J Neurology Neuromedicine
www.jneurology.com
Journal of Neurology & Neuromedicine

Mini Review Open Access

Fiberoptic Endoscopic Evaluation of Swallowing as possible index of ALS clinical development

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Article Info

Article Notes
Received: January 11, 2017
Accepted: February 14, 2017

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Keywords
Dysphagia
Amyotrophic Lateral Sclerosis
Fiberoptic Endoscopic Evaluation of Swallowing
ALSFRS
b-ALSFRS

ABSTRACT

Our purpose was to assess the relationship between the disease severity of Amyotrophic Lateral Sclerosis (ALS) and the main parameters of Fiberoptic Endoscopic Evaluation of Swallowing (FEES), indirectly hypothesizing for FEES a role as clinical indicator of the progression of ALS. We studied 220 patients (101 women, 119 men) with ALS; of these, 148 had spinal and 72 bulbar onset. They were analyzed according to the Amyotrophic Lateral Sclerosis Functioning Rating Scale (ALSFRS) and the b-ALSFRS subscale (bulbar scale). All subjects underwent FEES. Post-swallowing residue was classified into four classes (0-3); premature spillage and aspiration were considered either present or absent. An in-depth statistical analysis revealed a highly significant relationship between the FEES parameters studied and the severity of the disease assessed through ALSFRS and b-ALSFRS ($p < 0.0001$), no matter what bolus texture was used. Moreover, statistical analysis showed a highly significant association between the classes of severity in bulbar forms and all the FEES parameters, no matter what type of bolus was administered ($p <0.0001$), whereas a significant correlation in spinal forms only for post-swallowing residue with solid ($p= 0.025$) and semisolid ($p= 0.034$) boluses. FEES is a good indicator of the severity of dysphagia and of its progression in patients with ALS, as well as of the clinical progression of the disease.

Fiberoptic Endoscopic Evaluation of Swallowing (FEES) is an excellent method in the study of swallowing disorders: it allows to directly view the pharyngeal phase of swallowing, permitting precise assessment of any premature spillage, post-swallowing residue in the hypo-pharyngeal region, as well as penetration and/or aspiration incidents in the lower respiratory tract. It is easy to perform, well tolerated, not requiring exposure to radiation, suitable for bedside examination, inexpensive, and with rare side-effects[1]. It is necessary to remember that potential complications and adverse effects of FEES are very few. In one of our previous studies, we found significant complications such as posterior epistaxis in one patient (0.04%) and laryngospasm only in two patients (0.07%) out of 2,820 patients[1]. Moreover, its repeatability makes FEES especially suitable for the follow-up of dysphagic patients, in particular for patients suffering from Amyotrophic Lateral Sclerosis (ALS)[2-4].

ALS is a neurodegenerative disorder characterized by upper and lower motor neuron degeneration. Starting insidiously in adulthood, it leads to death within 1-5 year[5]. The body region of symptoms onset (spinal onset or bulbar onset), the predominant upper or lower motor neuron involvement and the rate of disease progression bring the phenotypic variability.

ALS is very frequently complicated with dysphagia, that may be the presenting symptom in 30% of the cases and nevertheless occurs in

about 80% of the cases during the course of the disease[6]. It is a mixed type of dysphagia, involving both the central motor neuron (pseudobulbar paralysis) and the second motor neuron located in the motor nuclei of the brainstem (bulbar paralysis)[7]. Dysphagia affects the first three phases of swallowing (buccal, oral and pharyngeal)[8,9] and progresses to make it impossible for the patient to feed orally. Dysphagia in patients with ALS has been studied with Videofluoroscopy, with FEES, and with Oro-Pharyngeal-Esophageal Scintigraphy (OPES)[3,10-13].

In a previous recently published work, we have demonstrated that in cases of oro-pharyngeal dysphagia, FEES, compared to Videofluoroscopy and OPES, presents a good overall validity in assessing dysphagia and, in particular, shows a good sensitivity to detect post swallowing residue and a good specificity for premature spillage[14].

With this in mind, we searched for a relationship between the clinical severity of ALS and the main FEES parameters (premature spillage, post-swallowing residue and aspiration), indirectly hypothesizing for FEES a role as clinical indicator of the progression of ALS.

220 patients with ALS were studied (101 women and 119 men, mean age 63.82 ± 12.16 yrs SD); the onset of the disease was spinal in 148 of these and was bulbar in 72.

The patients were classified according to the Amyotrophic Lateral Sclerosis Functioning Rating Scale (ALSFRS) and the b-ALSFRS subscale (bulbar scale)[15-17]. The ALSFRS scale is a validated questionnaire based on a score, which measures physical function while performing normal daily activities. It includes four domains (bulbar functions, gross motor tasks and fine motor tasks, respiratory function) with scores ranging from 0 (severe disability) to 4 (no disability). Based on the overall score and the b-ALSFRS bulbar score (3 items: language, salivation, swallowing), the 220 patients were divided into three classes with increasing severity (Table 1).

