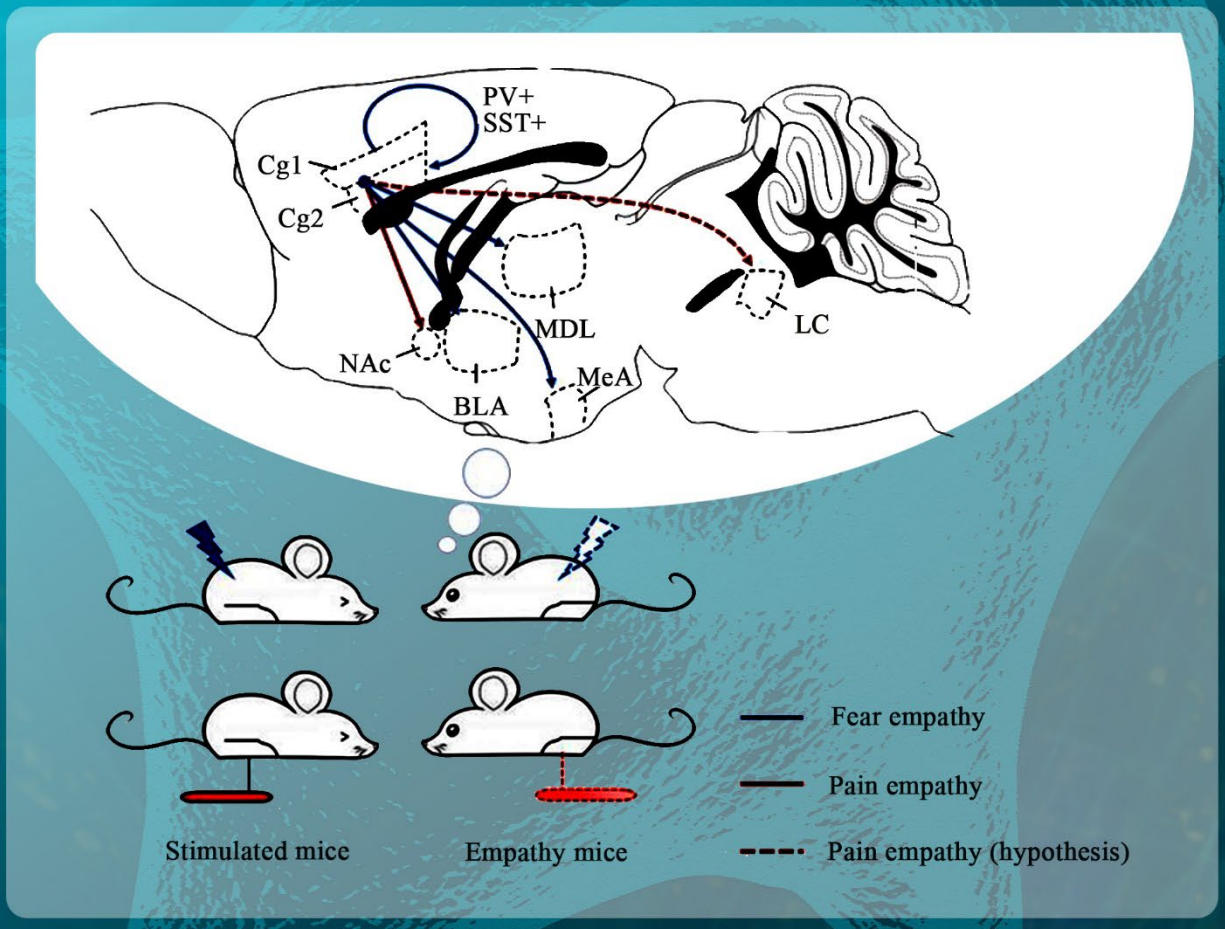
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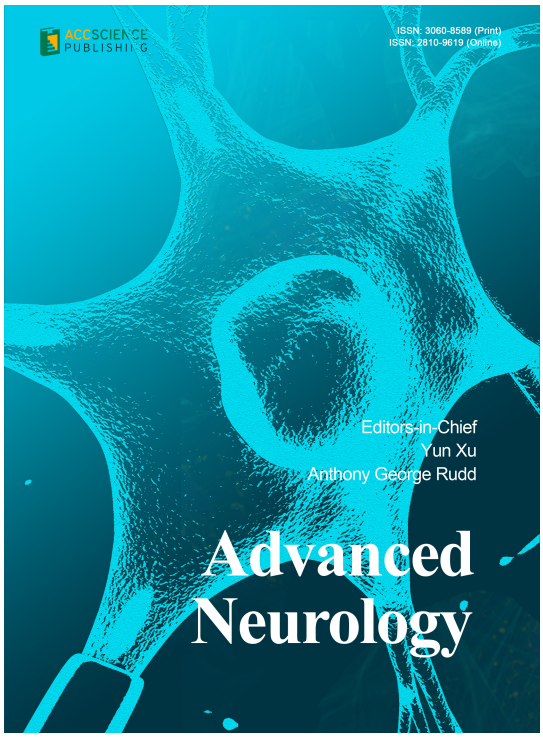
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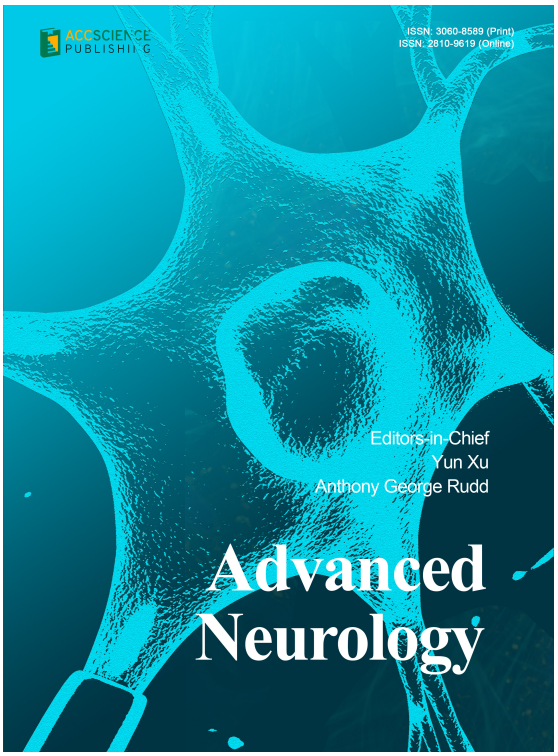
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Advanced Neurology

EDITORIAL

Advanced Neurology in 2023: A continued effort to soar higher

Yun Xu[†]*

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In 2022, we launched *Advanced Neurology* with the collaborative efforts of our editorial board members, experts, editors, and authors. We successfully published a total of three issues and 24 articles last year, which have been downloaded 1931 times and viewed 14,905 times by the end of March 2023. In 2023, we plan to publish four issues and continue to showcase cutting-edge and multi-dimensional articles on basic, translational, and clinical research in neuroscience and neurology. We also plan to gradually launch special issues and featured columns to complement the current scope of the journal, so as to cater to a broader audience.

We are pleased to announce the release of the first issue of 2023, which features articles that explore the frontiers of neurology. These articles include "An Update of the Axon Initial Segment Structure and Function"[1] and "The Neural Mechanisms of Social Empathy in the Anterior Cingulate Cortex"[2]. Besides, one of the articles introduces the comorbidity mechanism of neurodegenerative diseases, which we believe will be beneficial to clinical diagnosis and treatment[3]. In addition, we highlight the impact of restless legs syndrome, a common clinical syndrome, on the quality of life of patients and the outcome of the disease, to call for attention of physicians on this syndrome[4]. Furthermore, this issue also features a systematic review presenting an analysis of the treatment of traumatic brain injuries and the crucial role of successful treatment of depressed skull fractures in reducing its mortality and morbidity[5]. The authors analyzed currently used fillers, so as to identify the best treatment materials[5].

In 2023, we will continue to recruit editorial board members and reviewers from around the world. We will also encourage the submission of manuscripts that align with our journal requirements to ensure the publication of the most relevant and innovative research.

The goal of launching *Advanced Neurology* is to provide a platform to physicians and researchers working in this field to report scientific problems originated in clinical practice, and investigate these problems through basic research and clinical research, to explore new or alternative diagnosis and treatment options that can improve the prognosis of patients. Having achieved a new milestone in the beginning of 2023, we would like to express our sincere gratitude to the editorial board members, reviewers, authors, readers, and all practitioners in this field who have shown their unwavering support for the development of this journal.

[†]Professor Yun Xu is the Editor-in-Chief of Advanced Neurology

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The author declares that she has no competing interests.

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Advanced Neurology

REVIEW ARTICLE

An update on axon initial segment structure and function

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Abstract

The axon initial segment (AIS) is a specialized subcellular region located at the proximal end of the axon and serves as the action potential initiation site due to the high density of ion channels. The AIS plays a critical role in maintaining neuronal polarity by regulating the trafficking and distribution of proteins that function in the dendritic or axonal compartment of the neuron. Due to the adaptive nature of AIS location and length, the excitability of neurons can be altered in response to activity. In this review, we briefly introduce the structure and function of AIS as well as discuss the recent progress in our understanding of AIS ion channel distribution and plasticity in different types of neurons. These would contribute to a better understanding of the AIS and give us a new perspective on AIS-related diseases.

Keywords: Axon initial segment; Ankyrin G; Ion channels; Plasticity

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1. Introduction

There are approximately 100 billion neurons in our brains. Neurons, as the most basic structural and functional units of the nervous system, are responsible for receiving and transmitting electrochemical signals in the nervous system and are involved in perception, calculation, learning, and memory. Signals exist in the form of action potentials (APs), which contain information encoded either in the firing time of the APs or in certain shape characteristics, such as the amplitude of APs[1]. Almost all neurons are composed of three parts: the soma, axon, and dendrite.

The axon initial segment (AIS) is a highly specialized region in the axon of neurons[1-5]. The AIS, which starts right after the axon hillock, is located approximately 20–60 μm from the proximal end of the axon and is distinguished from the axon by the dense framework of ion channels and other linker proteins. The most important function of the AIS is AP initiation, which could trigger the release of neurotransmitters in the synapses at the end of the axon. *In vivo* axons are usually tightly wrapped by lipid layers called the myelin sheath. The myelin sheath insulates axons from the outside environment, and as a result, there is no loss of current, thus ensuring the efficiency and fidelity of AP conduction.

2. Structure of AIS

The molecular structure of the AIS is relatively complex and is maintained by the accumulation of ankyrin G (AnkG) and βIV-spectrin[6,7]. AnkG, a product of the *ANK3* gene, is an anchoring protein at the AIS[8]. It forms a "scaffolding" structure with βIV-spectrin to anchor ion channels to the actin cytoskeleton. AnkG has three isoforms in mammals: 190-kDa AnkG, which is distributed in the cytoplasm; and 270-kDa and 480-kDa AnkG, which are the major isoforms that are specifically located at the AIS and nodes of Ranvier[8-10]. Following axon differentiation, AnkG begins to cluster at the proximal end of the axon and then recruits the other components of AIS[11,12]. The aminoterminal end of AnkG inserts into the actin/spectrin submembrane scaffold and anchors specific membrane proteins, including γ-aminobutyric acid type A ($GABA_A$) receptors, voltage-gated sodium (Na_v), and potassium (K_v) channels, as well as cellular adhesion molecules (CAMs), specifically the 186 kDa isoform of neurofascin 186 (NF-186) and neuronal (Nr)CAM, to the AIS[13] (Figure 1). Moreover, Wang *et al.* reported that neurons with αII spectrin deletion also showed the absence of AnkG, suggesting that αII spectrin and βIV-spectrin can interact to form spectrin tetramers that link adjacent actin rings and are required for AnkG clustering in the AIS[14].

In addition to actin, AnkG also interacts with microtubules through microtubule-associated proteins. For instance, a previous study has shown that the microtubule plus-end-binding (EB) proteins EB1 and EB3 are highly concentrated in mature AIS and can directly bind to AnkG, thus suggesting that EB1 and EB3 can stabilize the structure and microtubule network together[15]. Not only that, the dynein regulator nuclear distribution element-like 1 (NDEL1) localizes to the AIS through interaction with AnkG and controls cargo transport at the AIS[16].

In addition, there is a layer of specialized extracellular matrix anchored to the AIS that promotes and regulates the production of APs by various ion channels, such as Na_v, K_v, and calcium channels (Ca_v)[17-20], allowing neurons to generate a wide variety of AP waveforms[21]. Although the basic components of the AIS have been known for more than two decades, recent studies have indicated an increasing complexity of its types and the molecular composition and distribution of ion channels enriched within it.

3. Ion channels in the AIS

The entire AIS is enriched with many sodium channels of different subtypes[22]. AnkG binds to the interaction motif within the II-III intracellular loop of Na_v channels[23-26]. Experiments have shown that the concentration of sodium ion (Na^+) channels in neuronal AIS is approximately 19-fold of that in the cell body[27], 50-fold of that in the proximal dendrite[28], and 30-fold of that in the distal axon[29]. The main subtypes of Na^+ channels at the AIS are $Na_v1.1$, $Na_v1.2$, and $Na_v1.6$[30,31]. During different developmental stages, the expression and subcellular distribution of various subtypes of Na^+ channels vary. For example, during early neuronal development, $Na_v1.2$ channels are initially found in the AIS, while $Na_v1.6$ is the dominant subtype in mature neurons[20,29,30,32,33]. Moreover, in cortical neurons, high-threshold $Na_v1.2$ channels are preferentially located at the proximal end of the AIS, while low-threshold $Na_v1.6$ channels are found at the distal end of the AIS[27]. Na_v channels are primarily responsible for the initiation of

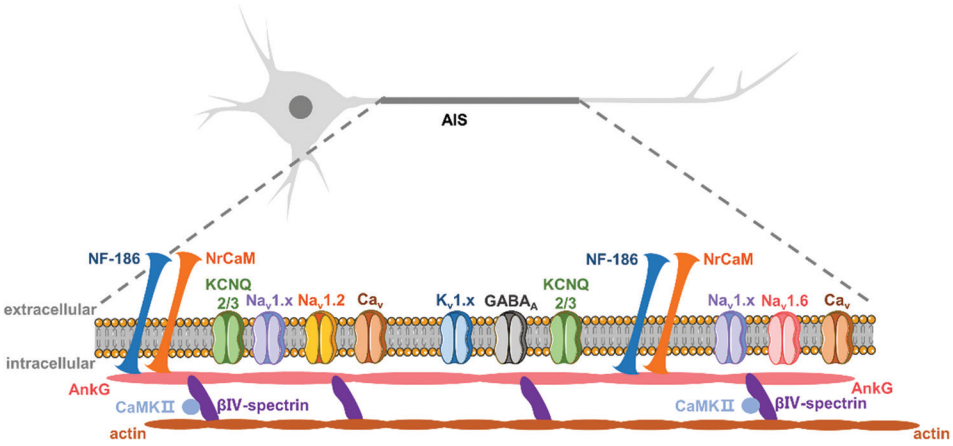


Figure 1. A simplified diagram of the molecular structure of the axon initial segment (AIS) in a neuron. AIS aggregates many anchoring and cytoskeletal proteins, such as ankyrin G (AnkG) and βIV spectrin. Skeleton proteins are anchored by a variety of ion channels, such as voltage-gated sodium channels ($Na_v1.x$), voltage-gated potassium channels ($K_v1.x$), voltage-gated calcium channels (Ca_v), and γ-aminobutyric acid type A ($GABA_A$) receptors. The AIS comprises many other component molecules and ion channels, and its complexity is constantly growing with advancements in research.

APs in the AIS[2,5]. This polarized distribution may reflect discrete functions of Na^+ channel subtypes in AP initiation and backpropagation.

Potassium ion (K^+) channels in the AIS are important for repolarization of AP. The density of K^+ channels in the distal AIS is also 10-fold of that in the cell body[34]. $K_v7.2$ and $K_v7.3$ (KCNQ2/3) channels form homomeric or heteromeric complexes, which interact with AnkG and gather in the AIS[35]. Although $K_v1.1$ and $K_v1.2$ channels do not bind to AnkG, they still cluster at the distal end of the AIS by binding to the scaffold protein postsynaptic density-93 (PSD93)[20,36].

Calcium ion (Ca^{2+}) channels have also been reported in the AIS[17]. Previous study has shown that Ca^{2+} channels may be modulated by dopaminergic signaling[37]. Unlike Na^+ and K^+ channels in the AIS, very little is known about the molecular mechanisms of Ca^{2+} channels.

There is usually only one axon in a neuron. The so-called somatic axon grows from the cell body through a short axon hillock. However, in cultured neurons, approximately 20% of neuronal axons grow from the dendrite, which we refer to as dendritic axons. This type of axon has been observed in rat pyramidal cells in previous studies[29,38,39]. According to a recent study, axons emanate from the basal dendritic arbor in more than half of all CA1 pyramidal neurons and 30% of those in rat pups[38]. Correspondingly, the AIS also has different origins. In this review, "dendritic AIS" refers to AIS with a dendritic origin, whereas "somatic AIS" refers to AIS with a somatic origin. Our previous study has shown that although somatic AIS has a similar length as dendritic AIS, the distribution of $Na_v1.2$ was significantly narrower in dendritic AIS[40].

4. Physiological functions of the AIS

APs are initiated at the AIS. In the 1950s when the structure and molecular composition of the AIS were mostly unknown, people speculated that the AIS or axon hillock was the AP initiation site based on intracellular recording observations[41-43]. The AIS has a lower AP threshold than the somatodendritic domain[42]. In an autoradiography study using Na^+ channel-binding ^{125}I-scorpion toxin, it was first revealed that Na^+ channel density was higher at the AIS[44]. In recent years, more and more studies have shown that the AIS is the AP initiation site in different types of CNS neurons[28,40,45,46]. Using quantitative freeze-fracture electron microscopy immunogold labeling, Lorincz *et al.* have confirmed that the concentration of $Na_v1.6$ channels at the AIS and nodes of Ranvier is approximately 40-fold higher than that at the soma in hippocampal neurons[29]. Our previous work has also confirmed that AP is initiated at the distal end of the AIS through voltage imaging technology[40]. As a result of its ability to determine the onset of AP, kinetic dysfunction in AIS can lead to neurological disorders, such as epilepsy[47-50].

Second, the AIS can "filter" molecules to separate the cell body from the axon, limiting the diffusion and exchange of molecules in different parts, and maintaining cell polarity[6,22,51]. Since it is located between the axon and the soma, it serves as a critical regulatory center that controls the proteins entering into the axon, and thus plays a crucial role in maintaining the neuron's polarity[52]. Either for cytoplasmic proteins or for vesicles, the AIS has been reported to have filtering functions. There is an actin-based cytoplasmic filter that could prevent the diffusion of soluble macromolecules larger than 13 nm. This has been proposed as a mechanism for regulating cytoplasmic protein movement[53,54]. Within the AIS, studies have shown different trafficking pathways in vesicles carrying axonal or dendritic protein. For instance, vesicles containing axonal proteins are preferentially trafficked into the axon[55]. On the other hand, the trafficking of vesicles carrying dendritic proteins is stopped in the AIS and redirected back to the soma[55-59].

5. Plasticity of the AIS

AIS plasticity refers to the adaptive responses in the nervous system to change its structure and function in response to neuronal activity[60,61]. Ion channel compositions at the AIS vary across different types of neurons. The differences in AIS length and location may be the basis for the different neuronal firing properties. For instance, retinal ganglion cells with different visual properties have different AIS lengths and locations in the axons[62]. Despite the importance of these differences for neuronal function, the mechanisms controlling AIS length and location remain largely unknown. Recent studies have revealed that AIS length or location is dynamically regulated in response to normal developmental and pathological conditions. For example, in rat cortical neurons, the length of AIS undergoes dynamic changes during their visual system development[63]. Previous studies have investigated the long-term activity-dependent plasticity regulation of the AIS in neurons *in vivo* and *in vitro* and found that the position and length of the AIS would make corresponding changes and adapt to changes in external factors[60,61,64,65]. This phenomenon, also known as AIS plasticity, is usually accompanied by alterations in neuronal excitability.

