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REVIEW ARTICLE

Diagnosis and differential diagnosis flow diagram of Chinese post-stroke aphasia types and treatment of post-stroke aphasia

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Abstract

This review aimed to explore the concept, etiology, classification, classical cortical mapping, assessment, diagnosis and differential diagnosis, treatment, rehabilitation, mechanism, recovery, prognosis, and influencing factors for Chinese post-stroke aphasia (PSA). The review emphasized the necessity and significance of neuroimaging assessment of brain and blood vessels and neuropsychological assessment in diagnosis and differential diagnosis of Chinese PSA. In addition, it suggested and recommended to use "dichotomies of internal and external, and anterior and posterior" as a starting point, based on the anatomic location of brain and blood vessels and their relationship with language area and language disorder. As a result, the formulated Chinese PSA classification was more suitable to guide the clinical treatment of cerebral stroke. Diagnosis, classification, and differential diagnosis of Chinese PSA types were performed according to the "dichotomy" and "four elements." The formulated "flow diagram" enabled to determine the classification of Chinese PSA types. It was beneficial for patients to establish targeted and individualized rehabilitation training plans. This review introduced the use of memantine, piracetam, donepezil, etc. in PSA treatment, evaluated clinical studies conducted in China and abroad, investigated the mechanism of action related to the use of drugs in PSA treatment, and explored the therapeutic mechanism of rehabilitation training. It suggested the use drugs of memantine, piracetam, donepezil, etc. combine with non-pharmacotherapy and rehabilitation training in clinical studies on PSA treatment and also in practical settings.

KEYWORDS

Chinese PSA types, dichotomy, differential diagnosis flow diagram, four elements, post-stroke aphasia, treatment

1 | INTRODUCTION

Cerebral stroke is common with high morbidity, mortality, and disability rates. It severely damages patients' health and life and also imposes a great disease burden on individuals and society. Aphasia symptoms are observed in 28%–30% of patients with acute stroke with post-stroke aphasia (PSA).

Chinese PSA has multiple symptoms and classifications. Neuropsychological assessment, diagnosis, and classification of aphasia require a high standard of professionalism. However, experienced professionals in this regard are not available because the differential diagnosis requires a higher level of expertise. Comprehensive assessments involve multiple methods and are time-consuming, whereas a single language ability scale cannot reflect the full view of aphasia. However, accurate diagnosis and classification are essential for the rehabilitation of aphasia to formulate individualized rehabilitation training programs for patients. This results in a multiplying effect and is therefore beneficial to patients. Diagnosis, treatment, and research of aphasia are inseparable from neuroimaging. Therefore, it is necessary to improve the diagnosis and treatment level of a multidisciplinary medical expert team specializing in aphasia; increase means of diagnosis, treatment, rehabilitation, and research; and eventually benefit patients.

Clinical researches on the use drugs of memantine, piracetam, donepezil, etc. combined with non-pharmacotherapy and rehabilitation training in PSA treatment are worthy of recommendation and are expected to provide valuable insights for future studies.

2 | OVERVIEW OF PSA

Language refers to expression, comprehension, reading, writing, and other aspects. Speech refers specifically to verbal language, which includes both talking and auditory comprehension. Aphasia is an impairment or loss of the acquired language ability caused by brain damage, leading to a language communication disorder. It is manifested as different levels of impairment or failure of the six basic abilities, including oral expression, oral comprehension, repetition, naming, reading, and writing. Aphasia causes communicative disorders. Aphasia caused by stroke is called PSA. PSA can be divided into multiple types according to different locations of stroke lesions.[1–8]

Cerebrovascular disease is a general term for localized cerebral circulatory disorders resulted from various vascular causes. It is mainly divided into ischemic and hemorrhagic disorders. Stroke is the "acute onset" of cerebrovascular disease. The causes of aphasia after the brain damage include stroke, brain trauma, brain tumors, hypoxic–ischemic encephalopathy, encephalitis, neurodegenerative diseases, and so forth.[9–11] Among all, stroke is the primary cause of aphasia in adults; with 28%–30% of patients with acute stroke who suffered from PSA after the stroke.[12,13]

A systematic review and meta-analysis[12] retrieved 2168 citations, reviewed 248 articles, and accepted 50. Flowers et al reported the median aphasia frequencies for mixed stroke (ischemic and hemorrhagic) were 30% and 34% for acute and rehabilitation settings, respectively. Bersano et al[13] selected 9594 cases out of 11,572 patients with acute stroke in Italy for the estimation of aphasia frequency. All patients underwent 2-year follow-up evaluation from 2001, 28% of alert patients with acute stroke had PSA.

3 | PATHOPHYSIOLOGICAL MECHANISM OF PSA

The language network of each cerebral hemisphere is divided into six modules[14]: Broca area and adjacent frontal lobe area, Wernicke area and adjacent temporal lobe area, part of the upper parietal cortex, central operculum, temporal lobe, and frontal lobe. The six modules are connected by white matter in the neural network. They are integrated into one whole to achieve normal processing of the language. In the process of PSA, the brain area near the lateral cerebral fissure of the dominant hemisphere plays a central role in language function. Stroke lesion impairs the function of the language area in the cerebral language center. In addition, it affects the functional connectivity of language areas in the brain,[14] causing a breakdown of white matter in neural networks and resulting in PSA.

