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ORIGINAL ARTICLE

Dementia trajectory for patients with logopenic variant primary progressive aphasia

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Abstract

Background The timing of progression of logopenic variant primary progressive aphasia (lvPPA) to severe dementia has not been elucidated. To address this shortcoming, 10 patients with lvPPA were continuously followed.

Methods Patients were assessed with the annual rate of change in the Clinical Dementia Rating (CDR) sum of boxes and period from lvPPA onset to the onset of benchmark signs, including mild, moderate, or severe dementia, episodic memory deficits, topographical disorientation, difficulties with using controls for electronic appliances, and conceptual apraxia. When severe dementia was evident, we also investigated the incidence of severe cognitive and behavioral signs such as neologistic jargon, difficulties in recognizing family members, pica, and mirror sign.

Results The mean time for patients to reach a particular CDR was as follows: CDR of 1, 4.1 ± 1.3 years post-onset; CDR 2, 5.7 ± 1.6 years; CDR 3, 7.3 ± 1.6 years. The annual rate of change in the CDR sum of boxes was 3.4 ± 1.1, corresponding to 1.7 years for the CDR to increase by 1.0. Difficulties with using electronic controls began at 3.3 ± 1.6 years, episodic memory deficits at 4.0 ± 2.0 years, topographical disorientation at 5.2 ± 2.1 years, and conceptual apraxia at 5.5 ± 2.1 years. For patients who progressed to severe dementia, six could not recognize family members, five exhibited pica, three experienced mirror sign, and one developed neologistic jargon.

Conclusions Our results suggest that patients with lvPPA progress rapidly to dementia and develop conceptual apraxia, episodic memory deficits, visuospatial deficits, and semantic memory deficits.

Keywords S: Logopenic variant primary progressive aphasia · Conceptual apraxia · Episodic memory deficits · Visuospatial deficits · Semantic memory deficits

Introduction

Owing to the nature of neurodegenerative disorders, it is expected that patients with logopenic variant primary progressive aphasia (lvPPA) experience cognitive decline over the course of the disease. The characteristics of linguistic decline for patients with lvPPA were recently documented [1–4], and these reports suggest that patients experience a deterioration in naming [1, 3], repetition [3, 4], and comprehension [3], and in rare cases, they progress to neologistic jargon aphasia [2]. However, linguistic function at the advanced stages has not been elucidated because the observation period reported for most studies has been only 3 years or less [1, 2, 4], and most studies were carried out with only a small patient group, i.e., a single case [2, 4] and a three-case series [1]. In addition, the progression of dysfunctions related to the nonverbal aspect of lvPPA has not been thoroughly investigated. Etcheverry et al. (2012) [1] reported a longitudinal study over a 3-year period, in which three patients with lvPPA presented with decreased non-verbal skills such as divided attention and increased apraxia. Leyton et al. (2013) [5] also conducted a 3-year evaluation of 13 lvPPA patients who had a more rapid and generalized cognitive decline compared with semantic variant PPA, i.e., deficits in visuospatial function, attention, or episodic memory. Our group reported three patients with lvPPA who

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subsequently showed difficulties with using controls for electronic appliances, conceptual apraxia, and severe semantic memory deficits, including pica and difficulties in recognizing family members [6]. Although few studies have addressed this issue, the existing reports suggest that patients with lvPPA might experience substantial cognitive decline over the course of the disease [1, 5, 6]. Because the vast majority of cases with lvPPA have Alzheimer's disease [7, 8], they presumably present with many cognitive and behavioral signs.

