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Original research article

Is descriptive writing useful in the differential diagnosis of logopenic variant of primary progressive aphasia, Alzheimer's disease and mild cognitive impairment?



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ABSTRACT

Current classification of primary progressive aphasia (PPA) encompasses three variants: non-fluent (nfvPPA), semantic (svPPA) and logopenic (lvPPA). Previously lvPPA was regarded as aphasic form of Alzheimer's disease (AD). However, not all patients with lvPPA phenotype present with AD pathology. Despite abundant literature on differentiation of lvPPA from svPPA and nfvPPA, studies comparing lvPPA with AD and mild cognitive impairment (MCI) are scarce. This study aimed at analyzing written descriptive output in lvPPA, AD and MCI. Thirty-five patients participated in the study: 9 with lvPPA, 13 with AD and 13 with MCI. Most aspects of writing performance were comparable in three groups. However, letter insertion errors appeared in 44% patients with lvPPA, while they were absent in AD and MCI. Patients with lvPPA used more verbs than patients with AD. Writing profile may complement other neuropsychological assessment results in the differential diagnosis of lvPPA. Letter insertion errors and frequent verb use may raise a query of lvPPA.

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1. Introduction

Primary progressive aphasia (PPA) is currently regarded as a spectrum of progressive language disorders due to either frontotemporal lobar degeneration (FTLD) or Alzheimer's disease (AD). The most recent PPA subdivision encompasses its three variants: non-fluent (nfvPPA), semantic (svPPA) and logopenic (lvPPA) [1,2]. The last, logopenic variant, described formally in 2004 by Gorno-Tempini et al. [3] was previously regarded as language variant of AD [4]. Logopenic progressive aphasia is characterized by word-finding difficulties (with preserved semantic knowledge and word comprehension), impaired phonological processing and short verbal span causing deficient repetition and comprehension of long sentences [5-9].

While svPPA has a clinically distinct profile, with generalized semantic impairment and circumscribed temporal pole atrophy, the differentiation of lvPPA from nfvPPA remains challenging in the clinic [1,10-12], especially in patients with more advanced disease. In the research setting beta-amyloid imaging and cerebrospinal fluid biomarkers profile assessment are very useful for the differential diagnosis between AD and FTLD pathology [13]. However, their availability is very limited. Moreover, a subset of patients with lvPPA has negative beta-amyloid imaging [14]. Thus, the diagnosis of lvPPA is established mainly on the basis of the clinical presentation and longitudinal observation. Patients with lvPPA show rapid and wide-spread cognitive deterioration [7,15,16] and decline in the activities of daily living [17]. Several algorithms have been proposed to differentiate between three variants of PPA [18-20]. However, in the clinical practice lvPPA needs to be differentiated not only from nfvPPA and svPPA, but also from AD and mild cognitive impairment. This differentiation is important for planning patient management, as patients with lvPPA require more frequent neuropsychological follow-ups and language intervention.

Thus, neuropsychological assessment is crucial for early differential diagnosis. Magnin et al. [21] has recently shown that lvPPA (in comparison to AD and MCI) is characterized by a recent onset or aggravation of anxiety, preserved orientation to time, poor verbal span and fluency, dissociation between poor verbal memory performance and much better visual memory performance as well as very impaired mental calculation. This is to our knowledge, the only paper addressing the neuropsychological differential diagnosis of lvPPA from MCI and AD.

Agraphia in the context of AD is quite well described in the literature [22] and written output is more sensitive than spoken output to early language problems in AD [23]. In the course of AD initial lexical dysgraphia (that affects spelling of irregular words) progresses to phonological agraphia (that affects also spelling of regular words due to graphemic buffer impairment). Moreover, agraphia in AD is closely related to cognitive impairment, mainly attentional and executive deficits [22], typical for the later disease stages. Writing assessment in the context of AD spectrum differential diagnosis may also be helpful to detect parkinsonian features (more likely in nfvPPA than lvPPA) or spatial problems, suggestive of posterior cortical atrophy.

The current diagnostic criteria for PPA highlight the role of writing assessment in the diagnosis of svPPA, which is characterized by surface dysgraphia [1]. However, psycholinguistic assessment of spelling in patients with nfvPPA, lvPPA, svPPA and unclassified PPA showed that spelling errors lack variant specificity and all PPA patients, regardless of the PPA variant, may present with impaired access to lexical or lexical-semantic representations, impaired sublexical phonology-to-orthography conversion and graphemic buffer impairment [24]. Most commonly, patients with lvPPA have lexical or surface dysgraphia, but there are also reports of graphemic buffer disorder [25].