4 | EVALUATION AND SIGNIFICANCE OF NEUROIMAGING ASSESSMENT IN PSA

Neuroimaging assessment of the brain and blood vessels plays an important role in the diagnosis and treatment of PSA. Although all kinds of stroke lesions can cause PSA, the most common cause is damage to the dominant (left) cerebral hemisphere due to left middle cerebral artery (MCA) ischemic stroke. Cerebral neuroimaging assessment shows the nature, location, and size of the lesion. It predicts the severity of the stroke, type of PSA, severity, and prognosis of aphasia.[9,15–17] The location of the lesion can provide information about possible cognitive impairments, whereas the size of the lesion can help predict the extent of cognitive defects.[9] It can be used to study the functional connection[14] between the language areas. The neuroimaging assessment of blood vessels can reveal the etiology, responsible lesions, and blood supply in PSA. Neuroimaging assessment can also guide the clinical diagnosis and treatment, and is used in theoretical research.

According to my clinical experiences and my concept of the PSA "Internal and external dichotomy" with the distribution of cerebral blood vessels, about the significance of neuroimaging assessment of vasculature in PSA, I think that the severity and prognosis of stroke, the aphasia types and associated clinical symptoms, cognition impairments are constrained by the underlying brain vasculature. Therefore, from the neuroimaging (computed tomography [CT] or magnetic

resonance imaging [MRI]) assessment of vasculature, the predictors of severe stroke, PSA, and cognitions impairments were as follows[8]:

1. The etiology of stroke was the left MCA (ischemic thrombosis or hemorrhage).
2. The infarction's corresponding blood supply vessel of the MCA and posterior cerebral artery (PCA).
3. The lesion's location in the dominant (left) cerebral hemisphere (more severe than in the right cerebral hemisphere); the lesion's location in the left temporal parietal junction area; near the lateral Perisylvian fissure.
4. The lesion's size (large more severe than small); the lesion's numbers (multiple more severe than single); the lesion's nature (ischemic infarctions more severe than hemorrhage).

The lesion location and its corresponding blood supply vessels can also be used to predict possible problems in speech expression, comprehension, naming, repetition, reading, and writing in these patients, thus predicting the type and severity of possible aphasia as well as the severity of stroke.[8]

The dominant (left) cerebral hemisphere was the dominant hemisphere of language and cognition functions. The brain areas of the left temporal parietal junction area near the Perisylvian fissure were very important language centers and cognition centers of the brain.

The language function is carried out by the temporofrontal network in the brain with lateralization majorly to the left hemisphere; the arcuate fasciculus structurally connects Broca's and Wernicke's areas, and is an important language pathway.[14]

Global aphasia is the most severe form of aphasia, and has been associated with extensive cortical damage in the region supplied by the left MCA. This type of aphasia was associated with damage to areas both Broca's area and Wernicke's area, as well as insular regions are damaged. Conduction aphasia has historically been associated with lesions of the arcuate fasciculus (a white-matter tract connecting Broca's and Wernicke's areas).[15]

5 | NEUROPSYCHOLOGICAL ASSESSMENT OF PSA AND ITS SIGNIFICANCE

In addition to language impairment of PSA, patients with stroke may also develop cognitive impairment, which lasts for 6 months. It is called "post-stroke cognitive impairment" syndrome, which affects the assessment of post-stroke aphasia. It needs to be identified, and vice versa.[9,11,18,19] Therefore, to correctly evaluate the language assessment results of PSA, patients with PSA need to undergo complete cerebral function assessment[1–8,11] to investigate whether they have memory, cognition, agnosia, apraxia, neglect, depression, and other disorders at the same time. PSA's language assessment and accurate classification of aphasia types are critical in the treatment of stroke. These are the keys to ensure that patients get the rehabilitation they need.

5.1 | Assess the severity of stroke using a stroke scale

5.2 | Systemic and comprehensive language assessment of aphasia by assessment methods used in China and abroad

Assessment methods cover six functions, including language expression, comprehension, repetition, naming, reading, and writing. It can systematically evaluate and classify aphasia. It facilitates localization and qualitative diagnosis by doctors. It is widely used in the clinical setting and research in China and abroad.[1–8,20–22]

1. Boston Diagnostic Aphasia Examination (BDAE), its third version (BDAE-third), and the modified version (BDAE-R).
2. Western Aphasia Battery (WAB), Western Aphasia Battery-revised version (WAB-R), and its Chinese version.
3. Standard Language Test for Aphasia.
4. China Rehabilitation Research Center Aphasia Examination.
5. Aphasia Battery of Chinese (ABC).
6. Chinese Aphasia Examination of Peking Hospital.

5.3 | Assessment of communicative abilities in aphasia

The assessment focused on interpersonal communicative abilities, such as oral expression, comprehension, and conversations.[7,23] For example: the Communicative Abilities in Daily Living Test; Functional Communication Profile; Porch Index of Communicative Ability; and American Speech-Language-Hearing Association Functional Assessment of Communication Skills.

5.4 | Assessment of single language ability

For patients with special or prominent language defects,[20,23–26] in-depth special evaluations can be conducted to guide treatment and formulate individualized rehabilitation treatment plans. For example, the verbal fluency test,[20] Boston naming test,[20] oral expression assessment, auditory comprehension assessment, repetition test, and token test.[23–26]

5.5 | Screening scale for aphasia

It is a simple and quick screening test that can be done at bedside or in outpatient clinics.[27]

1. Cognitive Linguistic Quick Test
2. Western Aphasia Battery-Bedside
3. Acute Aphasia Screening Protocol
4. Aachen Aphasia Bedside Test
5. The Language Screening Test

5.6 | Determining handedness

Judging of handedness should be done before the language assessment of aphasia.[28] Handedness, in combination with lesion location by neuroimaging and language assessment, can be used to determine the hemisphere in which the patient's language center is located.