Several studies have suggested that neurons may alter excitability by changing their AIS length or location in response to changes in developmental and pathological conditions. For example, when avian nucleus magnocellularis neurons are deprived of auditory inputs,

their AIS will be elongated and proximally shifted closer to the soma[61]. Moreover, electrophysiology recordings have shown that input-deprived neurons tend to be more excitable, indicating that to regulate neuronal excitability and homeostasis as well as maintain neuronal circuit output, neurons might need to adapt to presynaptic activity by altering their AIS properties.

In *in vivo* experiments using chicken embryos, Hiroshi Kuba *et al*. found that depriving chickens of auditory input (destroying the cochlea) resulted in the elongation of the AIS of chicken brainstem auditory neurons (Chick NM). In the experiment, 7 days after auditory input deprivation, the AIS length increased to 1.7 times the original length. The distribution of Na^+ channels and the excitability of neurons increased, but the density and distribution of Na^+ channels barely changed[61]. In addition, different decibels of auditory stimulation may cause the AIS to shorten or lengthen, suggesting that the AIS can change its length according to the activity level of presynaptic neurons.

In addition, Grubb and Burrone have demonstrated a distal shift in AIS location, up to 17 μm away from the cell body, after 48 h of *in vitro* culture of rat hippocampal neurons under high-concentration K^+ treatment (15 mM potassium chloride [KCl]) to the extracellular fluid. In the AIS, AnkG and other associated proteins, such as Na^+ channels and βIV-spectrin, moved accordingly, but there was no observable change in AIS length. After washing, the AIS returned to its original position in relation to the cell body, and after 48 h of treatment with 15 mM KCl, neuronal excitability reduced, and a stronger current stimulation was needed for the neurons to fire an AP[60].

Our previous study has shown that after treating cultured hippocampal neurons with 20 mM glucose for 3 h, the neurons from both rats and mice showed changes in AIS length or location but in different ways[40]: in rat neurons, the AIS length became shorter, and the distance from the cell body increased because the proximal end of the AIS was pushed away from the cell body, while the distal end did not change; in mouse neurons, the AIS was longer, but there was no change in distance from the cell body as the distal end of the AIS moved away from the cell body, while the proximal end of the AIS showed almost no change. However, in both mouse and rat neurons, the dendritic AIS barely changed after the 20 mM glucose treatment, indicating that even in the presence of the same external stimulus, AIS plasticity varies between different types of neurons.

AIS plasticity can also occur under certain pathophysiological conditions. A previous study has shown AIS plasticity in barrel cortex L5 pyramidal neurons in a mild traumatic brain injury model, where the AIS was shortened and AP intensity was attenuated[66]. Similarly, a previous study has reported a molecular remodeling of the AIS, which was observed in the surviving peri-infarct region after focal cortical stroke[67]. Moreover, *de novo* AIS formation has been observed within the peri-infarct cortex, suggesting that stroke-induced axonal sprouting may contribute to the formation of new functional axons[67].

6. Conclusions

The AIS is a remarkable neuronal structure comprising a complex assembly of membrane proteins, scaffold proteins, cytoskeletal adaptors, and voltage-gated ion channels. The precise molecular distribution of the AIS ensures proper neuronal excitability by regulating the generation of APs. The dynamic properties of the AIS allow the regulation of neuronal excitability in response to neuronal activities both inside and outside the cell, thereby maintaining homeostasis and the output of neural circuits. Dendritic AIS may play an important role in the homeostatic regulation of physiological functions in the nervous system due to its insensitivity to external stimulus. The AIS also demarcates the boundary between the dendritic-somatic and axonal compartments while allowing axonal proteins to pass through. Moreover, certain structural properties of the AIS, such as length and/or location, can change through activity-dependent manners. The structural plasticity of the AIS is known as an important factor for the establishment and maintenance of nervous system functions. During AIS plasticity, the proteins in the AIS may undergo a demolition and reconstruction process. However, we still have very limited knowledge of the AIS.

From research on the brain of Alzheimer's disease (AD) patients, we are aware that axonal pathology is associated with neuroaxonal dystrophy and amyloid plaque formation[68]. Our previous study has also shown that AIS pathology may occur even before axonal pathology[54]. As a result of the key role AIS plays in AP bursts, the dysfunction of AIS may lead to certain neurological diseases. For example, mutations in ion channel subtypes could cause epilepsy[48]. In addition, *ANK3* (gene encoding AnkG) mutation has been found to be associated with some neuronal diseases, such as bipolar disorder[69], intellectual disability[70], schizophrenia, and autism spectrum disorder[71,72]. In mouse models, the loss of βIV-spectrin function resulted in ataxia and central auditory deafness[73,74]. Moreover, patient with the pathogenic variant of *SPNB4* (gene encoding human βIV-spectrin) has also been associated with myopathies and auditory neuropathies[75]. Our previous study has shown that AnkG deficiency in the AIS could play a significant role in AD pathology[54]. Therefore, restoring or preserving the structure and function of the AIS will be an important strategy for the treatment of these diseases.

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Ethics approval and consent to participate

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Availability of data

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ACCSCIENCE PUBLISHING

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REVIEW ARTICLE

Outcomes of surgical management and implant consideration for depressed skull fractures: A systematic review

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ABSTRACT

Background: Traumatic brain injuries (TBIs) are associated with high mortality and morbidity. Depressed skull fractures (DSFs) are a subset of fractures characterized by either direct or indirect brain damage, compressing brain tissue. Recent advances in implant use during primary reconstruction surgeries have shown to be effective. In this systematic review, we assess differences in titanium mesh, polyetheretherketone (PEEK) implants, autologous pericranial grafts, and methyl methacrylate (PMMA) implants for DSF treatment.

Methods: A literature search was conducted in PubMed, Scopus, and Web of Science from their inception to September 2022 to retrieve articles regarding the use of various implant materials for depressed skull fractures. Inclusion criteria included studies specifically describing implant type/material within treatment of depressed skull fractures, particularly during duraplasty. Exclusion criteria were studies reporting only non-primary data, those insufficiently disaggregated to extract implant type, those describing treatment of pathologies other than depressed skull fractures, and non-English or cadaveric studies. The Newcastle-Ottawa Scale was utilized to assess for presence of bias in included studies.

Results: Following final study selection, 18 articles were included for quantitative and qualitative analysis. Of the 177 patients (152 males), mean age was 30.8 years with 82% implanted with autologous graft material, and 18% with non-autologous material. Data were pooled and analyzed with respect to the total patient set, and additionally stratified into those treated through autologous and non-autologous implant material. There were no differences between the two cohorts regarding mean time to encounter, pre-operative Glasgow coma scale (GCS), fracture location, length to cranioplasty, and complication rate. There were statistically significant differences in post-operative GCS ($p < 0.0001$), LOS ($p = 0.0274$), and minimum follow-up time ($p = 0.000796$).

Conclusion: Differences in measurable post-operative outcomes between implant groups were largely minimal or none. Future research should aim to probe these basic results deeper with a larger, non-biased sample.

Keywords: Autologous graft; Non-autologous graft; Implant material; Cranioplasty; Depressed skull fracture; Duraplasty

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1. Introduction

Traumatic brain injuries (TBIs) are a worldwide issue that is associated with high levels of mortality and morbidity[1,2]. Skull fractures vary in etiology as several factors influence the fracture such as bone mineralization and trauma type[3,4]. Depressed skull fractures (DSFs) are a subset of fractures characterized by a portion of the inner table of the skull displacing and lying above the outer table[5,6]. Incidence of depressed skull fractures (DSFs) within TBI patients ranges from 2% to 11%[5]. In DSFs, there is often underlying brain damage of two different varieties: direct damage to tissue and indirect damage via hematomas compressing the brain tissue[4]. Recent advancements of computed tomography (CT) and magnetic resonance imaging (MRI) provide better understanding of diagnosing DSFs and survival interventions.

Treatment for DSFs includes either surgical interventions, such as cranioplasty or conservative treatment. Surgery is pursued based on indications, such as neurologic, infective, and cosmetic issues and open skull fractures are managed in two stages: through primary reconstruction or delayed cranioplasty[5,7]. Previously, delayed cranioplasty was preferred due to reduction of infections such as meningitis and osteomyelitis[8]. However, several limitations are presented in these patients' lives. Furthermore, recent studies have shown no difference in infection rate between delayed cranioplasty and immediate titanium mesh reconstruction[8,9]. Although it is preferable to use patients' own bone material, due to several reasons, rather than artificial mesh during surgery, cases of DSF may be near impossible for bone material reconstruction[9,10]. Furthermore, recent work has demonstrated a higher failure rate with autologous bone due to infection and bone flap necrosis[10,11]. Urgent cranioplasty using artificial material such as titanium mesh, methyl methacrylate (PMMA), and several unique varieties has become more common[9].

Primary reconstruction for DSF was developed to avoid delayed cranioplasty, prevent further CSF complications, and for cosmetic reasons[12]. Variations and effectiveness of the different implants is a field of ongoing research. Differences in tissue tolerance, cost, and resistance to infections and other characteristics are considered when choosing the specific alloplastic material[13]. Titanium mesh bone grafts have been seen to be effective in preventing an inflammatory reaction[13]. PMMA, similarly, has been popular recently due to the ease of confirmation and application[13]. Studies have shown no significant difference between these two alloplastic materials, and both have demonstrated similar results, both functionally and cosmetically[10,13]. However, titanium mesh patients have been seen to develop less inflectional complications going forward[10,13].

With the goal of improving patient outcomes in addressing DSF, an effective route may involve optimization of the implantation approach required in surgical management. Specifically, the decision in implant material utilized can hold considerable weight. In the current review, outcome measures for the surgical management of DSF among various types of implant material are reported in a coherent fashion. We organized a systematic review by organizing the available data regarding outcomes of surgically treated DSF between different implant materials to address the question of how implant material may affect the post-operative outcomes of DSF patients.

2. Methods

2.1. Eligibility criteria

Retrospective cohort studies, case series, and case reports were included in this systematic review. Our analysis included the study design, country, number of patients, age, sex, preoperative Glasgow coma scale (GCS), fracture location, primary implant material, time to encounter, time to cranioplasty, presence of complications, postoperative GCS, length of stay, and follow-up duration. Inclusion criteria pertained to studies reporting use of specific implant material within treatment for depressed skull fractures. Exclusion criteria included studies not sufficiently disaggregated for extracting data pertaining to depressed skull fractures, those failing to specifically report surgical approach regarding implant material. Non-primary data including presentations, letters to the editor, editorials, and other sources that appeared non-peer-reviewed were strictly excluded. Articles written in languages other than English, or cadaver/non-human studies were excluded from the study. The selection process is shown in Figure 1.

2.2. Information sources

A literature search was performed in Web of Science, Scopus, and PubMed from their inception to September 2022 to identify studies reporting the outcome of implant usage in subsequent duraplasty in treatment of depressed skull fractures. The search strategy was developed by one reviewer (A.N.) by consulting the peer review of electronic search strategies (PRESS) criteria[14]. This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[9]. The search strategy is (depressed skull fracture) AND (implant OR shunt OR inlay OR onlay OR patch OR mesh OR titanium OR cranioplasty). Study selection was performed by one reviewer (A.N.) and data

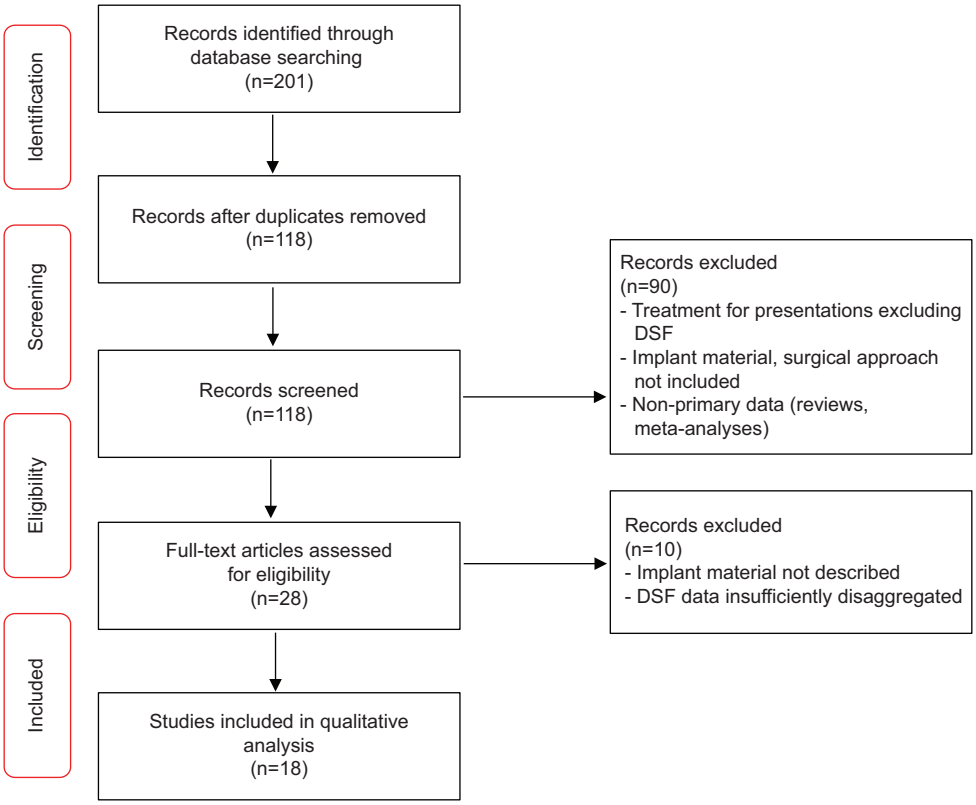


Figure 1. PRISMA study selection flow diagram.

extraction was performed by two reviewers (A.N., R.S.). Accuracy of data extraction was ensured through the use of a third reviewer, who monitored all data entries for correctness. When disagreements pertaining to study selection arose, an additional reviewer (M.D.) mediated the final decision. Full articles were retrieved when titles and abstracts potentially relevant to the inclusion criteria were found. The data from each study was then extracted and analyzed. With regard to the data points of interest, the corresponding values were extracted and collected for future analysis in an Excel spreadsheet. If a study did not explicitly mention the presence of a clinical characteristic, it was assumed that the characteristic was not present in that patient set.

2.3. Selection of sources of evidence

Titles and abstracts were screened by two reviewers independently (A.N., R.S.). Following individual screening, records identified through the searches were added to a database and duplicates were removed through Rayyan web app for systematic reviews.

2.4. Qualitative analysis

To assess the quality and risk of bias of the studies eligible for inclusion, Newcastle-Ottawa Scale (NOS) criteria were used to rate our included cohort studies and case reports/series[15]. The NOS cohort criteria allowed for a maximum of four stars in *selection*, two stars in *comparability*, and three stars in *outcome:* the total range was 0–9. Case reports and series were analyzed with NOS cohort guidelines without application of comparability questions, making their effective range 0–7. Two reviewers (M.D., A.N.) conducted this assessment.

2.5. Statistical analysis

Data were analyzed using JMP Statistical Software (SAS). Quantitative variables were analyzed through two-tailed independent samples t-tests. $p < 0.05$ was considered to be significant. Data were quantitatively pooled to present statistics in a coherent manner representative of the total patient set. Following this, analysis was conducted similarly, stratifying the dataset by autologous and nonautologous implant material. The implant material specifically dichotomized as autologous versus nonautologous material, and their respective outcomes were considered to be the primary analysis of the current review. Precluding this analysis, differences in age, sex, time to encounter, pre-operative GCS, and fracture location were assessed to determine the presence of confounding variables.

3. Results

3.1. Selection of sources of evidence

Figure 1 shows the study selection process. The literature search initially identified 201 studies, of which 118 were non-duplicate. Initially, 28 articles published between 1999 and 2022 were selected based on the inclusion and exclusion criteria for the present review of the literature. Eighteen articles were quantitatively analyzed following full-text analysis of the initial selected articles. These included 1 retrospective cohort study, 8 case series, and 9 case reports (Table 1)[7-9,16-30]. Five studies were conducted in the United States, three in China, and one each in Brazil, Egypt, Germany, India, Indonesia, Japan, Nigeria, South Korea, Switzerland, and Turkey (10).

3.2. Qualitative analysis

The eighteen studies were assessed with appropriate guidelines to characterize their quality based on several criteria (Table 2). NOS scores of 7–9 were deemed sufficient for the study as it fell in the region of high-quality study according to the NOS guidelines. The single retrospective cohort study was analyzed with the NOS for cohort studies. For case reports/series which had a maximum of 7, sufficient studies included those dissatisfying only 1 item per domain at maximum, with a total score of 5/7. The single cohort study scored a 7. Six case reports/series scored a 6 and eleven case reports/series scored a 5.

3.3. Analysis of confounding variables

From the extracted data, potential confounders were analyzed with respect to the two categories of implant type, that is, autologous and nonautologous. This included the age, gender, duration to hospital encounter, pre-operative GCS, and fracture location. With respect to all variables, barring age, there were no statistically significant differences observed between autologous versus non-autologous implant material. Age within the autologous patient sample set was skewed toward younger patients, particularly in a study by AbdelFatah *et al.*[16] Removal of this study in the same analysis revealed a transition to non-statistical significance of age. With this in mind, the study was included for outcome analysis acknowledging the large sample of younger patients in this study skewed autologous patient age toward the left.

3.4. Synthesis of results

The sample size across all studies was 177 patients after application of inclusion and exclusion criteria. The mean age was 30.77 years. There were 152 males (85.9%). Regarding duraplasty implant material, 82% utilized autologous pericranial grafts, 16% titanium mesh, 1% polyetheretherketone (PEEK), and 1% PMMA. After dichotomization, 82% utilized autologous implant material and 18% non-autologous implants. In the autologous group, the mean age of subjects was 25.2 years old, and the proportion of male was 64%. In the non-autologous group, the mean age of subjects was 42.0 years old, and the proportion of males was 16.5%.

3.5. Pre-operative characteristics

In total, the mean pre-operative GCS was 13.5, and time to initial encounter was 1.9 days. The proportion of fracture location was 44% frontal, 30% parietal, 15% occipital, and 11% temporal across the total patient sample. With respect to the autologous group, mean preoperative GCS was 12.8. Mean time to encounter was 1.67 days. Location of fracture was 36% frontal, 33% parietal, 17% occipital, and 14% temporal. In the non-autologous group, pre-operative GCS was 14.8. Mean time to encounter was 2.68 days. Location of fracture was 68% frontal, 22% parietal, and 10% occipital. There was no statistically significant difference between the two groups for preoperative GCS ($p = 0.1570$), time to encounter ($p = 0.4785$), or fracture location ($p = 0.09$) (Table 3).

3.6. Perioperative characteristics

Decision for cranioplasty was reported in 97% of the surgically treated patients. Mean length to cranioplasty 11.4 days. In the autologous group, mean length to cranioplasty was 10.3 days. The non-autologous group had a mean length to cranioplasty of 16.1 days. There was no difference between the two groups for days to cranioplasty ($p = 0.4780$) (Table 3).

3.7. Post-operative outcomes

The overall complication rate was 4.0%% including two cases of intraoperative epidural hematoma and postoperative wound infection. The mean post-operative GCS was 14.95. The mean length of stay was 18.6 days for the total sample size. Finally, the overall minimum follow-up time was 1.2 years. In the autologous group, the mean post-operative GCS was 15, while the non-autologous group had a mean of 14.74. In the autologous group, complication rate was 4.14%, and in the non-autologous group, the rate was 3.13%. There was no difference in complication rate ($p = 0.8584$). The autologous group had an average LOS of 36.3 days, and the non-autologous group had a LOS of 16.7 days. In the autologous group, minimum follow-up time was 1.21 years, and in the non-autologous group, the rate was 0.93 years (Table 4). There was a significant difference for GCS ($p < 0.0001$), LOS ($p = 0.0274$), and minimum follow-up time ($p = 0.000796$).

