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Original article

Semantic memory assessment in 15 patients with amyotrophic lateral sclerosis

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ABSTRACT

Introduction. – A total of 30 to 50% of amyotrophic lateral sclerosis patients suffer from cognitive disorders. The aim of the study is to characterize these disorders and to assess semantic memory in non-demented ALS patients. The secondary aim is to look for a link between disease type and neuropsychological characteristics.

Method. – Patients were followed in an ALS center in Dijon. The following neuropsychological tests were used in this study: Folstein test, BREF test, verbal fluency, Isaac test, GRESEM test and TOP 30 test.

Results. – Fifteen ALS patients were included. Nine of them (60%) were suffering from a semantic memory disorder. There was no correlation between ALS characteristics and the semantic memory disorder.

Discussion. – This is the first study to reveal a semantic memory disorder in ALS. This result accentuates the hypothesis that ALS and semantic dementia are two phenotypes of the same degenerative process linked to TDP 43 proteinopathy.

1. Introduction

Amyotrophic lateral sclerosis is a frequent neurodegenerative disease that leads to the progressive degeneration of motor neurons of the anterior horn of the spinal cord, the bulbar cranial nerves and the pyramidal tracts.

ALS has long been considered a purely motor disease. However, neuropsychological studies carried out in patients with ALS suggest that cognitive impairment does occur and affects executive functions in half of the cases [1]. In 15% of patients [2], symptoms evolve towards true dementia of the fronto-temporal lobar degeneration spectrum. Though some cases of ALS associated with primary progressive aphasia and semantic dementia have been described, the phenotype of the frontal variant of fronto-temporal dementia (FTD) is frequently associated with ALS. In addition, 15% of patients with FTD develop ALS [3,4].

A discovery in anatomic pathology reinforced the idea that ALS and FTD could be two clinical phenotypes of the same degenerative process. Indeed, in 2006, Neumman et al. identified the protein TDP 43 as the abnormally-folded protein of ubiquitin-positive inclusions found in both ALS and FTD patients: FTD-U patients. The clinical expression of this

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proteinopathy could therefore be purely motor (ALS) or purely cognitive (FTD) or cognitive and motor symptoms could overlap. Finally, more recently, mutation of the *c9ORF72* gene, which is situated on chromosome 9 and associated with the abnormal repetition of a hexanucleotide, was identified as the major mutation in forms of DFT-ALS. All of these patients had TDP 43 inclusions.

Semantic dementia, a clinical syndrome of the FTD spectrum, is almost exclusively a TDP 43 disease [5,6], in contrast to primary progressive aphasia and the frontal variant of FTD, which is frequently associated with tauopathy or Alzheimer-type lesions. It therefore seems logical that semantic memory is affected in patients with ALS. Neuropsychological studies conducted in ALS, however, have never specifically evaluated semantic memory. There have been several cases of ALS-related semantic dementia described in the literature, suggesting that there may be minor disorders of semantic functions in ALS [4,6–8].

The principal objective of our study was to assess semantic memory in patients with ALS and to determine whether the deterioration affected predominantly visual, verbal or global semantic memory. In order to do this, patients were asked to undergo psychometric tests with verbal and visual cues. Our secondary objectives were on the one hand to determine a particular profile of patients suffering from semantic memory disorder by comparing the normal group with the affected group and on the other hand to seek correlations between the results obtained in the cognitive screening tests used in routine practice (MMS and BREF) and the results of psychometric tests specific for semantic memory.

2. Materials and methods

Our study was approved by the Ethics Committee of Dijon CHU.

2.1. Selection of the population

For all of the patients, the diagnosis of ALS was raised or confirmed by a neurologist of the ALS center. The study took place between December 2009 and June 2010.

The exclusion criteria were the presence of any of the following clinical symptoms, which would have hampered the tests: anarthria, a severe visual or hearing disorder, vigilance disorders, dyspnea; a mother tongue other than French; a prior diagnosis of dementia; a hereditary form of SOD+ ALS. The presence of a single criterion was enough to exclude the patient.

The demographic characteristics of the patients were recorded: age, sex, profession, pre-morbid intellectual level. The pre-morbid intellectual level was determined using a scale based on the Signoret scale, which includes 3 levels: level 1: 8 years or less of formal education, corresponding to a school-leaving age of 16 years or less, with or without a school-leaving certificate; level 2: between 8 and 11 years of formal education, corresponding to school-leaving age of 17 years or more, with or without the various diplomas, but without the high-school diploma; level 3: 12 years or more of formal education, generally corresponding to higher education.

