaccid paresis, muscular atrophy and fasciculations and/or tongue fibrillations.[7,9]

Oro-facial function is an important contributor to an individual's general health and quality of life. The masticatory system is responsible for complex biopsychosocial functions, where basic functions such as chewing, swallowing, eating and yawning manifest simultaneously with emotional functions such as smiling, laughing, screaming and kissing. Functional limitation and disability can be measured with generic, disease-specific or organ-specific instruments. The 20-item Jaw Functional Limitation Scale (JFLS-20) is a reliable and valid organ-specific instrument for measuring limitations in mastication, jaw mobility and verbal and emotional expressions, together with a global functional limitation score. Global limitation can also be determined with a short version, the JFLS-8. These scales have three subscales that cover mastication, vertical jaw mobility and emotional and verbal expressions. The properties of the JFLS-8 scales are ideal for both research and patient evaluation when assessing global functional limitation of the jaw.[10]

Masticatory function includes phenomena such as bite force, mandibular mobility and masticatory performance[11-13] and has been studied by assessing these phenomena in other neurological diseases.[14-19] However, to the authors' knowledge, functional limitation of the masticatory system has not been assessed in a large sample of patients with ALS. The main objective of this study was to determine the effect of bulbar involvement on functional limitation of the masticatory system in patients with ALS. This study also aimed to compare the functional limitation of the masticatory system between patients with ALS and a pseudobulbar palsy (UMN involvement) and patients with ALS and a bulbar palsy (LMN involvement). The working hypothesis was that bulbar involvement would cause functional limitation of the masticatory system in patients with ALS.

2 | MATERIALS AND METHODS

2.1 | Participants

In this cross-sectional study, 153 patients diagnosed with ALS according to the revised El Escorial and Airlie House Diagnostic Criteria at the Motor Neuron Disease Unit of the Bellvitge University Hospital were selected. A control group was included that comprised 23 participants recruited from the families or caregivers of patients with ALS and other age- and gender-matched people. All subjects participated in a previous investigation.[20] Patients were excluded if they could not be evaluated because of their clinical condition or sensory deficits. All participants were fully informed and signed an informed consent form approved by Bellvitge University Hospital Ethics Committee (Code PR260/15), and all experiments were carried out in accordance with the principles of the Helsinki Declaration.

2.2 | ALS-related characteristics

Bulbar dysfunction involvement was determined as UMN, LMN or balanced (UMN + LMN) based on neurologic examination by a neurologist, using upper motor signs (ie brisk jaw jerk, tongue spasticity and spastic dysarthria) and lower motor signs (ie tongue wasting, tongue fasciculations and flaccid dysarthria).[21]

2.3 | Functional jaw limitations scale

Functional limitation of the masticatory system was assessed using the JFLS-8.[10] This scale evaluates 8 items: (1) chew tough food, (2) chew chicken (eg prepared in oven), (3) eat soft food requiring no chewing (eg mashed potatoes, apple sauce, pudding, pureed food), (4) open wide enough to drink from a cup, (5) swallow, (6) yawn, (7) talk and (8) smile. The participants rated the level of limitation for each item during last month using a 0-10 numerical rating scale, with 0 corresponding to "no limitation" and 10 corresponding to "maximal limitation." The examiner interviewed each participant orally asking all JFLS items. The patient's caregiver helped answering in case the patient had some difficulties. Questionnaires were filled when the patients were attended by the ALS unit multidisciplinary team for a check-up. The median time elapsed between the first symptom onset and the questionnaire was 31 months, and the median time elapsed between the diagnostic and the questionnaire was 16 months (Table 1).

2.4 | Data analysis

Participants were distributed into 1 of the 5 groups. The control group included 23 healthy participants, and the 153 patients with ALS were grouped as those with non-bulbar ALS, bulbar UMN-predominant ALS, bulbar LMN-predominant ALS and bulbar balanced ALS (with both UMN and LMN) groups. Items from the same subscale of the JFLS-8 with similar results were averaged, such as the chew tough food and chew chicken items, the swallow and talk items, or the yawn and smile items. The degree of jaw limitation for each subscale and for the eight items was compared between the different groups using the Kruskal-Wallis test with adjustment for pairwise comparisons. All analyses were performed in IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA), and P-values ≤.05 were considered statistically significant.

3 | RESULTS

3.1 | Participants

This study included 153 patients with ALS (mean age 62 years, SD 12 years; 46% women) and 23 controls (mean age 51 years, SD 12 years; 56% women). Patients with ALS were assigned to one of the four groups according to bulbar involvement, and their characteristics are summarised in Table 1. In total, 10% of patients with ALS received parotid botulin toxin injections, 32% required non-invasive ventilation, and although 76% had normal eating habits, 11% required supplemental tube feeding and 12% required either probe or oral feeding.

