Agraphia in Amyotrophic Lateral Sclerosis with Frontotemporal Lobe Degeneration

Bo Cui[1], Li-Ying Cui[1,2], Jing Gao[1], Cai-Yan Liu[1], Qing Liu[1], Ming-Sheng Liu[1], Dong-Chao Shen[1], Fang Liu[3]

[1]Department of Neurology, Peking Union Medical College and Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China
[2]Neurosciences Center, Chinese Academy of Medical Sciences, Beijing 100730, China
[3]Department of McKusick-Zhang Center for Genetic Medicine, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing 100730, China

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Frontotemporal lobe degeneration (FTLD) refers to a neurodegenerative dementia syndrome, which could be clinically classified into behavioral and language variant. Amyotrophic lateral sclerosis (ALS) is a progressive neurological disorder involving both upper motor neuron (UMN) and lower motor neuron (LMN), eventually leading to muscle atrophy and weakness, bulbar palsy, and respiratory failure. Once regarded as two independent entities, they now have been embraced into one continuum because of their clinical and pathological overlaps, namely ALS-FTLD and TAR DNA-binding protein 43. Deterioration in personality and behaviors serves as core feature in diagnosis while it seems difficult to identify language deficit due to dysarthria. Agraphia has been reported to appear before frank dementia/aphasia,[1] making it a potential clue to detect FTLD in the context of ALS. However, researches about writing ability of Chinese patients with ALS/FTLD spectrum disease turned to be limited. Hence, we described writing errors in a Chinese-speaking patient with ALS-FTLD.

The patient was a 67-year-old right-handed woman with 6-year formal education. She had neither history of neurological disorder nor family history of ALS and dementia. She was admitted to our hospital mainly due to progressive weakness of both upper limbs for almost 2 years and dysarthria for half a year. She became depressed shortly after her motor symptoms appeared, and she repeatedly claimed to commit suicide when upset. She recorded weather forecast and reported to the working staff of a supermarket nearby at a regular time every day. Her social, interpersonal conduct was also impaired – she excessively kissed her children and grandchildren, and she often divulges her privacy to neighbors or even strangers. She had difficulties in recognizing faces and recalling names of individuals who she used to be familiar with. No language disorder or psychotic symptoms were reported by her caregivers. Besides dysarthria, other salient neurological signs were moderate muscle wasting and weakness of her bilateral upper limbs, scoring 3/5 on proximal and 4/5 on distal muscles. No primitive or pathological reflexes were elicited except right palmomental reflex.

The clinical electrophysiological study indicated diffuse neurogenic change: Spontaneous potentials (fibrillations and positive sharp waves) and chronic denervation (motor unit potentials with increased duration and decreased motor unit recruitment) were recorded in all four regions (brainstem, cervical, thoracic, and lumbosacral spinal cords). The magnetic resonance imaging (MRI) of brain revealed focal atrophy in right temporal lobe while bilateral frontal lobes and left temporal lobe were relatively less affected [Figure 1]. The genetic test was performed with a panel of 27 genes [Supplementary Material 1], and a novel mutation was found in dynactin 1 (c. 1526 G>A).

In neuropsychological tests, she scored 21/30 in Mini–Mental State Examination, 14/30 in Montreal Cognitive

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Address for correspondence: Prof. Li-Ying Cui, Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100005, China
Neurosciences Center, Chinese Academy of Medical Sciences, Beijing 100730, China
E-Mail: pumchcuily@sina.com

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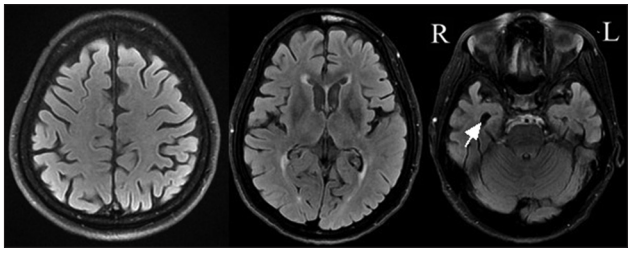

Figure 1: Neuroimaging of the patient. The MRI of the brain revealed right temporal lobe atrophy (white arrow) while bilateral frontal lobes and left temporal lobe were relatively less affected. R: Right; L: Left.

Assessment (version of Peking Union Medical College Hospital), and 12/72 in frontal behavioral inventory. Under the comprehensive cognitive evaluation system of Peking Union Medical College Hospital,[2] she showed impairment mainly in domains of executive function, memory, calculation, and abstract reasoning. She also underwent Aphasia Battery of Chinese, and the results as well as writing errors are summarized in Figure 2.

This patient demonstrated progressive impairment in both UMN and LMN. Her personality change, disinhibitive conducts, and stereotyped behaviors were also developed insidiously and aggravated in this course. Frontal executive dysfunction was also confirmed by neuropsychological evaluations. We diagnosed her as ALS-FTLD, based on these and evidence from neuroimaging and electrophysiology.

This patient unexpectedly displayed agraphia in language evaluation. Agraphia could be classified into pure agraphia, aphasic agraphia, agraphia with alexia, apraxic agraphia, and spatial agraphia. Despite right hand weakness, this patient could still manage a pen and finish the copying task which excluded the possibility of apraxia. A prominent problem lied in spontaneous writing – she claimed that she forgot how to write even those simple characters. In addition, writing errors (pictograph, strokes omission and addition, and phonological and morphological substitutions) were rather noticeable in writing to dictation and pictures tasks. On contrary, strokes were written in a right order and the configuration of these characters was also maintained well, even in the wrong ones, indicating relatively preserved visuospatial function. Interestingly, her spoken language remained intact at the time of evaluation, but whether agraphia would deteriorate to aphasia still need to be verified in the follow-up examination.

