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Amyotrophic lateral sclerosis with primary progressive aphasia: A case report and literature review

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Abstract

The association between amyotrophic lateral sclerosis (ALS) and primary progressive aphasia (PPA) is rarely seen in patients. A case of ALS-PPA with a possible reticulon 2 (RTN2) mutation was reported in this study. Moreover, we systematically reviewed the previous reports of 28 ALS cases with progressive non-fluent aphasia (PNFA) and semantic dementia (SD) to identified the unique pathologic features and strong heritability of ALS-PPA. There is a different heritability among the ALS-SD, ALS-PNFA, and the ALS-unclassified PPA groups (p=0.003). Males are more prone to have ALS-PPA than females in all the three groups (p=0.028). PPA-ALS usually starts with cognitive impairment, and the onset most often involves the bulbar. In addition, chromosome 9 open reading frame 72(C9ORF72) and TANK-binding kinase 1 (TBK1) are important pathogenic genes of PPA-ALS. Overall, heritability is of high certainty in ALS-SD, ALS-PNFA, and the ALS-unclassified PPA groups. TAR (Trans-Activator Regulatory) DNA-binding Protein 43 (TDP43) is a 100% predictive pathologic protein of ALS-PPA. C9ORF72 and TBK1 are important pathogenic genes of PPA-ALS.

Abbreviations:

PPA	- Primary progressive aphasia
PNFA	- progressive non-fluent aphasia
SD	- semantic dementia
FTD	- frontotemporal dementia
ALS	- Amyotrophic lateral sclerosis
RTN2	- reticulon 2
C9ORF72	- chromosome 9 open reading frame 72
TBK1	- TANK-binding kinase 1
TDP43	- TAR (Trans-Activator Regulatory) DNA-binding Protein 43
RNA	- ribonucleic acid
BvFTD	- Behavioral variant of frontotemporal dementia
RTN4	- reticulon 4
ER	- endoplasmic reticulum

INTRODUCTION

Primary progressive aphasia (PPA) is a language disorder with a gradual and occult onset that mainly manifests as difficulty in choosing and using words, impaired verbal comprehension, and awkward sentence construction (Gorno-Tempini *et al.* 2011). The subtypes of PPA include progressive non-fluent aphasia (PNFA), semantic dementia (SD), and logopenic aphasia (Gorno-Tempini *et al.* 2011; Staiger *et al.* 2021). PNFA and SD are categorized as frontotemporal dementia (FTD), which comprises a group

CASE STUDY

of neurodegenerative diseases characterized by progressive atrophy and neuron loss in the frontal and temporal lobe cortices (Younes & Miller, 2020). Amyotrophic lateral sclerosis (ALS) with primary progressive aphasia is a rare syndrome that not only meets the diagnosis criteria for ALS, but also the diagnostic criteria for PPA (Strong *et al.* 2017). ALS and FTD share a common molecular, pathologic, and genetic basis, and overlapping clinical features, thus are thought to belong to a disease continuum (Strong *et al.* 2017; Saxon *et al.* 2017). The association between ALS and PNFA or SD has rarely been reported. Here we report a case of ALS-SD with a possible reticulon 2 (RTN2) mutation. Moreover, we systematically reviewed the previous reports of 20 ALS-PNFA and 8 ALS-SD cases to determine the clinical features, pathology, and genotypes. Our review also identified the unique pathologic features and strong heritability of ALS-PPA.

CASE REPORT

History and examination

A 49-year-old man was admitted to the Department of Neurology at the Affiliated Hospital of Guizhou Medical University in July 2018 complaining of "right upper limb weakness and reduced speaking for over 6 months." The patient could not understand other people's words, often gave irrelevant answers 2 months ago, and could only utter brief sentences 1 month ago. No family history of dementia was reported. The patient was a 30-year smoker (20 cigarettes/day) with a documented history of kidney stones and gastric diseases. He had difficulty with comprehension and expression of words and a deterioration of semantic knowledge about places, people, objects, and general information. His spontaneous speech was fluent, and his ability to repeat and write was normal. The fasciculations were observed on tongue muscles. Uplifting of the pharyngeal arch and pharyngeal reflexes were normal. Of note, the neck was soft and muscle atrophy was present in the upper limbs bilaterally, especially the right upper limb. Muscle strength was grade 3 in the right upper limb, and grade 4 for the other limbs. The patient had bilateral pyramidal tract signs (brisk tendon reflexes and positive Babinski's sign), and frontal lobe signs (palmomental and snout reflexes).