According to Rohrer et al. [3], the primary brain regions that undergo atrophy in lvPPA patients are the posterior superior temporal and inferior parietal lobes as well as the posterior cingulate and medial temporal lobes with asymmetrical involvement, i.e., the left hemisphere greater than the right. They also found that patients with lvPPA at the advanced stages had increased involvement of other areas in the left hemisphere (temporal, parietal, frontal lobes, and caudate) and in the right hemisphere (temporal and parietal lobes, particularly the posterior cingulate/precuneus). Involvement of the parietal lobes often leads to apraxia [9] as well as visuospatial dysfunction [10], and atrophy in the posterior cingulate or medial parietal cortex can cause topographical disorientation [11, 12]. Likewise, involvement of the medial temporal lobes suggests that lvPPA patients might have episodic memory deficits similar to those exhibited by patients with typical Alzheimer's disease. In fact, these cognitive dysfunctions, i.e., apraxia, visuospatial deficits, and episodic memory deficits, have been documented in previous studies of lvPPA progression [1, 5, 6]. In our previous report on lvPPA progression [6], difficulties in using electronic appliances were the first sign other than linguistic dysfunction. The manipulation of electronic controls among people with degenerative disorders has now been deemed a relevant topic among clinical investigators [13–15] because electronic controls have mostly replaced the manual controls of many types of instrumentation. The neural basis for tool use has been mapped to the left parietal lobe [16–21] and, to a lesser degree, to the posterior part of the left temporal lobe [20]. Regarding manipulation of controls for electronic appliances or more complicated devices, the parietal cortex has again been regarded as a core area [22, 23] because it requires the integration of visual, visuospatial, conceptual, and motor information—a process subserved mainly in the left parietal lobe [19]. Considering that lvPPA has its neural basis in the left parietal and temporal lobes, patients with lvPPA would be expected to have difficulties using electronic appliances, as observed with our previous cases of lvPPA [6]. Thus, based on brain pathology, the potential benchmark signs for patients with lvPPA over the course of their cognitive decline include apraxia, difficulties using electronic appliances, visuospatial dysfunction, topographical disorientation, and episodic memory deficits.

In addition to those benchmark signs, certain severe cognitive and behavioral signs are easily observed during the course of Alzheimer's disease or lvPPA, and these include neologistic jargon [2]; difficulties in recognizing family members [24–26], pica, i.e., eating of non-food substances such as toothpaste, soap, or toilet paper, which is considered to be caused by temporal lobe dysfunction and its related semantic memory deficits [27, 28]; and mirror sign [29, 30]. The latter three are considered some of the most severe signs among people with dementia—in particular, those afflicted with Alzheimer's disease. The neural basis for pica is thought to involve mainly the posterior part of the left middle temporal gyrus [28], which is often affected in advanced stages of lvPPA [3]. In fact, lvPPA has often been the initial clinical manifestation for patients with Alzheimer's disease who present with pica in the later stages [27]. Mirror sign is common in patients with Alzheimer's disease [29, 30] and correlates with atrophy of the parietal lobe [31, 32]. Ishimaru et al. [32] reported a patient with lvPPA who developed mirror sign after progressing to severe dementia. Difficulty in recognizing familiar persons has been associated with Alzheimer's disease [24–26], and this difficulty involves the temporal lobes as well as parietal and frontal lobes [24–26]; this differs somewhat from delusional misidentification, which is the false identification of persons and is frequently apparent in dementia with Lewy bodies rather than Alzheimer's disease [33]. Neologistic jargon is one of the most severe forms of aphasia [34], especially for aphasia related to phonological dysfunction, i.e., conduction aphasia and Wernicke's aphasia in cerebrovascular diseases, which most closely resemble lvPPA in degenerative disorders [35].

Although these benchmark signs as well as severe cognitive and behavioral signs might be helpful for understanding the difficulties patients experience in daily life, few studies on lvPPA have considered these signs. Thus, to better understand the development of lvPPA, we studied those signs during the progression to dementia of lvPPA, for which 10 patients with lvPPA were followed until they manifested severe dementia, i.e., a Clinical Dementia Rating (CDR) of 3 [36].

Methods

Participants

Aspects of the study concerning ethics were approved by the Human Research Ethics Commitee of Ashikaga Red Cross Hospital. Patients with lvPPA were recruited from the Cognitive Function Clinic at Ashikaga Red Cross Hospital and Edogawa Hospital between January 2008 and December 2017. All patients were evaluated by neuropsychiatrists, each of whom had more than 10 years of experience in neuropsychology and clinical practice for degenerative disorders at the time of the study. A total of 14 patients met both the clinical and imaging-supported diagnostic criteria for lvPPA [37]. They all presented with length-dependent–impaired sentence repetition, phonological errors, and anomia while grammar,

articulation, and single-word comprehension were preserved. The imaging criteria for each patient were supported by both magnetic resonance imaging and single-photon emission–computed tomography, which revealed damage mainly affecting the left temporoparietal junction, including the left posterior superior and inferior parietal lobule. Of the 14 patients, 4 were not followed until they became severely impaired, i.e., CDR 3, and thus they were excluded from the study. The remaining 10 patients were included, i.e., those who had continuously been followed from lvPPA onset until they progressed to CDR 3. Informed consent was obtained from each patient and/or their spouse. A portion of the data for 3 of the 10 patients has been reported elsewhere [6]. All lvPPA patients had a CDR of 0.5 at the time they were recruited for the study except for one patient who had been undergoing therapy at a local clinic that specializes in treating patients with dementia, and this patient was referred to our clinic at the level of CDR 1 with a detailed medical referral of her disease course. All patients were observed until they reached CDR 3.

