SIALORRHOEA: HOW TO MANAGE A FREQUENT COMPLICATION OF MOTOR NEURON DISEASE

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ABSTRACT

Sialorrhoea, the unintentional loss of saliva through the mouth, is the frequent complication of neurological disorders affecting strength or coordination of oropharyngeal muscles, such as motor neuron disease/amyotrophic lateral sclerosis (MND/ALS) or Parkinson's disease. Sialorrhoea might affect up to 42% of ALS patients, with almost half of them having poorly managed symptoms. Sialorrhoea can impair patients' social life, while dermatological complications, such as skin rashes, may arise due to constant exposure to moisture. Moreover, the excess mouth-retained saliva in ALS patients may lead to serious complications, such as choking, which causes anxiety, and aspiration with the consequent pneumonia. The inclusion of a sialorrhoea-related item in the ALS functional rating scale testifies both the incidence and importance of sialorrhoea during the ALS clinical course. Because of the progressive nature of ALS, presence and severity of sialorrhoea should be assessed at every visit and, when present, active treatment pursued. Available treatments include behavioural therapy, i.e. techniques to enhance periodic swallowing of saliva, systemic or local anticholinergic medications, botulinum toxin injection, electron beam irradiation, and surgical techniques. This review paper briefly describes the available options with related side-effects and current guideline recommendations for managing sialorrhoea in ALS patients.

Keywords: Amyotrophic lateral sclerosis, motor neuron disease, sialorrhoea, drooling.

BACKGROUND

The term 'motor neuron diseases' (MNDs) describes a group of neurodegenerative disorders affecting motor neurons, among which amyotrophic lateral sclerosis (ALS) is the most frequent and best-characterised subset. ALS invariably leads to death due to respiratory insufficiency within, on average, 3-5 years from onset.[1] The disorder affects both upper and lower motor neurons: lower motor neuron degeneration causes muscle weakness, fasciculation, and progressive muscle atrophy; while the loss of upper motor neurons may cause spasticity and weakness. Sialorrhoea, or drooling, defined as the unintentional loss of saliva through the mouth, can often present in these patients, presumably due to lack of strength and coordination of oropharyngeal muscles. Sialorrhoea is a frequent and early feature of bulbar ALS presentations, but complicates later stages in spinal onset patients as well. Saliva is the mixed product of three pairs of major salivary glands: the parotid, submandibular, and sublingual. They account for 95% of saliva production; the remaining saliva is secreted by minor glands. Adult individuals produce approximately 1.5 litres of saliva daily, the secretion of which is modulated by the autonomic nervous system.[2]

Sialorrhoea should not be confused with hypersalivation, which is the increase of the amount of secreted saliva. Hypersalivation may sometimes cause sialorrhoea; however, an individual with preserved saliva clearance (i.e., the ability to swallow) can easily eliminate the excess. The main cause of sialorrhoea in ALS is the impairment

of saliva clearance due to degeneration of both upper and/or lower motor neurons controlling oropharyngeal muscles. Spasticity or weakness of such muscles causes dysphagia so that secretions build up in the mouth. Finally, weakness of buccal muscles impairs the ability to retain saliva, causing it to spill. Hypersalivation does not appear to be a prominent feature of ALS, while it may characterise other motor system disorders like Parkinson's disease (PD). For this reason, results of sialorrhoea trials in PD may not be applicable to ALS. These patients, rather than complaining of watery serous secretions, more often complain of the accumulation of thick mucous secretions. Indeed, salivary glands produce both. Serous secretions are controlled by parasympathetic, cholinergic, and sympathetic alpha receptors, while thick secretions are produced upon the activation of sympathetic beta-receptors.[2]

Sialorrhoea impairs quality of life by several means. It can impair mastication and speech, and it can embarrass patients engaged in social activities, prompting their isolation; often this latter issue is reported as the most disturbing complaint by patients. Constant exposure of the skin to moisture can cause skin lesions. Furthermore, pooled saliva can contribute to the sensation of choking and anxiety, while its aspiration may cause a life-threatening pneumonia. Such respiratory complications, however, are not the result of sialorrhoea; the loss of saliva through the mouth is, in fact, an alternative pathway of saliva clearance, which prevents aspiration. Instead, sialorrhoea and aspiration pneumonia share a common cause: dysphagia. For this reason, treatments aimed at reducing salivation could prevent both sialorrhoea and respiratory complications. Finally, tolerance of non-invasive ventilation, a key component of ALS care, also depends on successful control of sialorrhoea.[3]