Neuropsychological assessment

Neuropsychological assessment showed a 9-points score of Mini-Mental State Examination (Folstein *et al.* 1975) and a 4-points score of Montreal Cognitive Assessment (Nasreddine *et al.* 2005). The frontal lobe function score (Dubois *et al.* 2008) was 0 points. The ABC (age, biomarkers, clinical history) assessment (Hijazi *et al.* 2016) showed that verbal expression was fluent, listening comprehension was impaired, and repeating capability was normal. Serial language, naming, and writing capabilities were partially normal. Routine blood and laboratory examinations revealed no abnormalities.

Brain imaging

A cranial magnetic resonance imaging on admission displayed atrophy of the left temporal pole (Figure 1) and 18F-fluoro-2-deoxy-2-D-glucose positron emission tomography scanning exposed asymmetric metabolism reduction in bilateral temporal lobes, and the uptake of glucose in the left temporal parietal lobe was lower than the contralateral side.

Electromyography

An electromyography showed extensive progressive denervation and nerve regeneration in the muscles innervated by the medulla oblongata, intumescentia cervialis, and thoracic spine. The detailed report was as below: Medulla oblongata (sternocleidomastoid muscle), cervical enlargement (abductor digiti minimus, extensor digiti communis, deltoid muscle) and the muscles innervated by the thoracic spinal cord (paraspinal muscles) appeared extensive ongoing denervation and chronic dementia; regeneration phenomenon (mainly chronic neurogenic damage).

Cerebrospinal fluid testing

In the cerebrospinal fluid, the level of P-τprotein (181p) was normal - 38.70pg/ml (normal range: 35.84-66.26), while both Amyloid β-protein (1-42) level - 1166pg/ml (normal range: 792±182) and the T-tau level - 761pg/ml (normal range: 136±89) were elevated.

Genetic testing

Measurement of cognitive impairment and dyskinesia-related pathogenic genes showed a heterogeneous G>C mutation at chr19:45997789 of the RTN2 gene. This led to the missense mutation of the 185th amino acid from glutamine-to-arginine, which could impair the structure and function of the protein (Figure 2). The patient was not examined for chromosome 9 open reading frame 72(C9ORF72) or TANK-binding kinase 1 (TBK1) mutations.

Treatment and prognosis

This patient was diagnosed with ALS-SD with a possible RTN2 mutation. Riluzole was prescribed (50 mg twice per day) for neuroprotective treatment. The patient died 6 months later due to aspiration pneumonia caused by worsening bulbar paralysis.

SYSTEMATIC REVIEW OF THE LITERATURE

Methods

We carefully searched articles published in English and Chinese from the Wanfang, China national knowledge infrastructure, PubMed, and Cochrane Library databases from 1987 to 31 December 2021. We performed

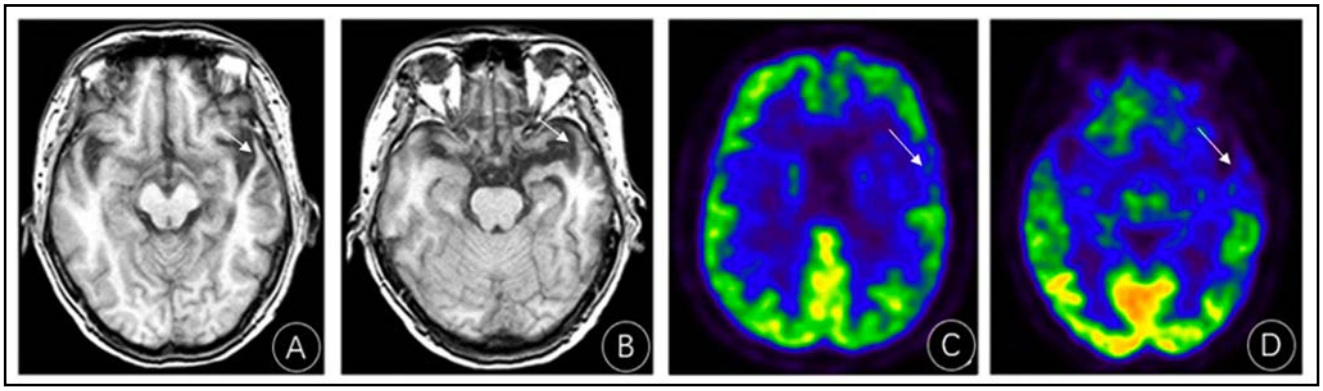

Fig. 1. Cranial images on admission. T1 weighted imaging of cranial magnetic resonance imaging (A, B) and 18F-fluoro-2-deoxy-2-D-glucose positron emission tomography imaging (C, D) show atrophy of the left temporal pole, and illustrates that glucose uptake in the left temporal parietal lobe is lower than the contralateral side.