3.2 | Comparison of the bulbar and non-bulbar groups

Two of the three mastication subscale items of the JFLS-8, chew tough food and chew chicken, were averaged because the results were similar. Although patients in the non-bulbar ALS group were similar to controls on the chewing measures, patients in the bulbar ALS groups had greater difficulties in chewing tough food or chicken compared to those in the non-bulbar group, regardless of the motor neuron affected (Figure 1). However, only patients in the balanced bulbar ALS group reported greater difficulties in chewing soft food compared with the non-bulbar ALS group (Figure 2). Patients in the balanced bulbar ALS group reported greater difficulties in opening their mouths wide enough to drink from a cup compared to those in the non-bulbar group (Figure 3).

Although patients in the non-bulbar ALS group had no significant differences in swallow and talk difficulties compared with the control group, patients in the ALS groups with bulbar involvement had greater swallow and talk difficulties compared with the non-bulbar group regardless of the motor neuron affected (Figure 4). However, there were no significant differences in smiling and yawning difficulties between any of the groups (Figure 5).

Considering all items of the three subscales, patients without bulbar involvement in ALS had similarly low functional jaw difficulties compared to healthy participants. By contrast, patients with bulbar involvement in ALS had greater functional jaw difficulties compared to those without bulbar involvement, regardless of the motor neuron affected (Figure 6).

TABLE 1 Characteristics of healthy and patients with amyotrophic lateral sclerosis

Characteristics	Healthy (n = 23)	ALS Patients (n = 157)				
		No Bulbar affectation (n = 47)	Bulbar UMN-predominant (n = 28)	Bulbar LMN-predominant (n = 18)	Balanced bulbar UMN and LMN (n = 60)	*P*-value between each subgroup[a]
Sex (% of Male)	44	64	36	56	53	NS
Mean age (years)	51	62	62	69	60	<.0005
Median time elapsed since symptom onset (months)		35.4	35.0	33.2	24.4	.015
Median time elapsed since ALS diagnosis (months)		18.8	19	12.5	13.3	.554
Botulinum toxin (%)		2.1	3.6	16.7	16.9	.034
Non-invasive ventilation (%)		36.2	25	55.6	25	.074
Oral feeding (%)		100	92.9	83.3	81.7	.015
Use of tube feeding (%)		6.4	14.3	50	31.7	<.0005

[a]Chi-squared test or Kruskal-Wallis test.

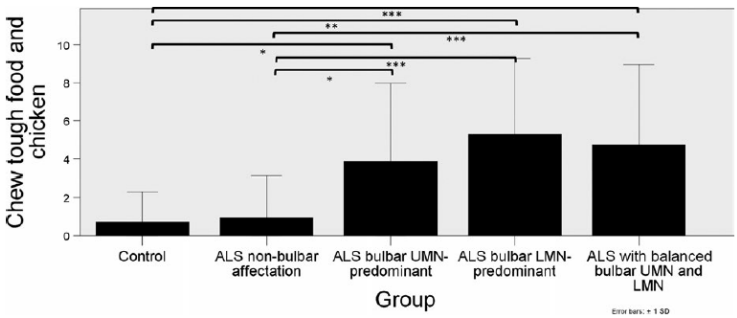

FIGURE 1 Means and standard deviation of limitation score of chewing tough food and chicken. *$P \leq .05$; **$P \leq .01$; ***$P \leq .001$ Kruskal-Wallis test and pairwise comparisons of different groups

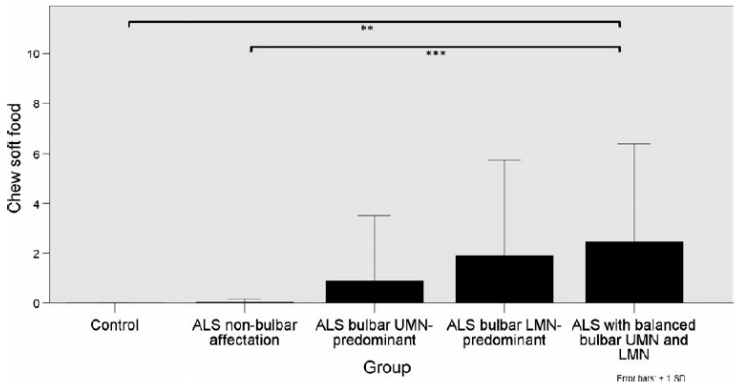

FIGURE 2 Means and standard deviation of limitation score of chewing soft food. **$P \leq .01$; ***$P \leq .001$ Kruskal-Wallis test and pairwise comparisons of different groups

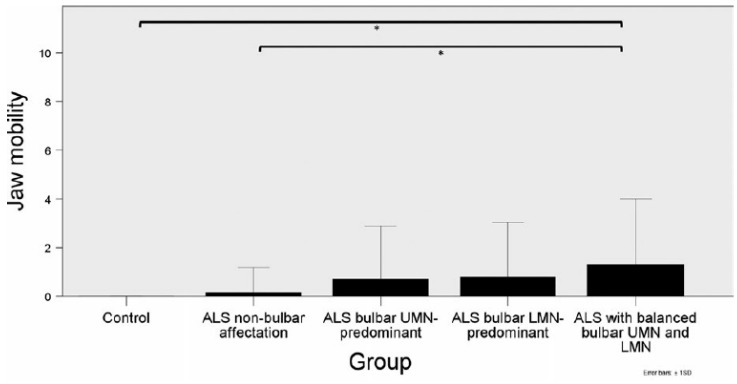

FIGURE 3 Means and standard deviation of limitation score of jaw mobility. *$P \leq .05$ Kruskal-Wallis test and pairwise comparisons of different groups

