OLFACTORY AND IMAGING FEATURES IN ATYPICAL ALZHEIMER’S DISEASE

Abstract

Objectives: Cognition and speech disorders are the most common symptoms of dementia in neurodegenerative disease. Here, we present a detailed clinical evaluation of a case of logopenic variant of primary progressive aphasia (lv-PPA), an atypical form of Alzheimer disease (AD), including cognitive testing over time, brain imaging, electrophysiology, and tests of olfactory function.

Case report: We present the case of a 58-year-old man suffering from progressive language difficulties who was finally diagnosed with lv-PPA. Clinical data included neuropsychological examinations, electrophysiology tests, neuroimaging, biomarkers, olfactory tests, and olfactory functional magnetic resonance imaging (fMRI).

Results and Discussion: The patient suffered from language disorders, including stumbling speech and forgetting appropriate words and how to pronounce some words. This had started 2 years earlier, and he had begun to deteriorate in recent months. In addition to his speech disorder, scores on the Mini Mental State Examination and Montreal cognitive assessment indicated that his cognition was affected. Structural imaging revealed no obvious hippocampal atrophy (score of 1), and molecular imaging showed hypometabolism and amyloid deposits in the temporal parietal region. The patient also presented with olfactory impairment. Although his odour detection threshold was normal, his cognitive threshold for scent recognition was significantly increased. Olfactory fMRI showed that activation of the whole brain and primary olfactory cortex was rare.

Conclusion: This case provides evidence suggesting that lv-PPA is an atypical form of AD, with symptoms including speech disorders and impaired cognition. This patient with lv-PPA presented with olfactory impairment.

Keywords
- Alzheimer’s disease (AD) • logopenic variant primary progressive aphasia (lv-PPA) • olfactory functional magnetic resonance imaging (fMRI).

1. Introduction

Alzheimer’s disease (AD) is the most common neurodegenerative dementia. The neuropathological process involves the accumulation of amyloid beta plaques and tau tangles. Typical AD is characterized by episodic memory loss. In other subtypes, dysfunctions of language, visual-spatial skills or executive function commonly accompany memory loss. Most often, speech disorders are the initial motivation for potential dementia patients to present to the hospital. The logopenic variant of primary progressive aphasia (lv-PPA), a unique primary progressive aphasia (PPA) syndrome, is characterized by anosmia, word-finding difficulties, and impaired sentence repetition [1, 2]. The neuropathology and biomarkers (molecular amyloid nuclear imaging) of lv-PPA frequently reveal AD, so it is defined as a variant of AD. Because there is no effective medication for lv-PPA, specific linguistic therapies are needed. Therefore, early diagnosis can improve patients’ quality of life.

Olfactory dysfunction was recently found to be associated with AD. AD causes neuropathological changes in entorhinal and trans-entorhinal areas that are critical to olfactory information processing. Olfactory deficits in AD include decreases in odour threshold sensitivity [3, 4], odour identification [5, 6], and olfactory event-related potentials [7]. In this case study, olfactory function was determined using the T&T olfactometer and olfactory functional magnetic resonance imaging (fMRI) was used to determine the threshold for odour sensitivity, odour identification and olfactory cortex function.

In this article, we present the case of a patient suffering from speech difficulties characteristic of lv-PPA. Data from cognitive testing, analyses of speech disorder, brain imaging, electrophysiology and olfactory function are carefully integrated to present a complete characterization of the development of cognitive defects in lv-PPA over time. We hope this will aid other clinicians in identifying lv-PPA and its progression.

2. Methods and results

2.1 Case report

The patient, a 58-year-old man, is right-handed, has a university degree, and has no history of stroke, nasosinusitis, chronic obstructive pulmonary disease, schizophrenia, depression or family dementia. He was admitted to our outpatient department for
diagnosis of his language disorders, which had persisted for approximately 2 years. He and his wife complained that he was unable to express himself and stumbled trying to find appropriate words. Moreover, he found it difficult to pronounce some words. His language comprehension was relatively well preserved. He could identify the appropriate word when others suggested words he might be trying to remember. During the previous 2 years, he insisted on driving to work by himself. During the past few months, his symptoms had worsened enough to limit his verbal contact with others, and he experienced memory impairment, such as forgetting his things and his co-workers' names, difficulty concentrating and with logic, and a poor temper.