Assessment

Disease progression of patients was assessed with the annual rate of change in the CDR sum of boxes, including mild, moderate, or severe dementia, i.e., CDR of 1, 2, or 3, respectively. The period from lvPPA onset to the onset of benchmark signs was also investigated, including episodic memory deficits, topographical disorientation, conceptual apraxia, and difficulties with using electronic appliances. Among various types of apraxias, conceptual apraxia is frequently noted in Alzheimer's disease [38–41] and was therefore employed as a benchmark sign in our study. Conceptual apraxia refers to a deficit in knowledge of tool use or semantic memory deficits [40, 41], and thus it impacts many aspects of daily life [42]. Here, the age of onset refers to the caregiver-reported time at which linguistic symptoms began. In addition, we investigated the incidence of severe cognitive and behavioral signs once each patient became severely impaired, including neologistic jargon, difficulties in recognizing family members, pica, and mirror sign.

To assess longitudinal linguistic changes, the Standard Language Test of Aphasia in Japanese [43] was administered. This standardized test is composed of 26 subtests concerning several language modalities, including auditory comprehension, speech, reading comprehension, writing, and arithmetic. For overall assessment of each patient, data from the 26 subtests were converted to a total score, which was then classified based on a scale of 0 to 10, with 0 being the worst performance and 10 being the best [43].

In addition, a new clinical scale for rating the mental states of the elderly (called the NM scale), which has been validated and proven reliable [44], was used to assess the cognitive functions of all 10 patients at each of our first and last longitudinal assessments. In contrast to the Japanese version of the Mini-Mental State Examination [45], which consists mainly of verbal tasks and therefore is not appropriate for assessing patients with aphasia, the NM scale was developed to assess the cognitive functions of patients with dementia, for whom verbal communication is a challenge. The NM score was calculated based on clinical observations, covering measures of memory, orientation, motivation, and speech along with the ability to do household chores with 10 points for each item (50-point maximum). The scores were grouped as follows: 48–50 points, normal cognition; 43–47, borderline condition; 31–42, mild dementia; 17–30, moderate dementia; and 0–16, severe dementia.

The lvPPA patients were evaluated approximately annually by neuropsychiatrists. For each cognitive and behavioral sign, each patient was given a semi-structured interview. Because some patients were unable to answer questions because of aphasia and/or severe cognitive impairment, the questions were asked to a caregiver who was most familiar with the patient's everyday life. The caregivers were asked to answer "yes" or "no" for each question. For any single question, a response of "yes" was taken to mean that the patient had the relevant deficit. The specific question related to difficulties with using electric appliances was "Do you often have trouble in using electric appliances at home?" The question for conceptual apraxia was "Are you often unable to use tools because you have lost the knowledge of their use?" For episodic memory deficits, the question was "Do you often forget recent events?" Regarding topographical disorientation, they were asked "Do you sometimes get lost on familiar routes?" The aspect concerning the difficulty in recognizing familiar faces focused on family members, and the question was "Is he or she sometimes unable to recognize family members?" The presence of pica was judged by asking "Does he or she sometimes eat non-food items?" The question for mirror sign was "Does he or she sometimes misidentify his or her own image reflected in a mirror as a different person and try to talk to the image?"

Results

The mean age at disease onset was 58.8 ± 6.4 years for the 10 patients, among whom 6 were male and 4 were female. They had an average of 13.2 ± 1.8 years of education. At the first assessment, the mean score for the NM scale for all patients was 43.0 ± 4.7 (50 points maximum), implying a borderline condition between normal cognitive function and dementia. The results for the subscales of the NM scale were almost normal, with mean values of 9.2 ± 0.9 for memory, 9.3 ± 0.9 for orientation, 8.8 ± 1.5 for motivation, and 9.1 ± 1.1 for household chores; only the score for the speech subscale was already low at this first assessment, with 6.6 ± 0.8, reflecting linguistic dysfunctions. At the last