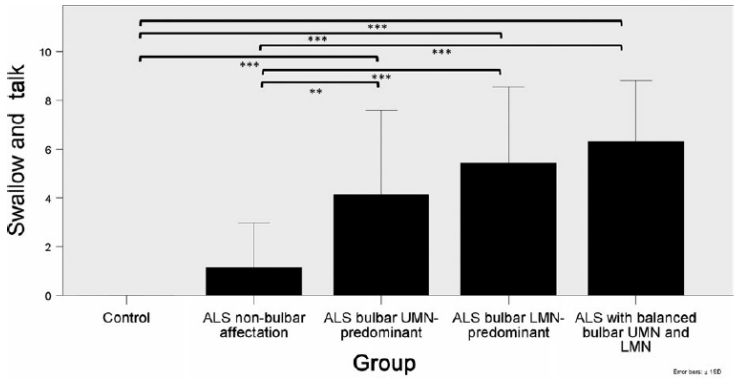

FIGURE 4 Means and standard deviation of limitation score of swallowing and talking. **$P \leq .01$; ***$P \leq .001$ Kruskal-Wallis test and pairwise comparisons of different groups

4 | DISCUSSION

The results of this study indicate that bulbar involvement was significantly associated with perceived functional limitation of the masticatory system in patients with ALS. In the bulbar group, the greatest impairment was seen in those with balanced UMN and LMN diseases, as evidenced primarily by difficulties in chewing soft food and opening the jaw widely, as well as difficulties in chewing tough food and chicken, swallowing and talking.

When patients have been grouped by symptom type at onset, aspects of masticatory function, like bite force and range of jaw mobility, were objectively shown to be reduced in bulbar-onset groups

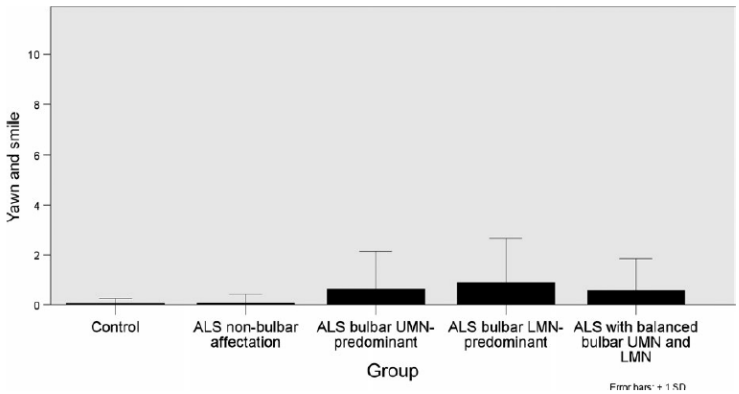

FIGURE 5 Means and standard deviation of limitation score of yawning and smiling. $P > .05$ Kruskal-Wallis test and pairwise comparisons of different groups

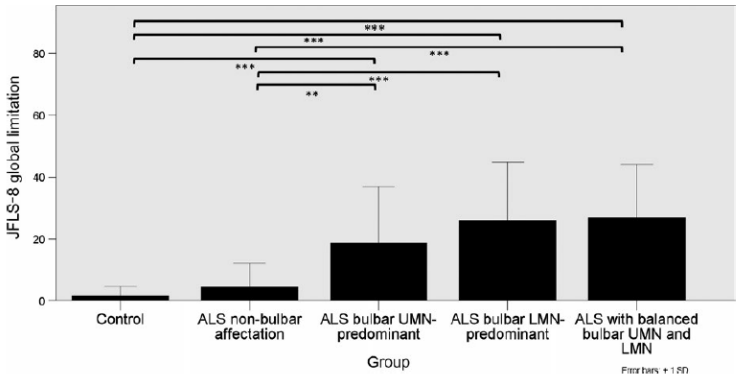

FIGURE 6 Means and standard deviation of JFLS-8 global limitation score. $^{**}P \leq .01$; $^{***}P \leq .001$ Kruskal-Wallis test and pairwise comparisons of different groups

compared with spinal or respiratory onset groups.[20] Moreover, the bulbar-onset group showed more severe oro-facial impairment than the spinal-onset group assessed with the Nordic Oro-facial Test-Screening.[21] Results of the present study suggest that masticatory function is also affected when the involvement of the bulbar region occurs during the evolution of the disease. This is consistent with the fact that the bulbar target damages neurons responsible for controlling facial, masticatory, pharyngeal and laryngeal muscles. There are differences in neurological symptoms between UMN and LMN involvement.[8] Emotional lability, nasal speech, nasal regurgitation, excessive saliva, slow tongue and brisk jaw jerk and facial reflexes are characteristics of UMN. Slurred speech, difficulty in swallowing, excessive saliva, small and fasciculating tongue are characteristics for LMN.[8] The difficulties in masticatory function are related to upper motor neuron signs as tongue spasticity or to lower motor neuron signs as tongue atrophy. Despite the neurological differences between patients with upper or lower motor neuron involvement, no differences in mastication, jaw mobility or verbal and emotional expression were observed. However, when both motor neurons were affected, there was a greater degree of functional limitation in these measures.