Assessment of Sialorrhoea

In a multicentre study[4] enrolling 143 ALS patients, 41% had saliva-related problems, and only 25% of those treated for sialorrhoea deemed their treatment effective. Therefore, any physician involved in ALS care should readily address sialorrhoea. Patients will often complain about the symptom because of its disturbing nature. As already stressed, sialorrhoea depends on the symptomatic involvement of bulbar-innervated muscles; this could be the result of the disease extending to bulbar segments or of an aggravation of the already present impairment. Dysphagia is frequently associated with this. Usually, overt sialorrhoea is preceded by loss of saliva during sleep; however, despite the potential benefit of early intervention (i.e., the prevention of aspiration pneumonia), such a strategy has never been investigated. Therefore, at this stage, assessment followed by treatment should be reserved for patients complaining about sialorrhoea or excess saliva.

The first step of sialorrhoea assessment should be the review of drug therapy for medications known to cause hypersalivation, such as cholinergic drugs (e.g., neostigmine, clozapine). Second, a quantification of sialorrhoea may help the physician to estimate symptom severity. Even if several objective measures of sialorrhoea are available (e.g., number of handkerchiefs used, weight gain of cotton rolls placed in the mouth for a set amount of time), clinical choices should be oriented by patient-reported distress. The salivary item of the ALS functionality rating scale is an already-known and easy-to-apply five-point scale for sialorrhoea quantification and could be sufficient for symptom staging.

Other ALS-dedicated tools measuring sialorrhoea severity[5] and patient-perceived impact[4] are the Oral Secretion Scale, the Sialorrhoea Scoring Scale, and the Clinical Saliva Scale for MND (CSS-MND). In particular, CSS-MND is a patient-reported measure for sialorrhoea impact, strongly correlating with a Likert scale measure of sialorrhoea severity. This scale may be a useful tool for research purposes because the impact of sialorrhoea over a patient's life appears to be a better outcome than its severity, as the two do not correlate.[6] Previous studies report the use of a 6-item tool for assessing the quality of daily living,[7] or of a 10-item dedicated tool, the drooling impact score.[8] General quality of life dedicated scales, such as the SF-36[9] have never been applied selectively to the assessment of sialorrhoea impact in ALS.

MANAGEMENT OF SIALORRHOEA

Non-invasive intervention modalities are often designated as the first-line therapy for sialorrhoea. In fact, treatments aimed at saliva flow reduction (i.e., drug therapy) may improve sialorrhoea without intervening over its cause. Rehabilitative and prosthetic treatments, on the other hand, may reduce sialorrhoea by re-establishing the physiological mechanism of saliva retention and clearance. Because of this, when postural deficits

(i.e., falling head/chin) are the putative cause of sialorrhoea, their correction should precede other treatments. In such cases, for example, a chin support could reduce the symptom. Analogously, sialorrhoea was successfully controlled by the application of a lip-sealing intraoral prosthesis in a single ALS patient.[10] Obviously, the use of a customised device limits the reproducibility of such a technique to the general patient population. Other rehabilitative interventions include oral motor therapy, behavioural modification via biofeedback, and orofacial regulation therapy;[11] these techniques, however, were developed for paediatric patients with neurological deficits and their applicability to ALS remains open to discussion. Finally, patients affected by sialorrhoea may benefit from aspiration devices, which can be operated by the caregiver or by the patient themselves. When no postural deficit causes sialorrhoea or when its correction is not sufficient to control the symptom, drug therapy should be the next step.