the literature search with the search term [("primary progressive aphasia" OR "PPA") OR ("progressive non-fluent aphasia" OR "PNFA") OR ("semantic aphasia" OR "SD")] AND ("amyotrophic lateral sclerosis" OR "ALS"). By hand screening references of literature reviews on this subject, we also identified additional citations. All types of case reports and cohort studies with ALS with PPA were selected. For repeated cases in different articles, preference was given to the article with more comprehensive clinical data. Six hundred eighty articles were identified for title and abstract review. Among these reports, 111 articles were excluded for other languages (not English or Chinese) and 106 clinical case reports were excluded. In the remaining 463 articles, 338 were not verified and 106 were excluded for duplication. Finally, 19 articles involving 29 patients were selected for analysis (Figure 3). Clinical information was extracted from each article as follows: genotype; pathologic subtypes; onset age; death; age; gender; family history; clinical phenotype; disease sequence; onset site of ALS; survival time; and electromyography. Two reviewers (A Zhang and H Xu) independently did the data extraction and if there was a disagreement about the classification, a third reviewer (D He) was consulted.

Statistical analyses

The statistical analysis was carried out using the SYSTAT 10.2 program (SYSTAT software Inc., CA, USA). The chi-square test or the Fisher's exact test were used to assess the enumeration data. One-way Analysis of Variance was used to analyze data reported as mean ± standard deviation (mean±SD), followed by a Student-Newman-Keuls post hoc test, and p-values of 0.05 were considered statistically significant.

Baseline data of literature review

Herein we summarized the clinical data of our case report and 29 possible or definite ALS-PPA patients from previous reports (Table 1). A total of 30 ALS-PPA patients were included in this study (males, 70.0% [21/30] and females, 30.0% [9/30]) and with a mean age of 58.07±8.55 years (39-74 years). We carefully categorized the cases into 3 subtypes (ALS-PNFA, ALS-SD and ALS-unclassified PPA), and compared the clinical data trying to find out the characteristics of genes and pathologic types other than clinical phenotypes (Table 2). ALS-PNFA was diagnosed in 66.7% of patients (20/30), ALS-SD in 26.7% of patients (8/30), and ALS-unclassified PPA in 6.6% of patients (2/30). There was a small difference in baseline characteristics of average age between the ALS-PNFA group (58.40±9.35 years), ALS-SD group (56.88±7.57 years) and ALS-unclassified PPA group (59.50±6.36 years). Males accounted for 60.0% of the patients (12/20) in the ALS-PNFA group, 87.5% of the patients (7/8) in ALS-SD group and 100% (2/2) in the ALS-unclassified PPA group (p=0.028, Table 2). 30% of patients in

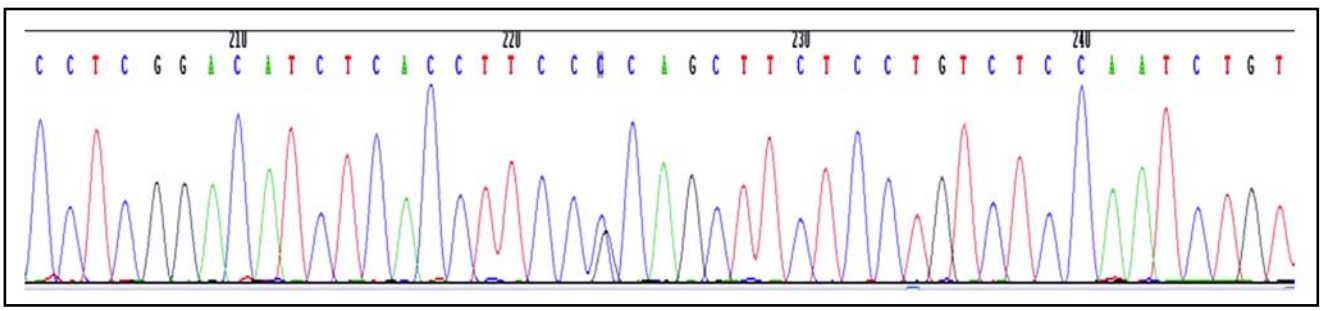

Fig. 2. Measurement result of cognitive impairment and dyskinesia-related pathogenic genes.