assessment, the mean score of the NM scale decreased substantially to 5.9 ± 4.2, reflecting severe dementia. Of the 3 patients who were employed at the time of lvPPA onset, each was unemployed 3 years hence. On average, the 10 patients reached CDR 3 at 7.3 ± 1.6 years (Table 1). Each subject's CDR trajectory is shown in Fig. 1. Seven patients were monitored for their longitudinal linguistic decline (Fig. 2). In Figs. 1 and 2, each line represents results for the same patient. In general, dementia progression paralleled linguistic decline. The annual change in the CDR sum of boxes during the period in which the CDR increased from 1 to 3 was 3.4 ± 1.1, which corresponds to an average interval of 1.7 years to worsen by one CDR level. Difficulties with using electronic appliances began at 3.3 ± 1.6 years post-onset, followed by episodic memory deficits, topographical disorientation, and conceptual apraxia (Table 1). It was notable that episodic memory deficits began at 4.0 ± 2.0 years post-onset, earlier than the other cognitive signs except for difficulties with using electronic appliances. Only one patient presented with neologistic jargon (Table 2). However, 5 patients became almost mute and occasionally responded with simple words when asked ordinary questions, although 9 patients never developed apraxia of speech, which is a typical sign for progressive non-fluent aphasia. No severely impaired patient showed any signs of marked Parkinsonism. Notably, 5 patients presented with logoclonia, i.e., meaningless repetition of part of a word, particularly the end syllables. Six patients could not recognize family members, 5 exhibited pica, and 3 exhibited mirror sign when they progressed to severe dementia (Table 2). Seven patients were admitted to nursing homes, and 4 of those patients became bedridden by the time when they had progressed to CDR 3.

Pica, i.e., eating of non-food substances [27, 30], and difficulties in recognizing family members [46] are considered to reflect semantic memory deficits, as is conceptual apraxia [40, 41]. Pica is considered to be caused by temporal lobe dysfunction and its related semantic memory deficits [27, 28], as is the difficulty in recognizing family members [46]. Topographical disorientation is one of the most common signs of visuospatial deficits. Likewise, mirror sign may be partially attributable to visuospatial deficits [30] along with body schema disorder.

Table 1 Interval from lvPPA onset to the onset of various cognitive and behavioral signs

Cognitive or behavioral sign	Years post-onset
CDR 1 (mild dementia)	4.1 ± 1.3
CDR 2 (moderate dementia)	5.7 ± 1.6
CDR 3 (severe dementia)	7.3 ± 1.6
Difficulties with using electronic appliances	3.3 ± 1.6
Episodic memory deficits	4.0 ± 2.0
Topographical disorientation	5.2 ± 2.1
Conceptual apraxia	5.5 ± 2.1

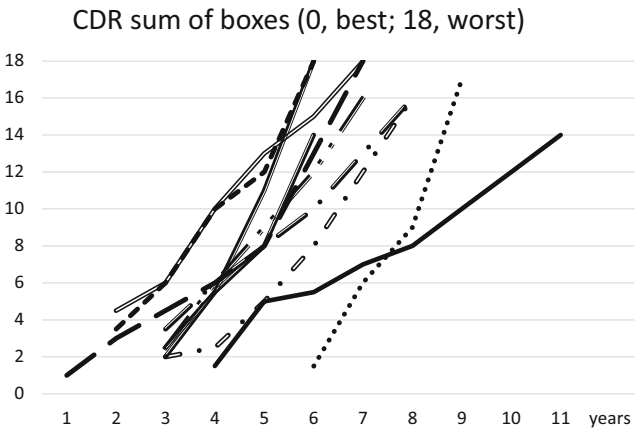

Fig. 1 Trajectory of the CDR sum of boxes for each patient

Therefore, our current data as well as published results suggest that patients with lvPPA develop conceptual apraxia, visuospatial deficits, and semantic memory deficits as the disease progresses.

Discussion

Because the observation period of our study was substantially longer than that of previous studies [1, 5, 6], our results clarify certain aspects of the later stages of dementia associated with lvPPA. Our results strengthen findings of previous reports [1, 5, 6] that advanced-stage lvPPA is characterized by the development of episodic memory deficits [5], conceptual apraxia [1, 6], visuospatial deficits [5], and semantic memory deficits [6]. Although semantic memory deficits are a hallmark of semantic dementia, other signs, i.e., episodic memory deficits and visuospatial deficits, are uncommon consequences of frontotemporal lobar degeneration—at least during the time a patient remains in the stage of moderate dementia [47]. In addition, as the name itself implies, i.e., the word "logopenic" in lvPPA, some of our patients became almost mute. Because most of them did not develop apraxia of speech, however, the