6 | CLASSIFICATION OF PSA IN THE NEUROPSYCHOLOGICAL UNIT, DEPARTMENT OF NEUROLOGY, PEKING UNIVERSITY FIRST HOSPITAL

No standard classification for aphasia is available yet. The classification of aphasia in the Neuropsychological Unit, Department of Neurology, Peking University First Hospital, is based mainly on the result of neuropsychological and neuroimaging assessments. It was developed in 1979 based on Benson and Kertesz's view on aphasia classification.[1–3,15,29–31] Related studies have been conducted on Chinese PSA in China for decades. In combination with the characteristics of stroke, it is believed that aphasia classifications are highly related to anatomic location and blood supply of lesions. Therefore, the Chinese aphasia classification was reformulated (Table 1)[32] based on the relationship between brain anatomy and language areas supported by the blood supply (dichotomy). The classification of aphasia helps guide the treatment of PSA and the formulation of targeted and individualized rehabilitation treatment plans. It can be used to predict prognosis and monitor disease progression.[12,13,31]

TABLE 1 Classification of Chinese PSA in the Department of Neurology, Peking University First Hospital

1. Perisylvian fissure aphasia syndrome: All the lesions are in the Perisylvian fissure area, and patients commonly have difficulty in repetition.
   a. Broca aphasia
   b. Wernicke aphasia (WA)
   c. Conduction aphasia
   d. Global aphasia
2. Transcortical aphasia, also known as border-zone aphasia syndrome: the lesions are located in the watershed area, and the common feature in these patients is relatively intact repetition function.
   a. Transcortical motor aphasia (TCMA)
   b. Transcortical sensory aphasia (TCSA)
   c. Mixed transcortical aphasia (MTA)
3. Anomic aphasia
4. Subcortical aphasia syndrome
   a. Thalamic aphasia (TA)
   b. Basal ganglion aphasia (BaA)
5. Alexia
6. Agraphia
7. Pure word deafness
8. Pure word dumbness
9. Crossed aphasia

Note: It refers to right-handed individuals who have aphasia caused by the right cerebral hemisphere lesions and develop the aforementioned types of aphasia.

PSA, post-stroke aphasia.

ABC's PSA classification system and fluent rating system have applied in clinical and research field very widely within our country. ABC (which includes the PSA classification system and fluent rating system) was used in clinics about 56.1% in China.[33]

The experts consider that ABC was a systematic evaluation system, enabled to determine the PSA types, helpful to get the localization and qualitative diagnosis, and be suitable to guide the treatment and rehabilitation in clinical practice. The rating system was very practical in clinic. The ABC got several recommendations of expert consensus.[9,17]

7 | CLASSIC CORTICAL MAPPING OF VARIOUS TYPES OF CHINESE APHASIA (THE SCHEMATIC DIAGRAM)

1. Broca aphasia (BA): Its core lesion is located in the posterior part of the dominant inferior frontal gyrus (Broca area; BA44 and 45).[1–8,14–17,29–32]
2. Conductive aphasia (CA): Its core lesion is located in the dominant supramarginal gyrus and Wernicke area, with left arcuate fasciculus damage (results in a disconnection between the Wernicke area and Broca area).
3. Wernicke aphasia (WA): Its core lesion is located in the posterior part of the dominant superior temporal gyrus (Wernicke area; BA22).
4. Global aphasia (GA): Its core lesion is extensively located in the dominant hemisphere, involving the left frontal, temporal, and parietal lobes, and the language area around the left Perisylvian fissure (a large lesion in the area supported by the left MCA).
5. Transcortical motor aphasia (TCMA): Its core lesion is located in the watershed area between the frontal lobe and the parietal lobe in the dominant hemisphere, and in the anterior superior cortex in the left Broca area, with fiber connections impaired in the left superior frontal gyrus; middle and posterior parts of the left middle frontal gyrus; anterior, superior, and middle parts of the left inferior frontal gyrus; and between language motor areas.
6. Transcortical sensory aphasia (TCSA): Its core lesion is located in the watershed area between the temporal and parietal cortices in the dominant hemisphere cortex and near the Wernicke area.
7. Mixed transcortical aphasia (MTCA): It is a large focal lesion in the watershed area of the dominant hemisphere, involving the cortices of the frontal, parietal, and temporal lobes.
8. Anomic aphasia (AA): Its core lesion is in the posterior part of the middle temporal gyrus in the dominant hemisphere, involving the cortices of temporal, parietal, and occipital lobe junctions between the left middle temporal gyrus and the angular gyrus.
9. Subcortical aphasia (SCA): Its core lesion is in the left thalamus and internal capsule area of basal ganglia, with impaired connections.