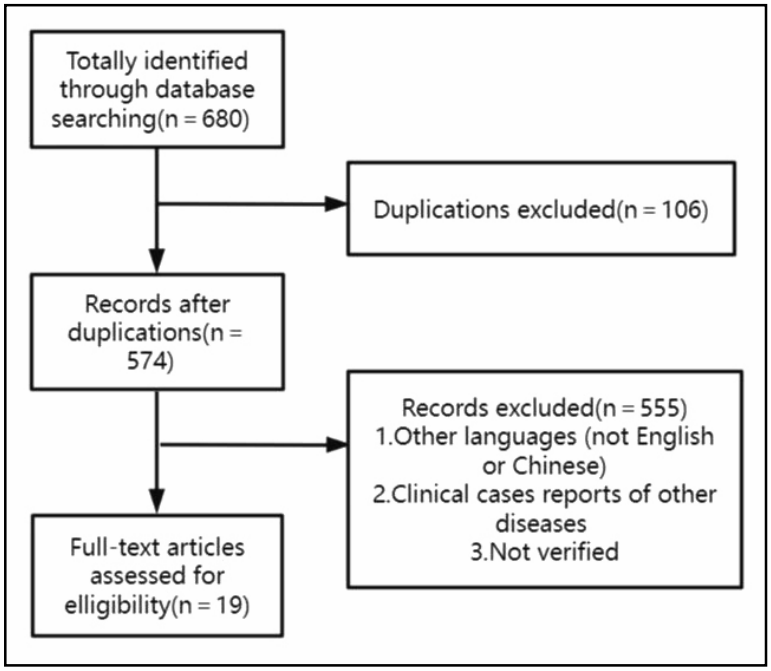

Fig. 3. Flowchart of literature search and selection criteria

the ALS-PNFA group and 50% of patients in the ALS-unclassified PPA had the disease related family history (p=0.003, Table 2)

Comparison of clinical, pathologic, and gene mutation characteristics between ALS-PNFA and ALS-SD patients

A family history of cognitive impairment and ALS existed in 6 patients in the ALS-PNFA group and 1 patient in the ALS-unclassified PPA. A family history of cognitive impairment was more common than a family history of ALS (6 patients vs. 1 patient; Table 1). The incidence of cognitive impairment was similar in the ALS-PNFA (9/20 [45%]) and ALS-SD groups (4/8 [50%]). Motor symptoms onset appeared to be similar in ALS-PNFA patients (4/20 [20.0%]) than ALS-SD patients (2/8 [25%]). The average interval between symptoms of cognitive impairment and motor symptoms was shorter in the ALS-unclassified PPA group (5.00±7.07months) than in the ALS-PNFA group (14.61±12.89 months) and in the ALS-SD group (19.50±28.72 months). The first onset of ALS was mainly bulbar among the 3 groups (Table 2). Survival in the ALS-PNFA group (38.87±24.87 months) was longer than in the ALS-SD group (25.14±18.47 months) and in the ALS-unclassified PPA group (20.00±5.66 months). TAR (Trans-Activator Regulatory) DNA-binding Protein 43 (TDP43) pathology was identified in 7 patients with ALS-PNFA and 2 patients with ALS-SD who had undergone autopsies. Five patients with ALS-PNFA had a C9ORF72 mutation, while one patient had a TBK1 mutation. There was one patient with a possible RTN2 mutation and one patient with a TBK1 mutation in the ALS-SD group. One patient with ALS-unclassified PPA had a C9ORF72 mutation (All $p > 0.05$, Table 2).

DISCUSSION

We have reported a patient with the ALS-SD phenotype, which manifest as an impaired understanding of words, atrophy and fasciculations of the tongue, muscle atrophy and weakness of the upper limbs bilaterally, and bilateral pyramidal tract signs. Involvement of the motor system achieved clinical ALS EI Escorial diagnostic criteria on clinical and electrophysiologic examination, which demonstrated clearly this was a case of ALS-SD. The results from the literature review (Table 1 for details and Table 2 for an overview) confirm that there is a different heritability among the ALS-SD, ALS-PNFA, and the ALS-unclassified PPA groups (p=0.003). Males are more prone to have ALS-PPA than females in all the three groups (p=0.028). Also, the results revealed that TDP43 pathology may be the predominant pathology in ALS-PPA.