Physical and neurological examinations identified no cardiac dysfunction, pulmonary disease, sensory deficiencies, muscular strength deficiencies or pyramidal symptoms, except the clumsy use of language. Laboratory examinations showed normal ranges of liver, kidney, and thyroid function, as well as normal levels of homocysteine, vitamin B12, and folic acid were in the normal range, and the levels of low density lipoprotein cholesterol (3.03 mmol/L) and total cholesterol (6.08 mmol/L) were slightly higher than the normal range. The apolipoprotein genotype was ε3/ε3. Neuropsychological examinations included cognition, executive function, and neuropsychiatric tests. The Montreal cognitive assessment (15 points) and clock drawing test (2 points) revealed symptoms of dementia, including impaired memory, executive function and language. He had no positive symptoms in the neuropsychiatric tests, but did present with increased levels of anxiety and aggression.

Magnetic resonance imaging (MRI), which was performed with a 3.0 T Siemens MR system using a standard head coil, included structural MRI and olfactory functional MRI. The structural MRI (Fig. 1) revealed demyelination of cerebral white matter (0–1 degree on the Fazekas scale) [8], and a hippocampal score of 1 using the medial temporal lobe atrophy score.

2.2 Electrophysiology test
During the electrophysiology study, cognitive and motor cortical functions were evaluated using the P300 and transcranial magnetic stimulation (TMS). The P300 wave is a prominent event-related potential (ERP) that indicates changes in the cognitive cortex [9]. The P300 wave is the most commonly recorded potential and can be elicited using the oddball paradigm. In this method, the patient was instructed to focus on an infrequent target stimulus (2,000 Hz, 100 dB) embedded in a series of frequent background stimuli (1,000 Hz, 100 dB). The P300 latency was 374 ms at the Cz-A1 site and 368 ms at the Pz-A1 site, and the amplitudes were 4.1 µv and -0.77 µv at different sites, which indicates cognitive impairment. In addition to the cognitive cortex, TMS was conducted to assess the motor cortex function. The cortical

Figure 1. MRI image of this patient
motor-evoked potential of the abductor pollicis brevis (left) showed that the resting motor threshold (RMT) was 40%, the facilitated motor threshold (FMT) was 31%, and the cortical silent period (CSP) was 145.1 ms for the right cortex. On the other side, the thresholds were 47%, 31%, and 146.4 ms, respectively. These results indicate that excitability of the motor cortex was increased in this patient compared with age-matched controls in our hospital.

2.3 Positron Emission Tomography Imaging (PET)
To further clarify the diagnosis, PET images were acquired on a GE Discovery LS PET/CT scanner in the three-dimensional scanning mode. Ten minutes before intravenous administration of the radiotracer, the patient rested in supine position in a quiet, dimly lit room. The 11\textsuperscript{C}-labeled Pittsburgh compound B (11\textsuperscript{C}-PIB) was injected into an antecubital vein at a mean dose of 370 MBq. PIB PET images were acquired during a 90-min dynamic PET scan. The same scanner was used for the 18\textsuperscript{F}-fluorodeoxyglucose (FDG) study conducted 30 min after the 11\textsuperscript{C}-PIB scan. The patient was intravenously injected with 250 MBq of 18\textsuperscript{F}-FDG and underwent a 10 min static PET emission scan 60 min after the injection. Cortical-to-cerebellar grey matter ratios (standardized uptake value ratio) were generated for regions of interest. The analysis was performed by two experienced nuclear medicine physicians.

The FDG scan revealed bilateral temporal-parietal junction regions, bilateral precuneus regions, and right frontal lobe hypometabolism. Among these regions, the right temporal-parietal junction hypometabolism was the most distinct (Fig. 2A). Moreover, the PIB scan revealed amyloid deposits in the temporal, parietal, and frontal regions (Fig. 2B), consistent with AD. Based on the patient’s clinical symptoms and examination results, we diagnosed him with lv-PPA [2].

2.4 Olfactory function
2.4.1 Olfactory test
To determine olfactory function, the patient underwent testing with a standard Toyoda and Takagi’s perfumist’s strip (T&T olfactometry, Japan) [10, 11]. We tested the thresholds of five odorants using T&T olfactometry. The 8 degrees (-2, -1, 0, +1, +2, +3, +4, +5) of odorant on the T&T olfactometry represent a concentration series from 10^{-2} to 10^{5}, and zero represents the average detection threshold of normosmic subjects. Lack of response to the highest concentration was scored as 6. For this patient, the detection threshold was -1.2 (degree 1), and the cognitive threshold was 6.