10. Pure word deafness: Its core lesion is in the posterior part of the left superior temporal gyrus, deep in the posterior part of the left temporal lobe.
11. Pure word dumbness: Its core lesion is in the inferior part of the left precentral gyrus and posterior cortex of left inferior frontal gyrus, below the left frontal cortex.
12. Alexia: Its core lesion is in the left angular gyrus of the parietal lobe, anterior part of the left occipital lobe, and posterior inferior part of the left frontal lobe.
13. Agraphia: Its core lesion is in the posterior part of the left middle frontal gyrus and left angular gyrus.
14. Crossed aphasia: The core lesion in right-handed patients is in the right cerebral hemisphere, corresponding to the homolog brain language area in the aforementioned aphasia types[1–7,10,14]

Noteworthy: Except for the classic cortical mapping of various aphasia types, the subcortical white matter, various cerebral language areas, and the two cerebral hemispheres are all interconnected and coordinate with each other to form a neural network to achieve language functions.[14,15,18]

8 | DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS: FLOW DIAGRAM OF APHASIA TYPES IN CHINESE PSA

8.1 | ABC and clinical research on Chinese PSA

Wang Yinhua translated WAB into the Chinese language in 1982 and applied it in the clinical setting.[34] Wan Yinhua and Gao Surong then formulated ABC[8,35] that examined the circumstances with reference to WAB[3]and BDAE.[4] This test is indeed a comprehensive assessment of cerebral function, including assessments on cerebral linguistic and nonlinguistic functions. Nonlinguistic functions include consciousness, attention, orientation, memory, visual–spatial skills, praxia, calculation, frontal lobe motor function, determination of handedness, and so forth. Since the beginning of 1988, it has been used in the clinical setting and gradually promoted to many provinces and cities nationwide.

Gao Surong and Wang Yinhua[28] performed clinical studies on Chinese PSA and found that although Chinese characters were different from Western alphabetic characters, the language centers were mostly located in the left cerebral hemisphere, which was the same as those in Westerner's language centers and is located in the left cerebral hemisphere for 96.88% of all patients with aphasia, whereas 2.34% have their language center located in the right cerebral hemisphere (crossed aphasia). The main types of Chinese aphasia are almost the same as those of Westerners. Wang Yinhua et al[19,24-26,28,33,36–48] used our ABC and the later created diagnosis and differential diagnosis flow diagram of Chinese aphasia types to do a series of clinical studies Separately on language disorders and neuropsychology of Chinese PSA, Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), Vascular Cognitive Impairment (VCI), Vascular Dementia (VaD), Semantic Dementia (SD), Primary Progressive Aphasia (PPA), etc.

8.2 | Developing the concept of "dichotomy," "four elements," "classification of Chinese aphasia," and "Diagnosis and differential diagnosis flow diagram of Chinese aphasia types"

Based on decades of clinical and neuropsychological assessment and practice,[32,34] Wang Yinhua believed that to adapt to the characteristics of stroke and Chinese PSA, aphasia types should be more closely associated with the location of the cerebral cortex lesions and the lesion's supplying vessels. This can further facilitate clinical practice. Therefore, it is suggested that the concepts of "dichotomy," "four elements," and "diagnosis and differential diagnosis flow diagram of Chinese aphasia types" have facilitated the clinical use of ABC. The flow diagram of classification, diagnosis, and differential diagnosis of Chinese aphasia types was created[7,8,32] using the concept of "dichotomy"; the assessment results on repetition, auditory comprehension, and speech fluency; and the "four elements" of differential diagnosis used for the differential diagnosis of aphasia types. It is also closely connected to the location of various types of aphasia lesions in the cerebral cortex and the associated cerebral vascular supply.

8.3 | "Dichotomy" of the classification, diagnosis, and differential diagnosis of Chinese aphasia types

Wang Yinhua split the "dichotomy" in the classification of Chinese aphasia types into "internal and external dichotomy" (distribution of cerebral blood vessels) and "anterior and posterior dichotomy" (localization of cerebral central sulcus).

1. "Anterior and posterior dichotomy": Localization of cerebral central sulcus is related to auditory comprehension and speech fluency (Figure 1).
2. PSA "Internal and external dichotomy": Distribution of cerebral blood vessels: related to repetition in speech (Figure 2).
3. Dichotomy of Chinese PSA aphasia types based on repetition, auditory comprehension, and speech fluency (Table 2).
4. Significance of "dichotomy" of aphasia.

About two thirds of the patient's oral speech with aphasia can be classified using this dichotomy. Here, the dichotomy of aphasia can be used to locate lesions responsible for stroke and vascular supply based on the type and severity of aphasia. The lesion location and its corresponding blood supply vessels can also be used to predict possible problems in speech expression, comprehension, naming, repetition, reading, and writing in these patients, thus predicting

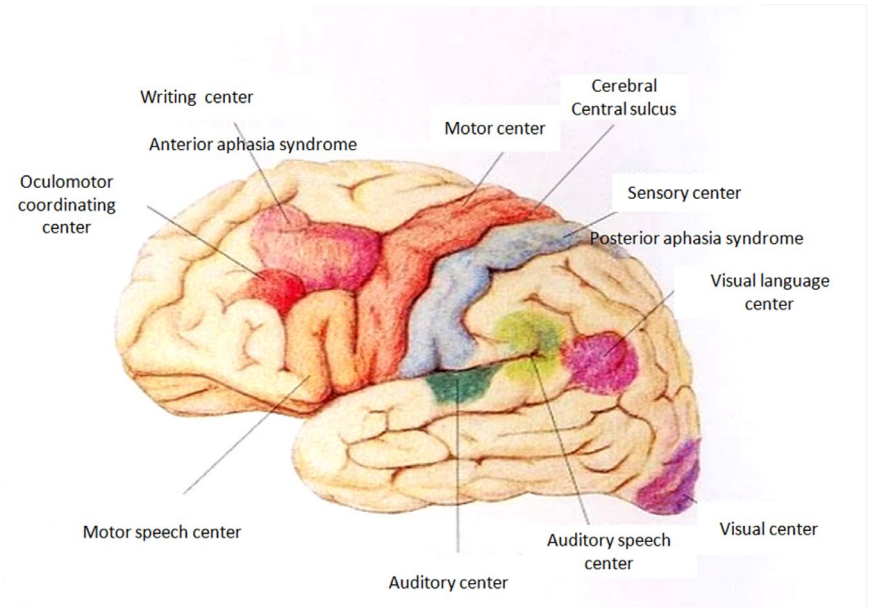

FIGURE 1 PSA "anterior and posterior dichotomy". Localization of the cerebral central sulcus. PSA, post-stroke aphasia