Although the jaw mobility is reduced in balanced bulbar UMN and LMN ALS, yawning was not affected in this study. It is known that excessive yawning occurs in a substantial number of patients with ALS specially in those with a bulbar onset.[8,22] Probably this could be related to the inhibition of normal control mechanisms of emotions, which would mean that neurological paths controlling voluntary mandibular opening and yawning are different. However, to date, no physiological significance has been associated with yawning, and the neural pathways underlying it are not known.[23] Moreover, even though patients with bulbar symptoms experience facial weakness affecting the lower half of the face, no patient in this study reported difficulty smiling.

Amyotrophic lateral sclerosis (ALS) is a low-prevalent disease, and therefore, it should not be considered as a first-line differential diagnosis in patients with temporomandibular disorders. Nevertheless, as most of the bulbar-onset patients reported the first symptoms in the oro-facial region, dentists should keep in mind this possibility in those situations in which, in a patient with apparent symptoms of temporomandibular disorders, there are incongruous signs or symptoms.[24] These signs and symptoms may include difficulty in mastication, speech or swallowing due to an impairment in tongue control or a weakness in masticatory muscles, and difficulty in mandibular mobility not attributable to muscular or articular pain or disc displacement.[7,8]

Mandibular mobility and/or bite force are also reduced in patients with other neuromuscular diseases, including spinal muscular atrophy,[14-16] bulbar myasthenia gravis[17,18] and Duchenne muscular dystrophy.[19] A reduced ability to open the mouth may hinder oral hygiene and perhaps even the efficacy of non-invasive ventilation. To minimise these complications, especially in patients with bulbar onset, an effective physiotherapy programme of active exercises is needed to slow the rate of reduction in mouth opening.[19] The physiotherapy programme could consist of moderate-load and moderate-intensity resistance and stretching exercise programme to improve mandibular mobility.[25] Moreover, the dentist could also manage ALS patients to avoid traumatic lesions in the lips, cheeks or tongue due to self-biting.[20] Recommendations for dental care in patients with ALS also include a regular oral maintenance care to maintain oral health and avoid dental disease, as well as counselling for dietary modifications.[26] Symptoms of dysphagia may occur at any time in the act of swallowing. Patients may report failure to chew or intolerance to texture in the oral preparatory phase and pocketing of food in the oral phase.[27] Recommendations to improve or mitigate swallowing function include compensatory manoeuvres, behavioural strategies, sensory tricks and dietary modifications such as mechanically altered food, thickened liquids, soft diet or liquidise food.[26] Consequently, dentists should also be included in the multidisciplinary team to improve the quality of life of patients with ALS.

The sample of this study was representative to the population of Catalonia, corresponding to 30% of the approximate 451 patients with ALS diagnosed among the 7 500 000 inhabitants.[2] However, the small sample size and recruitment method for the control group are potential limitations. Nevertheless, the prevalence of TMD and the range of mandibular motion in the control group were comparable to those reported in other studies.[28,29]

In conclusion, bulbar involvement in patients with ALS is associated with functional limitation of the masticatory system. However, balanced bulbar UMN and LMN involvement is associated with the worst impairments, affecting soft food chewing and opening the jaw widely.

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COMPETING INTERESTS

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHORS' CONTRIBUTIONS

Nina Riera-Punet contributed to the conception and design of the study, to the acquisition of data and analysis and interpretation of data. J Martinez-Gomis, E Willaert and M Peraire contributed to the conception and design of the study and analysis and interpretation of data. M Povedano contributed to the conception and design of the study, to the acquisition of data and analysis and interpretation of data. All co-authors participated in drafting the article and approved the version to be published.

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STUDY III

Satisfaction of patients with amyotrophic lateral sclerosis with an oral appliance for managing oral self-biting injuries and alterations in their masticatory system: A case-series study

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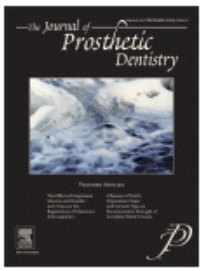

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CLINICAL RESEARCH

Satisfaction of patients with amyotrophic lateral sclerosis with an oral appliance for managing oral self-biting injuries and alterations in their masticatory system: A case-series study

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ABSTRACT

Statement of problem. About 10% of patients with amyotrophic lateral sclerosis (ALS) are candidates for oral treatment specifically because of traumatic injuries in the lips, cheeks, or tongue due to self-biting. However, patients with ALS have a prevalence of temporomandibular disorder (TMD) similar to that in the general population.

