Neuropsychologia 50 (2012) 1708–1718

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

The time course of neurolinguistic and neuropsychological symptoms in three cases of logopenic primary progressive aphasia

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ARTICLE INFO

Article history:
Received 22 June 2011
Received in revised form 12 March 2012
Accepted 22 March 2012
Available online 30 March 2012

Keywords:
Aphasia
Fronto-temporal degeneration
Attention
PPA
Apraxia
Cognition
Atrophy

ABSTRACT

Primary progressive aphasia (PPA) is a rare clinical dementia syndrome affecting predominantly language abilities. Word-finding difficulties and comprehension deficits despite relatively preserved cognitive functions are characteristic symptoms during the first two years, and distinguish PPA from other dementia types like Alzheimer's disease. However, the dynamics of changes in language and non-linguistic abilities are not well understood. Most studies on progression used cross-sectional designs, which provide only limited insight into the course of the disease. Here we report the results of a longitudinal study in three cases of logopenic PPA over a period of 18 months, with exemplary longitudinal data from one patient even over 46 months. A comprehensive battery of neurolinguistic and neuropsychological tests was applied four times at intervals of six months. Over this period, deterioration of verbal abilities such as picture naming, story retelling, and semantic word recall was found, and the individual decline was quantified and compared between the three patients. Furthermore, decrease in non-verbal skills such as divided attention and increasing apraxia was observed in all three patients. In addition, inter-subject variability in the progression with different focuses was observed, with one patient developing a non-fluent PPA variant. The longitudinal, multivariate investigation of logopenic PPA thus provides novel insights into the progressive deterioration of verbal as well as non-verbal abilities. These deficits may further interact and thus form a multi-causal basis for the patients' problems in every-day life which need to be considered when planning individually targeted intervention in PPA.

1. Introduction

Primary progressive aphasia (PPA) is a progressive neurodegenerative syndrome affecting predominantly language abilities (Mesulam, 1982). Word-finding difficulties and comprehension deficits despite preserved cognitive functions are characteristic symptoms during the early course of disease, i.e. during the first two years. Preserved cognitive functions distinguish PPA from other dementia types like Alzheimer's disease. Mild impairment in arithmetic operations (dyscalculia), ideomotor and/or buccofacial apraxia, and marginal deficits in constructional abilities can be present at the beginning of the disease but should not affect the normal day activities. At later stages, other verbal and non-verbal cognitive impairments may appear and, finally, the patients loose their ability to communicate verbally because of total loss of language and accompanying severe cognitive deficits. However, the longitudinal development of non-linguistic cognitive deficits accompanying or influencing language, or some of its aspects, remains largely unknown. Therefore, the present study provides a longitudinal, multivariate account on PPA in order to uncover the cognitive dynamics of its progressive nature.

When investigating the longitudinal cognitive characteristics of PPA, it is of note that the status of PPA as a unique clinical entity has been discussed controversially. First, this is due to heterogeneous neuropathological and clinical findings as well as controversial reports on different long-term developments in PPA, such as the average duration of the disease or developing

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http://dx.doi.org/10.1016/j.neuropsychologia.2012.03.028

co-morbid impairments. Moreover, there is an ongoing discussion whether PPA subtypes can be distinguished, and if so, on the basis of which symptoms. Sonty et al. (2003), Gorno-Tempini, Dronkers, et al. (2004), Rogalski and Mesulam (2007) and others differentiate three PPA-variants: a fluent form (fPPA), characterized by impaired comprehension with preserved syntactic abilities and word-fluency, a non-fluent form (nfPPA), which is labelled by impaired syntactic abilities and word-fluency with intact comprehension, and finally a logopenic variant (lPPA) which is a mixture of the two former variants: it is characterized by frequent disruption of oral fluency because of word-finding difficulties whereas syntactic abilities and comprehension are little impaired. According to Mesulam, Grossman, Hillis, Kertesz, and Weintraub (2003), those three variants of PPA finally converge in the progression of the disease and ultimately lead to mutism. Gorno-Tempini et al. (2006) report, that nfPPA leads earlier to mutism than fPPA and can develop into a corticobasal syndrome (Gorno-Tempini, Murray, Rankin, Weiner, & Miller, 2004). In opposition to this classification of PPA, authors like Snowden, Neary, and Mann (1996) as well as Garrad and Hodges (2000) regard nfPPA and fPPA as two separate disorders. Whereas the non-fluent type (including lPPA) is termed PPA, the fluent variant is called semantic dementia (SD) which is characterized by severe semantic impairment up to the total loss of the ability processing semantic information. Following this account, in order to diagnose fPPA, it is important to test whether or not semantic processing is intact. In Mesulam's classification of the semantic variant of PPA (i.e. fPPA in their terms) the semantic system itself is intact but access to it is impaired. The knowledge of the object is still intact and in case of word-finding difficulties the patient has the chance to make himself understood using circumlocutions or non-verbal expression like pantomime or gesture. In contrast, following the definition of SD by Snowden et al. (1996), representations in the semantic system are impaired. Hence, the patient cannot communicate by non-verbal expression, because the knowledge of meaning and use of objects is lost. In an attempt to unify the field by discussing and integrating the variety of approaches to PPA, Gorno-Tempini et al. (2011) have now published a new guideline paper for the classification of PPA in non-fluent/agrammatic, semantic, and logopenic PPA (for a quantitative template to dissociate these subtype on the basis of their performance in semantic and syntactic tests cf. Mesulam et al., 2009). When describing the relevant recent papers on PPA in the following paragraphs, we stick to the subtype labels originally given by the respective authors of the studies for the sake of scientific correctness; the reader may easily translate these labels to the now valid nomenclature just mentioned.