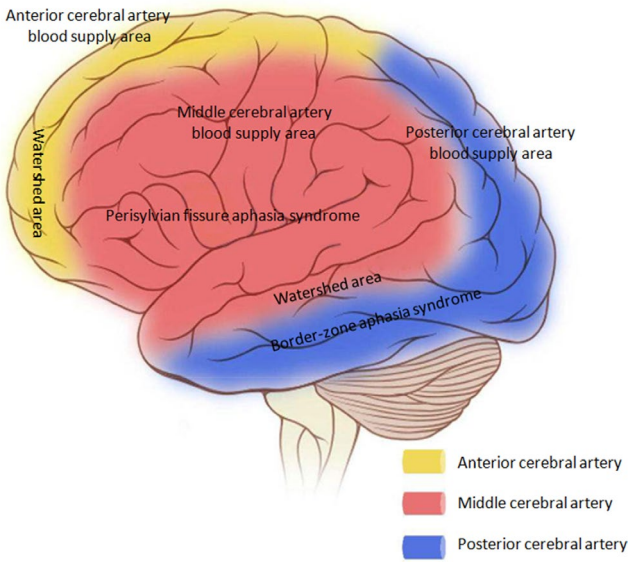

FIGURE 2 PSA "internal and external dichotomy". Cerebral blood vessel supply. PSA, post-stroke aphasia

the type and severity of possible aphasia. This facilitates the cause-finding, diagnosis, differential diagnosis, disease severity estimation, guidance of treatment and rehabilitation, and prognosis estimation of stroke and PSA.

8.4 | The "four elements" for the classification, diagnosis, and differential diagnosis of Chinese aphasia types

The four elements proposed by Wang Yinhua[32] are as follows: ability in terms of oral repetition, oral auditory comprehension, and verbal fluency (see Table 3 for fluency assessment[32]), and whether it is an

TABLE 2 Dichotomy of Chinese PSA aphasia types in the Department of Neurology, Peking University First Hospital

I. Internal and external dichotomy (distribution of cerebral blood vessels)	
Poor repetition Perisylvian fissure aphasia syndrome:	**Intact repetition Border-zone aphasia syndrome**
BA	TCMA
CA	TCSA
WA	MTCA
GA	AA
Pure word deafness	SCA
Pure word dumbness	
II. Anterior and posterior dichotomy (cerebral central sulcus localization)	
Anterior aphasia	**Posterior aphasia**
Intact auditory comprehension	**Poor auditory comprehension**
BA	WA
TCMA	TCSA
Pure word dumbness	Pure word deafness
CA	GA
AA	MTCA
SCA	
Nonfluent oral speech	**Fluent oral speech**
BA	WA
TCMA	TCSA
Pure word dumbness	Pure word deafness
GA	CA
MTCA	AA
SCA is the intermediate type	

Abbrevations: AA, anomic aphasia; BA, Broca aphasia; CA, conductive aphasia; GA, global aphasia; MTCA, mixed transcortical aphasia; PSA, post-stroke aphasia; SCA, subcortical aphasia; TCMA, transcortical motor aphasia; TCSA, transcortical sensory aphasia; WA, Wernicke aphasia.

impairment in "verbal speech" or "reading and writing of written language." These "four elements" not only are the decisive factors for the classification, diagnosis, and differential diagnosis of aphasia but can also indicate the location and size of the lesions and the severity of stroke in patients.

8.5 | Diagnosis and differential diagnosis flow diagram of Chinese aphasia types

The flow diagram for the classification, diagnosis, and differential diagnosis of Chinese aphasia types (Figure 3)[32] was made based on "dichotomy," "four elements," and classification according to repetition, auditory comprehension, fluency, and written language. Lesion location and schematic diagram of PSA Chinese aphasia types are shown in Figure 4.

9 | TREATMENT OF PSA

9.1 | Drug therapy

Cholinesterase inhibitors (donepezil, galantamine, rivastigmine, and physostigmine),[49–51] *N*-methyl-D-aspartate (NMDA) receptor antagonists (memantine),[50,51] nerve repair and brain-stimulating medications, and nootropic medications, such as piracetam, butylphthalide, ergoline, nimodipine, citicoline, Ginkgo biloba, and some proprietary Chinese medicines.

9.2 | Nonpharmacological therapy

Noninvasive brain stimulation, such as transcranial direct current stimulation, repetitive transcranial magnetic stimulation (rTMS),

TABLE 3 Fluency assessment of oral output of Chinese aphasia in the Department of Neurology, Peking University First Hospital

Oral output characteristics	1 point	2 points	3 points
1. Quantity	<50 words/min	51–99 words/min	>100 words/min
2. Intonation	Abnormal	Partially normal	Normal
3. Articulation	Dysarthria	Partially normal	Normal
4. Phrase length	Short (1–2 words, telegraphic style)	Some phrases are short	Normal (more than 4 words per sentence)
5. Level of effort	Obvious effort	Moderate effort	Effortless
6. Forced speech	No	Forced tendency	Yes
7. Wording	With content and meaning	Few meaningful words	Without content and meaning, meaningless
8. Grammar	No	Partially	Yes
9. Paraphasia	No	Occasionally	Frequent

Note: Sum of patients* score in the aforementioned nine items: 9–13 points represent the nonfluency type, 14–20 points represent the intermediate type; and 21–27 points represent the fluent type.