Purpose. The purpose of this case-series study was to determine the degree of satisfaction of patients with ALS with an oral appliance for managing oral self-biting lesions or symptoms related to TMDs. This study also assessed the degree of improvement of the chief complaint and the compliance with and adverse effects of this treatment.

Material and methods. Eleven patients with ALS who sought oral treatment because of oral self-biting or TMD-related symptoms were included. A custom complete-coverage acrylic resin device was fabricated and fitted to each participant. A follow-up visit was planned for 3 months after the placement of the oral appliance, at which point the patients would rate the degree of improvement or worsening of the chief complaint and their degree of satisfaction with the treatment. A 1-sample *t* test was used to assess whether the degree of improvement of the chief complaint was significant.

Results. Participants reported a mean of 61% (95% confidence interval [CI] 38% to 84%) improvement of the chief complaint and a mean of 84% (95% CI 72% to 97%) satisfaction with the treatment. The mean rate of compliance was 62% (95% CI 40% to 84%) of the recommended time, and only a few adverse effects were reported.

Conclusions. Participants with ALS were highly satisfied with the use of an oral appliance to manage oral self-biting or TMD-related symptoms. Adherence to this treatment was high, and no major adverse effects were observed. (J Prosthet Dent 2018;■:■-■)

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive muscular paralysis reflecting the degeneration of motor neurons in the primary motor cortex, corticospinal tract, brainstem, and spinal cord.[1] Its incidence rate is approximately 1.4 and 2.1 per 100 000 persons/year in Catalonia and Europe, respectively.[2,3] Because ALS is rapidly progressive in nature, life expectancy is 3 to 5 years after diagnosis, although approximately 10% of patients with ALS survive for 10 or more years.[4] The typical clinical characteristics of ALS are variable and depend on whether the site of onset is spinal, bulbar, or respiratory. Most patients with ALS have a spinal onset, referring with weakness, muscle atrophy, and fasciculations due to lower motor neuron involvement and hyperreflexia and hypertonia due to upper motor neuron involvement. In about 20% of patients, weakness starts in the bulbar muscles, with dysarthria, dysphagia, and tongue fasciculations. Bulbar onset ALS has a poorer

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Clinical Implications

Patients with amyotrophic lateral sclerosis referred for oral self-biting or temporomandibular disorder symptoms can be managed efficiently by means of an acrylic resin device.

prognosis because of swallowing difficulties, weight loss, aspiration, and respiratory involvement, with poorer adaptation to noninvasive ventilation. About 3% to 5% of patients have a respiratory onset, referring with orthopnea or dyspnea and mild or even absent spinal or bulbar signs.[1]

About 10% of patients with ALS are candidates for oral treatment specifically because of their disease. The chief complaint may include traumatic injuries to the lips, cheeks, or tongue due to self-biting in the case of bulbar involvement.[5] However, patients with ALS have a prevalence of temporomandibular disorder (TMD) similar to that of the general population. Almost 50% report grinding and clenching, and 9% may be diagnosed with myalgia.[5] Furthermore, bulbar involvement is associated with the perception of functional limitation of the masticatory system, especially when masticating tough food or chicken or when swallowing or talking.[6]

The dentist should be part of a multidisciplinary team for the management of patients with ALS.[5-9] The treatment options available to the dentist include the use of a palatal lift and/or palatal augmentation prosthesis to improve dysarthria, as described in several patients with ALS.[10] Other types of oral appliances have been reported in clinical reports to assist with noninvasive ventilation or to control drooling.[11,12] However, the authors are unaware of a study that considered how to manage traumatic injuries to the lips, cheeks, or tongue because of self-biting in patients with ALS. Customized oral appliances, acrylic resin devices, or mouthguards have been used in other patients with oral self-injury.[13-28] For example, an acrylic resin device with a labial bumper for displacing the lower lip forward was effective in preventing traumatic lesions in the lip due to self-biting in an adult with severe neurological impairment.[13] Oral appliances are also recommended for the treatment of TMDs.[29-34]

The purpose of the present study was to determine the degree of satisfaction in patients with ALS after treatment with an oral appliance to manage oral self-biting or symptoms related to TMDs. This study also assessed the degree of improvement in the chief complaint, the change in the quality of life due to changes in the chief complaint, and other aspects of the treatment including compliance, side effects, and technical failures. The research hypothesis was that patients with ALS are satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMDs.

Table 1. Clinical characteristics of patients with amyotrophic lateral sclerosis according to chief complaint

	Chief Complaint	
Clinical Characteristics	**TMDs (n=7)**	**Self-biting (n=12)**
Sex (% of male)	43	17
Median age (years)	61.8	61.7
Bulbar-onset ALS type (%)	43	58
Bulbar involvement (%)	71.4	100
Median time elapsed since symptom onset (mo)	27.2	24
Median time elapsed since ALS diagnosis (mo)	18.7	13.2
Botulinum toxin (%)	14	25
Noninvasive ventilation (%)	0	33
Oral feeding (%)	100	58
Use of tube feeding (%)	14	50
Median number of missing teeth	7	5.5

ALS, amyotrophic lateral sclerosis; TMDs, temporomandibular disorders.