Their neurological history and usual treatments were recorded. The characteristics of their disease were also noted: age at onset of the disorders, type of onset (spinal or bulbar), sporadic or hereditary form, evaluation of the severity of the bulbar involvement using the Norris bulbar score and assessment of severity using the ALSFRS-R score.

2.2. Psychometric tests

The neuropsychological evaluation was broken down as follows: evaluation of global cognitive performance using the MMS; rapid evaluation of executive functions using the BREF; evaluation of the lexico-semantic stock or access to the lexico-semantic stock using the verbal and category fluency test (Cardebat et al. for semantic fluency and GREFEX, Rosser et al., for initial-letter fluency) and the Isaac test [9]; evaluation of the identification, comprehension and naming of items presented in the verbal and visual BECS-GRECO battery; identification of famous persons test (TOP 30 battery, Catherine Thomas Anterion, Solal).

We then identified three distinct types of impairment, impairment of semantic knowledge on visual cues (right-side involvement), by using three tests: the visual items of the BECS-GRECO battery (GRESEM visual), the evocation tests of the TOP 30 battery and the recognition tests of the TOP 30 battery; impairment of semantic knowledge on verbal cues (left-side impairment), using three tests: the 2-minute category fluency test, the Isaac Set Test and verbal items of the BECS-GRECO battery; and finally, global impairment, diagnosed when the patient failed two tests for one sensory domain (visual or verbal) and at least one test from the other domain.

A test result was considered pathological if the Z-score was less than −2 standard deviations (−2 SD). In accordance with what is classically reported in neuropsychology research, we considered that semantic knowledge was impaired in a domain (verbal or visual) if the patient failed two out of three psychometric tests.

2.3. Statistical methods

We compared demographic and disease characteristics and the results obtained in MMS and BREF in normal groups with those in impaired groups. Given the small sample size, this comparison was done using the Mann–Whitney U test for quantitative variables.

We then looked for correlations between performances in the usual cognitive tests (MMS and BREF) and the degree of impairment of semantic memory. We also looked for correlations between demographic and disease characteristics of the patients and the existence of impaired semantic memory. The Spearman test was used to look for correlations.

3. Results

3.1. Selection of the population

During the study period, 45 patients consulted at the ALS center. For 11 of these, it was not possible to organize a neuropsychological examination on the day of the multidisciplinary consultation.

Four refused. Four others were lost to follow-up and 11 patients were excluded: three had an insufficient level of French, five had severe dysarthria, two suffered from dyspnea, and one had dementia.

3.2. Demographic characteristics of the patients

We therefore included 15 patients in our study between December 2009 and June 2010. Their demographic characteristics are presented in Table 1.

The mean age of included patients was 61.2 years. The mean age at the onset of the disorders was 59.86 years. The sex ratio was three men for one woman.

3.3. Clinical characteristics of the patients

According to the El Escorial criteria, eight of the 15 patients (53.3%) had definite ALS, 3/15 (20%) probable ALS and 4/15 (26.6%) possible ALS. No patients presented the bulbar form, 12 of the 15 patients (80%) had the spinal-onset form and three of the 15 patients (20%) had generalized-onset form. At the end of the study, 12 of the 15 patients (60%) presented generalized ALS. Only one patient had the hereditary form of ALS (SOD negative). All of the patients were treated with Riluzole and Vitamin E. Three patients were also treated with psychotropic agents (antidepressants and/or anxiolytics) (Table 1).

3.4. Analysis of the results of the psychometric tests

The results obtained in the MMSE and the BREF are presented in Table 1.

3.5. Interpretation of the results

3.5.1. Left-side semantic impairment

For all of the patients, the scores in the GRESEM verbal test were in the normal range. Patients with semantic deficits were therefore those who failed both the two-minute category fluency test and the Isaac Set Test. Patients 1, 2, 7, 8, 9 and 10 were in this group. Seven of the 15 patients thus presented impaired semantic knowledge for verbal cues (Table 2).

3.5.2. Right semantic impairment

The results are presented in Table 2. For all of the patients, the scores in the GRESEM visual test were within the normal range. Patients with impairments were therefore those who failed both the evocation test and the TOP 30 recognition test. Patients 2, 7, 8, 9, 10, 11, 14 and 15 were in this group. Eight of the 15 patients thus presented impaired semantic knowledge on visual cues (Table 2).

