LETTER

Sialorrhoea and reversals in ALS functional rating scale

INTRODUCTION

Sialorrhoea is a common debilitating symptom in amyotrophic lateral sclerosis (ALS). It occurs when there is excessive saliva in the mouth beyond the lip margin. In ALS, sialorrhoea is not related to the increased production of saliva but to the impaired swallowing resulting from dysfunction of bulbar muscles. Swallowing requires an efficient coordination of several muscles in the mouth, pharynx, larynx and oesophagus, involved in oral, pharyngeal and oesophageal phases of the swallowing process. The first phase is under voluntary control, while the remaining steps are automatic. Spontaneous swallowing is necessary for drool control. Salivary secretion is regulated via a reflex arc with the information processed in the salivary nuclei in the medulla oblongata. Theafferent pathway consists of chemoreceptors in taste buds, mechanoreceptors in the periodontal ligament and afferents in the V, VII, IX and X cranial nerves. Parasympathetic efferences enter the VII (submandibular, sublingual and minor glands) and IX cranial nerves (parotid gland). In bulbar patients, dysphagia, weak mouth occlusion, head drop, impaired tongue-palate coordination and swallowing reflex impairment increase the risk of sialorrhoea. Pharyngo-oesophageal dysfunction can lead to aspiration and the unpleasant feeling of thick saliva in the pharyngeal walls.

Excessive saliva in the mouth can cause halitosis and perioral skin erosion, which have professional and social implications. Increased risk of dehydration and reduced compliance with facial masks on non-invasive ventilation are relevant problems. Anticholinergic drugs, botulinum toxin injections and salivary gland irradiation are used to treat sialorrhoea, which can provide transitory or permanent relief.

With the present study, we aimed to evaluate the impact of sialorrhoea on the functional scoring as assessed by the ALS functional rating scale (ALSFRS). We anticipated that its treatment could impact on the ALSFRS scoring, thus having implications in the clinical trials that use this scale.

METHODS

Consecutive ALS patients observed in our unit from August 2000 to December 2014 were included. Patients with other medical or neurological conditions were excluded, including diabetes, lung disorders and clinical dementia. ALSFRS, ALSFRSb, the second question (Q2) of ALSFRS addressing sialorrhoea, as well as the first (Q1) and the third (Q3) questions addressing, respectively, dysarthria and dysphagia were recorded. All evaluations were performed by the authors (SP, MdC). Each question in ALSFRS is scored from 4 (normal performance) to 0, representing 3, 2 and 1 a progressive worsening of the functional status. ALSFRSb was calculated by adding Q1, Q2 and Q3.

Patients were evaluated at study entry (T0), 3 (T1), 6 (T2) and 9 months after (T3). Further assessments were not considered due to dropout and anticipated floor-effect. No patient had any therapeutic intervention to prevent sialorrhoea at T0. Anticholinergic drugs (amitriptyline and/or atropine sulphate) were prescribed to all patients with a Q2 score lower than 3. No patient received parotid irradiation or botulinum toxin injection. Progression of the total ALSFRS, ALSFRSb, Q1, Q2 and Q3 were considered. Decay between successive times was evaluated by repeated-measures ANOVA. Pearson’s correlation coefficient with the Bonferroni correction was used to correlate the pairs Q2–ALSFRSb, ALSFRS–ALSFRS, Q2–(Q1+Q3) and ALSFRSb–(ALSFRS-minus-ALSFRSb) in each evaluation period. Multiregression model analysis was used to test if Q1, Q2 and Q3 were independently related to the ALSFRSb decay. Values of p<0.05 were considered significant.

The local Ethics Committee approved the protocol described.

RESULTS

We included 533 ALS patients (295 men; mean onset age: 61.3±12 years; mean disease duration from onset: 17.3±21.6 months) followed for at least 6 months and with clinical progression. Spinal onset was reported in 352 patients, bulbar onset in 158 and respiratory/axial onset in 23. Evaluation at T3 was possible in 435 patients.

All variables decayed significantly between evaluations (p<0.001) (table 1). ALSFRS, ALSFRSb, Q1, Q2 and Q3 were all significantly intercorrelated at each time (p<0.001). Each score was intercorrelated in successive timing period evaluations (p<0.001). Q2 was significantly correlated with Q1 and Q3 at each time (p<0.001). ALSFRSb was not correlated with ALSFRS-minus-ALSFRSb score at any time (p>0.05). ALSFRSb was significantly dependent on all three bulbar questions (Q1, Q2, Q3) at each time (p<0.001), with similar coefficients for each question (Q1, Q2 and Q3: T0: 0.99, 0.99, 0.99; T1: 0.99, 1.00, 1.00; T2: 0.99, 1.00, 0.93; T3: 1.00, 0.99, 0.99, respectively).