2.4.2 Olfactory functional magnetic resonance imaging (fMRI)
Lavender oil is one of the most effective olfactory stimulants. It has minimal to no effect on the trigeminal system, and has been used in olfactory fMRI studies [12]. Lavender oil at concentrations of 0.10%, 0.33%, and 1.00% were used as stimuli. Olfactory stimuli were delivered through the tube of a custom-built olfactometer placed approximately 1 cm from the participant’s nose, with air flow at 8 L/min. Each odorant was presented in 6-second blocks separated by a 42-second interval of odourless air. Each concentration was repeated five times in succession, beginning with the weakest. Before fMRI, we explained the progression of the examination, instructed the subject to keep his head and body motionless, and to receive the odours without sniffing.

The olfactory fMRI showed that activation of the whole brain was rare, especially in the bilateral primary olfactory cortical (POC), which directly reflects the subject’s impaired olfactory function.

Figure 2. A. The 18F-FDG PET of this patient, B. The 11C-PIB image of this patient
2.5 Follow-up
Data from follow-up examinations at 6 months and 1, 1.5, and 2 years are shown in Fig. 3. At the 6-month follow-up, the Mini Mental State Examination score decreased (Table 1), whereas scores for activity of daily living and neuropsychiatric Inventory (NPI) were increased. At the 1.5-year follow-up, his sense of orientation and memory had deteriorated, which induced a gradual downward trend in his cognitive function.

3. Discussion
AD is one of the most common chronic diseases in the elderly, but there is currently no treatment that blocks the progression of AD. Moreover, patients whose initial symptoms are not memory impairment are often ignored or misdiagnosed. Atypical symptoms are present in at least 5% of AD patients over the age of 65 years and 1/3 of patients under the age of 65 [13, 14]. Lv-PPA is an atypical clinical variant of AD, which is characterized by anomia, word-finding difficulties, and impaired sentence repetition [2]. Imaging features include left temporal-parietal atrophy on MRI [1, 15] and hypometabolism on 18F-FDG PET [16]. Lv-PPA is not well understood, possibly because of the relatively small number of patients and a lack of comprehensive investigations. Therefore, we aimed to present a comprehensive description of brain imaging, electrophysiology, and olfactory function in a patient with lv-PPA. In our case, the patient initially presented with a speech disorder, characterized by difficulty in finding words and sentence-repeating. After 2 years of follow-up, his cognitive function, including orientation, delayed recall and ability to perform calculations deteriorated; all clinical symptoms consistent with AD. These results, combined with PET results, led to a diagnosis of lv-PPA [2].

Structural MRI revealed significant atrophy of the hippocampus, which might be a useful biomarker for distinguishing lv-PPA from typical AD and other degenerative diseases. Unlike typical AD, hippocampal regions are spared in lv-PPA [17], which is consistent with our results. In typical AD patients, PET shows some areas, including the frontal, temporal and parietal regions, with decreased metabolism, increased 11C-PIB uptake, and a decreased removal rate [18], which is similar to lv-PPA patients [16]. However, in lv-PPA patients, the degree of hypometabolism in the left parietal-temporal junction might be more severe, representing an anatomical signature of lv-PPA [19]. Conversely, our results showed more significant hypometabolism in the right parietal-temporal junction. This discrepancy might be attributed to lv-PPA endophenotypes with slightly different clinical profiles, disease severity and decline over time [20, 21]. The specific mechanisms underlying this difference should be studied in the future.