MATERIAL AND METHODS

Nineteen adult patients diagnosed with ALS according to the revised El Escorial diagnostic criteria and who were referred with alterations of the masticatory system were invited to participate in this prospective case series.[35] All patients were attending the Motor Neuron Disease Unit of the Bellvitge University Hospital between September 2015 and July 2016 and had participated in previous studies.[5,6] Patients who could not be treated with an orofacial device because of the advanced stage of their disease, those with severe periodontal disease, or those without a sufficient number of teeth to hold an oral appliance were excluded. The nature of the study was explained in full to all participants, and all signed an informed consent form approved by the Bellvitge University Hospital Ethics Committee (Code PR259/15). All experiments were carried out in accordance with the principles of the Helsinki Declaration.

One dental clinician (N.R.-P.) recorded chronologic variables including the time elapsed since symptom onset and since the ALS diagnosis. Demographics such as sex, age, and a phenotypic classification according to the site of onset were recorded. Medication, use of mechanical ventilation, and gastrostomy were also recorded (Table 1).

All participants were examined by the same dental clinician (N.R.-P.) and answered the symptom questionnaire of the Diagnostic Criteria for Temporomandibular Disorders protocol.[36] The clinical examination included the measurement of maximum opening, protrusion, and laterotrusion; palpation and auscultation of the temporomandibular joints; and palpation of the masticatory muscles.[36-38] Participants were also assessed by means of a questionnaire about awareness of clenching/grinding and self-biting of the tongue, lips, or cheeks with dichotomous no/yes answers. Patients were

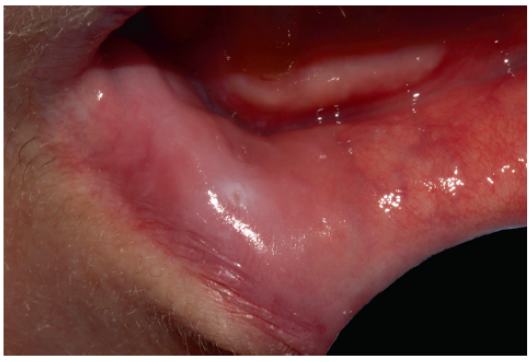

Figure 1. Lower lip self-biting lesion in patient with amyotrophic lateral sclerosis.

asked about the chief complaint because most had been referred with more than one. They were assigned to the TMDs or self-biting group accordingly. The most frequent complaints were lower lip self-biting, grinding/clenching, and masticatory muscle pain (Fig. 1).

The oral appliance was a custom complete-coverage acrylic resin occlusal device with a flat occlusal surface in contact with all antagonistic teeth at habitual closure and providing anterior guidance in lateral and protrusive movements (Fig. 2).[29,32] It was placed on the maxillary or mandibular arch depending on the chief complaint and on the dental conditions (Table 2). Alginate impressions of the maxillary and mandibular arches were used to make gypsum casts. Among the 19 participants, difficulties making the impression were encountered in 5 individuals, mainly because these patients were not able to open their mouth wide enough or keep it sufficiently open while the impression material was setting (Table 2). If the chief complaint was self-biting the lower lip or cheeks, the acrylic resin device could include a buccal bumper to move the lower lip forward (Fig. 2). If the chief complaint was self-biting the tongue, the acrylic resin device could include a lingual bumper to move the tongue backward. All oral appliances were fabricated by the same dental technician and fitted and adjusted by the same dental clinician (N.R.-P.). The patients were instructed to use the oral appliance every night during sleep and/or during the day at times they considered helpful.

During treatment, patients with technical complications involving the oral appliance and/or adverse effects involving the masticatory system were seen by the same dental clinician (N.R.-P.). The number of additional dental visits, the reason for each extra visit, and the number of oral appliance repairs in the dental laboratory were recorded.

The follow-up visit was planned for 3 months after the patient had worn the oral appliance normally. This follow-up consisted of a questionnaire to assess compliance as the percentage of time the oral appliance was used with respect to the recommended time and the adverse effects reported by the patients. This questionnaire also assessed the degree of improvement or worsening of the chief complaint after 3 months of oral appliance treatment by means of a visual analog scale (VAS), for which the patient made a mark on a 10-cm line anchored by "extreme worsening" (-100%) or "completely improved" (+100%) at either end and "no change" in the center of the line (0%).[39] The change in quality of life because of changes in the chief complaint after 3 months of treatment was assessed by using a similar VAS. Finally, patients also rated their degree of satisfaction with treatment by using a VAS anchored by "extremely dissatisfied" (0%) or "completely satisfied" (+100%) at either end.