PHARMACOLOGICAL TREATMENTS

First-Line Drug Therapy

Saliva production can be decreased by the blockade of parasympathetic stimulation to salivary glands. This is achieved by anticholinergic medications, whose efficacy in clinical practice is well documented. However, to date, no study has compared the efficacy of different anticholinergic medications for the treatment of sialorrhoea in ALS. Reportedly, the most commonly used drugs in this category are amitriptyline tablets/oral solution, and scopolamine patches.[12] Sometimes even a few milligrams of amitriptyline (e.g., 4-6 mg three times daily [t.i.d.]) or scopolamine (e.g., 1.5 mg patch every 3 days) might be sufficient to control sialorrhoea, albeit the doses can be slowly increased, carefully monitoring for side-effects. Butylscopolamine, i.e., scopolamine butylbromide, is another effective option and is also available for subcutaneous administration. Glycopyrrolate is a muscarinic antagonist that is widely used in anaesthesia and palliative care and has been identified as a potentially efficacious treatment for sialorrhoea.[13] This drug seems to produce fewer side-effects than alternative anticholinergic agents, due in part to poorer penetration across the blood—brain barrier[14] and a possible higher selectivity for muscarinic receptors in gastrointestinal rather than cardiac tissue.[15] A randomised double-blind crossover trial demonstrated that oral glycopyrrolate is an effective treatment for severe sialorrhoea in PD.[16] Although, as stated above, the results of PD trials cannot be generalised at the moment, a case of treatment-resistant bulbar ALS is described where subcutaneous glycopyrrolate was effective without significant side-effects.[17] In our anecdotal experience, an oral dose of 0.5 mg twice daily (b.i.d.) or t.i.d. is usually sufficient. This suggestion, however, has still to be tested in randomised controlled trials before concluding on its validity.

Unsurprisingly, the unselective blockade of muscarinic receptors frequently causes side-effects alongside therapeutic ones, albeit the use of locally administered drugs tends to confine them to the area of administration. For instance, atropine drops can be administered sublingually: a pilot study in patients with PD demonstrated a statistically significant decline in saliva production.[18] For ALS patients 0.25–0.75 mg t.i.d. is empirically recommended.[19] When a systemic drug is chosen, those that cannot pass the blood—brain barrier should be preferred in order to minimise the most distressing symptom. Finally, saliva is an important factor for the mineralisation and protection of teeth.[2] For this reason, a reduction in its production may have deleterious effects on dental health. Therefore, patients should be instructed to increase oral hygiene. Table 1 reports the initial doses of the most effective pharmacological options for managing sialorrhoea in ALS patients.

Patients under anticholinergic blockade may sometimes complain of increased thickness of secretion, often localised in the back of the mouth, so that patients may not clear it by coughing. This may be caused by the unopposed stimulation of sympathetic beta-receptors. This principle is supported by the study of Newall et al.,[20] in which patients reported subjective benefit over saliva thickness through the use of beta-blocker therapy. Other medications for this purpose include: guaifenesin, nebulised saline, or acetylcysteine.[21] When these secretions are not localised in the back of the mouth, aspiration devices may prove useful. Breath-stacking techniques and cough-assist machines,[22] which alternate positive and negative pressures to improve cough airflow[23] may also be useful.

Notably, at the highest tolerated doses, drugs not infrequently fail to control sialorrhoea in these patients, and both the American Academy of

Neurology (AAN) (2009) and the European Federation for Neurological Societies (EFNS) (2012) clinical practice parameters for ALS management[24,25] suggest the options of botulinum toxin (BTx) injection or parotid gland irradiation. The most frequently reported side-effect is drowsiness, followed by constipation (see Table 1); in our experience they occur in ALS patients with the same modalities observed in patients treated with anticholinergic medications for other conditions, such as amitriptyline for headache. Other side-effects might arise in susceptible patients (e.g., arrhythmia in patients affected by concomitant heart disease).

BOTULINUM TOXIN INJECTION

Much interest has grown around BTx injection, as it appears to be an easy-to-replicate, highly effective, reversible, safe, and cost-effective technique. This toxin is produced by *Clostridium botulinum* and other bacteria of the *Clostridium* species. *Clostridia* are Gram-positive, rod-shaped, spore-forming, obligate anaerobic bacteria. Seven distinct types of BTx serotypes have been identified, named A-G. However, only Type A and B are commercially available, marketed as Botox®, Dysport® and Xeomin® (BTxA), and Neurobloc/Myobloc® (BTxB). Both of these toxins act by cleaving the soluble N-ethylmaleimide sensitive factor attachment protein receptor (SNARE) proteins, responsible for acetylcholine release. An exhaustive insight into BTx molecular mechanism of action is available in a review by Kammerer and Benoit.[26]

BTx injection has been the main subject of several clinical trials, among which are two randomised double-blind trials.[27,28] BTxA was the most frequently used toxin in non-randomised trials; however, BTxB efficacy has a higher level of recommendation in clinical practice parameters because evidence comes from an AAN Class I study.[27] Also, a more recent trial[28] compared the efficacy of the two neurotoxins and found BTxB to have shorter latency and equal duration of effects in comparison with BTxA without an increase in adverse effects. The study, however, is biased by the inclusion of PD and MND patients together. Moreover, BTxB comes at lower pricing. Transcutaneous injection of BTx is preferred to the transductal approach because of the unacceptable side-effects of the latter.[29] Notably, regarding the BTx injection targets, the submandibular glands contribute 70% of the unstimulated saliva secretion (i.e., the secretion not depending on the saliva reflex),[2] while the stimulated secretion depends mainly on the parotid glands. Therefore, for control of saliva production under both stimulated and unstimulated conditions, both pairs of salivary glands should be targeted.