The PNFA phenotype of ALS-PPA accounted for 66.7% of patients and the SD phenotype accounted for 26.7% of the ALS-PPA population. A previous study also showed that ALS-PNFA was more common than ALS-SD in the ALS population (12 vs. 3) (Tan *et al.* 2019); however, this is different from the proportion of SD and PNFA in PPA. Previous studies showed that SD has a higher proportion of PPA than PNFA (Sajjadi *et al.* 2012; Hodges *et al.* 2010; Senaha *et al.* 2013). The prone pathologic changes in Brodmann areas 44 and 45 of ALS patients may lead to a higher PNFA incidence in ALS patients (Hodges, 1995). Therefore, language impairment selectively involves verbs, and impaired speech fluency is a common clinical manifestation in ALS patients (Bak & Hodges, 2004). From the present point of view, this finding supports the phenomenon that ALS-PNFA is the dominant phenotype in ALS-PPA.

Based on the literature review, we found a higher incidence of ALS-PPA in men than women, which is consistent with a higher incidence and prevalence of ALS in men than in women. This gender difference was noted in a large study (McCombe & Henderson, 2015) that included all patients with ALS (sporadic and familial), but not in independent studies of familial ALS (McCombe & Henderson, 2015). Further analysis of the ALS-PNFA and ALS-SD subgroups showed that the proportion of males in the ALS-PNFA group was 60% (12/20) and 87.5% (7/8) in the ALS-SD group. Possible reasons for differences in the incidence of ALS between males and females include differences in exposure to environmental toxins, biological responses to exogenous toxins, and underlying differences between the male and female nervous systems and the ability to repair damage (Woolley *et al.* 2011). The spinal column is more likely to be affected in males with sporadic ALS, while the medulla oblongata was more likely affected in females with ALS according to the Mccombe study (McCombe & Henderson, 2015). Our study showed that ALS-PPA was more likely to develop mainly in the bulbar area in males and females. These results are not sufficient to confirm the influence of gender on the onset sequence of motor symptoms in patients with ALS-PPA.

Patients with ALS-PPA are common to have symptoms like dysarthria, dysphagia, or upper limb weakness accompanied by muscle atrophy and fibrillation. The interval between the onset of ALS symptoms and cognitive symptoms in patients with ALS-PNFA and ALS-SD are similar, but the survival time is longer for patients with ALS-PNFA than ALS-SD. All of the reviewed studies were single-center retrospective studies, thus the prognosis of ALS-PPA patients remains to be further investigated.

Based on a previous report, among the cases of familial PPA with TDP43 in Australia, known FTD/ALS gene mutations accounted for 100%, but only 50% of the cases of familial ALS-PPA (Tan *et al.* 2019). In our study, TDP B type accounted for 89.9% (8/9) of TDP pathologic types in ALS-PPA. Therefore, TDP B type is the potential neurobiological basis for ALS-PPA rarity. There was only one case of familial PPA-ALS with FTD-TDP (1/9 [11%]), which may be mainly related to the low percentage of patients with familial PPA-ALS who were autopsied. Among the ALS-PPA patients with TDP43 in this study, the C9ORF72 gene mutation accounted for 44% (4/9), all of whom were from Canada. These results are similar to the data in the Australia report (Tan *et al.* 2019), which suggests that the patients in different locations may have the same genetic patterns.

In recent years, multiple genes have been found in PPA and ALS at the same time, and the common pathogenesis of PPA and ALS is the destruction of ribonucleic acid (RNA) and protein homeostasis. Most studies in European and American countries believe that repeated amplification of C9ORF72 gene in the non-coding region GGGGCC is the most common mutation type in ALS-PPA (DeJesus-Hernandez *et al.* 2011; Gijselinck *et al.* 2012; Majounie *et al.* 2012; Renton *et al.* 2011). Currently, there are two theories regarding the pathogenesis of C9ORF72. One theory holds that the repeated amplification of GGGGCC on the C9ORF72 gene leads to RNA toxicity, which leads to the isolation of RNA binding protein. Another theory is that the pathogenesis of C9ORF72 may be related to haploid deficiency. Behavioral variant of frontotemporal dementia (BvFTD) is the most common FTD variant associated with C9ORF72 amplification, while PNFA is the second most common and SD is rarely associated with C9ORF72 amplification (Cerami *et al.* 2013; Simón-Sánchez *et al.* 2012; Snowden *et al.* 2012). Therefore, the C9ORF72 gene is more closely related to the clinical characteristics of PNFA, and ALS-PNFA complex is more easily formed in ALS-PPA, which may be related to atrophy of the main frontal lobe in C9ORF72-related cases (Van Langenhove *et al.* 2013). It is worth noting that the ALS-PPA cases related to C9ORF72 reported in this paper were all patients from Canada, and there are no reports about C9ORF72 and ALS-PPA in China at present.