Our study aimed at establishing the value of written picture description in the differentiation of lvPPA from AD and MCI. It was hypothesized that lexical content will be most impoverished in lvPPA, due to prominent word-finding difficulties. Similarly, it was expected that spelling errors will be more common in lvPPA than in AD and MCI, because of primary phonological deficit in lvPPA.

2. Materials and methods

2.1. Participants

Thirty-five patients participated in the study: nine (seven women, two men) with the clinical diagnosis of lvPPA according to Gorno-Tempini et al. criteria [1], 13 with mild AD (seven women, six men) diagnosed according to the criteria by McKhann [26], scoring 1 on Clinical Dementia Rating (CDR) [27] and 13 patients with MCI (CDR = 0.5) (11 women, 2 men) according to the criteria by Petersen [28]. Within the MCI group eight patients had amnesic MCI and five multiple-domain MCI (amnesic with attentional deficits). The patients were diagnosed in two centers specializing in the differential diagnosis of neurodegenerative disorders. The groups were matched in terms of years of education (see Table 1), sex ($p = 0.196$) and time since onset ($p = 0.320$). The lvPPA group did not significantly differ in age either from MCI or AD group. The MCI group was significantly younger than the AD group. The median time since symptom onset was 2 years in both lvPPA and AD and it ranged from 1 to 10 years in lvPPA and from 1 to 6 years in AD. None of the patients reported the history of developmental language problems (e.g. dyslexia or dysgraphia). All participants volunteered for this study and provided informed consent to participate. The study procedures were approved by local Bioethics Committee.

2.2. Methods

To assess the patients' descriptive writing the untimed written description of one of three pictures was administered: Cookie theft picture from Boston Diagnostic Aphasia Examination-3 [29], picture from Frenchay Aphasia Screening test [30] or A beach scene by Prof. EK Warrington [31]. The choice of two pictures was due to the fact that most patients were administered an oral picture description task few days before the study procedure and the use of the same picture for a written task was not considered appropriate. Written picture description was administered by a neuropsychologist (EJS or

Table 1 – Demographic and clinical data in patients with logopenic progressive aphasia (LPA), Alzheimer's disease (AD) and mild cognitive impairment (MCI).

| | LPA n = 9 Mean (SD) | AD n = 13 Mean (SD) | MCI n = 13 Mean (SD) | p ^c | Significant intergroup differences |
|----------------------------------|---------------------------|---------------------------|----------------------------|----------------|--|
| Age | 70 (6) | 77 (5) | 67 (8) | 0.002 | AD vs. MCI ^a |
| Years of education | 13 (3) | 12 (4) | 13 (3) | 0.872 | – |
| MMSE | – | 24.23 (2.55) | 28.15 (1.41) | <0.001 | AD vs. MCI |
| Confrontation naming (% correct) | 49 (23) | 63 (23) | 74 (17) | 0.041 | LPA vs. MCI ^a |
| Verbal fluency | | | | | |
| -Phonemic | 8.44 (4.20) | 9.69 (5.10) | 12.04 (3.34) | 0.158 | – |
| -Semantic | 11.56 (6.54) | 11.31 (4.25) | 18.15 (4.99) | 0.003 | LPA vs. MCI ^a ; AD vs. MCI ^b |

^a p < 0.05.^b p < 0.01.^c The intergroup comparisons were performed with H Kruskal–Wallis test.

AB). All picture descriptions were subsequently scored by two independent raters specializing in speech pathology (KKK and MK). The raters were blinded to the clinical diagnosis in each patient. Divergent scores were discussed with the third rater (EJS) and scores reported were reached by consensus. For each assessed parameter raw scores (number of occurrence) were used in the analysis: number of words, lexical content (number of nouns and verbs), letter errors (omissions, additions, substitutions and transpositions), syntactic structure parameters (number of sentences, complex sentences and correct sentences, max. sentence length). Raters were also asked to detect features suggestive of micrographia, the presence of

omission of diacritical marks, punctuation errors and the use of mixed script (cursive and print). Subsequently, so as to make the results of lexical analysis independent of the variable sample length, percentage of nouns and verbs used was computed.