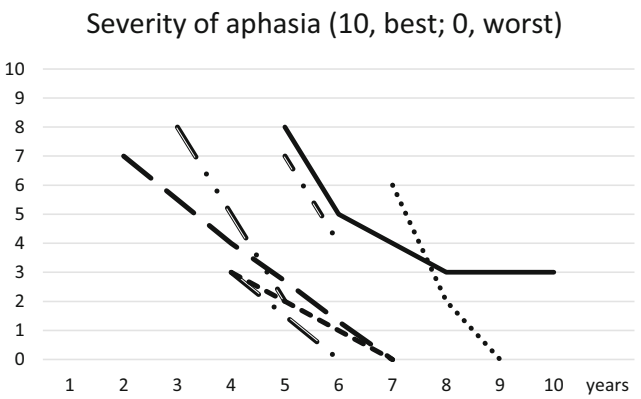

Fig. 2 Trajectory of aphasia for each patient as assessed with the Standard Language Test of Aphasia

Table 2 Incidence of severe cognitive and behavioral signs once a patient had progressed to severe dementia

Cognitive or behavioral sign	Incidence (%)
Difficulties in recognizing family members	60
Pica	50
Mirror sign	30
Neologistic jargon	10

extreme deficit of speech observed for these cases might reflect severe phonological dysfunction. Indeed, when the concept of lvPPA was first proposed, Gorno-Tempini et al. (2008) considered lvPPA to be a phonological variant of PPA, and the term logopenic was used to describe the commonly observed slow delivery of speech even without apraxia of speech [37]. Development of visuospatial deficits might also be explained by occasional clinical manifestations of overlap between lvPPA and posterior cortical atrophy, a neurodegenerative syndrome characterized by a progressive increase in visuospatial deficits [48, 49]. Semantic memory deficits have been linked to left temporal lobe damage [50], and patients with advanced-stage lvPPA almost always present with this type of damage.

The annual rate of change in the CDR sum of boxes in patients with lvPPA (3.4 ± 1.1) was greater than that of an entire group of 597 Alzheimer's disease patients, which, according to Doody (2010) [51], is approximately 2.3 during the period from CDR 1 to CDR 3. The more rapid disease progression we observed might be a result of any of a wide range of deficits of lvPPA that our new results clarify, i.e., episodic memory deficits, conceptual apraxia, visuospatial deficits, and semantic memory deficits. This rapid disease progression of lvPPA has been reported [5, 52, 53]. According to Matias-Guiu et al. (2015) [52] and Midorikawa et al. (2018) [53], lvPPA progresses more rapidly than the other variants of PPA, i.e., the non-fluent/agrammatic and semantic variants, in regard to cognitive domains such as episodic memory and visuospatial function. In contrast, behavioral symptoms, e.g., disinhibition, stereotypical behavior, and empathy loss, are less frequently found in lvPPA compared with semantic variant PPA [54]. In terms of etiology, many patients with lvPPA are diagnosed with having a type of early-onset Alzheimer's disease [7, 8], in which aphasia, rather than episodic memory deficits, is sometimes the initial symptom, followed by relatively rapid disease progression [55]. According to Chang et al. 2017 [56], patients with early-onset Alzheimer's disease are at greater risk for mortality compared with those with late-onset Alzheimer's disease.

Our study has several limitations that should be considered when interpreting the results. First, owing to the severe cognitive impairment and aphasia of our lvPPA patients, detailed testing of neuropsychological functions could not be carried out. Second, we did not test for an association between the results of the neuroanatomical analysis and cognitive decline. Third, the number of patients was small. To our knowledge, however, no larger study has addressed the severe cognitive and behavioral signs of lvPPA at the advanced stages. Fourth, we did not compare the rate of progression of cognitive and behavioral symptoms in these patients with that of a group of typical Alzheimer's patients, who show episodic memory deficits as an initial sign. Finally, lvPPA is a heterogeneous disorder [8], and our results do not represent all aspects of lvPPA. Despite these limitations, our study reveals that lvPPA progresses rapidly and that patients develop episodic memory deficits, conceptual apraxia, visuospatial deficits, and semantic memory deficits.

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Authors' contributions MF, YN, TT, YM, and AN acquired case data. MF designed the study, and drafted the manuscript. MM supervised the study.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Patient consent Informed consent was obtained from each patient and/or their spouse.

Ethics approval Aspects of the study concerning ethics were approved by the Human Research Ethics Committee of Ashikaga Red Cross Hospital.

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