Since 2015, the relationship between the TBK1 gene and FTD-ALS has received increased attention. Gijselinck *et al.* reported that the TBK1 gene loss of function is related to FTD and ALS, which is the most common pathogenic gene of FTD after C9ORF72 and progranulin genes (Gijselinck *et al.* 2015). TBK1 gene is also the most common ALS pathogenic gene after the C9ORF72 gene. Gijselinck *et al.* reported that the TBK1 mutation rate is 1.1% in FTD patients, 3.4% in ALS patients, and 4.5% in BvFTD-ALS patients (Gijselinck *et al.* 2015). TBK1 mutations are mainly mediated by the FTD-ALS complex, mainly the BvFTD phenotype. In China, however, TBK1 mutations in the ALS complex are all ALS-PPA; few family histories are positive. The age of onset of our case was 49 years, and the course of disease was 2 years. In the previous reports of the P. Glu643Del mutation in ALS-BvFTD patients, the patient was 62 years of age, and the course of disease was longer (11 years) (Gijselinck *et al.* 2015). Our study was different from the case in previous report (Gijselinck *et al.* 2015), suggesting that there may be great differences among different races in diseases mediated by TBK1 mutations. Therefore, the clinical heterogeneity among TBK1 mutation carriers warrants further study in the future.

To date, very few reticulon gene mutation-related cases have been reported, and the mutation directly related to ALS is the reticulon 4 (RTN4) gene mutation (Kulczyńska-Przybik *et al.* 2021). RTN2 and RTN4 belong to a gene family encoding the membrane protein of the endoplasmic reticulum (ER). RTN2B is a positive regulatory factor that promotes the release of excitatory amino acid carrier 1 from the ER to the membrane surface of the dendrite and spinous process, and consequently eliminates the excitatory toxic amino

Tab. 1. Demographic, clinical, genetic, and pathologic profile of the cases with amyotrophic lateral sclerosis and primary progressive aphasia

Order/Ref	Mutation	Pathology	Sex	Age of onset	Age of death	Family history	Phenotype	Order of disease	Interval (months)	First onset of ALS	Survival (months)	Electromyogram	Country
1 Caselli *et al.* 1993	NA	NA	male	57	58	four siblings had cognitive impairment	ALS-PNFA	ALS→PNFA	12	bulbar	12	Acute denervation, extensive fibrillation potential	America
2 Tsuchiya *et al.* 2000	NA	NA	female	74	75	N	ALS-PNFA	Simultaneously	0	bulbar	10	Neurogenic impairment	Japan
3 Bak *et al.* 2001	NA	NA	male	51	NA	sister had Down syndrome	ALS-PNFA	PNFA→ALS	24	bulbar	36	NA	Britain
4 Bak *et al.* 2001	NA	NA	male	67	NA	N	ALS-SD	SD→ALS	2	bulbar	18	NA	Britain
5 Bak *et al.* 2001	NA	NA	male	50	NA	NA	ALS-PNFA	PNFA→ALS	NA	NA	22	Denervation of biceps brachii	Britain
6 Bak *et al.* 2001	NA	NA	male	64	NA	N	ALS-unclassified PPA	Simultaneously	0	bulbar	24	Extensive chronic denervation	Britain
7 Bak *et al.* 2001	NA	NA	female	70	NA	N	ALS-PNFA	ALS→PNFA	12	bulbar	24	NA	Britain
8 Catani *et al.* 2003	NA	NA	male	71	NA	NA	ALS-PNFA	PNFA→ALS	3	bulbar	15	Extensive denervation potential	Britain
9 Ishihara *et al.* 2006	NA	NA	female	52	NA	N	ALS-PNFA	PNFA→ALS	6	cervical	90	Damage to anterior horn of the right hand and lower limb	Japan
10 Kim *et al.* 2009	NA	NA	male	61	NA	NA	ALS-SD	SD→ALS	17	bulbar	NA	Denervation of the upper extremity, large action potential	Korean
11 Östberg &Bogdanović, 2011	NA	TDP43	male	63	NA	NA	ALS-SD	SD→ALS	84	bulbar	36	Neurogenic impairment of the tongue and proximal arm	Swedish
12 Coon *et al.* 2012	NA	NA	female	64	NA	NA	ALS-SD	ALS→SD	12	cervical	48	NA	America
13 Pelin *et al.* 2012	NA	NA	female	64	NA	mother cerebral infarction	ALS-PNFA	ALS→PNFA	6	bulbar	NA	Bulbar, cervical motor potential, denervation potential	Turkey
14 Cerami *et al.* 2013	C9ORF72	NA	male	55	NA	mother ALS	ALS-unclassified PPA	PPA→ALS	10	cervical	16	Neurogenic impairment	Italy