Detailed investigations of writing ability have been performed to Japanese patients with ALS and writing errors turned to be frequent among them.[1,3] These errors were highlighted for their potential to be harbinger of comorbid dementia or aphasia. Ichikawa *et al*.[1] found that agraphia tended to precede or occur independently from overt cognitive decline, rather than appear as a consequence of it. Japanese writing system contains two types of letters such as kanji (morphogram) and kana (phonogram). Similar to the case we presented, phonological and morphological substitutions for kanji

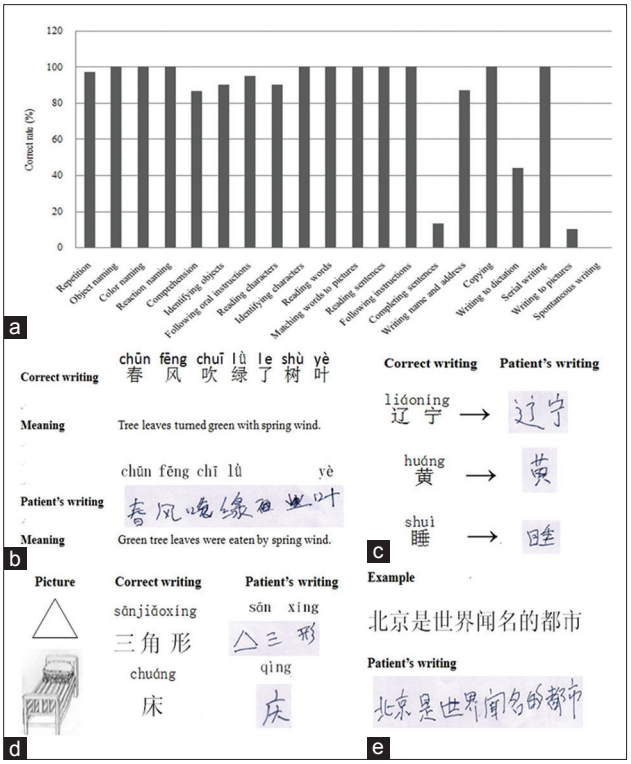

Figure 2: Results in Aphasia Battery of Chinese and writing errors of the patient. (a) Correct rate of every Aphasia Battery of Chinese subset: Correct rates in writing subsets were rather low while other language territory remained relatively unaffected. (b) Phonological substitution in writing to dictation task: "吹/chui/" was substituted by "吃/chi/", similar pronunciation but with a different meaning. Besides, the patient could not write "了" and "树". (c) Strokes addition and omission: An unnecessary dot was added to "辽", and a horizontal stroke and two vertical strokes were missed in "黄" and "睡", respectively. (d) Pictograph and morphological error in writing to pictures task: The patient could not write the character "角" and she draw a triangle instead. "床" was substituted by "庆", similar grapheme but with a different pronunciation and meaning. (e) Patient's copying: Copying ability of this patient was preserved as configuration of these characters was maintained well.

letters were found in Japanese patients. Kana letters are more comparable to alphabetical letters, and problems concerning them seemed to be more common, such as letter omission and syntactic errors.

Left frontotemporal lobe was supposed to be responsible for agraphia in Japanese patients. Through single-photon emission computed tomography analysis, reduced uptake was shown to be predominant in this area in more than half of these cases, and symmetric bilateral reduced uptake was found in the rest cases.[1] Unlike these Japanese patients, the case we presented exhibited right temporal lobe atrophy (RTLA). RTLA-FTLD, also known as right variant semantic dementia (SD), is marked by early personality change, prosopagnosia, and topographagno while language deficit would appear in intermediate stage.[4] It is rather different from classic SD characterized by left temporal lobe atrophy and early aphasia. This might imply a different pathomechanism of Chinese agraphia – right

hemisphere also contributed in processing auditory and visual information to writing. Evidence in favor of this hypothesis came from a case of vascular lesion. Similar type of writing errors such as phonological substitutions was also reported in a Chinese patient with right thalamic hemorrhage.[5]

In conclusion, we described writing features of a Chinese patient with ALS-FTLD, and agraphia could appear independently from aphasia. However, the reliability of writing errors in predicting dementia/aphasia in ALS still needed to be tested. Moreover, neuropsychological mechanism of agraphia might indicate the vulnerable cortical area of ALS.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Material 1: Genes tested in the panel of next generation sequencing

Name of genes	Abbreviation
Amyotrophic lateral sclerosis 2	*ALS2*
Angiogenin	*ANG*
Androgen receptor	*AR*
Ataxin 2	*ATXN2*
Ataxin 3	*ATXN3*
Ataxin 8 opposite strand	*ATXN8OS*
Chromosome 9 open reading frame 72	*C9ORF72*
Charged multivesicular body protein 2B	*CHMBP2B*
D-amino acid oxidase	*DAO*
Dynactin 1	*DCTN1*
Factor-induced gene 4	*FIG4*
Fused in sarcoma	*FUS*
Progranulin	*GRN*
Microtubule-associated protein tau	*MAPT*
Neurofilament heavy polypeptide	*NEFH*
Optineurin	*OPTN*
Profilin1	*PFN1*
DNA polymerase gamma	*POLG*
Peripherin	*PRPH*
Senataxin	*SETX*
Sigma receptor 1	*SIGMAR1*
Superoxide dismutase 1	*SOD1*
TATA box binding protein-associated factor 15	*TAF-15*
TAR DNA-binding protein	*TARDBP*
Ubiquilin-2	*UBQLN2*
Vesicle-associated membrane protein-associated protein B	*VAPB*
Valosin-containing protein	*VCP*