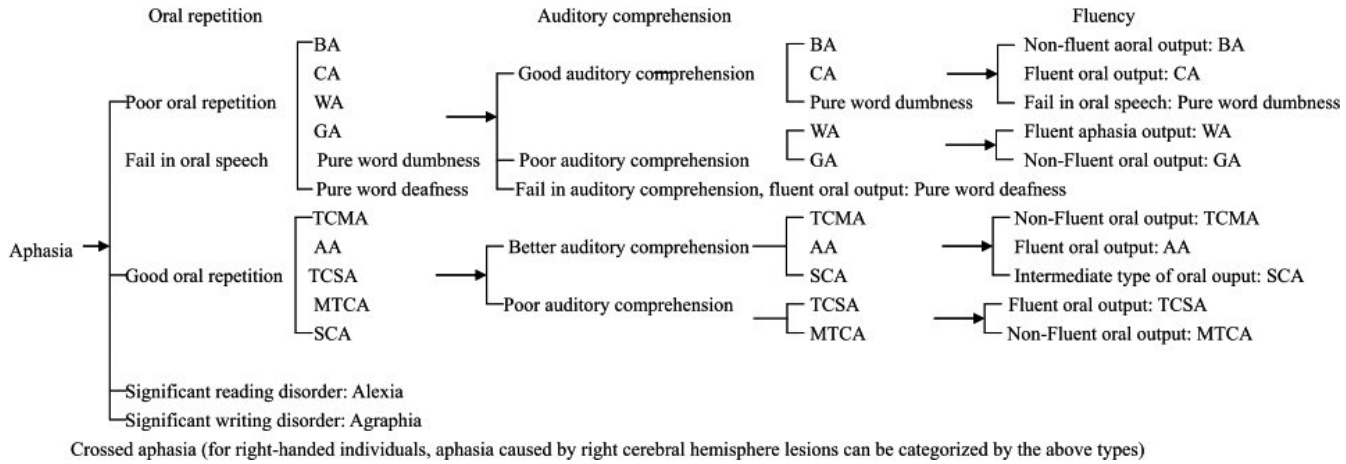

FIGURE 3 The diagnosis and differential diagnosis FLow Diagram of Chinese aphasia types of the department of Neurology, Peking University First Hospital. AA, anomic aphasia; BA, Broca aphasia; CA, conductive aphasia; GA, global aphasia; MTCA, mixed transcortical aphasia; SCA, subcortical aphasia; TCMA, transcortical motor aphasia; TCSA, transcortical sensory aphasia; WA, Wernicke aphasia