Table 1: Drugs for sialorrhoea treatment.

Drug	Route	Suggested initial dose	Notable side-effects
Amitriptyline	Tablets, oral solution	4 mg t.i.d.	Anticholinergic effects*, REM sleep abnormalities, seizures, orthostatic hypotension, nausea, vomiting, increased appetite, mental status changes. Withdrawal symptoms are possible, careful de-escalation is advised.
Scopolamine Butylscopolamine	Patches Subcutaneous	1.5 mg patch every 3 days	Anticholinergic effects*, rash, dryness of the skin, erythema and dermatitis (at the application site). Unilateral eye dilatation/anisocoria may result from eye contamination (hand wash is suggested after drug application). Rebound cholinesterase activity may develop after drug discontinuation.
Glycopyrrolate	Tablets Subcutaneous	0.5 mg b.i.d.	Anticholinergic effects*, headache, mental status changes.
Atropine	Sublingual drops	0.25 mg t.i.d.	Anticholinergic effects*, hypotension, hallucinosis, seizures, delirium.

*Anticholinergic effects are particularly disturbing when drugs are received systemically and include: drowsiness, mydriasis and cycloplegia (resulting in blurred vision), tachycardia, arrhythmias, flushing, constipation, and urine retention.
b.i.d.: twice daily; t.i.d.: three times daily; REM: rapid eye movement.

The main injection patterns found throughout studies were four-gland injection (i.e., bilateral parotid and submandibular glands) and bilateral parotid injection alone. There are no studies, however, comparing injection patterns. Glands can be identified either by palpation or by ultrasound imaging. BTx injection under continuous guidance with a 7.5 MHz superficial probe has been shown to reduce the amount of injected toxin; this could reduce side-effects caused by the diffusion of the toxin to oropharyngeal muscles.[30] The most consistently used dose of BTxB is 2,500 U diluted in 1 ml of saline,[7,28,31] of which 1,000 U (in 0.4 ml of saline) are injected in each parotid gland at two different sites, and 250 U (in 0.1 ml of saline) in each submandibular gland in one site. Alternatively, the injection of 500 U in each parotid and 750 U in each submandibular gland, with two injection sites each, is reported.[27] BTxA equivalent dose depends on the brand; Guidubaldi et al.[28] described an equivalent dose of Dysport® being 250 U diluted in 1 ml of saline with 100 U injected in two sites in each parotid gland, and 25 U in one site in each submandibular gland. A review of the most commonly used doses is available in literature.[32]

A suggested approach is to begin treatment at low doses, which can be cautiously increased if the patient does not show side-effects.[33] Benefits arise as early as the first week after injection, peak for 1 or 2 months, and last up to 3 months.[28] At 4 weeks, 90% of patients treated with BTxB report an improvement of symptoms against the 40% of those treated with placebo.[27] In our experience, the rate of response may be variable. The main side-effects of the procedure are local, such as pain at needle injection sites and swelling. Some patients will complain about dry mouth, which can be a distressing symptom especially during sleep; in this case the interruption of other anticholinergic medications can partially release parasympathetic blockade and improve the symptom. Alternative short-term treatments are hydration during day time or environmental humidifier for night time mouth dryness. Otherwise, a BTx dose reduction in the following treatments is advised.

Increased saliva thickness is possible, and has already been addressed above. More disturbing side-effects include a worsening of dysphagia and problems in chewing. An author reported acute deterioration of bulbar function after BTxA treatment.[33] This is probably caused by the diffusion of BTx outside salivary gland boundaries, and the effects upon oral and pharyngeal muscles; evidence also shows that the injection of more diluted solution may facilitate toxin diffusion.[34] The exact advantage of repeating doses of BTx has never been consistently investigated as well as the most advantageous time interval among different doses. Anticholinergic drug treatment could be discontinued upon reduction of sialorrhoea, albeit a pragmatic approach based on a gradual dose reduction should probably be recommended at this stage, aiming at defining the minimum optimal dose controlling each patient's symptoms.