Table 1. Newcastle-Ottawa Scale qualitative analysis

Case series/report										
		Selection				Comparability	Outcome		Adequacy of follow up of cohorts	Total
Author and year	Study type	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur		
Wylen *et al.*, 1999 [29]	Case series	1	n/a	1	1	n/a	1	1	1	6
Ebel *et al.*, 2000[20]	Case series	1	n/a	1	1	n/a	1	1	1	6
Marbacher *et al.*, 2008[7]	Case series	1	n/a	1	1	n/a	1	1	1	6
McCall *et al.*, 2008[25]	Case series	1	n/a	1	1	n/a	1	0	1	5
Hewitt *et al.*, 2009[24]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Forbes *et al.*, 2010[22]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Bot *et al.*, 2013[19]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Muderris *et al.*, 2013[26]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Wan *et al.*, 2013[28]	Case series	1	n/a	1	1	n/a	1	1	1	6
Sheng *et al.*, 2017[27]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Ballestero *et al.*, 2019[18]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Faried *et al.*, 2019[21]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Hitoshi *et al.*, 2019[9]	Case series	1	n/a	1	1	n/a	1	1	1	6
Eom *et al.*, 2020[8]	Case series	1	n/a	1	1	n/a	1	1	1	6
Haider *et al.*, 2020[23]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Yang *et al.*, 2021[30]	Case series	1	n/a	1	1	n/a	1	1	0	5

(Cont'd...)

Table 1. (*Continued*)

		Case series/report								
		Selection				Comparability	Outcome			
Author and year	Study type	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
Anehosur *et al.*, 2022[17]	Case report	1	n/a	1	1	n/a	1	1	n/a	5
Cohort										
AbdelFatah *et al.*, 2016[16]	Retrospective cohort	1	1	1	1	1	1	1	0	7

n/a: Not available

4. Discussion

Surgical reconstruction of DSFs has been achieved using various implant materials; however, comparative analysis of post-operative outcomes associated with the type of implant material has yet to be conducted[31-33]. With the goal of improving outcomes in patients presenting to the emergency department with DSFs, the authors conducted a systematic review to explore the outcomes and operative considerations associated with DSF reconstruction achieved through use of either autologous or non-autologous implant material (Tables 1 and 2).

Comparative analysis of pre-operative factors, such as GCS, was conducted between patients in whom DSF reconstruction was achieved using either autologous or non-autologous implant material to identify the implications of pre-operative GCS assessment on surgical approach (Table 3). Despite the lack of a statistically significant difference in pre-operative GCS between the two groups, there was an advantageous trend toward the use of an autologous implant among patients with a lower pre-operative GCS (GCS: 12.8 vs. 14.8) (Table 3). Although there is limited evidence in the literature citing a preference towards the use of either an autologous or allogenic graft in patients with lower GCS, it is hypothesized that autologous grafts are preferred in patients with lower GCS scores to prevent further complications related to graft rejection[34]. It is also possible that patients with the lower GCS scores were deemed to require more urgent intervention that did not allow ample opportunity for sourcing an appropriate HLA-matched allogenic graft; however, further investigation is needed to ascertain whether autologous grafts may enable reduced post-operative complication in patients with lower GCS scores[34]. Further evaluation of the association between the time to encounter – defined as the duration between injury and arrival at the ER – and its implications on the use of either an autologous or non-autologous implant also did not reveal any statistically significant differences. However, comparative analysis suggests a trend towards the use of an autologous implant for DSF reconstruction in patients with a shorter time to encounter (1.67 days vs. 2.68 days), which may support the hypothesis that autologous implants are preferred in cases of greater interventional urgency (Table 3). In addition, the association between fracture location and the type of implant material utilized for reconstruction was evaluated to identify whether differences in selection of implant material are preferentially attributable to fracture location (Table 3). The frontal region of the skull was the most common location of reconstruction within both cohorts of patients; however, reconstruction of the frontal region of the skull occurred in 68% of patients in

Table 2. Characteristics of included studies and patient demographics

Study	Study type	Country	Number of total subjects	Mean age (year)	Sex (M/F)	Implant material
Wylen *et al.*,1999[29]	Case series	United States	32	n/a	27/5	Pericranial graft
Ebel *et al.*, 2000[20]	Case series	Germany	2	49	2/0	Pericranial graft
Marbacher *et al.*, 2008[7]	Case series	Switzerland	5	32.2	5/0	Titanium mesh
McCall *et al.*, 2008[25]	Case series	United States	1	49	1/0	Pericranial graft
Hewitt *et al.*, 2009[24]	Case report	United States	1	14	1/0	n/a
Forbes *et al.*, 2010[22]	Case report	United States	1	6	1/0	n/a
Bot *et al.*, 2013[19]	Case report	Nigeria	1	40	1/0	Methylmethacryalte (PMMA)
Muderris *et al.*, 2013[26]	Case report	Turkey	1	45	1/0	Pericranial graft
Wan *et al.*, 2013[28]	Case series	China	18	41	11/7	Pericranial graft
AbdelFatah *et al.*, 2016[16]	Retrospective cohort	Egypt	87	21	76/11	Pericranial graft
Sheng *et al.*, 2017[27]	Case report	China	1	22	1/0	Pericranial graft
Ballestero *et al.*, 2019[18]	Case report	Brazil	1	0	1/0	n/a
Faried *et al.*, 2019[21]	Case report	Indonesia	1	19	1/0	Pericranial graft
Hitoshi *et al.*, 2019[9]	Case series	Japan	2	8	2/0	Titanium mesh
Eom *et al.*, 2020[8]	Case series	South Korea	19	50.4	18/1	Titanium mesh
Haider *et al.*, 2020[23]	Case report	United States	1	27	1/0	Titanium mesh
Yang *et al.*, 2021[30]	Case series	China	2	47	1/1	PEEK
Anehosur *et al.*, 2022[17]	Case report	India	1	6	1/0	Titanium mesh
Total (mean)			177	30.77	152/25	

n/a: Not available

Table 3. Pre- and peri-operative characteristics

Autologous			
Pre-operative GCS	**Time to encounter (days)**	**Fracture location**	**Length to cranioplasty (days)**
12.8 (10–15)	1.67 (0–21)	36% frontal 33% parietal 17% occipital 14% temporal	10.27 (0–210)
Non-autologous			
14.8 (8–15)	2.68 (0–45)	68% frontal 22% parietal 10% occipital	16.10 (0–210)
p-value			
p=0.1570	p=0.4785	p=0.09	p=0.4780
Overall			
13.5 (10–15)	1.9 (0–45)	44% frontal 30% parietal 15% occipital 11% temporal	11.43 (0–180)

All values reported as either means with standard deviations or sole proportions

Table 4. Post-operative outcomes

Autologous			
Post-operative GCS	**Length of stay (days)**	**Complication rate**	**Minimum follow-up time (years)**
15	36.3 (7–42)	4.14	1.21 (0.25–2)
Non-autologous			
14.74 (10–15)	16.7 (3–75)	3.13%	0.93 (0.20–2.67)
p-value			
p<0.0001	p=0.0274	p=0.8484	p=0.000796
Overall			
14.95 (10–15)	18.6 (3–75)	4 0.0%	1.15 (0.20–2.67)

All values reported as either means with ranges or sole proportions

the non-autologous cohort, versus 36% in the autologous cohort (Table 3). Assessment of variation in reconstruction location revealed a coinciding trend among both cohorts of patients, with DSF reconstructions of the parietal and occipital regions being the second and third most common, respectively. Interestingly, however, while reconstruction of the temporal region was conducted in 14% of patients within the autologous implant cohort, reconstruction of the temporal region among the non-autologous implant cohort was not reported in the analyzed patient sample. As some studies have reported greater occurrences of

post-operative complications associated with autologous implants, it is possible that there may be a preferential bias towards the use of allogenic grafts for reconstruction of the frontal skull bone; however, it is also possible that these observations could be due to the relatively small sample size of the studied patient population[35]. Thus, further investigation of the association between the location of fracture reconstruction and post-operative outcomes associated with the type of implant material is warranted.

Perioperative characteristics were also comparatively assessed to identify differences associated with operative considerations and selection of implant material. Although studies have reported reduced incidence of post-operative infection attributable to delayed surgical intervention, clinical equipoise remains as to the optimal timing of operation post-injury given conflicting evidence in the literature[36-38]. There is more consensus in the literature, however, that immediate cranioplasty following injury should be restricted to the removal of damaged bone, and later followed by cranioplasty in a staged surgical approach[8,33,38]. As such, we investigated whether this equipoise persists in consideration of DSF reconstructions utilizing autologous or non-autologous implant material (Table 3). In comparing the duration of time between injury and cranioplasty between both cohorts, we identified a mean duration of 11.43 days among the autologous implant cohort as compared to a mean duration of 10.27 days in the non-autologous implant cohort (Table 3). This slight delay in intervention time among the autologous cohort may be indicative of a deliberate attempt to reduce postoperative infection, which is supported as a precautionary measure given the lower preoperative GCS observed in this cohort (Table 2). We additionally compared the average length of stay between both cohorts to determine whether DSF reconstruction utilizing either autologous or non-autologous implant material was associated with improved post-operative outcomes. This revealed a significant statistical difference between the autologous and non-autologous cohorts (36.3 days vs. 16.7 days, $p = 0.0274$), which supports the possibility that enhanced postoperative outcomes can be achieved through use of non-autologous implant material (Table 4).

In addition, post-operative outcomes were analyzed between patients with autologous or nonautologous implant material. The previous literature has shown no significant difference in post-operative outcomes between different implant materials[39,40], but male patients, patients with complex injuries, and cases with involvement of the frontal sinus experienced a higher risk of postoperative complications[39]. Zanotti et al. additionally reported that complications after cranioplasty are influenced by implant design (Y). Although autologous implants show desirable biomimetic properties, they display a variable reabsorption rate between 3% and 50%, leading to failure of the implant (Y). Nonautologous implants may overcome these disadvantages of autologous material; however they may be associated with their own shortcomings such as higher infection rate or higher costs. Due to these proposed differences, we analyzed post-operative complication rates between patients utilizing autologous or nonautologous graft material (Table 4). Of 145 patients with an autologous graft, 4.14% (6/145) had experienced at least one post-operative complication. This was compared against the nonautologous patient sample in which 3.13% (1/32) of patients reported at least one post-operative complication, resulting in a mean complication rate of 4% across groups. Thus, there was no significant difference in complication rate between both groups. The previous literature reports minor complications usually occur within the first 2 – 3 months after cranioplasty, and major complications occur around 6 months after surgery (Y). Both patients in the autologous and nonautologous groups had a mean follow-up time of 13.2 months, 14.5 months in the autologous group and 11.2 months in the nonautologous group, thus allowing adequate time for the occurrence of complications. The outcome of depressed skull fractures has been significantly associated with GCS, with patients scoring between 13 and 15 having fewer complications (Z)[41], which allows for accurate comparison between both autologous and nonautologous groups with a similar GCS of 15 and 14.75 for the autologous and nonautologous groups, respectively. The length of stay was significantly different between the two groups, with 36.3 days for patients receiving an autologous implant and 16.7 days for patients receiving a nonautologous implant ($p = 0.0274$). Although hospital length of stay is commonly used as a measure of quality of care, there were no significant differences in post-operative complication rates with longer hospital stay following cranioplasty with an autologous implant when compared with shorter hospital stay in the nonautologous implant group.

We confer there were few limitations to the present systematic review. Due to the stringency of the chosen inclusion criteria, a minority of studies that met the requirements were included in the present analysis. The relationship between perioperative characteristics and outcomes were also difficult to establish across groups due to the variable length of follow-up across studies. Moreover, a larger, non-homogeneous sample is desired to resolve a generalizable relationship between patient outcomes related to receiving autologous or nonautologous implants. The autologous patient population was predominantly young adult males, whereas the non-

autologous patient population was predominantly middle-aged females (Table 2). In addition, significant differences were reported between post-operative GCS and minimum follow-up times between both groups. This was likely due to small sample size leading to differences that may not be representative of patients receiving autologous and nonautologous implants. In addition, the country of origin for included studies should be further analyzed with a report of justification regarding chosen implant material. Finally, pooled effect sizes described here could not be rigorously adjusted for covariates.

With the goal of improving patient outcomes in addressing DSF, we hope to address how implant material may affect post-operative outcomes. Future research should be conducted, adjusting for standard of care across national health systems, patient socio-demographic factors, and patient comorbidities. We also require a clearer focus on primary outcomes evaluated to better compare across groups.

5. Conclusions

The current study represents a scoping systematic review of the Web of Science, Scopus, and PubMed databases. Here, we provide novel efforts to elucidate depressed skull fracture outcomes in patients receiving autologous-based interventions compared to non-autologous-based interventions. We identified trends toward autologous implant usage among low preoperative-GCS patients, though DSF patients receiving autologous grafts reported greater likelihood of postoperative complication. Still, however, these data largely corroborate previous research indicating little-to-no statistically significant contributions of selected implant material towards post-operative complication rates among neurosurgical patients. Limitations of the present review include uncontrolled cofounders in patient and hospital factors, distinctly heterogenous patient cohorts, and inconsistent follow-up times. Future investigation of implant considerations for depressed skull fractures should focus its efforts on studying large, non-biased treatment cohorts with adequate control measures in place for differences attributable to interacting factors.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

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Ethics approval and consent to participate

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Consent for publication

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Availability of data

All data generated or analyzed during this study are included in this published article.

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Neural mechanisms of social empathy in the anterior cingulate cortex

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Abstract

Empathy is a prosocial behavior that perceives the emotional state of others, expresses similar perceptions that match those of others, and mediates different social behaviors. Empathic behaviors for pain and fear also exist in primates and rodents. In the past decades, the neural mechanisms of empathy have been defined as a result of various sensations and perceptions, such as visual and hearing stimuli, which cause mirror activations in brain regions, such as the insular, the inferior frontal, and the medial frontal cortices, among which the anterior cingulate cortex (ACC) has been identified as a core region of the neural network that is associated with the empathic activity in mammals. Most studies on the neural mechanisms underlying empathy have been based on rodent models, which allowed for single-cell resolution mapping of neuronal activity; moreover, the application of optogenetic techniques in rodent models has led to a deeper delineation of neural circuits. Here, we review the role of the ACC in two behavioral paradigms, pain and fear empathy, in rodents at the neuronal and neural circuit levels. Understanding how the ACC mediates empathic behavior in the brain will provide new targets in the treatment for neuropsychiatric disorders characterized by empathic disorders.

Keywords: Empathy, Anterior cingulate cortex, Mirror neurons, Somatostatin neurons, Neural circuits

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1. Introduction

Empathy is a cognitive process of perceiving and sharing an animal's emotional state, encompassing both affective empathy (emotional contagion and prosocial behavior), which retains primitive features across species, and higher-level cognitive empathy, which exists in human and nonhuman primates. Emotional contagion and imitative behaviors are considered to be the basis of empathy, including behaviors, expressions, or emotional states that match those of others, whereas cognitive empathy focuses more on the observer's understanding of emotions and the demonstrator's motivation to share[1,2].

The existence of cognitive empathy in rodents has been controversial, and there is no ideal way to analyze it directly. However, it has been argued that empathy can serve as a motivation to drive prosocial behavior among rodents[3-5]. Although it has been proposed that empathy serves as a motivation to drive prosocial behavior among rodents, the same motivation to share among demonstrators may also be based on receiving help from others to relieve their own pain, and thus prosocial behavior may indirectly reflect the animal's understanding of emotions.

Initially, empathy was thought to be unique to humans and primates, but subsequent studies have shown empathic behavior in various other mammals[2,6]. It follows that this conserved empathic behavior is crucial for population survival. In rodents, for example, when observers receive threat signals from the social group, they can react accordingly without experiencing them firsthand through passive defense or active helping behavior, which greatly enhances the survival rate of individuals and the stability of the society as a whole. A study has shown that the presence of social buffers caused stimulated rats to exhibit less freezing caused by fear[7], and thus the ability to empathize, allowing for enhanced social roles in the group and leading to better survival. In addition, many psychiatric disorders exhibited diminished or absent empathic abilities, such as autism and schizophrenia[8,9]. Therefore, the exploration of the neural mechanisms underlying empathic behaviors is gaining significance.

Rodents and other non-primates possess an observational learning capacity similar to that of humans, and this highly conserved ability underlies the retention of emotional empathy among animals across species[10]. As a result, behavioral neuroscientists have established empathic rodent models, which include numerous behavioral paradigms for both pain and fear empathy. In these paradigms, the neuronal activity in the brain can be artificially manipulated to further investigate the neural mechanisms underlying empathy. Many excellent literature reviews in the past have provided a relatively clear picture of the neural mechanisms of empathy[11,12]. These include the insular, inferior frontal cortices, medial frontal regions around the cingulate cortex (Brodmann's area [BA] 24, BA32, and BA6), as well as the amygdala, thalamus, putamen, caudate, and primary somatosensory cortex (SI, BA2), where brain activities are highly correlated with empathic activity.

Empathy depends on these neural networks. Beyond the core brain regions that are typically activated in pain empathy research (the insula and the anterior cingulate cortex [ACC]), other secondary networks with more specific processes may be revealed by the diversity of paradigms used. Pain empathy relies on a core network that is regulated by multiple secondary networks, which improves emotional sensitivity by promoting the integration of internal/external sensory information. These changes may eventually promote empathy in the subjects. The co-activation of the higher visual cortex and core region has been observed during empathy[13]. These evidence shows that the core area of empathy must have the ability to integrate external information, especially visual information. In an experiment based on a model of observational fear, when an opaque partition was used to replace a transparent partition, the freezing of observers significantly decreased[14]. This finding is similar to human beings. The social acceptance of visual stimuli is higher, and painful stimuli are more likely to activate the ACC/medial prefrontal cortex (mPFC)[15]. Some studies have shown dense bidirectional projection nerve fibers between the ACC and the visual cortex (VIS) by using virus tracing technology. ACC and VIS neurons have projections from other regions, and these regions constitute a tightly coordinated anterior cingulate area (ACA)-posterior parietal association cortex (PTLp)-retrosplenial cortex (RSP)-VIS network for visual processing[16,17]. These connection networks are the structural basis for the ACC to collect and process information, and as a result, the ACC becomes the core region of empathy activation. According to several studies, children or adolescents with autism have insufficient functional connectivity between the left anterior insula and bilateral visual cortex, but there is no evidence that insufficient connectivity could directly lead to changes in empathy[18]. In brief, it appears that the ACC is more capable of mediating empathy than the insula in the process of empathy.

Human neuroimaging experiments have shown that the ACC is activated when people experience distress or witness the distress of others and that the intensities of ACC activation are higher in individuals with greater empathy but lower in those with mental illnesses[19-21]. Studies in rodent models have shown that rodents without prior experience of footshock exhibited stronger freezing behaviors when they observed other rats receiving the same footshock[22]. In addition, increased expressions of immediate early proteins have been observed in some ACC neurons, and a decrease in passive defense behaviors has been observed following either destruction or functional inhibition of the ACC[14]. Therefore, the ACC might be considered as a core brain region in the neural network of empathy.

In the present review, we summarize the neural mechanisms at the neuronal, neural circuit, and synaptic plasticity levels in the ACC based on two different behavioral

paradigms: pain and fear empathy in rodents. The study of the neural mechanisms in the ACC during empathic behavior is of great importance for the exploration of new therapeutic targets for patients with psychiatric disorders.