ALSFRS	Class I (score 40-31)	Class II (score 30-11)	Class III (score 10-0)
	102 pts	109 pts	9 pts
b-ALSFRS	Class I (score 12-10)	Class II (score 9-4)	Class III (score 3-0)
	74 pts	121 pts	25 pts

Table 1: Classification of studied patients according to ALSFRS and b-ALSFRS scores.

All subjects underwent a medical history evaluation (in particular, investigating the dysphagia symptom and episodes of aspiration), a phoniatric examination and Fiberoptic Endoscopic Evaluation of Swallowing (FEES) using boluses of different texture: Liquid, 5cc of water marked with methylene blue; Semi-solid, 5cc jellied drink (jellied drink, Novartis SA®); Solid, bolus (¼) of cracker biscuits. All the patients signed a specific informed consent[18].

The post-swallowing residue parameter of the FEES investigation was divided into four classes of increasing severity (score from 0 to 3) according to the pooling-score of the Farneti scale[19,20], while for the premature spillage parameter and for penetration/aspiration we considered either presence (score 1) or absence (score 0) (Table 2). This further division allowed us to compare any possible correlation between the clinical status of the disease (average score and ALSFRS and b-ALSFRS classes) and the parameters obtained with the FEES investigation.

Statistical analysis was performed in the following way: sample characteristics were assessed using descriptive statistics and categorical variables were expressed as percentages. We performed the Spearman correlation test (Spearman's Rho) between the classified variables (premature spillage, post-swallowing residue, aspiration) and the continuous variable (ALSFRS and b-ALSFRS). The correlation is inverse (negative) because the FEES parameters worsen from 0 to 1, while the ALSFRS score worsens contrary-wise from class III to II to I. Comparison between the classified variables for the different bolus textures (premature spillage, post-swallowing residue, aspiration) and the continuous variable (ALSFRS, b-ALSFRS), analysis of variance (ANOVA) or Independent T-Test models and post-hoc tests (Bonferroni) were performed. Then, we performed a non parametric analysis of the variance (Kruskal-Wallis test) between the categorized variables (premature spillage, post-swallowing residue, aspiration) and the scores in the classes (Classes I, II and III for the ALSFRS and b-ALSFRS scores).

Statistical analysis aimed to study the correlation between the clinical severity of ALS (assessed through ALSFRS and b-ALSFRS) and the main FEES parameters. As we have demonstrated in our recently published study, statistical analysis performed on 202 patients showed that FEES not only detects the presence of bolus aspiration, but also correlates the progressive worsening of some

Premature spillage	0 Absent	1 Present		
Aspiration	0 Absent	1 Present		
Post-swallowing residue	0 Absent	1 Coating	2 Minimum	3 Maximum

Table 2: FEES parameters considered in the study.

Parameters of FEES	Spearman's Rho ALSFRS	p	Spearman's Rho b-ALSFRS	p
Premature spillage-L	-0.304	**Liquid** p<0.0001	-0.428	**Liquid** p<0.0001
Residue-L	- 0.500		- 0.525	
Premature spillage-SS	- 0.338	**Semisolid** p<0.0001	- 0.421	**Semisolid** p<0.0001
Residue-SS	-0.509		-0.482	
Premature spillage-S	- 0.328	**Solid** p<0.0001	- 0.446	**Solid** p<0.0001
Residue-S	- 0.510		- 0.455	

Table 3: Spearman correlation test (Spearman's rho) ALSFRS and b-ALSFRS for premature spillage and post-swallowing residue with liquid (L), semisolid (SS) and solid (S) bolus.

Aspiration	Spearman's rho	p
ALSFRS (mean±SD)	- 0.335	p < 0.0001
b-ALSFRS (mean±SD)	- 0.405	p < 0.0001

Table 4: Spearman correlation test (Spearman's rho) ALSFRS and b-ALSFRS for aspiration.

Aspiration	NO	YES	Independent T-Test
ALSFRS (mean±SD)	32.27±10.3	23.86±9.6	p < 0.0001
b-ALSFRS (mean±SD)	10.02±1.9	5.98±5.2	p < 0.0001

Table 5: Statistically significant difference between mean ALSFRS and b-ALSFRS scores in the presence/absence of aspiration.

swallowing parameters, such as premature spillage and post-swallowing residue, with severity of the disease[21].