NON-PHARMACOLOGICAL TREATMENTS

Photocoagulation and Radiation Therapy

Gland and salivary duct photocoagulation is an innovative, minimally invasive technique that has been used to reduce sialorrhoea in children affected by cerebral palsy.[35] It consists of gland and related duct coagulation though the use of laser light, via a catheter introduced through the parotid duct. Reported complications were haematoma, infection, and cystic formation. Facial swelling is possible but transient. This technique may be preferred to surgical procedures; however, it has not yet been tested in ALS.

Salivary gland irradiation is a non-invasive alternative to BTx injection for medical refractory sialorrhoea, endorsed by both AAN and EFNS clinical practice guidelines. It presents the theoretical advantage of reduced side-effects. Furthermore, it may be used as a third-line approach for patients not tolerating BTx injection or not achieving an adequate control of secretion. Response duration lasts for 4-9 months[36] so that patients tolerating the first treatment may need a re-irradiation. Another drawback is the reproducibility of the technique, being limited to centres with adequate infrastructure. Borg and Hirst[37] report that a reduction of sialorrhoea can be obtained with five 4 Gy fractions (20 Gy total dose) of electron beam irradiation both to the parotid and submandibular glands. Care has to be taken to spare the upper part of the parotid from the radiation field, in order to avoid the increase of secretion thickness. The low-dose radiation should also prevent temporomandibular joint fibrosis. This radiation dose has also been tested in ALS patients by Guy and colleagues.[38] In this retrospective case report, no patient treated with electron beam irradiation reported side-effects; on the contrary, those irradiated with photons

reported immediate and delayed side-effects (mucositis, oral pain, oedema, dry mouth). Therefore, we suggest using electron rather than photon beam irradiation. Other reported schemes include single parotid gland radiation[39] or use of 7.5-8 Gy single fraction.[40,41] A trial directly comparing BTx injection and radiation therapy has never been performed.

SURGERY

Invasive interventions for the management of sialorrhoea are neurectomy and salivary gland/duct procedures. Use of surgery in the care of ALS is discouraged by the EFNS clinical practice guidelines, while no recommendation is given by the AAN. They present the theoretical advantage of withstanding results. Furthermore, they may control sialorrhoea that is inadequately controlled by previous treatments or in patients not tolerating BTx. At present, the application of surgical techniques for sialorrhoea has not been investigated in ALS. Neurectomy consists of the destruction of the chorda tympani or the tympanic plexus. The destruction of nerve bundles carrying the parasympathetic innervation reduces saliva secretion by the submandibular and sublingual glands.

Bilateral neurectomy is believed to carry disadvantages (e.g., hearing loss) that outweigh the benefits, and appears to control sialorrhoea poorly when used alone. The chorda tympani also carries taste information for the anterior two-thirds of the tongue; an ethical dilemma arises regarding the reduction of a sense in patients who already have a reduced quality of life.[42] Surgery of the salivary glands and duct has reliably been applied to sialorrhoea, mainly in the field of paediatric surgery, due to their long-lasting effects and low side-effects. Bilateral ligation of the parotid gland duct with the combined removal of the submandibular glands appears to be a simple and effective procedure. Other techniques have also been applied.[11] Explorative studies regarding this topic are advised before clinical implementation.

CONCLUSION

Sialorrhoea assessment and treatment represent common issues of palliative care in ALS patients. Besides improvement in quality of life, sialorrhoea management might reduce the risk of aspiration-related complications, potentially resulting in extremely relevant benefits for these patients. Although anticholinergic drugs are most commonly used, they are often insufficient to control these symptoms, unless at the cost of severe side-effects. Therefore, physicians should be aware that different techniques are at hand for overcoming these limitations. These can be easily introduced in clinical practice; if required, patients should be referred to the closest specialised centre. Other studies are certainly required to provide more satisfactory options for managing this still troublesome problem. Currently, ongoing randomised clinical trials are predominantly focussed on exploring BTx options (ClinicalTrials.gov Identifier: NCT01565395, NCT01551940, NCT01994109), but other drugs might be considered as well, for example, those coming from similar fields, such as mirtazapine or guanfacine for clozapine-induced sialorrhoea.

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