2. Anatomical division of the anterior cingulate cortex

The human ACC is located in the anterior third of the cingulate cortex, surrounding the cephalic end of the corpus callosum (area [A]24a–c, A25, A32, and A33), while the midcingulate cortex (MCC) is located in the middle third of the cingulate cortex (A24a–c', A32', and A33'). The ACC can be divided into posterior ACC (pACC) and subgenual ACC (sACC) (Figure 1A). For rodents, there is a gradual shift in the nomenclature of the cingulate region. The cingulate cortex was initially divided into cingulate area 1 (Cg1) and Cg2, with Cg1 containing A24b and A24b' and Cg2 containing A24a and A24a'. However, a problem exists, in which the boundaries of the conventional cingulate cortex partition in rodents are perpendicular to those between ACC and MCC in primates[23], suggesting that Cg1 and Cg2 cover parts of what would be considered the ACC and MCC in other mammalians. It has been shown that there is a significant gap between rodent ACC and MCC in terms of anatomical structure, cellular architecture, connections to different brain regions, and the functions involved[24]. However, to the extent of differentiation, rodent ACC and MCC are functionally complementary and coordinated[25]. Therefore, in the last decade or so, some researchers have re-delineated the cingulate cortex of rodents by using a method that follows the distinction between the cingulate cortex of other mammals (MCC and ACC) to facilitate the study of brain function across species homologies. Rodent ACC ranges from A24a–b, A25, A32, and A33 (A33 is present in rats only), with A25 corresponding to subgenual ACC and A32 and A24a and b roughly coinciding with pACC.

Although the extent of the brain regions corresponding to rodent ACC has been re-normalized, there is still no way to clarify the boundary between the ACC and the PFC, especially the mPFC, because the prefrontal lobes of primates and rodents are fundamentally different in development. In general, the lateral prefrontal lobes of rodents, that is, prefrontal lobes with the granular layer, are underdeveloped[26], and researchers tend to use rodent PFC to refer to primate mPFC. It has been found that the ACC is homologous to the granule-free cellular structures in the mPFC, and therefore primate ACC is often treated as a subregion of the medial prefrontal lobe[27]. A large part of the current data on rodent prefrontal lobe comes from studies of the prelimbic (PL), infralimbic (IL), and cingulate regions[28]. Therefore, the definitions of the cingulate cortex, PFC, and mPFC remain ambiguous. As mentioned earlier, a nomenclature change has redefined these two regions and the anterior part of the cingulate cortex as the ACC, but because of the controversy, PL and IL are

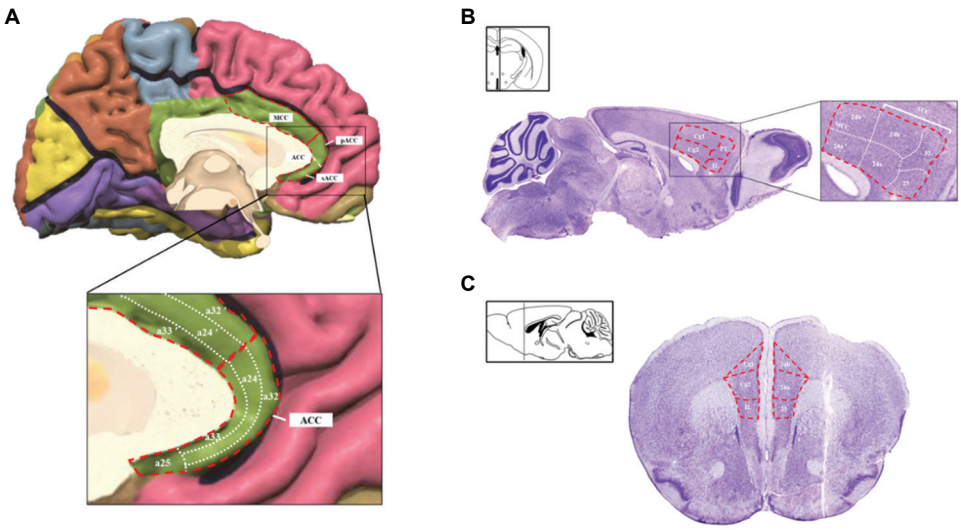


Figure 1. Anatomical division of the ACC. **(A)** The human ACC is located in the anterior third of the cingulate cortex, surrounding the cephalic end of the corpus callosum (area [A] 24, A25, A32, and A33), while the midcingulate cortex (MCC) is located in the middle third of the cingulate cortex (A24', A32', and A33'). The ACC can be divided into posterior ACC and subgenual ACC. **(B and C)** For rodents, the cingulate cortex was initially divided into Cg1 and Cg2, with Cg1 containing A24b and A24b' and Cg2 containing A24a and A24a'. Meanwhile, we define the ACC, IL, PL, and other areas of the mPFC as the ACC.

ACC: Anterior cingulate cortex; Cg1: Cingulate area 1; Cg2: Cingulate area 2; IL: Infralimbic cortex; MCC: Midcingulate cortex; pACC: posterior ACC; PL: Prelimbic cortex; sACC; subgenual ACC.

still considered by many as dorsomedial prefrontal cortex (dmPFC) and ventromedial prefrontal cortex (vmPFC)[27]. Regardless of the change in nomenclature, the ACC is a part of the prefrontal lobe according to anatomy and three-dimensional (3D) stereoscopic imaging. The whole prefrontal lobe is composed of several areas, including the ACC, secondary motor cortex (M2), PL, IL, orbital cortex (ORB), and agranular insular cortex (AI)[29-31]. Since the boundaries between the ACC and the surrounding adjacent areas are unclear and the localization of the ACC varies from experiment to experiment, the ACC, IL, PL, and other areas of the mPFC are defined as the ACC (Figure 1B and C).

3. Involvement of the anterior cingulate cortex in empathy

3.1. Anterior cingulate cortex and pain empathy

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. It is significantly influenced by environmental and psychosocial factors and a social cue that can be recognized and understood by others through emotional contagion in social interactions, thus inducing a corresponding state in oneself, which plays a positive role in self-defense or in triggering prosocial behaviors, such as empathy and helping[32,33]. Therefore, the social transmission of emotional information encoded by painful stimuli may be an important behavioral paradigm for studying the neural mechanisms of empathy. Pain empathy in mice, other than humans and nonhuman primates, has gradually gained recognition[34]. A study in mice has demonstrated that cagemates similarly exhibited pain sensation without pain stimuli under social conditions[35-37]; however, the underlying neural and molecular mechanisms of pain empathy are still largely unknown. The existence of pain empathy among rodents resulted in mechanical nociceptive sensitization in observers.

With the advancement of neuroimaging technology, the ACC has been accepted as the core brain region activated by pain empathy in humans, and its alternative pain production is positively correlated with ACC activity[38]. Although the lateral prefrontal lobe is neurodevelopmentally underdeveloped in rodents, the mPFC, including the ACC, is homologous across species, and therefore, combined with neuroimaging studies in humans, it would be inferred that the core region of pain empathy in rodents is still the ACC. In addition, when mechanical pain sensitivity is observed, neurons in the ACC are activated, and the activity of neurons in the dorsal horn of the spinal cord increases accordingly, suggesting that pain is real, rather than simply imitated. These experiments show that the ACC plays an important role in rodent pain empathy through a top-down regulatory mechanism during pain empathy[37,39].

Witnessing pain in others can produce or reinforce behavioral signs of injurious pain. However, individuals who are innately insensitive to injurious pain show a delayed response to empathic pain. This suggests that there may be overlapping neural representations between injurious pain and empathic pain[40]. The previous studies have suggested that pain-activated brain regions form a complex neuromodulatory network with different regions. The ACC is primarily involved in the production and modulation of the emotional component of direct pain[41].

3.2. Anterior cingulate cortex and fear empathy

In fear empathy, the perception of the emotions of others may further trigger empathic experiences of the self. Rodents have been found to acquire vicarious fear by sharing and perceiving threatening information in the environment, and many studies have also shown that the brain regions activated in empathic pain are also recruited in vicarious experiences associated with other aversive stimuli[42]. This observational fear can help mice avoid risks, and the presence of social buffers that allow for post-fear freezing in stimulated mice is behaviors that could better sustain the population.

Alternative fear is highly correlated with the characteristic empathy in humans[43]. Therefore, the rodent model of observational fear has become another important approach to further study the neuronal, circuit, and molecular mechanisms of empathy. In this model, the freezing behavior of observer mice was enhanced after observing the painful state of the demonstrator experiencing footshock and was consistent with that of the demonstrator, suggesting that the social transmission of fear or fear empathy does exist between rodents in this observational fear model. Further experiments revealed that the neural activity of the ACC increased during this observational learning process and the electrical stimulation of the ACC promoted alternative freezing behaviors; conversely, damage to the ACC reduced alternative behaviors[44]. All the above studies suggest that the ACC plays a very important role in fear empathy.

The development of optogenetic techniques has greatly facilitated the underpinnings of empathy mechanisms at the neuronal and neural circuit levels. It has been found that both ACC internal neurons and projection neurons play important roles in the formation of fear empathy and the ACC plays a dominant role in the neural circuitry. The downstream regions are still dependent on the ACC for encoding social information[45], indicating that the ACC

plays an important role in perceiving social fear as well as receiving and encoding social cues.

4. Neuronal types associated with empathy in the anterior cingulate cortex

Considering the versatility of the ACC and the universality of its connections with various brain regions, the neural mechanisms underlying empathy need to be further studied from the perspective of specific neurons. The previous studies have only focused on the functional connections between brain regions, neglecting the classification of neurons. Here, two types of neurons that mediate empathy in the ACC are discussed: Mirror neurons and somatostatin (SST) neurons (Table 1). As for whether there are other types of neurons that mediate empathy, more in-depth research is needed.

4.1. Mirror neurons in empathy

The ACC has proven to be important not only in the generation and processing of painful, negative emotions, but also in recognizing and perceiving the painful states in others. It has been speculated that the ACC might be the intersection for processing both empathic and painful emotions[46,47]. With the advancement of single-cell resolution techniques, a class of emotional mirrors has been identified within the ACC in A24 extending toward M2 and A32[19]. According to several studies, the specific types of ACC neurons are responsive to both the observation and the experience of overlapping emotions[48-50]. Similarly, the subtype ACC neurons can be activated by observational fear and classical fear[40,51]. More than 50% of the neurons that are activated by observational fear have mirror image properties, that is, they can be activated by both observational fear and pain[48]. Only a very small proportion of this group of neurons can be activated by both nociceptive and conditioned fear responses at the same time. The peaks of neurons have been shown to correspond to different conditions. In an algorithmic analysis of the peaks of neurons in the ACC after pain and observational fear tests, the alternative pain induced by observational fear did have the same code as the pain experience[52,53], but with an asymmetry of coding overlap, where neurons encoding ShockObs signals also encoded signals for pain, whereas neurons encoding pain signals did not necessarily encode signals for ShockObs[48]. The alternative activation of mirror neurons, which can also elicit pain behaviors, is explained through the results. The difference in the peak of mirror neurons under different signal stimuli provides greater selectivity in the activation of downstream neurons. These experimental results suggest that mirror neurons may be the biological basis for the overlap of the ACC in processing painful emotions and emotional empathy functions. Some experiments have even observed mirror neuron properties in ACC-basolateral nucleus of amygdala (BLA) neural pathway, with previously pain-activated neurons being

Table 1. Specific neurons and neural circuits associated with empathy

Neurons and neural circuits	Empathic behaviors	Methods and mechanisms	References
Mirror neurons	Pain empathy Fear empathy	A mirror neuron system located in A24b.	[48,54,55]
SST+neurons	Fear empathy	Associated with the recognition of emotional states Reducing inhibitory synaptic transmission in Nrxn3-dependent SST neurons enhances alternative fear responses	[46,58]
ACC-NAc pathway	Pain empathy	A neural circuit from the ACC to the NAc that mediates the rapid transfer of pain sensitivity and analgesia. A familiar social environment is important for pain empathy	[36,65,66]
ACC-BLA pathway	Fear empathy	ACC neurons rapidly alter basal firing rates during social fear transmission ACC input dominates the BLA encoding of social cues and subsequent behaviors	[44,45,71]
ACC-MDL pathway	Fear empathy	The optogenetic activation of the ACC to MDL reduces freezing behavior The destruction of ACC-MDL projection neurons delays the onset of the alternative behavior	[22,77]
ACC internal microcircuits	Fear empathy	Abnormal connections of interneurons induce severe deficits in social functioning SST + neurons in the ACC in the social transfer of fear	[46,94]

A24b: Area 24b/cingulate cortex 1; ACC: Anterior cingulate cortex; BLA: Basolateral nucleus of amygdala; MDL: Mediodorsal thalamic nucleus; NAc: Nucleus accumbens, Nrxn3: Neurexin 3; SST: Somatostatin

recruited preferentially in the social transmission of fear that follows[54], suggesting that mirror neurons may be directly involved in the presence of empathically activated neural circuits.

At the single-cell level, specific neuronal populations in the ACC have shown to create shared neural representations between direct pain and pain empathy, and the shared neural representations depend on a mirror neuron system (MNS) located in A24b, which is activated both when an action is actively performed and when it is observed[48,55]. Therefore, it has been hypothesized that mirror neurons might be involved in the encoding of painful emotional states transmitted during social interactions and might be the biological bases for the shared neural mechanisms of direct pain and pain empathy[56]. However, it is still uncertain whether mirror neurons are capable of encoding the emotional component of pain. Furthermore, although the neurons that are co-activated by empathy and pain have been identified in the ACC, the exact location of the overlapping neurons and whether they are involved in specific neural circuits remain unclear.

4.2. Somatostatin neurons in empathy

SST neurons release gamma-aminobutyric acid (GABA) ergic transmitters and affect the excitability of neighboring neurons to regulate the cortical state of certain regions[57]. Studies have shown that SST neurons in the ACC are associated with the discrimination of emotional states and the optogenetic inhibition of these neurons would eliminate social discrimination[58]. Therefore, it has been hypothesized that specific SST neurons in the ACC may be responsible for the emotional states of others in empathy and that social cognitive function depends on an intact balance of cortical neuronal excitation and inhibition[59]. Other experimental studies have shown that neurexin (Nrxn)3-dependent SST interneurons in the ACC can control the degree of socially transmitted fear in mice. SST neurons contribute to the hyperactivity of ACC pyramidal neurons by decreasing inhibitory synaptic transmission, thus driving enhanced alternative fear responses[46]. Therefore, the inhibition of ACC neurons through SST neurons can be said to regulate empathy-related behaviors. However, the molecular mechanisms underlying the mediation of SST neurons in the occurrence of fear empathy are unclear. Previous studies have shown that SST neurons with different molecules at different levels or in the same region may result in different function and distribution[60,61]. Therefore, further investigations are required to determine whether there are co-expressed molecules that dictate the specific roles of SST neurons in empathy.

5. Neural circuits associated with the anterior cingulate cortex in empathy

Both neural circuits from the ACC projecting to other nuclei and from other nuclei projecting to the ACC underly the neural mechanisms for social empathy. The neural circuits from the ACC projecting to other nuclei include ACC-nucleus accumbens (NAc), ACC-mediodorsal thalamic nucleus (MDL), ACC-BLA, and local neural circuits in the ACC (Figure 2). ACC appears to have a top-down regulation mechanism in the sensitization of social pain, but the mechanism in which sensitivity is regulated at the spinal cord level remains unclear. According to research, when noradrenergic neurons in the locus coeruleus (LC) are activated, the concentration of norepinephrine in the circulation increases, and alpha-1 adrenergic receptor blockers can be used to block mechanical pain hypersensitivity[62]. The previous studies have shown a bidirectional synaptic connection between the LC and the ACC, and the excitability of its neurons is regulated by the ACC[63,64]. Although it has been suggested that ACC-LC might mediate the top-down regulation of social pain, this hypothesis needs to be further investigated with photogenetic technology. In addition, a study has found that the inactivation of the lateral amygdala (LA) and the medial amygdala (MeA) can decrease emotional transmission and alternative learning in rats[12]. The LA-MeA circuit can connect social cues with environmental cues and use these environmental cues to guide social behaviors in fear conditioning. The stronger the functional connection of the neural circuit, the more the conditional freezing of social fear. According to Allsop *et al*., the inner amygdala path between the LA and the MeA might be the basis for linking the emotional content of social cues with other external prediction cues[45]. Since previous studies have observed a dense projection between the ACC and the amygdala, it is speculated that the ACC-MeA may be a potential neural mechanism for the ACC to adopt corresponding social behaviors after decision-making empathy. Furthermore, the MNS in the ACC may be the biological basis of the neural mechanism shared by pain and pain empathy; this remains to be further investigated.

5.1. Anterior cingulate cortex-nucleus accumbens pathway

Recent studies have shown that the neural circuit from the ACC to the nucleus accumbens (NAc) mediates the rapid transfer of pain sensitivity and analgesia in bystanders, but not the expression of mechanical pain sensitivity[35]. In a study, pain empathy was not detected in unfamiliar mice, which suggested the importance of a familiar social environment for pain empathy[65]. In addition, the

social transfer of pain was found to be more dependent on olfactory perception[36], while visual and auditory sensations contributed equally to the social onset of pain[66]. This is very different from the social transfer of fear, which relies on visual and auditory sensations[67]. Although the ACC encodes our own pain emotions and the emotional states of others[68], further research in rodents is needed to determine whether social cues transmitted through multiple sensory inputs can mediate pain empathy.

5.2. Anterior cingulate cortex-basolateral nucleus of amygdala pathway

The ACC and the amygdala are associated with observational learning and social decision-making. Studies have shown that the pharmacological inhibition of both the ACC and the BLA significantly decreased freezing behavior in observer mice[14,44,69] and there was a synchronous increase in the theta rhythm between the ACC and the BLA during the transmission of social fear in rodents[44,70]. In addition, ACC neurons have been observed to rapidly alter basal firing rates during social fear transmission[45,71]. Kim *et al.* have shown that the optogenetic inhibition of ACC-BLA projections did not affect the freezing behavior of observational fear but the inhibited fear memory in observational fear the next day[72]. The above findings suggest that the neural circuit from the ACC to the BLA is involved in the transmission and encoding of social fear information (Table 1), where ACC input dominates BLA encoding of social cues and subsequent observational fear memory but does not affect the re-expression of memory[14,45,71]. Post-long-term potentiation (LTP) activation depends on the de-silencing of silent synapses in the ACC-BLA pathway that occurs after observational fear[73]. However, no experiments have been conducted to demonstrate the extent to which this change in synaptic plasticity after observational fear affects behavior. Instead, combining observational fear experiment with inhibitory avoidance experiment (IA) has revealed a rapid disappearance of LTP after the IA test, along with observed rapid maturation of silent synapses and enhanced excitatory synaptic transmission, which facilitated the ACC-BLA circuit[74]. This is in contrast to previous studies, which found that the maturation of silent synapses is able to promote the expression of post-LTP[73].

5.3. Anterior cingulate cortex-mediodorsal thalamic nucleus pathway

Recent studies have found that the optogenetic activation of ACC to lateral MDL circuit reduces the occurrence of freezing behavior (Table 1), suggesting that ACC-MDL can modulate alternative freezing behavior. Studies have also found that rats that experienced foot stimulation were more likely to induce alternative freezing behavior[22,75,76]. In addition, resting state-functional magnetic resonance imaging (rs-fMRI) has revealed significantly enhanced regional connectivity of the ACC after electric shock, suggesting that the plasticity of ACC neurons may also be altered in rodents with the same painful experience[77]; similar to the preferential recruitment of hippocampal neurons in learning and memory with synchronous excitation in recall, there may also be a preferential recruitment of neurons activated by previous painful experiences when reactivated by observational fear. Determining the subpopulation of ACC-MDL projection neurons is thus necessary to further explore the mechanisms of empathy at the neuronal level.

Experiments in which rats were under observational fear stimuli followed by conditioned fear experiments have revealed enhanced conditioned fear, and the dynamic tracking of neurons activated by both types of fear has revealed that conditioned fear preferentially activated neurons in the CA1 region of the dorsal hippocampus, which were also activated by observational fear, suggesting that the overlapping activated neurons may have the ability to integrate both types of fear learning[78]. This may also be the neuronal basis of the alternative freezing behavior that is more likely to be evoked in foot-stimulated rats, suggesting that there may be a bidirectional positive feedback neural mechanism between observational and conditioned fears. As mentioned in the previous section, mirror neurons in the ACC have the dual property of encoding signals for pain signals and observational fears[48]. Mediodorsal (MD)-ACC projections, in turn, are involved in the development of pain emotions and sensations as well as in the enhancement of pathological states[79-81]. Although there is still no experimental confirmation of an overlapping relationship between activated ACC neurons and mirror neurons in this circuit, the speculation that the mechanism by which the formation of observational fear shares a neural loop with affection pain awaits further investigation.