Our analysis of olfactory function included perception and recognition, as determined by detection and cognitive thresholds. Many previous studies found decreased recognition of olfactory stimuli in the elderly [22], and impairment may occur several years before the onset of AD symptoms [23, 24]. Some researchers have suggested that there is a relationship between olfactory recognition and cognition. It is noteworthy that our lv-PPA patient had a significantly impaired recognition of odours with no obvious impairment of detection threshold. The detection threshold reflects the function of peripheral olfactory structures, whereas the cognitive threshold mainly reflects the function of the olfactory centre [25]. Our patient’s limited olfactory dysfunction, difficulty recognizing odours, was related to the olfactory centre, which is consistent with a previous study [26]. The olfactory centre includes the anterior olfactory

| Table 1. Scores of sub-item of the MMSE scale |
|---------------------------------------------|
| orientation | memory | repetition | Attention and computation | recall | naming | reading | executive | writing | copying |
|-------------|--------|------------|---------------------------|--------|--------|---------|-----------|---------|---------|
| First visit | 10     | 3          | 0                         | 1      | 3      | 2       | 1         | 2       | 1       | 0       |
| 6 Mon       | 10     | 3          | 0                         | 0      | 3      | 2       | 1         | 2       | 1       | 0       |
| 12 Mon      | 10     | 3          | 0                         | 0      | 3      | 2       | 1         | 1       | 0       | 0       |
| 18 Mon      | 7      | 3          | 0                         | 0      | 2      | 2       | 1         | 2       | 1       | 0       |
| 24 Mon      | 8      | 3          | 0                         | 0      | 2      | 2       | 1         | 2       | 1       | 0       |
4. Conclusion

In conclusion, the results of our molecular imaging studies indicate that lv-PPA is an atypical subtype of AD. Symptoms include speech disorders and cognitive impairment. Patients with lv-PPA may present with olfactory impairment.

Acknowledgements

This work was supported by the technology fund of the Tianjin City Department of Health (Grant No. 13KG121).

The authors have no conflicts of interest to declare.

All authors had full access to all data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Zhou Yuying and Zhang Huihong.

Acquisition of data: Zhang Huihong, Wang Pan, Zhang Chunfeng and Zhang Hui.

Analysis and interpretation of data: Zhou Yuying, Zhang Huihong, Cai Li and Wang Yan.

Writing the manuscript: Zhang Huihong.

Critical revision of the manuscript for intellectual content: Yuying Zhou.

Study supervision: Yuying Zhou.

References

[1] Gorno-Tempini M.L., Drorone D., Rankin K.P., Ogar J.M., Phengrasamy L., Rosen H.J., et al., Cognition and anatomy in three variants of primary progressive aphasia, Ann Neurol, 2004, 55, 335-346

[2] Gorno-Tempini M.L., Hillis A.E., Weintraub S., Kertesz A., Mendez M., Cappa S.F., et al., Classification of primary progressive aphasia and its variants, Neurology, 2011, 76, 1006-1014

[3] Murphy C., Gilmore M.M., Seery C.S., Salmon D.P., Lasker B.R., Olfactory thresholds are associated with degree of dementia in Alzheimer's disease, Neurobiol Aging, 1990, 11, 465-469

[4] Bacon A.W., Bondi M.W., Salmon D.P., Murphy C., Very early changes in olfactory functioning due to Alzheimer's disease and the role of apolipoprotein E in olfaction, Ann N Y Acad Sci, 1998, 855, 723-731

[5] Serby M., Olfaction and Alzheimer's disease, Prog Neuropsychopharmacol Biol Psychiatry, 1986, 10, 579-586

[6] Doty R.L., Perl D.P., Steele J.C., Chen K.M., Pierce J.D., Jr., Reyes P., et al., Odor identification deficit of the parkinsonism-dementia complex of Guam: equivalence to that of Alzheimer's and idiopathic Parkinson's disease, Neurology, 1991, 41, 77-80; discussion 80-71

[7] Morgan C.D., Murphy C., Olfactory event-related potentials in Alzheimer's disease, J Int Neuropsychol Soc, 2002, 8, 753-763

[8] Wahlund L.O., Barkhof F., Fazekas F., Bronge L., Augustin M., Sjogren M., et al., A new rating scale for age-related white matter changes applicable to MRI and CT, Stroke, 2001, 32, 1318-1322

[9] Bennys K., Portet F., Touchon J., Rondouin G., Diagnostic value of event-related evoked potentials N200 and P300 subcomponents in early diagnosis of Alzheimer's disease and mild cognitive impairment, J Clin Neurophysiol, 2007, 24, 405-412

[10] Gilbert A.N., Human olfaction : Sadayuki F. Takagi, University of Tokyo Press, Tokyo, 1989, $127.00, ISBN 4-13-068148-6. ISBN 0-86008-434-S, Appetite, 1991, 16, 166-167