Order/Ref	Mutation	Pathology	Sex	Age of onset	Age of death	Family history	Phenotype	Order of disease	Interval (months)	First onset of ALS	Survival (months)	Electromyogram	Country
15 De Marchi *et al.* 2019	N	NA	male	60	NA	N	ALS-PNFA	PNFA→ALS	22	bulbar	36	Neurogenic impairment of the bulbar, cervical and lumbar spinal cord	Italy
16 Rajagopalan & Pioro, 2019	C9ORF72negative	NA	female	69	NA	N	ALS-PNFA	PNFA→ALS	12	bulbar	NA	N	America
17 Lee *et al.* 2020	NA	TDP B	male	59	NA	NA	ALS-PNFA	PNFA→ALS	NA	NA	NA	NA	America
18 Lee *et al.* 2020	NA	TDP B	male	64	NA	NA	ALS-PNFA	PNFA→ALS	48	bulbar	84	NA	America
19 Lee *et al.* 2020	NA	TDP B	male	60	NA	aunt dementia	ALS-PNFA	PNFA→ALS	24	bulbar	60	NA	America
20 Lee *et al.* 2020	NA	TDP B	male	51	NA	NA	ALS-SD	SD→ALS	36	bulbar	48	NA	America
21 Li *et al.* 2013	NA	NA	male	70	NA	N	ALS-PNFA	PNFA→ALS	4	bulbar	NA	Denervation potential of sternocleidomastoid muscle	China
22 He *et al.* 2018	TBK1	NA	female	51	53	father Parkinson	ALS-PNFA	Simultaneously	0	cervical	24	Neurogenic impairment of cervical, thoracic, and lumbar spinal cord	China
23 Cui *et al.* 2016	N	NA	male	51	NA	N	ALS-SD	Simultaneously	0	bulbar	6	NA	China
24 Wu *et al.* 2017	N	NA	male	47	NA	mother cerebral infarction	ALS-PNFA	PNFA→ALS	30	cervical	60	Extensive neurogenic damage	China
25 Wan *et al.* 2019	TBK1	NA	male	49	NA	N	ALS-SD	SD→ALS	5	bulbar	8	Extensive neurogenic damage	China
26 Hsiung *et al.* 2012	C9ORF72	TDP B	female	54	58	NA	ALS-PNFA	PNFA→ALS	24	NA	48	NA	Canada
27 Hsiung *et al.* 2012	C9ORF72	TDP B	male	52	55	NA	ALS-PNFA	PNFA→ALS	24	NA	36	NA	Canada
28 Hsiung *et al.* 2012	C9ORF72	TDP B	male	54	56	NA	ALS-PNFA	ALS→PNFA	12	NA	24	NA	Canada
29 Hsiung *et al.* 2012	C9ORF72	TDP B	female	39	41	NA	ALS-PNFA	Simultaneously	0	NA	24	NA	Canada
30 our report	RTN2	NA	male	49	50	N	ALS-SD	Simultaneously	0	cervical	12	Chronic denervation potential of cervical onset	China

Footnotes: PPA: Primary progressive aphasia; PNFA -progressive non-fluent aphasia; SD -semantic dementia; ALS -Amyotrophic lateral sclerosis; RTN2-reticulon 2; C9ORF72:chromosome 9 open reading frame 72; TBK1:TANK-binding kinase 1; TDP43: TAR (Trans-Activator Regulatory) DNA-binding Protein 43

Tab. 2. Comparison of clinical features, gene findings and pathology results among the ALS-PNFA, ALS-SD and ALS-unclassified PPA (n, %)