Among the 220 patients studied, the correlation between the value of the scores (ALSFRS and b-ALSFRS) and the parameters obtained through the FEES investigation (premature spillage,post-swallowing residue and aspiration), revealed a highly significant correlation for all the bolus textures administered (p <0.0001), showing a close relationship between severity of the disease (assessed by the ALSFRS and b-ALSFRS scores) and severity of dysphagia (assessed by the categorized premature spillage, post-swallowing residue and aspiration variables). The FEES parameters considered in our study (premature spillage, post-swallowing residue, aspiration) are hence strongly correlated with the severity of the disease, both in bulbar onset forms and in spinal onset types, regardless of the bolus consistency used (Tables 3, 4).

By performing an analysis of variance between the mean value of the score (ALSFRS and b-ALSFRS) and presence/absence of aspiration, we found a highly significant difference (p <0.0001) between the mean ALSFRS and b-ALSFRS score and the presence/absence of aspiration. In particular, patients with spinal onset had a higher mean ALSFRS score in the absence of aspiration (absence of aspiration: 32.27 ± 10.3 vs. presence of aspiration: 23.86 ± 9.6) with a statistically significant difference (p <0.0001). Similarly, the mean b-ALSFRS score in patients with bulbar onset was higher in the absence of aspiration (absence of aspiration: 10.02 ± 1.9 vs. presence of aspiration: 5.98 ± 5.2) with a highly significant difference (p <0.0001) (Table 5). These data indicate that patients with aspiration events have lower mean scores, therefore the disease is more serious in their case. Thus, even this statistical analysis confirms that aspiration assessed by FEES is closely related with the clinical stage of disease severity.

Among the FEES parameters, post-swallowing residue

FEES parameters	p ALSFRS	p b-ALSFRS
Aspiration	0.486	< 0.0001
Residue-Solid	0.025	< 0.0001
Premature spillage-Solid	0.148	< 0.0001
Residue-Semisolid	0.034	< 0.0001
Premature spillage-Semisolid	0.281	< 0.0001
Residue-Liquid	0.093	< 0.0001
Premature spillage-Liquid	0.246	< 0.0001

Table 6: Kruskal - Wallis Test.

resulted the most significant one for correlating the endoscopic investigation with the clinical stage of the disease. Moreover, in patients with bulbar onset, who have greater difficulty in managing the boluses, particularly since the oral-pharyngeal muscles are involved, the post-swallowing residue parameter detected with the liquid bolus correlates the severity of the disease better (compared to other consistencies) with the result of the FEES. In fact, patients with spinal onset had a more significant value for the post-swallowing residue parameter with all three consistencies (Spearman's Rho ≤ - 0.500), while in those with bulbar onset the most significant value was always for post-swallowing residue, but only in the case of the liquid bolus administration (Spearman's Rho = - 0.525).

The analysis of variance between variables and the FEES scores categorized into classes (Class I, II and III for the ALSFRS and b-ALSFRS scores) showed that the classes of severity in the bulbar forms (b-ALSFRS) are associated in a highly significant manner with all the FEES parameters studied, no matter what type of the bolus was administered (p <0.0001), whereas in the spinal forms (ALSFRS) it revealed a statistically significant correlation only for the post-swallowing residue parameter in the case of solid boluses (p= 0.025) and semisolid boluses (p= 0.034) (Table 6). Hence, in the bulbar form of ALS evaluated according

to the b-ALSFRS scale, which takes into account language, salivation and swallowing, the FEES investigation allows to follow the clinical course of the disease through all the parameters considered, regardless of the texture of the bolus. In fact, the severity of the disease and its evolution is mainly linked to deficit of the oro-pharyngeal-laryngeal structures involved, that is to say, swallowing. However, in patients with spinal onset form, evaluated into classes of gravity through the more general ALSFRS scale (which globally considers bulbar functions, gross motor tasks, fine motor tasks and respiratory function), the most sensitive FEES parameter for monitoring the severity of the disease in classes is post-swallowing residue of solid and semisolid boluses. The post-swallowing residue parameter with FEES and its division into subclasses (0 = Absent, 1 = Coating; 2 = Minimum, 3 = Maximum) demonstrate an overall remarkable precision, and in particular a considerable sensitivity for monitoring the progressive worsening of the symptoms even in the spinal forms.

The FEES parameters studied and the severity of the disease assessed through ALSFRS and b-ALSFRS revealed a highly significant relationship: in patients belonging to classes of greater severity, a greater deterioration of the FEES parameters is also observed. FEES is a good indicator of the severity of dysphagia and of its progression in patients with ALS, as well as of the clinical progression of the disease. It makes FEES a suitable, useful and reliable test for the follow-up of oro-pharyngeal dysphagia in patients with ALS, whether of spinal or bulbar onset.

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