Additionally, the patients were administered a confrontation naming task (60-item Boston Naming Test, BNT [29]; 30-item naming subtest from Sydney Language Battery [20], 15-item short version of BNT or 12-item Naming component from Addenbrooke's Cognitive Examination-III [32]. As different tests were used in two centers, the naming test results are presented as percentage of correct answers. Moreover, the

Table 2 – Comparison of descriptive writing in patients with logopenic progressive aphasia (LPA) to patients with Alzheimer's disease (AD) and with mild cognitive impairment (MCI).

| | LPA n = 9 | AD n = 13 | MCI n = 13 | p ^c | Significant intergroup differences |
|--|-------------------------------|--------------------------------|--------------------------------|----------------|------------------------------------|
| Lexical content | | | | | |
| Number of words (rs) | 23.33 (7.19) ^a | 19.00 (11.92) | 25.77 (10.35) | 0.255 | – |
| Nouns (rs) | 10.44 (2.74) | 9.69 (4.91) | 11.85 (3.93) | 0.407 | – |
| % of nouns | 45.83 (7.14) | 54.62 (19.40) | 47.58 (7.38) | 0.248 | – |
| Verbs (rs) | 5.78 (1.79) | 2.85 (2.19) | 4.23 (1.96) | 0.008 | LPA vs. AD |
| % of verbs | 26 (17–29) | 17.88 (20.10) | 18 (0–30) | 0.320 | – |
| Spelling errors | | | | | |
| Deletions (rs) | 0 (0–5) ^b | 1 (0–3) | 0 (0–2) | 0.415 | – |
| Insertions (rs) | 0 (0–2) | 0 | 0 | 0.02 | LPA vs. AD; LPA vs. MCI |
| Substitutions (rs) | 1 (0–4) | 1 (0–4) | 0 (0–2) | 0.240 | – |
| Transpositions (rs) | 0 | 0 | 0 (0–1) | 0.429 | – |
| Letter errors – sum (rs) | 1 (0–8) | 2 (0–5) | 1 (0–3) | 0.180 | – |
| Sentence | | | | | |
| Max. sentence length | 9 (5–22) | 6 (0–19) | 9 (0–22) | 0.138 | – |
| Sentences (rs) | 3.89 (1.05) | 2.08 (1.71) | 2.85 (1.41) | 0.025 | LPA vs. AD |
| Complex sentences (rs) | 1 (0–2) | 0 (0–1) | 1 (0–2) | 0.237 | – |
| Correct sentences (rs) | 2 (1–5) | 1 (0–3) | 2 (0–5) | 0.021 | – |
| Script | | | | | |
| Omission of diacritical marks (n of cases/percentage) | Yes – 4 (44%) No – 5 (56%) | Yes – 10 (77%) No – 3 (23%) | Yes – 6 (46%) No – 7 (54%) | 0.191 | – |
| Punctuation errors (n of cases/percentage) | Yes – 8 (89%) No – 1 (11%) | Yes – 12 (92%) No – 1 (8%) | Yes – 11 (85%) No – 2 (15%) | 0.826 | – |

rs, raw score.

^a Mean (SD).^b Median (range).^c Intergroup comparisons were performed with one-way ANOVA, its non-parametric equivalent H Kruskal–Wallis test or chi-square test.

Table 3 – Profile of spelling errors in patients with lvPPA.

| | Age | Time since onset (years) | Deletions | Insertions | Substitutions | Transpositions |
|--|-----|--------------------------|-----------|------------|---------------|----------------|
| Case 1 | 68 | 1, 5 | 5 | 2 | 1 | 0 |
| Case 2 | 72 | 4 | 0 | 0 | 1 | 0 |
| Case 3 | 63 | 1 | 0 | 1 | 4 | 0 |
| Case 4 | 61 | 3 | 0 | 0 | 0 | 0 |
| Case 5 | 79 | 5 | 1 | 0 | 0 | 0 |
| Case 6 | 65 | 2 | 1 | 0 | 0 | 0 |
| Case 7 | 77 | 2 | 0 | 1 | 3 | 0 |
| Case 8 | 76 | 10 | 0 | 1 | 3 | 0 |
| Case 9 | 70 | 2 | 0 | 0 | 0 | 0 |
| Number of cases presenting with a given error type (%) | | | 3 (33%) | 4 (44%) | 5 (55%) | 0 (0%) |

patients were administered at least one phonemic and one semantic 60-s verbal fluency trials. If the patient was administered two fluency tasks, the mean score from these two tasks was used for further analyses. Mini-Mental State Examination was administered in all AD and MCI patients.

2.3. Statistical analysis

Normality of distribution was assessed with Shapiro–Wilk test and homogeneity of variance was verified with the use of Levene's test. The differences between three groups were analyzed with the use of one-way ANOVA (with Tukey's post hoc test) for variables that were normally distributed or with *H* Kruskal–Wallis test with post hoc comparisons for non-normally distributed variables. The differences between two groups were analyzed with the use of *U* Mann–Whitney test. The differences in distribution of qualitative variables were analyzed by chi-square test. The statistical significance level was set at 0.05 for all analyses.