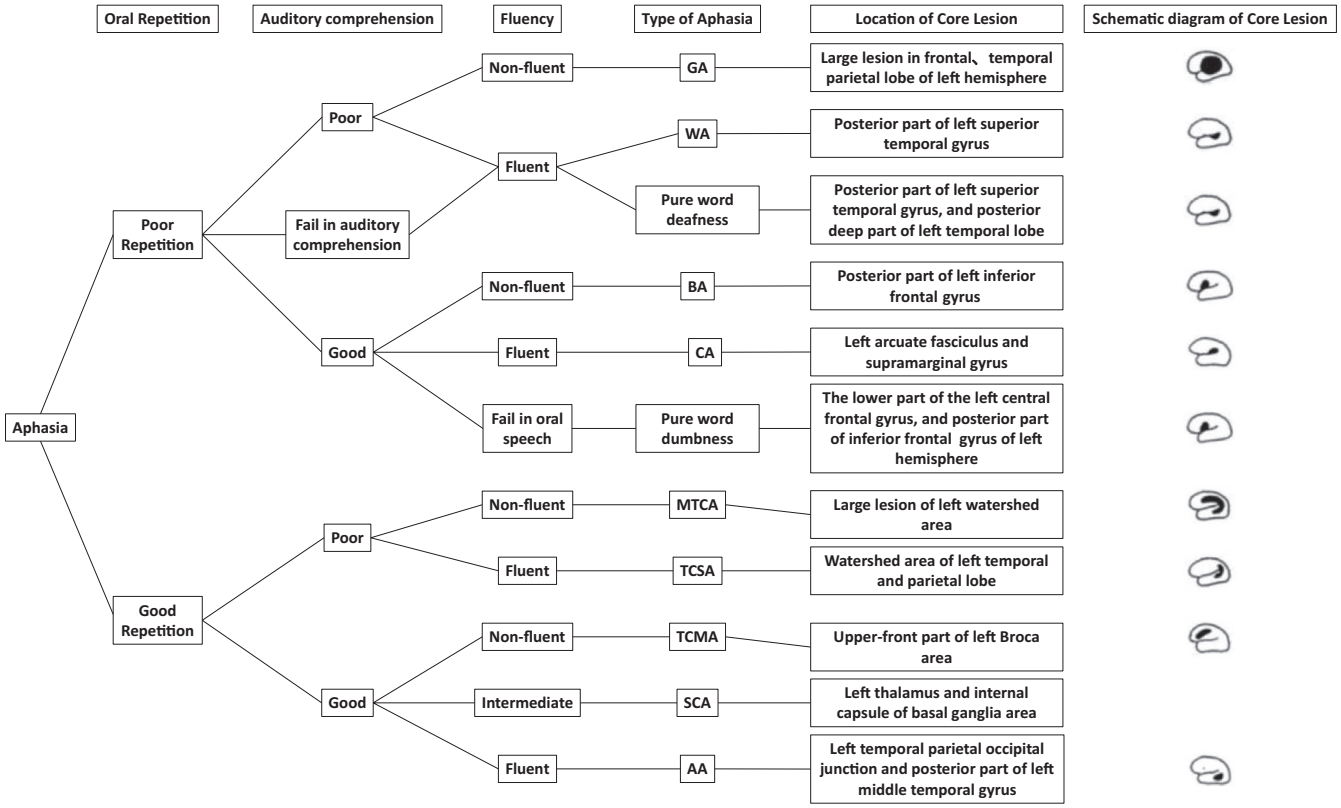

FIGURE 4 Lesion location and schematic diagram of PSA Chinese aphasia types of the Department of Neurology, Peking University First Hospital. AA, anomic aphasia; BA, Broca aphasia; CA, conductive aphasia; GA, global aphasia; MTCA, mixed transcortical aphasia; SCA, subcortical aphasia; TCMA, transcortical motor aphasia; TCSA, transcortical sensory aphasia; WA, Wernicke aphasia

theta-burst stimulation, hyperbaric oxygen therapy, acupuncture therapy, and so forth.[52]

9.3 | Rehabilitation training program

Wang Yinhua, Li Shengli, and Chen Zhuoming[21,52–54] introduced rehabilitation training therapy, which included language function training, daily communication training, grouping, and practicing, family management, drug therapy, and traditional rehabilitation therapy:

1. Training methods to improve patients' language function: Schuell stimulation approach, speech and language training, modular model therapy, cognitive training (attention and memory training), neuro-linguistic programming, constraint-induced aphasia therapy (CIAT), melodic intonation therapy, computer-aided training, and so forth.
2. Training aims to improve daily communication skills: Functional communication therapy, promotion of aphasic communicative effectiveness, communication/conversation therapy, grouping, and practicing, family training, and so forth.

Based on the results of aphasia assessment, individualized rehabilitation treatment plans were formulated focusing on patients' impaired language function, with the aim to promote language reconstruction and recovery of patients with aphasia, to integrate the training into daily life communication, and, eventually, achieve the goals of best recovery of patients' language communication skills and enhance the reintegration of patients with their families and society.[21,51,53,54]

10 | PROGNOSIS AND FACTORS AFFECTING PSA

Wang Yinhua et al[21] suggested that the factors affecting prognosis were related mainly to stroke and progression of PSA: the severity of the stroke at the time of onset; nature, size, and location of the lesions; whether it affected the essential language area in the brain (such as the left perisylvian fissure cortex and subcortical white matter in the left cerebral hemisphere); whether the location of the lesion affected the patient's other cognitive functions; the severity of PSA at the time of onset; type of aphasia; and whether it was accompanied by other cognitive functions. The prognosis was related to the patient's neuroplasticity and brain reserve capacity.[16,17,21,55,56]

The severity of aphasia at the time of onset (including the lesion location, size of lesion, and type of aphasia) was the most important factor affecting the prognosis of PSA. If cerebral infarct lesion in the left MCA was large in size, it damaged mainly the left temporal parietal junction area. Under such circumstances, it damaged the

essential and core modular neural network function[14] (Broca area, Wernicke area, part of the superior parietal cortex, central operculum cortex, temporal lobe, frontal cortex, and subcortical white matter). Undoubtedly, the degree of this aphasia was severe, and the prognosis of language recovery after stroke was poor. In patients with initially severe aphasia, large infarct size or critical damage in the left temporoparietal junction is associated with poor language outcome. The view that the linguistic features of severe aphasia after acute stroke-poor repetition indicated the adverse outcome of PSA was also supported by the location of the lesions. Language features in the acute phase of post-stroke severe aphasia could predict the outcome. Word repetition was a more relevant predictor of recovery.[55,56]

Wang Yinhua, Chen Zhuoming, et al[21,52] suggested other harmful factors, including bilateral brain damage, prolonged coma, accompanying memory and attention or cognitive deficits, depression, mental illness, alcoholism, drug abuse, or other substance abuse. The prognosis of aphasia after stroke varied greatly among individuals, with many influencing factors related to patient, family, and treatment.