3.5.3. Global semantic impairment

Multi-domain or global semantic impairment was defined as impaired semantic knowledge whatever the type of cue (here, verbal or visual). We reached a diagnosis of global impairment when patients failed two tests based on one type of cue and one test based on the other type of cue.

Global impairment of semantic knowledge was thus found in patients 1, 2, 4, 5, 8, 9, 10, 11 and 15. Nine of the 15 patients thus presented global impairment of their semantic knowledge (Table 2).

3.6. Comparison of patients according to their cognitive profile

Finally, we compared the disease and demographic characteristics and the results of the cognitive screening tests in patients presenting a global semantic deficit with those in the other patients. Once again, no significant difference was found between these two groups whatever the variable tested.

3.7. Correlation studies

There was no significant correlation between the demographic characteristics of patients and the presence of global semantic impairment, nor was there a correlation between the

Table 1 – Demographic and disease characteristics of patients and memory assessments.

Patient	Age	Sex	SCL	Duration of the disease (months)	Type of onset	Type of ALS	ALSFRS-R score	Norris Bulbar score	MMSE	BREF	Hand laterality Right/Left
1	47	M	1	24	Generalized	Fam (SOD-)	46	34	25	10	R
2	76	M	1	8	Spinal	Spo	41	33	30	17	R
3	63	F	3	6	Spinal	Spo	30	34	NE	NE	R
4	50	M	1	5	Spinal	Spo	44	39	26	13	R
5	40	F	1	13	Generalized	Spo	32	33	29	18	R
6	56	M	1	5	Spinal	Spo	37	39	25	15	R
7	62	M	3	108	Spinal	Spo	43	39	27	18	R
8	66	M	1	18	Spinal	Spo	36	37	29	14	R
9	63	M	1	7	Spinal	Spo	36	37	22	17	R
10	71	F	1	72	Spinal	Spo	27	33	20/25	NE	R
11	77	M	1	16	Spinal	Spo	32	36	21	8	R
12	61	M	1	3	Generalized	Spo	NE	NE	26	14	R
13	80	F	1	17	Spinal	Spo	36	36	27	17	R
14	20	M	1	6	Spinal	Spo	48	39	30	18	R
15	87	M	1	9	Spinal	Spo	48	39	30	15	R

NE: not evaluated; SCL: sociocultural level.

Table 2 – Results of left and right semantic memory tests and integrative analysis. Left semantic memory tests: category fluency, Isaac Set Test and GRESEM verbal. Right semantic memory tests: GRESEM visual and TOP 30. Global impairment: two failed tests on either verbal or visual cues associated with one failed test on the other domain (Semantic memory tests results).

Patient	C Fluency (Z-score)	Isaac (Z-score)	GRESEM Verbal (Z-score)	left impairment	GRESEM Visual (Z-score)	Top 30 Evoc (Z-score)	Top 30 Rec (Z-score)	right impairment	global impairment
1	11 (−11,56)	21 (−9,61)	39 (0,07)	+	40 (1,22)	41 (−0,44)	23 (−7,01)	–	+
2	17 (−4,1)	26 (−3,23)	40 (0,62)	+	40 (1,07)	4 (−11,55)	5 (−16,2)	+	+
3	14 (−4,13)	37 (−1,14)	39 (−1,15)	–	40 (1,07)	49 (−5,8)	29,5 (0,58)	–	–
4	15 (−9,33)	26 (−7,23)	40 (0,62)	+	40 (1,07)	58 (1,28)	29,5 (1,14)	–	+
5	20 (−2,92)	31 (−3,92)	39 (0,07)	+	40 (1,07)	30,5 (−1,56)	21 (−3,52)	–	+
6	42 (5,56)	32 (−4,38)	39 (0,07)	–	40 (1,07)	41 (−2,16)	29 (0,57)	–	–
7	38 (−0,7)	48 (1,76)	40 (0,62)	–	40 (1,07)	43,5 (−4,33)	25,5 (−6,6)	+	–
8	17 (−2,03)	32 (−4)	40 (0,62)	+	40 (1,07)	20,5 (−7,38)	18 (−8,59)	+	+
9	19 (−2,22)	21 (−11,3)	38 (−0,48)	+	40 (1,07)	24 (−6,41)	22,5 (−5,02)	+	+
10	11 (−5,41)	25 (−2,58)	39 (0,07)	+	40 (1,07)	14 (−9,07)	17,5 (−7,52)	+	+
11	12 (−0,88)	28 (−2,71)	36 (−1,59)	–	40 (1,07)	2 (−12,04)	0 (nc)	+	+
12	30 (−0,55)	30 (−3,42)	40 (0,62)	–	40 (1,07)	60 (2,39)	30 (1,32)	–	–
13	12 (−1,05)	27 (−2,25)	40 (0,62)	–	40 (1,07)	50 (1,45)	29 (2,41)	–	–
14	9 (−2,52)	32 (−1,46)	40 (0,62)	–	40 (1,07)	13 (−7,61)	16,5 (−9,09)	+	–
15	41 (1,62)	28 (−2,71)	40 (0,62)	–	40 (1,07)	0 (nc)	0 (nc)	+	+