	ALS-PNFA (n=20)	ALS-SD (n=8)	ALS-unclassified PPA (n=2)	ANOVA (F)/ χ^2	*p* value
Onset age (years, mean ± SD)	58.40±9.35	56.88±7.57	59.50±6.36	F=0.114	0.893
Gender, male	12/20 (60.0)	7/8 (87.5)	2/2 (100)	χ^2 =4.80	0.028
Family history	6/20 (30.0)	0/8 (0)	½ (50.0)	χ^2 =8.533	0.003
Cognitive impairment onset	9/20(45)	4/8(50.0)	2/2 (100)	χ^2 =2.200	0.333
Motor symptoms onset	4/20(20.0)	2/8(25.0)	0/2 (0.0)	χ^2 =0.625	0.732
Interval between cognitive and motor symptoms (months, mean ± SD)	14.61±12.89	19.50±28.72	5.00±7.07 (5)	F=0.523	0.599
Bulbar onset	11/20 (55)	6/8 (75)	½ (50)	χ^2 =1.042	0.594
Cervical onset	3/20 (15)	2/8 (25)	½ (50)	χ^2 =1.563	0.458
Not clear onset	6/20 (30)	0/8 (0)	0/2 (0)	NA	NA
Survival time (months, mean ± SD)	38.87±24.87(36)	25.14±18.47(18)	20.00±5.66 (20)	F=1.139	0.338
Gene mutation					
C9ORF72	5/20 (25)	N/A	1/2 (50)	χ2 =0.573	0.449
RTN2	N/A	1/8 (12.5)	N/A	NA	NA
TBK1	1/20 (5)	1/8 (12.5)	N/A	χ^2 =0.485	0.486
Pathology/TDP 43	7/7 (100)	2/2 (100)	N/A	NA	NA

Footnotes: PPA: Primary progressive aphasia; PNFA -progressive non-fluent aphasia; SD -semantic dementia; ALS -Amyotrophic lateral sclerosis; RTN2-reticulon 2; C9ORF72: chromosome 9 open reading frame 72; TBK1:TANK-binding kinase 1; TDP43: TAR (Trans-Activator Regulatory) DNA-binding Protein 43; ANOVA : Analysis of Variance; mean ± SD: mean ± standard deviation

acid (glutamic acid) that is released from the synapse (Liu *et al.* 2008). Glutamic acid-mediated excitatory toxicity is the initiating factor for the spiral of events in neurodegenerative cell death in ALS, including mitochondrial dysfunction, oxidative stress, and protein aggregation. The ER contact site damage is one pathogenic mechanism underlying the occurrence of ALS, which could induce morphologic and functional abnormalities of Golgi bodies, calcium disturbance, and autophagy disorders of neurons (Farhan *et al.* 2006). Previous studies have shown that after knockout of the RTN2 gene, neurons have distal ER and mitochondrial localization sequence loss, as well as presynaptic terminal mitochondria enlargement and loss, which consequently induces the ER dynamic changes in axons of neurons, leading to lipid, Ca^{2+}, and organelle homeostatic damage (Liu *et al.* 2008; Diekmann *et al.* 2005). The exact mechanisms, though, remain unclear. Previous studies have reported that hereditary spastic paraplegia induced by the RTN2 gene mutation could be manifested as a spinal cord anterior horn injury (Mishra & Pandey, 2006). Specifically, the clinical manifestations of reticulon mutations included progressively worsening body rigidity accompanied by rapidly progressing muscle fasciculations and atrophy (Liu *et al.* 2008; Farhan *et al.* 2006; Diekmann *et al.* 2005; Mishra & Pandey, 2006), the mechanisms of which might involve an interaction of RTN2 protein with spastin protein that influence injuries of the spinal cord anterior horn. The onset of this disease in the patient study was 49 years of age with a rapid progression of muscle fasciculations and atrophy within 2 months. We speculated that such clinical characteristics could be associated with a RTN2 gene mutation.

In summary, our case was a patient of ALS-PPA with a possible RTN2 mutation. PPA-ALS is a rare disease, which is familial in some foreign patients. PPA-ALS usually starts with cognitive impairment, and the onset most often involves the bulbar. TDP43 is a 100% predictive pathologic protein of ALS-PPA. In addition to C9ORF72 and TBK1 are important pathogenic genes of PPA-ALS; however, this study was limited by the small number of cases, incomplete comparative clinical data, and selection bias. Most of the identified literatures were case reports with less data, resulting in inaccurate statistical results. Further large cohort studies are therefore needed.

DECLARATIONS

Ethical Statement

The study was approved by the ethics committee of our hospital. The research was conducted ethically in accordance with the World Medical Association Declaration

of Helsinki. Written informed consent to participate in the study has been obtained from the patient.

Consent for publication

Written informed consent of the publication of this study has been obtained from the patient.

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Authors' contributions

All the authors have participated in the clinical data collection and analysis, AZ and HX did the literature review and analysis, and wrote the 1st draft of the manuscript. JH, TT and SG did the validation of the data. XL and DH did critical review and revisions on the manuscript draft. All the authors have approved the final draft for submission.

Conflicts of Interest

None.

Acknowledgment

None.

Availability of data and material

The data of this study was restricted for public access for the privacy but could be achieved on reasonable request to the corresponding author.

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