Another interesting phenomenon is that the destruction of ACC-MDL projecting neurons delays the onset of alternative behavior but does not completely prevent it, so there may be other neural loops mediating alternative freezing behavior in rodents[77]. Uncertainty surrounds the ability of ACC interneurons and ACC neurons projecting to the MDL regulating alternative freezing behavior and whether there is a more precise microcircuit mechanism between projecting neurons and interneurons.

5.4. Local neural circuits in the anterior cingulate cortex

In the cerebral cortex, information processing relies on a highly interconnected microcircuit that is composed of excitatory glutamatergic pyramidal neurons and GABAergic inhibitory neurons[82]. The ACC is no exception; as a center of social interaction and information integration, the activation and inhibition of its internal pyramidal neurons depend not only on the direct projections of superior neurons, but also on the dynamic modulation and filtering of information by intermediate neurons[83]. The interaction of different neurons allows the ACC to process the input and output signals differently. Inhibitory interneuron dysfunction is more likely to cause dysregulation of neural homeostasis, thus resulting in psychiatric symptoms[84]. This includes both parvalbumin (PV)+ and SST+ neurons[85]. Results of a viral bundle pathway tracing have shown that both PV+ and SST+ neurons receive monosynaptic excitatory inputs from the BLA and midline and intralaminar thalamic nuclei (MITN)[16,86]. Fast-spiking PV+ neurons in the ACC mainly receive information filtered by the thalamus[83,87] and mediates feed forward inhibition around L2/3 pyramidal cells to control excitatory inputs to pyramidal neurons[88]. SST+ interneurons, on the other hand, target the distal dendrites of pyramidal cells and play a prominent role in regulating distal dendritic excitability[89]. SST+ interneurons also receive direct projections from L5 pyramidal neurons or the cortex. There is also a reciprocal inhibitory effect between these two interneurons[89,90]; an increase in PV neuron-mediated perisomatic feed forward inhibition of pyramidal neurons leads to a compensatory decrease in (SST+ neuron-mediated) dendritic inhibition[83,91]. The modulation of pyramidal neurons by interneurons is seen to be a dynamic balance[83,92]. However, less dendritic inhibition decreases the threshold at which pyramidal neurons are activated, lowering the neurons' capacity to filter information, and thus causing behavioral abnormalities. However, the effect of these two modes of inhibition differs in that an increase in input from PV+ neurons significantly decreases E/I, whereas the input from SST+ neurons to the distal dendrites of pyramidal neurons significantly increases E/I. As a result, the modulation of pyramidal neurons by interneurons is more flexible and dynamic, thus facilitating the processing of information from different brain regions. Recent studies have found that oxytocin can bind to postsynaptic oxytocin receptors on fast-spiking interneurons in the ACC and enhance inhibitory input to pyramidal neurons by lowering the action potential (AP) threshold and resting membrane potential of interneurons, and thus promoting depolarization of interneurons and inducing a decrease in the E/I ratio[93]. Therefore, the modulation of social cognition in rodents by ACC relies heavily on the modulation of these interneurons, that is, receiving remote projections from cortical or subcortical areas or receiving local neurotransmitter modulation to achieve a shift in excitatory or inhibitory effects on pyramidal neurons following information integration. This ability to dynamically regulate interneurons is necessary for social interaction, and deficits or abnormal connections of interneurons within the ACC can cause severe deficits in social functioning in animals, as shown in a study in which participants with high autistic traits showed elevated observational fear responses[94]. In contrast, when PV+ neurons are absent, there is a deficit in information filtering in the cortex that leads to autism[83,95]. This is consistent with the neuroanatomical findings of autistic individuals or model rats exhibiting PV+ neuron deficits[96,97]. Past experiments have revealed a unique role for specific SST+ neurons in the ACC in the social transfer of fear in rodents, but the inhibition of PV+ neurons did not alter the level of alternative freezing in experimental animals[46]. The possible reason for this is that PV+ neurons in the ACC have a weaker direct modulation of pyramidal neurons and are more involved in the modulation of SST+ neurons. However, it is undeniable that the microcircuits composed of PV+ neurons, SST+ neurons, and pyramidal neurons will be an important neurobiological basis for decoding social cues in the ACC and the balance of microcircuits homeostasis within the ACC is crucial for decoding the behavior of social cues, such as empathy (Table 1).

There appears to be a top-down regulatory mechanism in the ACC for social pain sensitization. More and more neural circuits are likely to be identified in the involvement of empathy with the development of neural modulations.

6. Clinical studies

Numerous clinical studies have confirmed that there are variations in the empathic abilities of patients with different neuropsychiatric disorders[98-100]. Patients with Alzheimer's disease (AD) and Parkinson's disease (PD) have significantly lower social emotion recognition ability than their respective caregivers; meanwhile, changes in emotion perception and empathy in patients with AD and PD have an impact on the perceived burden and depression among caregivers. Therefore, an early identification of the changes in empathic abilities in those patients may be effective for interventions in both patients and their caregivers[98]. As an other-oriented form of emotional empathy, empathic concern was found to be higher in AD patients than in controls. fMRI can be used to assist in the assessment of functional changes in empathy-related brain areas. A higher connectivity between the ACC

and periaqueductal gray matter predicts a longitudinal increase in empathic concern in AD patients. These results suggest that the acquisition of empathic concern may be a very early feature of AD pathophysiology, involving hyperconnectivity in a system that supports emotion generation and perception[101]. Therefore, an early identification of changes in empathic abilities may help in the early detection of neuropsychiatric disorders in some patients.

Patients with autism spectrum disorder (ASD) tend to exhibit reduced empathic abilities and impaired emotional empathy[102,103]. Imaging studies have demonstrated structural defects in the core empathic network in autism, such as reduced volumes of gray matter in bilateral superior temporal gyri (STG) and disturbances in resting-state functional connectivity between the ACC and prefrontal lobes[99]. However, another study has shown that patients with autism lack the ability to recognize, understand, and describe their own emotions. On that account, while ASD patients with alexithymia may experience emotional empathy differently, it should not be described as a lack of ability to empathize with emotions[104]. Since there is no standard, consistent definition of empathy, controversial views have emerged. Although there are consistent assessment scales and evidence of reduced empathy in people with autism from the data on Empathy Quotient (EQ), a 60-item self-report measure[8], the questions in such measures may be vague and imprecise as it is not clear to whom or which group one should be comparing with[105]. Further grouping of individuals with autism, and thus individualizing treatment, will be necessary. The use of different behavioral paradigms combined with neurophysiological markers measured by fMRI-based blood oxygen level dependent (BOLD) response for the assessment of ASD patients might be a good way[106]. As mentioned earlier, the MNS plays an important role in the perception of emotions and the imitative behaviors of individuals with ASD, which would further help to mediate empathic behaviors[107]. Future studies examining the effects of specific treatments on specific neurophysiological markers of MNS may reveal diagnostic subgroups of patients with ASD, with each subgroup requiring a specific treatment approach[106].

Central or peripheral oxytocin injections are clinically used to treat diminished empathic abilities in patients with neuropsychiatric disorders[108-110]. Previous studies in rodent models of observational fear have shown that intranasal oxytocin enhanced freezing behavior following observational fear transmission[54,111]. Recent studies have also shown that intranasal oxytocin administration might act on the MSN in the sensorimotor circuit of

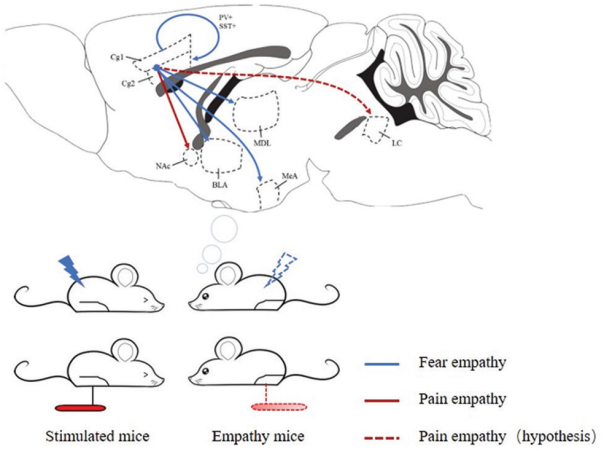


Figure 2. Neural circuits of ACC neurons projecting to the neural nuclei in pain and fear empathy. When empathy mice observe stimulated mice receiving click and mechanical tingling stimuli through visual, olfactory, and auditory sensory organs, there is activation of ACC neurons projecting to downstream nuclei through the stimulation of ACC-BLA, ACC-MDL, and ACC-MeA neural circuits as well as ACC internal microcircuits in fear empathic behaviors (blue arrows), while the ACC-NAc and the ACC-LC neural circuits mediate pain empathic behaviors (red arrows). The neural circuit from the ACC to the LC has been proposed to mediate pain empathy.
ACC: Anterior cingulate cortex; BLA: Basolateral nucleus of amygdala; Cg1/2: Cingulate cortex 1/2; LC: Locus coeruleus; MDL: Mediodorsal thalamic nucleus; MeA: Medial amygdala; NAc: Nucleus accumbens.

social perception and behavioral understanding[112]. Therefore, further investigations are required to determine whether oxytocin contributes to prosocial behavior by acting on ACC mirror neurons. In addition, it has been proposed that oxytocin release is potentially environment-dependent and might be involved in stress response, with a potential synchronous activation with cortisol; however, the two hormones are secreted independently, and stressor exposure is not the primary trigger for oxytocin secretion[113,114]. Oxytocin may bind to postsynaptic oxytocin receptors in fast-spiking interneurons in the ACC, significantly decreasing the action potential threshold and resting membrane potential of interneurons, promoting the depolarization of interneurons, resulting in a decrease in the E/I ratio, as well as enhancing the input from inhibitory to pyramidal neurons[93]. The above studies suggest that the modulatory neural circuitry of oxytocinergic projections to the ACC from other brain regions or subcortical nuclei may be involved in the treatment of neuropsychiatric patients with impaired empathic abilities.

7. Perspective significance

The development of fMRI has greatly facilitated the understanding of the neural basis behind empathy and depicted a vast neurofunctional network of various

neural circuits of the brain associated with empathy and brain areas that are causally associated with empathic behaviors, such as the ACC. Over the years, a wealth of data has been accumulated, which include not only the emotional states of their conspecifics, but also the prosocial behaviors driven by such shared experiences in rodents. The establishment of rodent empathy models has provided more possibilities to precisely modulate neural networks and delineate the connected neural circuits underlying empathic behaviors using techniques that monitor and manipulate neural activities at higher resolution. It also allows for thorough preclinical screening of potential therapeutic agents. This gives an opportunity to explore pharmacological treatments for certain psychiatric disorders with diminishing empathic capacity.

The current research still faces some challenges; although the development of optogenetic techniques is accompanied by a proliferation of studies on neural circuits, the majority of these studies still focus on inter-regional connections and are inactive in tracing the specific neurons behind the neural circuits. This may be a hindrance to the study of inter-brain regions. Therefore, future studies should focus on the neural representation of emotional state perception and behavioral decision in empathic behavior at the single-cell and population levels; further differentiate the neuronal types and map neuronal connectivity networks to further characterize the neural circuits underlying empathic behaviors.

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Conflict of interest

The authors declare that they have no competing interests.

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REVIEW ARTICLE

Treatment of Parkinson's disease with piribedil: Suggestions for clinical practices

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Abstract

With rapidly growing rates of prevalence, disability, and mortality, Parkinson's disease (PD) has become a global healthcare burden. Increasing elderly population increases the incidence of neurodegenerative diseases in China. Hence, PD poses a huge burden to Chinese economic and healthcare system. PD is a movement disorder that affects the motor and nonmotor functions. Dopamine agonists are used in the management of PD. Piribedil is an antiparkinsonian drug and piperazine derivative, which acts as D2/D3 receptor agonist. Piribedil is one of the non-ergot dopamine receptor (DR) agonists and has been used in China for many years as monotherapy or in combination with levodopa. In this paper, we present a review of clinical application of piribedil, management of adverse events, and drug interactions, and discuss the results of clinical trials of piribedil on motor and non-motor symptoms of PD.

Keywords: Neurodegenerative disease; Levodopa; Dopamine receptor; Non-ergot dopamine receptor agonists; α2-adrenoreceptor; Dyskinesia; Hypotension orthostatic

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease[1]. PD affects 41 and 107 persons/100,000 people who were in the fourth and fifth decade of age, respectively[2]. It affects 1903 persons/100,000 people who were aged above 80 years, with peak age group between 85 and 89 years[3].

According to the reports of Global Burden of Disease Study 2016, the prevalence of patients with PD in 2016 was approximately 6.10 million in 2016 compared with 2.50 million in 1990. China reports a higher rate of incidence of PD compared with the rest of the world. The prevalence of PD is higher in men (52.5%) than in women (47.5%). It is estimated that in China, nearly 23.9 – 26.9% of the population will be aged above

65 years by 2050. This will result in an expansion of aging population[4], which might further increase the incidence of PD in China. It is expected that by 2030, China will contribute to over half of the world's PD patients[5]. The global burden of PD has been doubled as the age and life expectancy of the population increases. PD resulted in approximately 3.2 million disability-adjusted life years and caused >210,000 deaths worldwide[6].

Motor symptoms such as akinesia and bradykinesia, tremor, and rigidity[7], and non motor symptoms such as depression, fatigue, altered gait, psychosis, apathy, sleep disorders, and sensory abnormalities[8,9] affect the patient and caregiver's quality of life. Thus, PD causes heavy economic burden to families and society[10,11]. Levodopa, dopamine receptor agonists (DRA), monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors, anticholinergic agent, and amantadine are the most common first-line therapy for PD. In patients with chronic PD, the long-term use of levodopa would result in decreased response to the drug, dose adjustments, and frequent emergence of motor complications. DRA have multiple advantages, such as direct dopamine receptor (DR) agonistic effect, long half-life, and antidepressant effect. No evidence of oxidative metabolism and interactions with food amino acids with DR agonists was observed. Daytime somnolence and behavioral changes are some of its drawbacks. DR agonists have been increasingly recognized in the treatment of PD, of which non-ergot DR agonists are highly recommended because of their less adverse effects[12].

Non-ergot DR agonists were approved as the first-line medications for the treatment of PD according to multiple national and international authoritative guidelines. Piribedil has been used as the first non-ergot DR agonist in China. Piribedil improves patient's motor and non-motor symptoms, and prevents motor complications in an advanced stage of PD with minimal adverse reactions such as somnolence[12-16].

However, there is no standardized guideline for the use of piribedil in PD. Based on the evidence-based medical research and domestic practical experience, experts put together comprehensive and reliable instructions on piribedil administration for clinicians. In this review article, we highlight the pharmacological properties of piribedil and its clinical applications in PD, management of adverse events and drug interactions.

2. Pharmacological properties of piribedil

2.1. Pharmacological mechanism

Clinical manifestations of patients with PD are mainly characterized by the degeneration of nigral dopaminergic cell bodies in the substantia nigra pars compacta (SNc) and dysfunction of neurons, which produces dopamine (DA)[17]. It is commonly regarded that the death of dopaminergic neurons in SNc is influenced by DA metabolism, oxidative stress and mitochondrial dysfunction, endoplasmic reticulum stress, impaired protein degradation mechanisms, and neuroinflammation. Dopaminergic neurons are susceptible to mitochondrial oxidative stress induced by DA oxidation. Mitochondrial oxidative stress leads to an accumulation of oxidized DA that suppresses the activity of glucocerebrosidase, lysosomal dysfunction, and α-synuclein accumulation in PD neurons[18,19]. The accumulation of DA in cytoplasm is neurotoxic, resulting in selective death of neurons in SNc[20]. Endoplasmic reticulum stress also causes neuronal death, which is caused by the accumulation of misfolded or unfolded proteins[21,22]. In addition, PD pathology affects autophagy, and stimulation of autophagic activities may be a compensatory mechanism induced by persistent reticulum stress. Impairment of autophagy tends to accumulate abnormal α-synuclein in the Lewy bodies which subsequently causes parkinsonism[23,24].

DA binds to G-protein coupled receptors or DA receptors. These receptors can be classified as D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, D4). These receptors mediate all physiological functions of catecholaminergic neurotransmitter, DA. D4 and D5 receptors may have limited effects on motor or cognition function[25,26]. DR agonists can stimulate DR to produce dopaminergic-like effects, thus improving motor and non-motor symptoms. D2 and D3 receptors are the DRs mainly related to PD. Stimulating the D2 receptors can improve motor function and cognitive functions, such as learning and memory, through prefrontal cortical regulation. D3 receptors can slightly regulate cognitive functions through hippocampal and play a key role in reward and reinforcement mechanisms. Evidence shows that D1 receptors might be related to motor function. Piribedil is a D2-like agonist but the D1 agonist (S584) is one of its metabolites[27]. Relevance of D1 agonistic activity remains speculative but it is thought to have consequences regarding efficacy and tolerability of piribedil. A combined stimulation of D1 and D2 receptors in animal model potentiates antiparkinsonian responses of piribedil and participates in the pathophysiology of dyskinesia[28].

DRA acts as adjuncts to levodopa. DAs can be divided into ergot derivatives and non-ergot derivatives. Piribedil, pramipexole, apomorphine, ropinirole, and rotigotine are the common non-ergot DR agonists. These will bind to DA D2-like family of DA receptors[12,17]. Neuroprotection conferred by DA agonists is thought to be provided by

different mechanisms. They decrease DA turnover and free radical generation in the substantia nigra, and possess antioxidant properties. Pathological conditions were reversed by piribedil in a dose-dependent manner, which showed to increase the expression of lactate dehydrogenase and reduce the expression of tyrosine hydroxylase positive/total neurons ratio after infusion[29]. The mechanisms and pharmacokinetics of non-ergot DR agonists are shown in Table 1[12]. In 1969, piribedil was marketed as the first non-ergot partial DA D2/D3-selective agonist. Piribedil 1-(2-pyrimidyl)-4 piperonyl piperazine is a non-catechol analog of DA[29].

Mechanisms of piribedil include the following:

i. Acting as signal-specific partial agonists at D2/D3 receptors. Partial agonism is sufficient to improve motor dysfunction in PD. While improving motor dysfunction, the avoidance of potentially excessive stimulation of D2/D3 receptors may reduce the incidence of complications, such as cognitive dysfunction and abnormal prolactin excretion. The combined stimulation of D1 and D2 receptors can increase the anti-PD effect and reduce the intensity of dyskinesia[17].
ii. α2-adrenoreceptor antagonistic effects. Piribedil blocks the α2-adrenoreceptor and reinforces dopaminergic, adrenergic, and cholinergic transmission. This effect may decrease the incidence of dyskinesia, improve the motor function and cognition, elevate the mood, and reduce the risk of daytime somnolence[30].
iii. Low affinity to multi-subtype 5-HT receptors. Piribedil may decrease serotonergic 5-HT1-related and 5-HT2-related side effects, such as valvular heart diseases[17].
iv. Minimal interaction with histaminergic and cholinergic receptors[12].

2.2. Pharmacokinetics

Piribedil is used as an oral medication. It reaches maximum concentration 1 hour after single oral dose with rapid absorption. Oral bioavailability is low due to an extensive first-pass metabolism. Hepatic metabolism produces many metabolites, which are excreted through kidney. The elimination of piribedil follows biphasic kinetics and is composed of a first phase characterized by a half-life of 1.7 h and a second, slower phase characterized by a half-life of 6.9 h[12,30]. A sustained-release formulation has a half-life of up to 21 h once steady state is attained, which is longer than levodopa and multiple DR agonist-like pramipexole (8 – 12 h) and ropinirole (6 – 8 h)[30,31]. According to Chinese Guidelines for the Treatment of PD (4th Edition), piribedil sustained-release tablets can be split in half in special cases to reduce the side effects. Continuous dopaminergic stimulation of DA receptors will delay the motor complications. Piribedil has a longer half-life than that of levodopa. It stimulates DA in a less pulsatile manner and avoids adverse effects due to DR-pulsed stimulations[12,32,33].