The outcome variables were the degree of improvement of the chief complaint, the change in quality of life because of changes in the chief complaint, and the degree of satisfaction with the treatment. The degree of improvement of the chief complaint and the change in quality of life because of changes in the chief complaint were assessed by using a 1-sample *t* test. The degree of satisfaction with the treatment was expressed as mean (95% confidence interval [CI]) (α=.05).

RESULTS

Among the 19 treated participants, 8 were excluded because they did not attend the 3-month evaluation (7 from the self-biting group and 1 from the TMD group). Of these 8 participants, 4 did not attend the evaluation because their disease had worsened, 1 because the individual considered the oral appliance no longer necessary, 1 because she had developed hypersalivation and had stopped using the oral appliance, and 2 because they preferred not to attend the clinic, even though the treatment had apparently improved the chief complaint. Therefore, 11 participants were included in the study and performed their evaluation for a mean of 4.4 months after being fitted with the oral appliance.

The participants reported a mean of 61.2% (95% CI 38% to 84.4%) improvement in the chief complaint (P<.001, 2-tailed 1-sample *t* test) and a mean of 84.3% (95% CI 72% to 96.6%) satisfaction with the treatment. Because of changes in the chief complaint, quality of life improved by a mean of 58.6% (95% CI 23.5% to 93.7%) (P=.004, 2-tailed 1-sample *t* test). Of the 11 participants, only 1 reported a reduction in quality of life because the chief complaint had not improved (Table 3).

Of the participants who attended the 3-month evaluation, 5 had needed at least 1 extra visit because of technical complications with the oral appliance, 3 of them for adjustment and 2 for loosening. Only 1 oral appliance

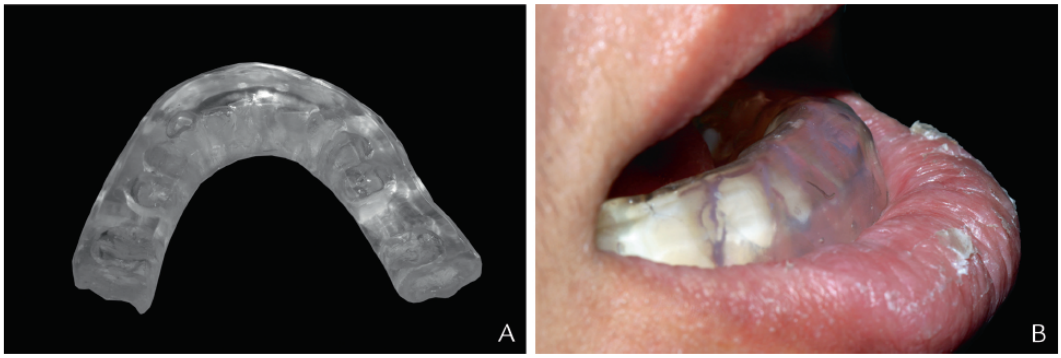

Figure 2. A, Mandibular acrylic resin occlusal device with buccal bumper. B, Device inserted in participant with lip biting.

Table 2. Characteristics of oral appliance and degree of difficulty when making impressions according to chief complaint

Characteristics of the Oral Appliance	Chief Complaint	
	TMDs (n=7)	Self-biting (n=12)
Maxillary oral appliance (%)	29	0
Mandibular oral appliance (%)	71	100
Presence of buccal bumper (%)	14	67
Presence of lingual bumper (%)	0	17
Difficulty making impressions (%)	14	33

TMDs, temporomandibular disorders.

Table 3. Treatment success perceived by participants according to chief complaint

Treatment Success	Chief Complaint	
	TMDs (n=6)	Self-biting (n=5)
Mean (95% CI) improvement of chief complaint (-100 to 100)	56.8 (16.4-97.2)	66.4 (25.7-100)
Mean (95% CI) satisfaction with treatment (0 to 100)	83.8 (62.0-100)	85.0 (64.5-100)
Mean (95% CI) improvement in QoL (-100 to 100)	55.8 (0-100)	62.0 (25.4-98.7)

CI, confidence interval; TMDs, temporomandibular disorders; QoL, quality of life.

needed to be repaired at a dental laboratory because of the lack of retention. The mean rate of compliance was 62.3% (95% CI 40.3% to 84.2%) of the recommended time. The main reason for not having used the oral appliance 100% of the recommended time was discomfort, as reported by 4 participants (36%). Only 3 participants reported no side effects at the evaluation, and the most reported side effect was excessive salivation, affecting 64% of the participants (Table 4). The participant who reported worsening of the chief complaint and had stopped using the oral appliance reported all types of side effects (Table 4).