[11] Ishimaru T., Shimada T., Miwa T., Furukawa M., Electrically stimulated olfactory evoked potential in olfactory disturbance, The Annals of otology, rhinology, and laryngology, 2002, 111, 518-522

[12] Wang J., Eslinger P.J., Doty R.L., Zimmerman E.K., Grunfeld R., Sun X., et al., Olfactory deficit detected by fMRI in early Alzheimer's disease, Brain Res, 2010, 1357, 184-194

[13] Balasa M., Gelpi E., Antonell A., Rey M.J., Sanchez-Valle R., Molinuevo J.L., et al., Clinical features and APOE genotype of pathologically proven early-onset Alzheimer disease, Neurology, 2011, 76, 1720-1725

[14] Snowden J.S., Stopford C.L., Julien C.L., Thompson J.C., Davidson Y., Gibbons L., et al., Cognitive phenotypes in Alzheimer's disease and genetic risk, Cortex, 2007, 43, 835-845

[15] Rohrer J.D., Ridgway G.R., Crutch S.J., Hailstone J., Goll J.C., Clarkson M.J., et al., Progressive logopenic/phonological aphasia: erosion of the language network, NeuroImage, 2010, 49, 984-993

[16] Rabinovici G.D., Jagust W.J., Furst A.J., Ogar J.M., Racine C.A., Mormino E.C., et al., Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia, Ann Neurol, 2008, 64, 388-401

[17] Teichmann M., Kas A., Boutet C., Ferrieux S., Nogues M., Samri D., et al., Deciphering logopenic primary progressive aphasia: a clinical, imaging and biomarker investigation, Brain, 2013, 136, 3474-3488

[18] Edison P., Archer H.A., Hinz R., Hammers A., Ottesen N., Tai Y.F., et al., Amyloid, hypometabolism, and cognition in Alzheimer disease: an [11C]PIB and [18F]FDG PET study, Neurology, 2007, 68, 501-508
[19] Ridgway G.R., Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum, Neurology, 2010, 75, 479; author reply 479-480

[20] Leyton C.E., Ballard K.J, Piguet O., Hodges J.R., Phonologic errors as a clinical marker of the logopenic variant of PPA, Neurology, 2014, 82, 1620-1627

[21] Madhavan A., Whitwell J.L., Weigand S.D., Duffy J.R., Strand E.A., Machulda M.M., et al., FDG PET and MRI in logopenic primary progressive aphasia versus dementia of the Alzheimer's type, PLoS One, 2013, 8, e62471

[22] Rezek D.L., Olfactory deficits as a neurologic sign in dementia of the Alzheimer type, Arch Neurol, 1987, 44, 1030-1032

[23] Peters J.M., Hummel T., Kratzsch T.,Lotsch J., Skarke C., Frolich L., Olfactory function in mild cognitive impairment and Alzheimer's disease: an investigation using psychophysical and electrophysiological techniques, Am J Psychiatry, 2003, 160, 1995-2002

[24] Wilson R.S., Arnold S.E., Schneider J.A., Tang Y., Bennett D.A., The relationship between cerebral Alzheimer's disease pathology and odour identification in old age, J Neurol Neurosurg Psychiatry, 2007, 78, 30-35

[25] Kovacs T., Mechanisms of olfactory dysfunction in aging and neurodegenerative disorders, Ageing research reviews, 2004, 3, 215-232

[26] Koss E., Weiffenbach J.M., Haxby J.V., Friedland R.P., Olfactory detection and identification performance are dissociated in early Alzheimer's disease, Neurology, 1988, 38, 1228-1232

[27] Li X., Jiao J., Shimizu S., Jibiki I., Watanabe K., Kubota T., Correlations between atrophy of the entorhinal cortex and cognitive function in patients with Alzheimer's disease and mild cognitive impairment, Psychiatry Clin Neurosci, 2012, 66, 587-593

[28] Vasavada M.M., Wang J., Eslinger P.J., Gill D.J., Sun X., Karunanayaka P., et al., Olfactory cortex degeneration in Alzheimer's disease and mild cognitive impairment, J Alzheimers Dis, 2015, 45, 947-958

[29] Christen-Zaech S., Kraftsik R., Pillevuit O., Kiraly M., Martins R., Khalili K., et al., Early olfactory involvement in Alzheimer's disease, The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, 2003, 30, 20-25