3. Clinical applications of piribedil in the treatment of PD

The goal of PD treatment is to effectively improve patients' motor and non-motor symptoms, prevent complications, and improve patient's workability and quality of life[15]. The International Parkinson and Movement Disorder Society considered piribedil efficacious and clinically useful for the treatment of PD[29].

A meta-analysis only involving randomized controlled trial (RCTss) showed that the combination of piribedil and levodopa is more effective compared with levodopa monotherapy (mostly focused on motor symptoms and few on mood) without significant worsening of drug-related adverse reactions that include gastrointestinal tract reactions and neuropsychiatric disorders[34]. Although this meta-analysis on RCTs revealed that the combination of piribedil and levodopa did not significantly increase the drug-related adverse reactions of patients with PD, these adverse reactions can still happen in clinical practice.

3.1. Motor symptoms

Piribedil can improve motor symptoms in patients with PD by increasing DR excitability[34]. In early untreated or levodopa-treated non-fluctuating PD patients, piribedil has shown superiority to placebo (level 1 evidence) for the alleviation of all cardinal motor symptoms. The typical

Table 1. Mechanisms and pharmacokinetics of non-ergot DR agonists

Parameters	Piribedil	Pramipexole IR	Ropinirole IR	Rotigotine transdermal patches
DR effects	D_2, D_3	D_3>D_2, D_4	D_2>D_3, D_4	D_1, D_2, D_3>D_4, D_5
Half-life (h)	1.7 – 6.9	8 – 12	6	5 – 7
Dose (mg/day)	150 – 250	1.5 – 4	8 – 24	8 – 16
Excretion pathway	68% through kidneys; 25% through bile	90% through kidneys	88% through kidneys	71% through kidneys; 23% through small intestine

DR: Dopamine receptor; IR: Immediate-release

piribedil dosage advised is 150 – 300 mg/day, usually taken 3 times daily[29]. Studies have demonstrated piribedil efficacy as monotherapy and in combination therapy. In this section, the results of clinical trials of piribedil on motor symptoms are reviewed. Table 2 summarizes the evidence for the improvement of motor symptoms by piribedil[34-42].

3.1.1. Monotherapy for early patients with PD

Piribedil monotherapy may improve motor symptoms, such as tremor, rigidity, and bradykinesia, in patients with early PD, and delay the need for levodopa[30,40].

A 7-month, randomized, double-blind, placebo-controlled trial (REGAIN study) showed that the piribedil monotherapy (150 – 300 mg/day) could achieve comprehensive control over motor symptoms, with proportion of both responders and patients remaining on monotherapy significantly higher than that of the placebo group. Researchers presumed that the treatment effect of piribedil monotherapy (effect size of 7.26 points for UPDRS III score) may be higher than or comparable with other dopaminergic agonists, including ropinirole (effect size of about 5 points), pramipexole (effect size of about 6 points), pergolide (effect size of about 5 points), and rotigotine (effect size of about 4 points)[39].

3.1.2. Patients with early PD insufficiently controlled by levodopa

A 6-month, open-label, multicenter trial showed that piribedil (150 mg/day) in early combination with levodopa and then a switch to piribedil monotherapy may improve motor symptoms and was well tolerated[41]. A 6-month RCT showed that piribedil (150 mg/day) as adjunct to levodopa may significantly improve motor symptoms, with a good safety and tolerance profile[42]. A 12-month multicenter RCT showed that the early combination of piribedil (150 mg/day) or bromocriptine (25 mg/day) and levodopa resulted in a similarly significant improvement of all motor symptoms in patients with PD; however, less dose of levodopa is required when piribedil is used, as compared to bromocriptine[38].

3.1.3. Patients with moderate and advanced PD

A previous review on piribedil indicates that the PD treatment generally requires long-term medication, and the long-term use of piribedil may not aggravate motor complications, with low incidence of dyskinesia[30]. Due to the restrictions of the number of cited papers, these results may be not comprehensive.

3.1.4. Patients with advanced PD treated with levodopa

An Asian phase IV, open-label, clinical study showed that an 8-week short-term combination therapy of piribedil (up to 150 mg/day) and levodopa may improve motor symptoms, such as tremor, with good tolerance. Moreover, piribedil reduces the dose of levodopa and prolongs the duration of its effect and may help to decrease the risk for levodopa-induced motor complications, and prolong the "ON" time[36]. Due to the limitations of the design in this study, the results need to be cautiously interpreted.

3.2. Non-motor symptoms

Studies on patients with early PD showed that piribedil monotherapy or as an adjunct to levodopa both resulted in some improvement in patient's non-motor symptoms, including mental state, depression, and sleep disorders. The early combination of piribedil may improve patients' quality of life[29]. Table 3 summarizes the evidence for the improvement of non-motor symptoms by piribedil.[35,38,40,43-47]

3.2.1. Apathy

Apathy is a common feature in end-stage PD that affects up to 42% of patients with PD. Apathy is associated with cognitive impairment and depression[48]. Many studies have shown that they are two different but commonly co-occurring syndromes, and depression can occur simultaneously with or after apathy[12,49].

A 12-week, randomized, double-blind, and placebo-controlled trial showed that (n=37) treatment of piribedil (maximum dose 300 mg/day) may effectively reverse postoperative apathy symptoms (Starkstein Apathy Scale score: -34.6% vs. -3.2%, P = 0.015, Robert Inventor score: improved by 46.6% vs. worsened by 2.3%, P = 0.005) after deep brain stimulation of the subthalamic nucleus. The remission rate of clinical symptoms was also higher than the control group (47.4% vs. 16.7%), and the treatment response was usually achieved in the first 6 weeks after treatment. It was suggested that piribedil should be initiated quickly in patients with postoperative apathy. Moreover, the piribedil group presented a trend towards improvement in symptoms of anhedonia[47].

3.2.2. Cognitive and executive functions

In a 12-month, multicenter, randomized, double-blind, Phase IV trial, and 425 patients with incomplete levodopa response were enrolled, and a subgroup analysis (n = 178) showed that only the combination of piribedil (150 mg/day) and levodopa may significantly improve the scores of Wisconsin Card Sorting Test (WCST) rather than other scales in patients with PD compared with bromocriptine (25 mg/day) and levodopa. The cognitive and executive functions were tested by the widely used WCST, which requires the participation of all cognitive processes needed

Table 2. Evidences for piribedil in treatment of motor symptoms of PD

Study, year	Region	Trial design	Patients	Treatment	Primary outcome	Main results	Evidence levela
Rondot and Ziegler, 1992[40]	France	Multicenter, open-label, single-cohort study	Patients with PD, mainly I–II stages (n = 113)	Piribedil monotherapy (150 – 250 mg/day)	NA	Three-month treatment with piribedil monotherapy may significantly improve motor symptoms, such as tremors, bradykinesia, and rigidity	IV
Ziegler *et al*., 2003[42]	France	Multicenter, randomized, double-blind, placebo-controlled trial	Non-fluctuating PD patients insufficiently controlled by levodopa (n = 115)	Piribedil (150 mg/day, n = 61) as adjunct to levodopa placebo group (n = 54)	The percentage of responders defined by a 30% decrease from baseline on the UPDRS III score and the change from baseline	In 6 months, the response rateb in the piribedil group was significantly higher than that in the placebo group (61.8 vs. 39.6%; P = 0.02)	I
Suwantamee *et al*., 2004[41]	Thailand	Multicenter, open-label, single-cohort clinical trial	Patients with early PD, poorly controlled by levodopa (n = 29)	Piribedil (150 mg/day, combined with levodopa in the first 3 months, and later switched to monotherapy)	The change in UPDRS part III score versus baseline and the percentage of responders defined by at least 30% decrease from baseline of the total UPDRS part III score	Through 6-month treatment of piribedil, UPDRS III scores were decreased significantly by 13.3±10.3 points (P < 0.0001), response rate was 93.1%b	IV
Evidente *et al*., 2004[36]	Philippines	Phase IV, open-label, prospective clinical trial	Advanced PD patients with fluctuating symptoms (n = 49)	Piribedil (up to 150 mg/day) combined with levodopa	Part III of UPDRS	An 8-week treatment of piribedil may improve UPDRS scores by 48% (tremors are improved mostly) and daily living ability by 43%, and may decrease the dose of levodopa and increase its duration of effect	IV
Rascol *et al*., 2006[39]	Multi-national	Multicenter, randomized, double-blind, placebo-controlled clinical trial (REGAIN)	Patients with early PD (n = 401)	Piribedil monotherapy (150 – 300 mg/day, n = 197) Placebo group (n = 204)	UPDRS III score as the last observation on monotherapy over 7 months was the primary outcome	After 7 months, UPDRS III scores were improved (–4.9 points) in the piribedil group, and exacerbated in the placebo group (+2.6 points; P<0.0001), and the response rateb in the piribedil group was also higher than that in the placebo (42% vs. 14%, P < 0.001)	I

(Cont'd...)

Table 2. ***(Continued)***

Study, year	Region	Trial design	Patients	Treatment	Primary outcome	Main results	Evidence levela
Castro-Caldas *et al*., 2006[38]	Multi-national	Multicenter, randomized, double-blind, controlled clinical trial	Patients with stages I–III PD, poorly controlled by levodopa (n = 425)	Piribedil (150 mg/day, n = 210) or Bromocriptine (25 mg/day, n = 215) combined with levodopa	Improvement of the UPDRS III score from baseline over 12 months, expressed as the change from baseline to the last observed value, and second as the response rate defined by a 30% or more decrease on the UPDRS III score at the last value	A 12-month treatment in the piribedil or bromocriptine group may fully improve motor symptoms of patients with PD, and the dose increase requirement of levodopa was less in the piribedil group	I
Xiao-ying *et al*., 2016[71]	China	Retrospective cohort study	PD patients (n = 140)	Compound levodopa combined with piribedil (100 – 150 mg/day, n = 76); compound levodopa monotherapy (n = 64)	NA	The overall effective rate in the piribedil combined group was significantly higher than that in the control group (92.10 vs. 62.50%, P < 0.05), and the decrease of UPDRS scores was significantly larger than that in the control group (P < 0.05)	III
Peihua and Jianqin, 2018[34]	China and France	Meta-analysis involving 11 studies	PD patients	Piribedil combined with levodopa (50~300 mg/day, n = 433); levodopa monotherapy (NA)	NA	The combination therapy group showed greater overall improvement of response rate and UPDRS scores than levodopa monotherapy group	I

[a]The evidence's levels were made with reference to the 2004 EFNS Guideline. [b]Defined as at least 30% decrease from baseline of UPDRS III score.
NA: Not available; PD: Parkinson's disease; UPDRS: Unified Parkinson's disease rating scale.

for executive functions during the test. The WCST can recognize early cognitive impairments and has a good sensitivity to identify frontal cortical dysfunction. This finding was more prominent in younger patients aged 50 – 70 years based on age stratification[38].

Pilot clinical trials demonstrated that piribedil may improve the frontal lobe dysfunction of patients with PD. Randomized, placebo-controlled, and double-blind clinical trials also showed that patients with mild cognitive disorder achieved some improvement in the overall cognitive function after receiving piribedil treatment (63.3% vs. 26.7%, P < 0.01); however, this requires to be further investigated by large-sample studies involving patients with PD[46,50].

3.2.3. Depression

Patients with depression show distinctly negative mood, which causes emotional suffering.

This is different from apathy, which is a mental disorder characterized by decreased goal-directed speech, motor activity, and emotion. Patients with apathy have indifference, but their mood is neutral[51].

Depression is the most common psychiatric non-motor symptom in PD patients with a high prevalence rate of

Table 3. Evidences for piribedil in the treatment of non-motor symptoms of PD

Study, year	Region	Trial design	Patients	Treatment	Primary outcome	Main results	Evidence level[a]
Mentenopoulos *et al.*, 1989[45]	Greece	Open-label, single-cohort clinical study	Stage II–IV PD patients (n = 30)	Piribedil (200 mg/day) combined with prior anti-PD drugs	NA	Through 20-week treatment, tremor showed greatest change, and an improvement of depression was observed in 14 patients	IV
Rondot and Ziegler, 1992[40]	France	Open-label, multicenter, single-cohort study	PD patients, mainly I–II stages (n = 113)	Piribedil monotherapy (150 – 250 mg/day)	NA	The depression score was decreased from 10.2 to 7.3 (P < 0.001), and moods were improved obviously (28%, P < 0.01)	IV
Nagaraja and Jayashree, 2001[46]	Indian	Randomized, double-blind, placebo-controlled clinical trial	Healthy elderly patients with mildly cognitive impairment (n = 60)	Piribedil group (50 mg/day, n = 30); placebo group (n = 30)	Change in MMSE score	Through 3-month treatment, the cognition scores in the piribedil group were improved more significantly (63.3% vs. 26.7%, P < 0.01)	II
Castro-Caldas *et al.*, 2006[38]	Multi-national	Multicenter, randomized, double-blind, controlled clinical trial	Stages I–III PD patients, poorly controlled by levodopa (n = 425); subgroup analysis on cognitive function (n = 178)	Piribedil (150mg/day,n=210) or bromocriptine (25 mg/day, n = 215) combined with levodopa	Improvement of the UPDRS III score from baseline over 12 months, expressed as the change from baseline to the last observed value, and second as the response rate defined by a 30% or more decrease on the UPDRS III score at the last value	A 12-month piribedil treatment may significantly improve cognitive function in PD patients	I
Yan-Bo *et al.*, 2007[72]	China	Prospective cohort study	Patients with early PD (n = 67)	Piribedil monotherapy group (n = 25, 50 – 100 mg/day); piribedil adjunct to compound levodopa (n = 20); and compound levodopa monotherapy (n = 22)	NA	UPDRS scores, depression, sleep quality and quality of life in the combination group were improved significantly at each follow-up time point; the depression scores in the piribedil group were decreased from baseline in any observation window	III
Thobois *et al.*, 2013[47]	France	Randomized, double-blind, placebo-controlled clinical trial	Patients with mid-stage and advanced PD presenting with apathy after deep brain subthalamic nucleus stimulation (n = 37)	Piribedil group (maximum dose 300 mg/day, n = 19); placebo group (n = 18)	The improvement of apathy under treatment, as assessed by the reduction of the Starkstein Apathy Scale score, in both treatment groups	After 12 weeks, the apathy scores in the piribedil group were decreased more significantly (34.6% vs. 3.2%, P = 0.015), and apathy symptom was also improved more (improved by 46.6% vs. worsened by 2.3%, P = 0.005). Piribedil also has a tendency to improve quality of life and anhedonia	II

(Cont'd...)

Table 3. ***(Continued)***

Study, year	Region	Trial design	Patients	Treatment	Primary outcome	Main results	Evidence level[a]
Eggert *et al.*, 2014[44]	Germany	Prospective, multicenter, randomized, active-controlled, rater-blinded phase III study	White men and women aged 35 – 80 years with a diagnosis of PD in Hoehn and Yahr stages 1 – 4 (n = 80)	Piribedil (213.2 mg/day), pramipexole (2.7 mg/day) or ropinirole (10.9 mg/day)	Median reaction time during the second half of the subtest "vigilance," test condition "moving bar" of the test battery for attention performances at the end of treatment	After 11 weeks of study, piribedil reduced daytime sleepiness with lower Epworth Sleepiness Scale scores at the end of treatment compared with the comparator (−4 vs. −2 points; P = 0.01)	I

[a]The evidence levels were made with reference to the 2004 EFNS Guideline

MMSE: Mini-mental state examination; NA, N = Not available; PD: Parkinson's disease; UPDRS: Unified Parkinson's disease rating scale

up to 35%[52], which may impact patients' quality of life and may lead to suicide. Piribedil produced significant antidepressant effects in multiple behavior models of depression, and its antidepressant effects are comparable with or better than those of multiple antidepressant drugs (e.g., imipramine, tricyclic antidepressant drugs, and selective serotonin reuptake inhibitors)[30].

A few open clinical studies have shown that piribedil may significantly relieve depression symptoms in an effective dose for motor symptoms control; however, these studies have no placebo control group[40,45]. More randomized, placebo-controlled, and double-blind studies are needed to verify these results.

3.2.4. Somnolence

A few studies revealed that piribedil may improve the somnolence in patients with PD. A RCT showed that switching from pramipexole or ropinirole to piribedil could decrease daytime sleepiness to a clinically relevant degree in PD patients with excessive daytime sleepiness[44].

3.3. Dyskinesia

The REGAIN study demonstrated that the incidence of dyskinesia in piribedil is comparable with placebo (8% vs. 7.5%)[17]. A RCT showed that the incidences of dyskinesia in piribedil and bromocriptine were 2.9% and 4.7%, respectively[38]. An animal-model study revealed that switching from levodopa to piribedil decreased the dyskinesia intensity without changing the improvement in motor deficits; however, switching from piribedil to levodopa resulted in a rapid increase in dyskinesia[53]. Animal models also demonstrated that α2-adrenoreceptor antagonists counter the dyskinesia induced by acute and chronic treatment of D2/D3 receptors agonists, such as piribedil, and while retaining or strengthening restoration of motor function[17,35]. No data are available to show that the incidence of dyskinesia on piribedil is different from that of other DRA.

3.4. Recommendations for dosage of piribedil

Piribedil is used in clinical practice since 1969 as 50 mg tablets. However, because of the limitations such as very low (< 10%) oral bioavailability due to extensive first pass metabolism and short biological half-life, piribedil is prescribed in high dosing frequencies with 3 – 5 tablets/day[54]. The dosage of sustained release formulation is 50 mg per tablet and the therapeutic effect will be lasting for 20 h. It is recommended to start with 50 mg once daily and an addition of 50 mg/week. Generally, the average effective dose is 150 – 200 mg/day, and the maximum dose is 250 mg. In combination therapy, the daily recommended maintenance dose of piribedil is 50 – 150 mg/day[55].

4. Management of adverse events caused by piribedil

Piribedil is generally safe and well tolerated. Most adverse reactions of piribedil overlap with those of all DRAs. The most commonly reported adverse reactions were gastrointestinal and cardiovascular responses. Neuropsychiatric disorder or daytime somnolence was also reported[29,30]. Thirteen percent of patients have to change the medication due to adverse effects. Suggesting the management of adverse reactions is highly important[12].

4.1. Gastrointestinal tract reactions

Gastrointestinal tract reactions, including nausea, vomiting, anorexia, and constipation, are the most common adverse reactions during treatment. The incidence ranges from 0% to 33%, but most of those are not severe[12]. During the 12-month follow-up, the gastrointestinal adverse reaction rate of piribedil was similar to that of bromocriptine, but

the latter had a higher risk of drug withdrawal due to gastrointestinal adverse events[38].

Piribedil-induced gastrointestinal tract reactions are short-term conditions and tend to disappear gradually. The undesired effect can be relieved by dose titration control or by administration of food. If the symptoms cannot be relieved, then domperidone, a peripheral DR inhibitor, could be used, but it is prohibited in patients with arrhythmia due to the risk of CT interval prolongation[56].

4.2. Daytime somnolence and sleep attack

As piribedil has α2-adrenoreceptor antagonistic effects, its incidence of daytime somnolence might be lesser than that of other DR agonists. The incidence of piribedil-related daytime somnolence is approximately 2% to 30%; however, it rarely results in drug withdrawal[12]. In over 30 years of clinical use, few cases of sudden sleep onset associated with piribedil have been reported. A position statement from the European Medicines Agency on sleep events and dopaminergic medications indicated that piribedil is "very rarely" associated with the incidences of excessive daytime somnolence[30]. A RCT showed that in patients with PD who developed daytime somnolence on pramipexole or ropinirole, switching to piribedil significantly reduced daytime somnolence compared with those continued on original treatment[44].