During the progression of logopenic PPA, the principle linguistic symptoms are increasing word-finding difficulties and comprehension deficits as well as naming dysfunctions. Fluent speech production can become non-fluent because of emerging word-finding problems. Only after the first two years after the onset of PPA, other cognitive impairments such as problems in orienting or memory may develop. Some PPA patients develop striking personality changes characteristic for fronto-temporal dementia. Other patients show signs of corticobasal degeneration (such as extrapyramidal dysfunction) or a motor neuron disease with associated aphasia. Those co-morbid diseases are called PPA-plus syndromes (Mesulam, 2001).

The assessment of neuropsychological abilities is important for a first diagnosis of PPA. At the very onset of PPA, skills like visuo-spatial processing as well as visual memory should be in a normal range. However, light impairment of arithmetic operation, constructional and ideomotor skills as well as light impaired ability of inhibition in go/nogo tasks may exist because of the closeness of the corresponding cortical regions and language-relevant regions. Yet, for the diagnosis of PPA, they should not affect everyday activities (Mesulam, 2001).

Multidimensional neuropsychological assessment may be useful for the distinction between cases of fronto-temporal dementia (FTLD) and Alzheimer's disease (AD) (Giovagnoli, Erbetta, Reati, & Bugiani, 2008), in particular in the domains of memory, attention and visuo-constructive abilities. Similarly, Wicklund, Rademaker, Johnson, Weitner, and Weintraub (2007) reported that the cognitive decline in PPA patients differed predominantly from Alzheimer's dementia and fronto-temporal dementia in the domains of language, verbal memory, and attention. In 2009, Libon et al. investigated the longitudinal course of neuropsychological performance in a large number of patients with AD and subtypes of FTLD (among others, SD and nfPPA) over the course of 100 months. They reported a double dissociation between SD and nfPPA in naming test and executive control, in terms of better results for nfPPA over SD in naming and worse results in letter fluency. Another double dissociation was found between patients with corticobasal degeneration and nfPPA: the nfPPA group performed better in visuo-constructive test than in tasks requiring executive control. However, in this study, no patients suffering from logopenic variant of PPA participated. Moreover, within the test battery, no tests assessing attention and apraxia were included. Considering these factors would thus be advantageous for the better understanding of the time course of the different variants of PPA.

In the case of PPA variants, neuropsychological performance may differ depending on the particular subtype. Gorno-Tempini, Dronkers, et al. (2004) found different patterns of neuropsychological deficits in the three subtypes of PPA. The authors tested verbal fluency, verbal recognition, verbal and non-verbal memory, executive functions, and praxis. For the nfPPA, Gorno-Tempini, Dronkers, et al. (2004) reported significant better performance in verbal memory tasks in comparison to fPPA and lPPA. The nfPPA patients did not differ from the other groups on non-verbal memory or executive functions. However, the nfPPA patients also showed the worst performance in the praxis test. In contrast, the logopenic PPA group had the worst results in tests of verbal recognition. In the test of semantic word recognition they scored significantly worse than the nfPPA but performed best on a test of verbal working memory. Finally, the lPPA group performed worst on immediate and 30-s recall of verbal information.

Such neuropsychological deficits in PPA may not simply co-occur but also intermingle with the patients' language deficits; a distinction between these two options via standard tests is not always possible. Sonty et al. (2003) and Gorno-Tempini, Dronkers, et al. (2004) reported that PPA patients performed significantly worse than healthy controls in a word-fluency task supposed to measure executive functions. Additionally Sonty et al. (2003) report significantly worse performance in naming. Consequently, when applying neuropsychological tests requiring verbal processing, there is a risk that PPA patients score significantly lower than a control sample only because of their aphasic symptoms (Le Rhun, Richard, & Pasquier, 2005; Mesulam et al., 2003; Sonty et al., 2003). Thus, a detailed knowledge of verbal and non-verbal neuropsychological profiles of PPA as well as their development during the progression of the disease seems relevant for the appropriate evaluation of a patient's level of cognitive performance. Such knowledge may, in turn, inform the planning of therapeutic interventions in individual cases. More generally, the data contribute to a better understanding of one subtype of PPA and may thus, in future, help characterize commonalities and differences to other PPA variants.

1.1. Aim of the study

The aim of the present study was to investigate the progression of neuropsychological abilities in three patients with a logopenic