duration of disease, the severity of the impairment or the presence of bulbar symptoms and global semantic impairment. There was no correlation either between the scores obtained in the MMS and BREF tests and the presence of global semantic impairment.

4. Discussion

This is the first study to specifically evaluate semantic memory in a cohort of ALS patients. Until now, only rare clinical observations concerning the association of semantic dementia (SD) and ALS have been published. However, the recent discovery of a pathological continuum between ALS and SD and the clinical observation of frequent cognitive-behavioral disorders of the FTD spectrum in patients with ALS led us to investigate this rarely studied cognitive domain.

4.1. *Impairment of the semantic memory in ALS*

Seven of the 15 patients suffered from impaired semantic knowledge on verbal cues. When their performances were examined in detail, it was discovered that none failed the GRESEM verbal test. Their impairment of semantic memory on verbal cues was only revealed by the category fluency test and the Isaac Set Test.

How can this dissociation be explained? Fluency tests do not concern the domain of semantic knowledge alone, but they also bring into play abilities in verbal initiation and mental flexibility, which depend on executive functions. The question thus arises as to whether failure in fluency tests was only due to executive dysfunction. Several arguments go against this hypothesis because in frontal diseases both types of fluency are impaired, with perhaps a predominance of alphabetic fluency.

In this study, among the nine patients presenting pathological category fluency scores, only two also had pathological alphabetic fluency scores. This result is clearly in favor of a disorder affecting the stock of semantic knowledge. In the same way, among the eleven patients who failed the Isaac Set Test only one patient also failed the alphabetic fluency test.

Finally, among the seven patients suffering from left semantic impairment, only three had a pathological BREF score. Their difficulties therefore seemed to be due to a true impairment of semantic memory.

The lack of sensitivity of the GRESEM could also explain this result, indicating that our patients were in the initial stages of semantic memory impairment. It is known that patients with Alzheimer disease suffer from impaired semantic knowledge early on in the disease, but at these initial stages, they can do the GRESEM test without fault.

The verbal fluency test is the only test that ALS patients with cognitive disorders invariably failed. This result is constant and generally concerns both alphabetic and category fluency, thus suggesting the presence of executive dysfunction [2,10–15]. In contrast, our results showed that patients predominantly failed the category fluency test. It is possible that by excluding dysarthric patients with predominant bulbar impairment, we selected patients with a different profile.

Eight of the 15 patients suffered from impaired semantic memory on visual cues. Again, all of our patients completed the GRESEM visual tests without fault and it was failure in the evocation and recognition tests of the TOP 30 battery that revealed the deficit, in particular for the identification of famous people.

How can this dissociation be explained? It is clear that unique items, such as famous people, are particularly difficult given their semantic specificity. In addition, in everyday life, patients are far less likely to come across images and names of famous people than an orange or a hammer, for example, which they are asked to identify in the GRESEM visual tests. It is therefore likely that the TOP 30 is more sensitive than an evaluation battery for semantic knowledge to reveal a disorder of semantic memory on visual cues.

Nine of the 15 patients (60%) in our cohort, suffered from global impairment of semantic memory. This is the first study to show that this cognitive domain is impaired in ALS.

This is the only study to investigate semantic memory in ALS patients without known dementia. The only other data on this subject are the rare clinical observations that describe patients with SD and ALS: two authors reported clinical observations of SD-ALS in which an impaired ability to name famous people led to a diagnosis of a right temporal form of semantic dementia [7,8].