Patients should be informed of the potential adverse reactions. Caution must be taken while driving or operating the machine and while taking this drug. Those who have experienced this adverse reaction should avoid driving or operating the machine, and consider to reduce the dose or discontinue the treatment. It is suggested to reduce the dose to achieve satisfying response, keep sleep hygiene, and treat actively, if necessary, with modafinil or amantadine drugs[14,57].

4.3. Neuropsychiatric disorders

Piribedil-induced neuropsychiatric disorders, such as psychosis and hallucination, have an incidence of 4 – 23% and are more frequent in patients with preexisting cognitive deficits[12]. This phenomenon may be dose-dependent, and elderly and advanced patients with PD are at a higher risk[30]. Hallucination is a major cause for drug withdrawal[39]. However, a double-blind RCT showed that there was no significant difference in the incidence of neuropsychiatric disorders through 7-month treatment of piribedil compared with placebo[57]. As only 35 patients were enrolled in this trial, the insignificant results may be due to insufficient power.

It is not recommended for the elderly patients with neuropsychiatric symptoms to take piribedil if they have never used piribedil. If neuropsychiatric symptoms are well tolerated by patients and family members, they may not need to be actively treated, or a reduction of the drug dose that might have triggered psychosis syndrome can be considered under the guidance of experts. For PD patients without cognitive disorder, quetiapine may be used for the treatment of hallucination and delusion, although the risk of deterioration in motor function cannot be excluded. If standard therapy failed, clozapine may be considered by carefully monitoring the blood cell count. Olanzapine or other antipsychotic drugs (phenothiazines or butyrophenones) are not recommended because they may result in confused symptoms or deterioration of parkinsonian motor symptoms[14]. Bromocriptine is not in use anymore because it is an ergot derivative.

4.4. Hypotension orthostatic

Hypotension orthostatic is common at the onset of therapy and caused by the agonistic effect on DA receptors at the presynaptic level of the orthosympathetic system, and usually becomes tolerable over time. It mainly occurs in the 1st week after the use of piribedil, accounting for 5% of the adverse drug reactions[58,59].

Animal experiments showed that intravenous injection of piribedil may decrease hypertension and heart rate[30]. During the clinical use of piribedil, decreased systolic pressure and a slight decrease of heart rate and body temperature may also occur especially in patients with advanced PD[29].

The antihypertensive drug history should be traced, including antihypertensive drugs (including diuretics), dopaminergic drugs, alpha-blockers, and antidepressant drugs. These drugs may be tapered or stopped, if possible. Midodrine, an alpha-1 agonist, could be used. If there are contraindications for midodrine, using the mineralocorticoid fludrocortisone can be considered; however, attention should be paid to cardiac risk factors[14].

Droxidopa is "clinically useful" for the short-term treatment of orthostatic hypotension, whereas no data from RCTs on treating PD with droxidopa for a longer treatment time are available[60]. If there are concurrent cardiovascular reactions, such as heart rate change, it is suggested to stop medication and adopt fluid infusion measures[59]. Other patient's management includes education, advice and training on factors influencing blood pressure, and special aspects to be avoided (i.e., foods, habits, and positions). Physical measures include leg crossing, squatting, elastic abdominal binders, and stockings. Furthermore, careful exercise will improve the orthostatic hypotension[61].

4.5. Impulse-control disorders

Impulse-control disorders (ICDs) occur in 2% to 13.7% of patients with PD and are more prevalent at a high dose;

moreover, the use of dopaminergic agonists is considered one of the main pathogenic factors[62-64]. Among dopaminergic agonists, pramipexole was more frequent with ICD[62]. Impulse behaviors caused by piribedil are rarely reported and also tended to be dose-related[65,66]. According to epidemiological survey and spontaneous reports system of adverse reactions in France, no obvious increased risk of ICDs was observed after piribedil intake, and the risk was lower than other DR agonists, such as ropinirole or pramipexole[63,67].

Although the risk of ICDs with piribedil might not be as important as with other DR agonists, definite conclusions can only be achieved with head-to-head comparisons due to the method limitations of the study.

The hazard for switching to another DR agonists is unknown and needs further investigation. Only in some infrequent cases, symptoms were relieved by dose reduction or switching to another drug. Dose reduction to cessation of DR agonists, compensated by a concomitant increase in levodopa dose, is a preferred option to resolve ICD[68]. For patients who have developed impulse behaviors, caution must be taken before resuming piribedil, considering the potential risk of ICD relapse[62,63,69].

5. Drug interactions

Combination treatment with any drug that blocks DA receptors is contraindicated. Antiemetic drugs that do not cross the blood-brain barrier (e.g., domperidone) should be recommended. Using antiemetics that can cross blood-brain barrier in patients with PD is generally contraindicated due to worsening of Parkinsonism. As PD patients with psychosis or hallucination are difficult to be managed, antipsychotics, such as quetiapine, clozapine, and pimavanserin, have been approved for treating PD psychosis[70]. DRA must be tapered gradually until the complete discontinuation of the drug[53].

6. Conclusion

Piribedil is the first and unique non-ergoline, primarily partial D2/D3 receptor agonist among the first generation of DRA. It is the only drug used for about half of the century, which has unique pharmacodynamic profiles with α2-adrenoreceptor antagonistic effects. Many clinical studies have demonstrated that both piribedil monotherapy or combination of piribedil and levodopa may effectively improve the motor and some non-motor symptoms of PD patients at any stage, with a good safety and tolerance. Hereby, piribedil is recommended by multiple authoritative guidelines as the first-line therapy for patients with PD. This clinical suggestion may help neurologists to appropriately use piribedil in patients with PD.

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ORIGINAL RESEARCH ARTICLE

Restless legs syndrome in end-stage renal disease patients on maintenance hemodialysis: Quality of life and sleep analysis

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Abstract

Vitamin D insufficiency, calcium/phosphate imbalance, iron deficiency, anemia, pregnancy, and end-stage renal disease (ESRD) are all thought to be involved in the pathogenesis of restless leg syndrome (RLS). The prevalence of RLS ranging from 6.6% to 83% has been reported in another study. It is one of the illnesses that affect the quality of life of ESRD patients on maintenance hemodialysis. Unfortunately, RLS has not received enough recognition and attention, and the underdiagnosed and undertreated rate can reach more than 10%. This study aimed to look at the sleep quality and quality of life of people with RLS who were on maintenance hemodialysis. The present study included 286 individuals on chronic dialysis. The International Restless Legs Syndrome Study Group Diagnostic Criteria and the International RLS Rating Scale were used as recommendations to diagnose and assess the severity of RLS. The Pittsburgh sleep quality index (PSQI) and the Short Form-36 Health Survey (SF-36) were employed to evaluate sleep quality and quality of life. All patients' biochemical and demographic data were reviewed, and statistical analyses were carried out. In conclusion, there were no statistically significant variations in demographic information or clinical and laboratory characteristics between RLS patients and those who did not have RLS. Specifically, among dialysis patients, those with RLS had higher PSQI and SF-36 ratings.

Keywords: Restless legs syndrome; End-stage renal disease; Maintenance dialysis; Quality of life; Quality of sleep

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1. Introduction

Restless legs syndrome (RLS) is a prevalent sensory-motor problem in hemodialysis (HD) patients that causes sleep disruptions, harms the quality of life, and has been linked to increased morbidity and mortality in patients on maintenance hemodialysis. However, no consistent results have been obtained regarding the relationship of RLS with quality of life and sleep quality in patients on maintenance hemodialysis. There was an extensive range in the outcomes of prior investigations due to complicated etiology, pathophysiology, reference standards, race, regional disparities, study technique discrepancies, and diversity.

Despite the significant frequency of sleep disruption in MHD patients, the causes remain unclear and are likely multifaceted. RLS has been shown to harm many elements of quality of life and sleep quality, which may trigger sadness and anxiety[1]. Furthermore, studies have found that premature dialysis termination is linked to RLS symptoms, poor transferrin saturation levels due to iron insufficiency, and sleep start delay[2]. In addition, RLS was associated with an increased risk of death, and the relationship was somewhat reduced when controlling for sleep-related disorders[1,3,4]. Furthermore, after correcting for comorbidities, demographic factors, and possible clinical confounders, severe restless legs symptoms were independently related to elevated mortality risk[5]. A recent study by Kambampati *et al.*[6] has shown that sleep fragmentation and sleep deprivation induced by RLS may contribute to cardiovascular problems and inflammatory infections, frequently resulting in a poor prognosis in dialysis patients. Complete analyses of RLS-related quality of life and sleep disruption, which may lead to specialized treatment, are time-consuming and difficult. We anticipated that RLS is a prevalent illness in these individuals because of concomitant conditions, such as iron metabolism disorders, dialysis-related variables, systemic inflammation, peripheral neuropathy, diabetes mellitus, and electrolyte imbalance[7]. In general, the purpose of this study was to investigate the link between LRS and common sleep disorders, as well as the possible consequences on quality of life parameters[2]. RLS treatment improves clinical outcomes in dialysis patients. The general measures include reduced possible aggravating variables such as living standards, medical issues, and drugs[8]. The revious research has suggested that a dopamine receptor agonist treatment drug might help with RLS symptoms[4].

2. Methods

2.1. Participants

From September 2012 to September 2017, 286 patients with end-stage renal disease (ESRD) on maintenance hemodialysis participated in our research at the Affiliated Hospital of Weifang Medical University. The Ethics Committee approved the protocol for the study of Weifang Medical University's Affiliated Hospital (wyfy-2022-ky-183), and all subjects provided informed consent. Inclusion criteria of the present study are as follows: (i) Patients aged from 18 years to 80 years; (ii) those who met the diagnostic criteria for chronic renal failure with uremia; (iii) those who received maintenance hemodialysis 3 times/week, 4 h per time and for a period of over 3 months; (iv) those who used the same hemodialysis and dialysis; and (v) those who were in stable condition during the study. Exclusion criteria of then present study are as follows: (i) Those who had disturbance of consciousness, severe dysarthria, aphasia and cognitive disorders; (ii) those who had severe auditory or visual impairment, and physical frailty that prevented interview attendance; (iii) those who had severe comorbidities (e.g., heart disease, lung disease, liver disease, kidney dysfunction, nutritional deficiency, electrolyte disorder, severe endocrine and infectious diseases, neuropsychiatric complications, and mental illness) that could affect follow-up assessment; (iv) those who were using antipsychotics, dopamine agonists, and nerves nutritional drugs; (v) those with a history of central nervous system disease (such as tumor, trauma, hydrocephalus, Parkinson's disease, dementia), malignancies, human immunodeficiency disease and opportunistic infections; (vi) those who did not provide comprehensive records and lost to follow-up; and (vii) those who refused to participate and sign the written consent. Figure 1 shows the flow chart of study and patient selection.

2.2. Clinical assessments

2.2.1. Patient characteristics

We collected the basic demographic parameters related to age, gender, smoking, alcohol intake, history of renal disease, and comorbid disease (chronic glomerulonephritis, diabetic mellitus, and hypertension), information regarding dialysis therapy (such as age at initiation, duration of chronic kidney disease, time of dialysis, the delivered dose of dialysis [Kt/V], dry weigh, ultrafiltration volume, pre/post-dialysis mean systolic/diastolic blood pressure [BP]), biochemical parameters (blood urea nitrogen [BUN], creatinine, albumin, hemoglobin, ferritin, serum iron, total iron-binding capacity [TIBC], calcium, phosphorus, Ca × P product, intact parathyroid hormone [i-PTH], and C-reactive protein [CRP], β2-MG) in the two groups with or without RLS.

2.2.2. International Restless Legs Syndrome Study Group (IRLSSG) criteria for the diagnosis of RLS

The RLS patients were diagnosed according to the criteria of the IRLSSG[9,10]. The four minimal criteria include: (i) Urge to move the legs, usually accompanied or caused by uncomfortable leg sensations; (ii) temporary relief with movement, partial or total relief from discomfort by walking or stretching; (iii) onset or worsening of symptoms at rest or inactivity, such as when lying down or sitting; and (iv) an aggravation or onset of symptoms in the evening or at night. To assess the severity of RLS, we used the IRLSSG severity scale. Severity classification is as follows: Mild (1 – 10 points), moderate (11 – 20 points), severe (21 – 30 points), and very severe (31 – 40 points).

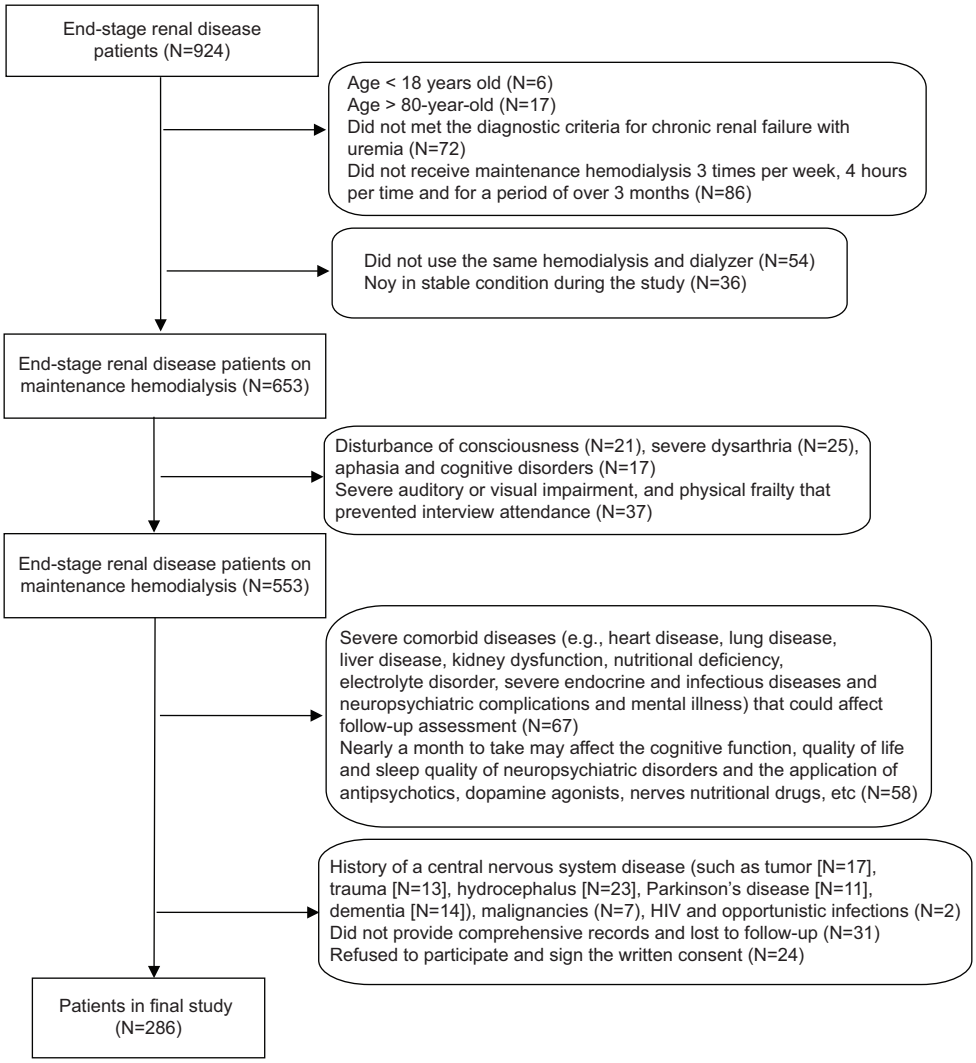


Figure 1. Flow chart of study search and selection. "→" indicates exclusion criteria.

2.2.3. Short form 36 (SF-36) health survey

The SF-36 was used to assess quality of life. The data from 36 items in eight subscales were integrated to measure the nutrition-associated quality of life in eight dimensions: Physical functioning, emotional role, physiological pain, general health, vitality, social functioning, and mental health. The SF-36 total score ranges from 0 to 100. The higher the score, the greater the quality of life; otherwise, the worse.

2.2.4. Assessment of sleep quality

The Pittsburgh sleep quality index (PSQI) is a method for measuring sleep quality. Seven component ratings ranging from 0 to 3 are generated from 19 individual items. PSQI may be classified into seven factors: subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, sleep disruption, usage of sleep medication, and daytime dysfunction. The total scores for these seven components result in a single global score. Lower ratings indicate better sleep quality. A global score of 5 or higher implies clinically severe sleep disruption.

2.3. Statistical methods

The SPSS 20.0 statistical program was used to analyze the data. The mean, standard deviation, or median (interquartile range) represent numerical data, while percentages are used to express data of categorical variables. To investigate differences between continuous variables, the Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed variables were employed. Correlation analysis also be performed to better describe the RLS-sleep or RLS-quality of life association. In contrast, the Fisher's exact test was used to analyze correlations between categorical variables. $P < 0.05$ indicates that the difference was statistically significant.

3. Results

The demographic data and clinical analysis results of the 286 patients on hemodialysis are shown in Table 1. Of the total, 41 patients (14.34%) were diagnosed with RLS with a male/female ratio of 16/25. Chronic glomerulonephrites is the primary disease in 155 patients (54.2%). The RLS severity score was 14.39 ± 9.75; there were 8 mild cases (19.51%), 25 moderate cases (60.98%), 6 severe cases (14.63%), and 2 very severe cases (4.88%). There was no significant association between RLS and gender, mean age, body mass index (BMI), smoking, drinking, mean age at the initiation of hemodialysis, hemodialysis duration, primary disease, and drug usage ($P > 0.05$).

The means of laboratory data, including hemoglobin, serum creatinine, uric acid, plasma albumin, calcium, phosphorus, magnesium, i-PTH, ferritin, and transferrin saturation, are shown in Table 2. No significant difference between the two groups (RLS-positive and RLS-negative patients) regarding all the laboratory data, including pre/post-dialysis mean systolic/diastolic BP, BUN, creatinine, albumin, hemoglobin, ferritin, iron saturation, iron, TIBC, calcium, phosphorus, Ca×P product, i-PTH, CRP, and β2-MG, was observed. There was a significant relationship between RLS severity and all SF-36 subscale scores, except the subscales "physical component score," "social functioning," and "general health" ($P < 0.005$). The RLS-negative patients had higher scores on the subscales physical functioning ($P = 0.019$), role limitations due to physical health ($P = 0.018$), pain ($P = 0.011$), mental component score ($P = 0.009$), energy/vitality ($P = 0.009$), vitality ($P = 0.005$), emotion ($P = 0.027$), and mental health ($P = 0.010$) than those RLS-positive patients (Table 3). Sleep disorders were considered more common in RLS-positive patients. These disorders included total PSQI global score, subjective sleep quality, sleep latency, duration of sleep, habitual sleep efficiency, and sleep disturbances ($P < 0.05$). However, there was no difference in the use of sleep medication and daytime dysfunction ($P > 0.05$), as shown in Table 4 and Table 5.