In 40 (7.5%) patients, ALSFRSb improved between T0 and T1 (p<0.001, mean±SD: 8.2±2.7 and 9.6±2.1, respectively), including Q1 in 10 patients (p=0.006), Q2 in 22 patients (p<0.001) and Q3 in 16 patients (p=0.003). ALSFRS was stable (29.8±5.5 and 29.6±6.5, p=0.19), but ALSFRS-minus-ALSFRSb score declined significantly (21.7±5.26 and 19.4±6.4, p<0.001). From these 40 patients, ALSFRSb improved in 4 between T1 and T2 and in 2 between T2 and T3 due to the Q2 improvement. Between T1 and T2, ALSFRSb improved in 49 (9.2%) patients (7.5±3.07 and 8.9±2.9, respectively, p<0.001) and Q2 (p<0.001) and Q3 (p=0.038) also improved, but not Q1 (p=0.13). ALSFRS and ALSFRS-minus-ALSFRSb scores decayed significantly (26.7±7.4 and 25±8.04, respectively, for ALSFRS, p=0.039; 19.2±6.6 and 16.2±7.1, respectively, for ALSFRS-minus-ALSFRSb, p<0.001). Between T2 and T3, ALSFRSb improved in 45 (8.4%) patients (6.7±3.3 and 7.87±3.2, respectively).

Table 1 Mean values of amyotrophic lateral sclerosis functional rating scale, ALSFRSb, Q1, Q2, Q3 at T0 (study entry), T1 (3 months after T0), T2 (6 months after T0) and T3 (9 months after T0)

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>p Value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALSFRS</td>
<td>32.5±5.2</td>
<td>29.4±6.7</td>
<td>26.3±8.2</td>
<td>24.8±8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALSFRSb</td>
<td>32.0±2.34</td>
<td>29.6±2.26</td>
<td>27.4±4.3</td>
<td>25.8±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Q1</td>
<td>3.3±0.95</td>
<td>3.0±0.12</td>
<td>3.1±0.13</td>
<td>3.0±0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Q2</td>
<td>3.5±0.87</td>
<td>3.3±0.87</td>
<td>3.1±0.13</td>
<td>3.0±0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Q3</td>
<td>3.4±0.74</td>
<td>3.3±0.87</td>
<td>3.0±0.17</td>
<td>2.9±0.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

p Value (ANOVA repeated measures for T0–T1, T1–T2, T2–T3) is given for the decay between each evaluation period for each variable. ALSFRSb, bulbar score of ALSFRS; ALSFRS-R, revised ALSFRS; Q1, first question of ALSFRS, addressing dysarthria; Q2, second question of ALSFRS, addressing sialorrhoea; Q3, third question of ALSFRS, addressing dysphagia; T0, time evaluation at study entry; T1, time evaluation 3 months after study entry; T2, time evaluation 6 months after study entry; T3, time evaluation 9 months after study entry.
p<0.001). In these patients, Q2 also improved (p<0.001), but not Q1 (p=1) and Q3 (p=0.54). ALSFRS remained stable (26.0±7.2 and 25.5±7.5, respectively, p=0.4), but ALSFRS-minus-ALSFRSb continue declining significantly, although with a lesser step decrease when compared with the significant decrease in the other described groups in earlier evaluation periods (19.3±7.0 and 17.67±7.7, respectively; p=0.002).

DISCUSSION

In our population, the three questions of ALSFRS were highly intercorrelated and with ALSFRSb. All scores declined significantly in each 3-month interval. However, we observed that 7–9% of the ALS patients followed for 9 months showed improvements in ALSFRSb. These improvements, nevertheless, were not powerful enough to cause reversals in the total ALSFRS. In fact, we considered ALSFRS and not the revised ALSFRS to avoid improvements derived from the respiratory symptoms, as described elsewhere.9

Interestingly, improvements in ALSFRSb involved dysarthria–sialorrhoea–dysphagia in the first 3-month period, sialorrhoea–dysphagia in the next period and only sialorrhoea in the last period. This later symptomatic improvement could be due to the anticholinergic treatment prescribed to the patients. The initial transitory improvement of dysarthria and swallowing is more difficult to explain. We speculate that in this population, it is possible that a transitory adaptation to bulbar dysfunction may have had a positive impact on symptoms and improvement in sialorrhoea may also impact improvement in the other bulbar questions. Plateaus (periods during which there is no ALSFRS change) and short lasting reversals (periods with improvement in ALSFRS scores) in ALS progression have been recently shown, but there is no generally accepted explanation for it.9 10

We conclude that short lasting reversals are observed in bulbar symptoms and longer sialorrhoea-symptom reversals probably derive from the sialorrhoea treatment. This additional information should be considered in clinical trials.

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