3. Results

Most writing parameters were comparable in lvPPA, AD and MCI (see Table 2). In terms of lexical content patients with lvPPA used more verbs than patients with AD or MCI. Among spelling errors, letter insertion errors were present only in individuals with lvPPA (see Table 3). In lvPPA substitution errors were most common, followed by insertion and deletion errors.

Patients with lvPPA wrote more sentences than patients with AD. Punctuation errors and omission of diacritical signs were quite common in all patient groups. All but one patient produced the whole writing sample in cursive. One patient with lvPPA wrote in upper-case print. In none of the participants inappropriate mixing of case form was present.

4. Discussion

Our study shows that written description of a complex pictures is not as good as verbal fluency tasks or confrontation naming task at detecting word-finding or phonological problems, being the hallmark of lvPPA [6]. On the one hand, this can be interpreted as an evidence of lack of sensitivity of written picture description to word-finding and phonological impairment. On the other hand, these results can be viewed as an

indirect sign of possible common underlying pathology in lvPPA, MCI and AD groups.

Obviously, word-finding difficulties are more likely to manifest during a confrontation naming task than in a written picture description, as in the latter context the patient may use the words that come to his/her mind and unless a major element of the picture remains unnamed, anomia does not have to be clearly manifested. Similarly, written picture description is less challenging phonologically than writing to dictation as the patient may choose to write only short words with simple phonological structure that he/she is able to spell correctly. In our study written picture description was chosen instead of writing to dictation as it is not dependent on preserved hearing and examiner's articulatory proficiency. Thus, as it is less likely to be biased by these confounding factors such assessment is more practical for clinicians that are not speech and language therapists. Unfortunately, written picture description, similarly as oral and written confrontation naming, may be compromised because of visual problems.

Our findings can also be regarded as an indirect hint of common underlying pathology in all three patient groups. The majority of patients with MCI presented with amnesic MCI, that is likely to be MCI due to AD. Logopenic variant of PPA is very often referred to as linguistic/language/aphasic variant of AD [4,33]. However, not all patients with a clinical diagnosis of lvPPA have positive beta-amyloid imaging [14] and only half of them have AD pathology in neuropathological examination [34]. Thus, at least some of patients from lvPPA group may suffer from focal presentation of AD [4].

Despite the overall similarity of writing performance in lvPPA, AD and MCI, observed in our study, few aspects differentiated between the groups. Patients with lvPPA used more verbs in their descriptions than individuals with AD. This higher use of verbs may be due to anomia in lvPPA. The higher percentage of verbs was observed in descriptive speech of patients with lvPPA relative to controls [35] and patients with nfvPPA [36]. While patients with nfvPPA present with more impaired verb naming than noun naming, this effect is not present in lvPPA [37].

Spelling deficit may be one of the earliest symptoms of lvPPA [38]. Patient recently diagnosed by one of the authors (AB) provided such information spontaneously during interview, stating “I can't repeat words and omit letters while writing”. Usually, in lvPPA both phonologically plausible and non-phonologically plausible errors are present [24,39–42].

Of note, in our study only letter insertion differentiated between the groups, while letter deletions and substitutions appeared in all groups with low but comparable frequency. Thus, it is likely that some spelling deficits were present in all groups. It was demonstrated that in AD non-phonologically plausible letter errors are more frequent in writing nonwords than regular words [43]. As mentioned before, written picture description is less likely to provoke non-phonologically plausible errors than writing irregular words or non-words to dictation. As evidenced by lack of transpositions in lvPPA and AD, this type of error is unlikely to reflect phonological problems. Transposition errors, typical for graphemic buffer disorder, are sequence errors more typical for non-fluent aphasia, that may be related with visuospatial sketchpad [39].

Allographic agraphia was absent in all patient groups. As it is more likely to appear in severe than in mild AD [44], lack of allographic errors in our AD sample comprising patients with mild AD is in accordance with the literature. Writing assessment can complement neuropsychological assessment in the differential diagnosis of lvPPA, AD and MCI. It seems to be more convenient and less stressful for patients with anomia than oral picture description. However, written picture description cannot serve as a stand-alone tool to differentiate between lvPPA and AD. Verbal fluency and confrontation naming tasks are more sensitive to anomia than written picture description.

5. Conclusions

Descriptive writing assessment is helpful in the differential diagnosis of lvPPA, AD and MCI. Its results may only complement neuropsychological assessment and serve as a secondary tool in the diagnostic process. Spelling errors were present in all patient groups. Only letter insertion errors differentiated lvPPA from AD and MCI, as insertions were present in 44% of patients with lvPPA and absent in AD and MCI.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving

humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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