Table 4. Number of participants (percentage) who reported side effects related to use of oral appliance at 3-mo evaluation according to chief complaint

Side Effects	Chief Complaint	
	TMDs (n=6)	Self-biting (n=5)
Excessive salivation	3 (50%)	4 (80%)
Dry mouth	1 (17%)	0 (0%)
Tooth discomfort or pain	2 (33%)	1 (20%)
Mucosal irritation	1 (17%)	0 (0%)
Muscular discomfort	1 (17%)	0 (0%)
TMJ discomfort or pain	1 (17%)	0 (0%)
TMJ sounds	1 (17%)	0 (0%)
Bite change	2 (33%)	0 (0%)
Other	1 (17%)	0 (0%)
At least 1 side effect	4 (67%)	4 (80%)

TMDs; temporomandibular disorders; TMJ, temporomandibular joint.

DISCUSSION

The results of this study suggest that patients with ALS are satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMDs, and therefore, the hypothesis was not rejected. The effectiveness of this treatment can be demonstrated by a mean of 61% improvement of the chief complaint, implying improved quality of life, and by a mean of 84% degree of satisfaction with the treatment. Furthermore, compliance was high, and few and nonrelevant side effects or technical complications were detected.

The effectiveness of an oral appliance in preventing self-biting has also been reported in other neurological diseases but not in ALS and only in case reports.[13,14,17-24] However, the authors are unaware of previous prospective case series studies that evaluated effectiveness in patients with ALS. In some individuals, the increased vertical dimension produced by the oral appliance was sufficient to avoid oral self-biting because the lips, tongue, or cheeks did not invade the interocclusal space. In others, a bumper was needed to separate the lower lip from the teeth because the increased vertical dimension was not sufficient to stop the soft tissues encroaching on

the interocclusal region. Before fabricating the oral appliance, the dentist should explore the placement of the tissues being traumatized in several mouth opening increments, from the intercuspal position to the resting position, to determine the required increase in vertical dimension increase and whether a bumper is required in the oral appliance.

The degree of patient satisfaction with the acrylic resin device and the compliance rate of participants with ALS were similar to those reported in those without ALS but with TMD symptoms.[29] Oral appliance therapy is a common approach to manage patients with TMDs. Although the mechanism of action of this approach remains unclear, multiple effects may be present, including allowing an orthopedically comfortable jaw position, reducing masticatory muscle activity and joint loading, and increasing patients' awareness and ability to reduce bad oral habits.[30-34] Therefore, patients with ALS with the chief complaint of clenching/grinding and/or muscular pain can be managed using an acrylic resin occlusal device.

The most common complication encountered in these patients during treatment was difficulty in making impressions due to the evolution of their disease. A poor impression can compromise the quality of the cast and therefore the acrylic resin device. Only one impression of one arch without the antagonist and/or the anterior region of this arch can be made in those who cannot be fed orally and when the dental occlusion has lost its normal function.[13] Intraoral scanning could be an alternative to traditional impression procedure in cases where patients are not able to keep their mouth sufficiently open while the impression material was setting.[40] Another option could be a removable lip bumper fabricated at the chairside without making an impression.[17] Similarly, custom mouthguards have been described as an option for the treatment of self-inflicted oral trauma.[16,25] A self-modeled mouthguard was reported to protect against cheek biting in a patient under orthodontic treatment,[26] although the self-modeled mouthguard is worn on the maxillary arch and this could be inconvenient.

Although the prevalence of ALS is low and the percentage of patients with ALS who require an oral appliance treatment is only about 10%, this disease is highly disabling; patients will appreciate any help that improves their quality of life. The use of an oral appliance permits daily oral care; its maintenance is straightforward, it can be placed and removed easily by the patient or the caregiver, it can be repaired or modified, and treatment can be conducted by a general dentist. Using an oral appliance can help the patient avoid the more extreme solution of extraction of all teeth.[27,28]

Side effects were generally the same as those reported in other studies of oral appliances.[29,37,41] However, excessive salivation could exacerbate the problem of drooling, which is common in ALS. Moreover, sialorrhea itself is already common in ALS and can be treated with amitriptyline, oral or transdermal hyoscine, or sublingual atropine drops.[7]

This study has several limitations. First, no control group was used, and a cause-and-effect relationship between the improvement of the chief complaint and the use of an oral appliance should be assumed with caution. The present findings encourage further studies with appropriate controls to demonstrate the effectiveness of the oral appliance in patients with ALS. Moreover, the initial sample size and the high proportion of dropouts could reduce the validity of these results. The fact that patients with ALS may have difficulty traveling from their homes to the clinic, mainly because of the evolution of their disease, could make it difficult to monitor treatment for longer periods. In the 4 patients excluded because of worsening of the disease, it is not known whether the acrylic resin device was effective or not. This suggests that patients with ALS should use the acrylic resin device in the first phase of their disease and not wait until their condition deteriorates, at which point compliance might decline. An early diagnosis and appropriate dental approach are indispensable to avoid severe injuries to the oral mucosa.[26]

CONCLUSIONS

Within the limitation of this case-series clinical study, the following conclusions were drawn:

1. Patients with ALS were highly satisfied with the use of an oral appliance to manage oral self-biting or symptoms related to TMDs because of the improvement in the chief complaint, which increased their quality of life.
2. Compliance regarding the use of an oral appliance was high, and few side effects and technical failures were observed.

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