11 | CLINICAL STUDY AND THE MECHANISM OF ACTION OF THERAPY ON THE TREATMENT OF PSA

11.1 | Clinical study on the treatment of PSA

1. Berthier et al[57] conducted a randomized, double-blind, placebo-controlled, parallel-group study of both memantine and CIAT on chronic poststroke aphasia for 1 year or longer. Twenty-seven patients completed both treatment phases. The effect on the patients' communication function using memantine alone or combined with CIAT was observed. In this study, WAB and the measured aphasia quotient (AQ) were used to reflect the severity of verbal language disorder and evaluate the efficacy of memantine in aphasia after chronic stroke. The results indicated that memantine had a significant effect on aphasia after chronic stroke whether it was used alone or combined with CIAT. It improved the speech and communication function of patients with PSA and reduced the severity of aphasia. It is safer with good tolerance, and the beneficial effect was maintained for a longer time and was more sustainable. This was due to the fact that memantine could reduce glutamate-induced neurotoxicity in the cerebral ischemic area and improve aphasia by significantly improving cognitive function.
2. Barbancho et al[58] conducted a randomized, double-blind, placebo-controlled trial of both memantine and constraint-induced aphasia therapy study on event-related evoked potentials (ERPs) using memantine alone and combined with CIAT for 28 patients with chronic PSA. The result confirmed that memantine alone significantly improved ERPs of language tasks in patients with chronic PSA; memantine combined with CIAT significantly improved the aphasia severity and ERPs of language tasks in patients with chronic PSA, and the effect was stably maintained. It was believed that the treatment effect was due to the reorganization of the bilateral brain.
3. Study on the use of memantine in the treatment of PSA in China: Fu et al[59] conducted a randomized study on 24 patients with lateral fissure aphasia after stroke. Both groups received speech training. The treatment group received oral administration of memantine. It confirmed that memantine alone or in combination with rTMS and language training therapy significantly improved aphasia after stroke. The meta-analysis of Zhang et al[49] reviewed four studies (124 participants) evaluating memantine and confirmed that memantine can significantly improve the speech, repetition, naming, and auditory understanding of PSA patients, increase AQ, and improve the prognosis of PSA.
4. Berthier et al[60] conducted a review of current evidence on drug therapy of PSA. Preliminary data revealed that combining neuroscience-based intensive aphasia techniques (constraint induced aphasia therapy) and drugs acting on cholinergic and glutamatergic neurotransmitter systems are associated with better outcomes than other strategies and long-term maintenance of benefits. Current state of the evidence suggested that drug therapy may play a key role in the treatment of post-stroke aphasia.

Piracetam: Positive effects in the acute PSA on overall language measures, spontaneous speech, and written language. Language improvements correlate with an increase in blood flow in the left peri-Sylvian cortex. Mechanisms of action: GABA/Glutamate/Acetylcholine.

Donepezil: Mechanisms of action: Acetylcholinesterase inhibition. Positive effects on aphasia severity and everyday functional communication. Significant benefits on spontaneous speech, comprehension and naming in chronic aphasia. Efficacy maintained at long-term follow-up.

Memantine: Mechanisms of action: Uncompetitive NMDA receptor antagonism, voltage-dependent. Positive effects on aphasia severity and everyday functional communication. Significant benefits on spontaneous speech, comprehension, and naming. Efficacy maintained at long-term follow-up.

According to the above two reviews and three clinical studies, the similarities of them were: the treatment methods were drug therapy plus non-pharmacological therapy (rTMS) or rehabilitation training program (CIAT); subjects in clinical trials were patients with PSA; outcomes were significantly improved and the effect maintained.

The differences of them were: agent and mechanisms of action; acute or chronic PSA; outcome measurement (ERPs, or blood flow or AQ of WAB); and improved the different speech functions.

11.2 | Mechanism of action of memantine therapy for PSA

Extracellular release of glutamate in large amounts causes excessive activation of NMDA receptors after acute cerebral ischemia.[50,61–65] This triggers the activity of pathological molecules and a cascade

effect, leading to cell death. As a reversible NMDA receptor antagonist, memantine blocks the excessive activation of neurons by glutamate. As a result, it prevents cell death due to apoptosis and necrosis, decreases infarct size, and reduces neurological and behavioral defects. Memantine NMDAR can regulate tau phosphorylation. Long-term use of memantine after the acute phase can also improve sensorimotor deficits, aphasia, and cognition through multiple mechanisms, including angiogenic, neurogenic, and astrocyte-derived mechanisms, eventually increasing neural plasticity and remodeling and restoring the brain.

11.3 | Therapeutic mechanism of rehabilitation training program for PSA

Rehabilitation training program of PSA and the recovery mechanism of acute and subacute PSA[14]: Plasticity of the isotopic brain area of ipsilateral or contralateral brain replaced the function of the damaged core language area. Neuroplasticity changed the functional connectivity of the brain.[14] The function was replaced or supported by a cerebral language area different from the original one. The research proved that, after stroke, language tasks could be completed by the activation of the right brain or both sides of the brain. When a stroke occurred in the left cerebral hemisphere, the right cerebral hemisphere could perform language functions and promote recovery. Brain plasticity and brain reserve capacity of patients were important factors for language recovery after suffering from PSA.

12 | SUMMARY

The "dichotomies of internal and external, and anterior and posterior," "four elements," and "differential diagnosis flow diagram" were created from our clinical practice and experiences. They were based on the anatomic location of brain and blood vessels' supply and their tight relationship with language area and language disorder. They were enabled to determine the classification of Chinese PSA types, severity, and prognosis and to guide clinical treatment and research.

Our ABC and the diagnosis and differential diagnosis flow diagram of Chinese aphasia types to be a research instruments could be also used to do a series of clinical studies on language disorders and neuropsychology researches of all kinds of the brain diseases (including their aphasia, agnosia, apraxia, executive functions, hemineglect, acalculate, body schema disturbances, memory, intelligence and dementia, MCI, AD, VCI, VaD, SD, PPA, etc.)

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CONFLICT OF INTEREST

All authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Wang Yinhua defined the thesis statement and was involved in idea design, literature review, thesis writing, revision, and editing. Yang Xiaona was responsible for thesis revision. Other authors were the ABC clinical practitioners and the first authors of clinical researches on Chinese PSA and the language disorders and the neuropsychological researches in MCI, AD, VCI, VaD, SD, and PPA, respectively.

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