4.2. *Search for a particular phenotype associated with semantic memory disorders*

We compared patients suffering from global impairment with the rest of the cohort. We found no significant difference between the groups with regard to their demographic and disease characteristics or their MMS and BREF results. As we have seen, the bulbar-onset forms and generalized forms associated with a high ALSFRS score are the forms most likely to develop into cognitive impairment. Here, we cannot comment on bulbar-onset forms as our cohort did not contain any. In our study, however, we found no evidence of a predisposition to cognitive impairment in patients with severe forms of ALS.

4.3. *Relationship between demographic and disease variables or MMS and BREF scores and impaired semantic memory*

Again, there was no statistical relationship between the patient's age, sociocultural level, sex or hand laterality and the existence of semantic disorders.

In the same way, there was no link between the patient's age at symptom onset, the type of onset, the sporadic or hereditary form or the severity of the ALS and the existence of semantic impairment.

Interestingly, there was no correlation either between the MMS and BREF scores and the presence of semantic impairment. Only five patients in our cohort had a pathological BREF score even though nine patients presented global impairment of semantic memory. Four patients therefore had a normal BREF score but semantic disorders. In contrast, patient 12 presented a pathological BREF score but not global semantic impairment.

The conference consensus issued by the HAS in 2006 on the management of patients with ALS recommends using the BREF in cases when the patient and his/her entourage report disorders concerning the psycho-behavioral domain. The text points out that there is no specific evaluation battery for this disease, but that the BREF is the most sensitive to screen for executive dysfunction, which essentially resumes cognitive impairment in patients with ALS.

Unfortunately, it seems that impairment of the memory and notably of semantic memory has been underestimated. It seems necessary to develop an evaluation battery for cognitive function adapted to ALS, which takes the domains of language and memory into account.

4.4. *Study limitations*

4.4.1. *Small sample size*

Given the small sample size, we cannot claim that the results are representative of all ALS patients. Our interesting results, however, deserve to be completed by a study involving a larger number of patients. This severe disease soon becomes extremely disabling and given the short median survival, it is difficult to gather large cohorts.

4.4.2. *Selection bias*

One exclusion criterion of our study was the presence of anarthria or dysarthria that was too severe to allow patients to take the tests. Because of this, we certainly excluded patients with a predominant bulbar form of the disease. Given the link between bulbar forms and the greater risk of executive dysfunction-type cognitive disorders, our results may not be representative of the cognitive disorders found in ALS patients.

4.4.3. *Absence of imaging*

The absence of morphological imaging is a major limitation of our study car because we cannot be certain that the cognitive disorders in our patients were the result of degeneration. Lesional causes should have been eliminated. It is, however, unlikely that the cause was stroke-related as none of the patients presented a sudden onset of the disorders. A chronic condition leading to leukoaraiosis could cause executive dysfunction, but no patients presented symptoms suggesting expansive focal lesions. Nonetheless, though a degenerative cause of the disorders seems most likely, imaging is an essential examination.

4.4.4. *Absence of a control group*

With regard to our results, the absence of a control group does not seem to be a true limitation as all of the psychometric tests we used are normalized for age, the intellectual level and sex.

As our aim was not to test the validity of the tests employed, we did not need a control group to determine whether or not our patients presented semantic disorders.

5. Conclusion

Thirty to 50% of patients with amyotrophic lateral sclerosis (ALS) suffer from cognitive disorders. This impairment has not yet been clearly characterized. Clinical observations of frequent cognitive-behavioral disorders of the FTD spectrum in non-demented ALS patients, the discovery of a common anatomic pathology in semantic dementia (SD) and ALS and the clinical observations of patients with both ALS and SD led us to explore the domain of semantic memory in ALS patients. This domain has rarely been studied in this disease. We found nine patients out of 15 (60%) with impaired semantic memory. This impairment did not correlate with either the characteristics of the disease or the MMSE and BREF scores. These results are of scientific interest because they support the notion that SD and ALS could be two clinical phenotypes of the same neurodegenerative process involving TDP 43 proteinopathy. They also raise questions of medical ethics because disorders of the semantic memory in this disease could affect the expression of autonomy in patients notably with regard to decisions at the extreme phase of the disease. Increasing the number of patients and including morphological and functional imaging data would have strengthened the validity of our results and provided more satisfactory responses in this

research into this degenerative semantic memory disorder in patients with ALS.

Disclosure of interest

The authors declare that they have no competing interest.

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