4. Discussion

Even though investigations into the etiopathogenesis of RLS have been conducted for many years, RLS is regarded as a complex condition in which genetic background, environmental variables, and gene-environment interactions are more likely to cause illness. Thousands of genetic studies have shown the hereditary variability of the illness and RLS is now considered a complicated congenital disorder. Large-scale genome-wide association study

Table 1. Clinical characteristics of patients on hemodialysis with and without RLS

	RLS	Non-RLS	*P*-value
Sex (female/male)	25/16	132/113	0.3979
Mean age (years)	56.37±14.35	54.64±15.13	0.4954
BMI (mean±SD)	22.58±3.41	23.61±3.62	0.090
Smoking	22 (53.66%)	141 (57.55%)	0.217
Drinking	23 (56.10%)	145 (59.18%)	0.1380
Mean age at the initiation of hemodialysis (years)	48.26±11.26	51.26±13.17	0.1698
Hemodialysis duration (years)			
≤5	25 (60.98%)	153 (62.45%)	0.8571
5–10	10 (24.39%)	66 (26.94%)	0.7324
≥10	6 (14.63%)	26 (10.61%)	0.4496
Primary disease			
Chronic glomerulonephritis	18 (43.90%)	137 (55.92%)	0.1529
Diabetic nephropathy	7 (17.07%)	29 (11.84%)	0.3459
Hypertensive nephropathy	9 (21.95%)	35 (14.29%)	0.2080
Others	7 (17.07%)	44 (17.96%)	0.8909
Drug			
Vitamins	17 (41.46%)	71 (28.98%)	0.1089
Anti-osteoporosis	27 (65.85%)	167 (68.16%)	0.7695
Erythropoietin and iron supplements	31 (75.61%)	203 (82.86%)	0.2655

BMI: Body mass index; RLS: Restless legs syndrome. Categorical variables are expressed as percentage while continuous variables are expressed as mean±standard deviation. *P<0.05

Table 2. Prevalence rate of RLS in maintenance hemodialysis patients from other studies

Study	Country	Prevalence rate (%)	Study	Country	Prevalence rate (%)
Xiao *et al.* 2017[1], Lin *et al.* 2013 (Taiwan)[18]	China	14.5%, 25.3%	Soumeila *et al.* 2015[36]	Maroc	41.7%
Jaber *et al.* 2011[19], Stefanidis *et al.* 2015[35],	USA	15.6%, 40%	Wali *et al.* 2015[37]	Saudi Arabia	19.4%
Tuncel *et al.* 2011[28], Demircioglu *et al.* 2015[38], Örsal *et al.* 2017[39], Kaya *et al.* 2015[44], Dikici *et al.* 2014[53]	Turkey	12%, 15.6%, 15.9%, 41.53%, 45.9%	Merlino *et al.* 2012[30], La Manna *et al.* 2011[31], Pizza *et al.* 2012[32], Baiardi *et al.* 2017[41]	Italy	19%, 31%, 32%, 36.7%
Esteve *et al.* 2017[40]	España	21.21%	Lee *et al.* 2013[33]	Canada	26%
Cengić *et al.* 2012[29]	Bosnia and Herzegovina	20.5%	Salman *et al.* 2011[34]	Allepo, Syria	20.3%
Neves *et al.* 2017[43]	Brazil	28.7%	Rohani *et al.* 2015[46]	Iran	37.4%
Higuchi *et al.* 2015[45]	Japan	22%	Beladi-Mousavi *et al.* 2015[47], Chavoshi *et al.* 2015[48]	IR Iran	15.8%, 31.7%
Bathla *et al.* 2016[50]	India	5.2%	De Santo *et al.* 2010[52]	Egypt	42%
Giannaki *et al.* 2017[49]	Cyprus	27.06%	Stefanidis *et al.* 2013[51]	Greece	26.6%

discovered apparent genetic risk variations replicated in 23 genomic locations[11]. Furthermore, a study showed that heritability contributed to RLS with common genetic variations amounting to 19.6% (single-nucleotide polymorphism [SNP]-based heritability), indicating the importance of these variants in RLS susceptibility[12]. In terms of etiological insights, numerous mechanisms, such as brain iron shortage, dopamine dysregulation, and hyper-glutamatergic condition, have been found and postulated to play a crucial role in pathophysiologies[13-14]. The previous studies have been conducted to determine the risk factors for RLS in patients on maintenance hemodialysis, but the results have been inconsistent, varied greatly, and have remained contentious. Unlike previous reports, we have not found an association of sleep quality index with serum creatinine, serum urea, cystatin-C, hemoglobin, and hematocrit levels, which might be attributed to the erythropoietin therapy and hemodialysis procedure. The main strengths of this study include the large number of patients studied and the comprehensive review process.

In our investigation, we found no change in parathyroid hormone (PTH) levels in two groups. The previous research has shown conflicting outcomes. In a prior study[15,16], PTH levels were observed to be lower in ESRD patients with RLS than in those without RLS. Recent investigations, on the other hand, have found that PTH is an independent risk factor[17], which is corroborated by the discovery that parathyroidectomy improved RLS in ESRD patients in one study[18]. Nonetheless, several research revealed that there is no link between PTH and RLS in ESRD patients. As a result, investigations involving larger sample size are needed to determine the link between PTH and RLS in ESRD patients[19,20].

Other risk factors for RLS include marital status, educational level, work status, dialysis type, dialysis frequency, and history of renal transplantation. However, we did not examine if there were any significant variations in these potential risk variables in the current subject population. Future research into the effects of these intervention variables on RLS-positive and RLS-negative patients is required. Studies on its relationship with laboratory data produced inconsistent findings. We found no link between hemoglobin, ferritin levels, and the Kt/V index in RLS patients. These findings were consistent with those of other investigations[8]. Sleep difficulties, depression, and polyneuropathy are known to follow these individuals and impact their quality of life, adherence to therapy, and overall health[4,5]. Serum albumin, i-PTH level, hemoglobin, urea, phosphorus, calcium, Kt/V index, and dialysis time have all been proven to have a significant impact on RLS patients' quality of life[15,17]. Furthermore, no correlation was detected between RLS and hematocrit, serum sodium, serum potassium, serum magnesium, Ca×P product, serum creatinine, BUN, serum albumin, CRP, uric acid, serum β2-MG, or iron metabolism markers.

Quality of life dimensions such as SF-36 total score, physical and mental component scores, bodily pain, general health perceptions, vitality, role functioning, emotion, and maintenance hemodialysis (MH) were significantly linked with RLS patients in our study. Sleep issues are widespread in ESRD patients, especially those with RLS, and contribute

Table 3. Laboratory and clinical indicators data of hemodialysis patients with and without RLS

	RLS	Non-RLS	*P*-value
Hemoglobin (g/dL)	105.34±15.12	101.86±17.32	0.2268
Hematocrit (%)	32.35±7. 12	33.65±6. 87	0.2655
Serum sodium (mmol/L)	134.24±13.68	137.15±10. 45	0.1168
Serum potassium (mmol/L)	4.46±0.72	4.53±0.68	0.5457
Serum magnesium (mmol/l)	1.15±0.24	1.12±0.21	0.4078
Serum phosphate (mmol/L)	4.46±0.72	4.53±0.68	0.5457
Serum calcium (mmol/L)	2.14±0.23	2.17±0.25	0.1515
Ca×P product (mg^2/dL^2)	51.43±15.12	52.95±13.76	0.5192
Serum creatinine	785.36±248.85	790.78±243.61	0.8955
BUN (mmol/L)	24.86±8.34	23.12±9.61	0.2756
Serum albumin (g/dL)	38.74±3.15	39.53±4.82	0.3118
i-PTH (pg/mL)	312.45±246.87	326.87±231.62	0.7150
Serum β2-MG (g/dL)	21.56±6.73	22.14±7.34	0.6361
CRP (mg/L)	13.86±4.57	12.43±5.81	0.1348
Uric acid (μmol/L)	345.53±101.67	336.41±117.82	0.6407
Ferritin (μg/L)	386.86±254.31	374.93±267.87	0.7906
Transferrin saturation (%)	24.85±3.14	26.13±4.26	0.0667
Iron saturation (%)	25.44±10.07	24.26±9.91	0.4820
Iron (μmol/L)	51±24	53±21	0.5810
TIBC (μmol/L)	223.12±42.38	217.86±48.24	0.5118
Kt/V	1.41±0.21	1.46±0.23	0.1933
Dry weight (kg)	61.58±9.76	58.13±11.24	0.0651
Ultrafiltration volume (kg)	1.62±1.13	1.57±1.34	0.8215
Pre-dialysis mean systolic BP (mmHg)	138.4±12.8	136.7±15.4	0.4810
Pre-dialysis mean diastolic BP (mmHg)	88.7±7.3	85.7±10.1	0.3922
Post-dialysis mean systolic BP (mmHg)	135.5±10.2	132.4±12.3	0.1277
Pre-dialysis mean diatolic BP (mmHg)	78.3±6.9	75.7±8.5	0.0642

β2-MG: β2-microgloblin; BUN: Blood urea nitrogen; CRP: C-reactive protein; i-PTH: intact parathyroid hormone; RLS: Restless legs syndrome; TIBC: Total iron binding capacity; Categorical variables are expressed as percentage while continuous variables are expressed as mean±standard deviation. *P<0.05

to a worse quality of life. In this patient population, the severity of RLS during sleep has been connected to an increased risk of cardiovascular and cerebrovascular illness and an increased risk of mortality[21-25]. RLS was linked to less peaceful nocturnal sleep, daily somnolence, and excessive daytime drowsiness, which led to symptoms of other sleep disorders, including insomnia, and lower overall sleep quality. Cederberg discovered that anxiety was much worse in individuals with MS and RLS, as well as higher levels of weariness and fear, compared to patients without concomitant RLS, which is similar to those with optic neuromyelitis[26].

Iron has been utilized to treat RLS in the general population. L-dopa and dopamine agonists are medications used to treat RLS[5,24,25]. RLS treatment aims to alleviate symptoms while also increasing sleep quality and quantity[26-28,42]. Non-pharmacologic treatment (for example, exercise training) or iron deficiency repair, common in ESRD, may be an effective therapy for people with moderate or occasional symptoms. Pharmacologic therapy, on the other hand, is frequently necessary for individuals with more severe illnesses.

Several limitations should be addressed when interpreting our findings. The most significant disadvantage of this study is the absence of metabolism gained from information on pharmaceuticals other than those that show the role of iron metabolism. Second, the sample size in this study is limited. Third, even after accounting for confounding factors, we cannot rule out the potential that unmeasured factors may explain some of our findings.

Table 4. SF-36 scores for RLS and non-RLS patients

	RLS	Non-RLS	*P*-value
Physical component score	42.56±12.91	45.86±16.18	0.2157
Physical functioning	62.31±18.62	71.14±22.76	0.0192*
Role physical	44.47±24.12	56.76±31.53	0.0179*
Bodily pain	51.43±23.56	64.17±30.49	0.0113*
General health	44.83±19.47	48.76±23.49	0.3114
Mental component score	45.21±11.47	51.65±14.84	0.0090*
Vitality	52.84±19.35	63.87±23.52	0.0050*
Social functioning	58.17±22.74	62.34±25.81	0.3314E
Emotion	40.32±32.74	54.65±39.15	0.0270*
Mental health	62.51±16.34	71.32±20.75	0.0101*

RLS: Restless legs syndrome; SF-36: Short Form-36. Categorical variables are expressed as percentage while continuous variables are expressed as mean±standard deviation. *P<0.05.

Table 5. PSQI scores for RLS and non-RLS patients

	RLS	Non-RLS	*P*-value
Sleep quality	1.76±0.75	1.43±0.61	0.0049*
Sleep latency	2.18±1.22	1.57±1.18	0.0025*
Sleep duration	1.28±0.87	1.01±0.61	0.0149*
Habitual sleep efficiency	1.47±0.72	1.24±0.45	0.0065*
Sleep disturbance	2.31±0.85	2.02±0.57	0.0057*
Use of sleep medication	1.28±1.14	1.19±0.92	0.5766
Daytime dysfunction	1.12±0.93	0.95±0.76	0.2011
PSQI global score	9.83±5.15	7.43±4.62	0.0027*

PSQI: Pittsburgh sleep quality index; RLS: restless legs syndrome; SF-36: Short Form-36. Continuous variables are expressed as mean±standard deviation. *P<0.05

Finally, whether additional variables such as weariness, sadness, patient disease uncertainty, nursing care, social and family support, and limited diets impact sleep quality and quality of life remain unknown.

5. Conclusions

This study found that RLS is a significant symptom of dialysis patients. Since the intensity of restless legs symptoms in ESRD patients is linked to lower sleep quality, impaired physical functioning and lifestyle standards, and increased mortality risk, management and treatment of this syndrome necessitates a long-term investment. Furthermore, RLS patients had poor sleep quality, particularly in subjective sleep quality, sleep latency, sleep duration, sleep efficiency, and daytime dysfunction. Moreover, RLS patients have a lower quality of life in terms of physical functioning, role restriction, pain, vitality, emotion, and mental health.

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Conflict of interest

The authors declare that they have no competing interests

Author contributions

Conceptualization: Ning Xu
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All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee approved the protocol for the study of Weifang Medical University's Affiliated Hospital (wyfy-2022-ky-183), and all subjects provided informed consent.

Consent for publication

Consent was obtained from all the participants.

Availability of data

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Alpha-synuclein at the interface between depression and neurodegeneration: Evidence from epidemiological and genetic data

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Abstract

Parkinson's disease (PD) and Alzheimer's disease (AlzD) are the two most common neurodegenerative disorders. Although these two disorders differ in terms of their underlying pathophysiology, clinical features, and course, there is a certain degree of overlap between them. This overlap may be partly related to alpha-synuclein (α-synuclein)-mediated neuropathological changes. Recent evidence has found that depression is associated with increased subsequent risk of both these neurological disorders and α-synuclein may also play a pathogenic role in depression. In the current study, epidemiological, population genetic, and environmental exposure data were examined in relation to the estimated prevalence of depressive disorders, PD, and AlzD using a cross-sectional, country-level analysis. The results showed a significant relationship between depressive disorders and neurodegenerative disorders, a possible shared genetic vulnerability related to the functional polymorphisms of *SNCA* gene, and potential gene-environment interactions involving fine particulate matter pollution. The significance of these results is discussed in light of existing translational, clinical, and epidemiological research on the links between these disorders.

Keywords: Alpha-synuclein; *SNCA*; Major depression; Dysthymia; Parkinson's disease; Epidemiology

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1. Introduction

Alzheimer's disease (AlzD) and Parkinson's disease (PD) are the most prevalent neurodegenerative disorders globally[1,2]. The burden associated with these disorders is expected to increase substantially over the next three decades, particularly in low- and middle-income countries, largely due to demographic shifts[3,4]. Both these disorders are chronic and progressive in nature, and they are associated with substantial disability, caregiver burden, and financial loss[5-8]. AlzD is mainly characterized by progressive memory impairment and loss of other cognitive functions[9], while PD is characterized by progressive motor symptoms and disability[10]. Despite their clinical and pathophysiological distinctiveness, there are significant clinical and neuropathological overlaps between them. Clinically, PD is associated with high rates of cognitive impairment, including dementia[11]; likewise, a subset of patients with AlzD tend to show signs of parkinsonism[12]. Pathologically, beta-amyloid (β-amyloid) deposition, which

is typical of AlzD, has been reported in patients with PD and related syndromes, in which it appears to correlate with cognitive impairment[13,14]. Similarly, alpha-synuclein (α-synuclein), which is specifically associated with PD, has been found to be elevated in the cerebrospinal fluid of patients with AlzD and may be linked to the severity of cognitive deterioration[15]. At a molecular level, α-synuclein appears to increase the production of β-amyloid from amyloid precursor protein (APP), and this effect may be mediated through the induction of beta-secretase, an enzyme that converts APP into β-amyloid[16].

Both PD and AlzD are associated with neuropsychiatric manifestations, particularly symptoms of depression and anxiety[17-19]. In PD, depressive symptoms are associated with more severe cognitive and motor coordination deficits[20,21], and fluctuations in mood and anxiety are associated with motor fluctuations[22], thus suggesting a shared pathophysiological link between these symptoms. Symptoms of anxiety and depression are also common in patients with AlzD and may reflect neurodegenerative changes in their cortical and limbic brain regions; however, such symptoms tend to be more severe in the early stages of the disease but decrease in severity as cognitive deficits worsen[23].

The chronic and progressive nature of both these disorders and the lack of effective disease-modifying treatment in patients with well-established motor or cognitive symptoms of either disorder have led researchers and clinicians to consider the possibility of early intervention in both PD and AlzD[24,25]. For such an approach to be effective, it would require early identification of specific biomarkers of disease risk and progression[26,27], early or "prodromal" symptoms that are associated with progression to marked neurodegeneration, and overt cognitive or motor symptoms[25,28], or both.

Recent research has drawn attention to a link between certain psychiatric disorders, particularly depression, anxiety disorders, and post-traumatic stress disorder, and the subsequent emergence of either PD or various subtypes of dementia, including AlzD[29,30]. Among these psychiatric disorders, the most consistent and significant associations have been reported for depression[31]. In a study of patients with severe depression without signs of parkinsonism, 6.5% of them developed PD over a nine-year follow-up[32]. A meta-analysis of eleven studies has found that depression is associated with at least a two-fold increase in risk of subsequent Parkinsonism regardless of age; the results remained significant even after adjusting for potential confounders[33]. Likewise, a meta-analysis of longitudinal studies has found a significant association between depression and the subsequent risk of AlzD, with stronger effects observed in severe- or late-life depression[34]; according to a review of six meta-analyses, syndromal depression is associated with a 1.5-fold increase in rates of subsequent AlzD[35]. The exact mechanism underlying these associations is unknown, but various mechanisms have been suggested to account for these links. These include immune-inflammatory dysfunction, dysfunction related to monoaminergic pathways, altered microglial or astrocytic functioning, and shared risk factors, such as stress or environmental toxins. There is a significant degree of overlap between these proposals; for instance, air pollution or stress can cause altered immune-inflammatory activity, which can lead to alteration in microglial activity, in turn causing neural inflammation and cell damage[36-40]. At a molecular level, there is now significant translational and clinical evidence suggesting that α-synuclein may also play a role in this association. In animal models, increased expression of α-synuclein is associated with depressive- and anxiety-like behaviors, and treatments that reverse depression are associated with reduced α-synuclein aggregation[41-43]. Similarly, chronic exposure to corticosterone, mimicking the biochemical effects of chronic stress, worsened the neural and behavioral changes in a mouse model of α-synucleinopathy[44]. Studies in human patients with depression without features of PD or AlzD have shown increased serum α-synuclein and α-synuclein expression, as indicated by increased messenger RNA (mRNA) levels[45-47]. In addition, a study has found an indirect association between the cerebrospinal fluid levels of α-synuclein and cognitive impairment in patients with depression[48]. Variations in the expression of *SNCA* gene, which encodes α-synuclein, have also been associated with the response to antidepressants in elderly individuals with depression[49]. It is therefore plausible that alterations in the expression of α-synuclein may represent a common pathway linking depression with the subsequent risk of PD or AlzD. The aim of the current study was to examine the plausibility of this association through the analysis of epidemiological, population genetic, and environmental risk factor data.

The objectives of this study were as follows:

(i) To examine the cross-sectional and longitudinal associations between the prevalence of depression, AlzD and PD over a certain period (1990 – 2019) using data from the global burden of disease study;
(ii) To examine the relationship between population-level variations in specific polymorphisms of *SNCA* gene and the prevalence of these disorders, both cross-sectionally and longitudinally;
(iii) To examine whether these associations remain significant after correction for two established environmental risk factors for AlzD and PD: air pollution and pesticide exposure.

2. Materials and methods

2.1. Materials

The Global Burden of Disease Study, which began in the year 1990 and was most recently updated in 2019, represents a systematic attempt to estimate the prevalence, burden, and outcome associated with diseases and their risk factors at a global level[50]. Data on the estimated prevalence of depressive disorders (major depressive disorder [MDD] and dysthymia), PD, and AlzD and related dementias were retrieved for the years 1990 and 2019 through database queries from the Global Health Data Exchange, which provides access to the entire data set of the Global Burden of Disease Study[51]. MDD, which is characterized by distinct episodes of depression with total or partial inter-episode recovery, has been consistently associated with both PD and AlzD[32-34]. Since older research has suggested that dysthymia may be associated with PD[52], it was also included in the analyses.

Several polymorphisms of *SNCA* gene have been associated with the risk or symptomatology of PD[53,54]. Although the association between this gene and AlzD has not been subjected to a comparable level of study, there is both direct and indirect evidence that variants in *SNCA* are correlated with the risk of AlzD and its underlying pathophysiology[55-58]. Recent research has suggested that *SNCA* may also be a candidate gene for major depression[59]. In light of these findings, the relationship between selected functional polymorphisms of the *SNCA* gene and the prevalence of major depression, PD, and AlzD was examined at a population level.

For the purpose of this analysis, data on allele frequencies for these polymorphisms were obtained from the Allele Frequency Database, a public-domain repository that contains data on over 660,000 genetic polymorphisms in 762 distinct populations[60,61]. Although this database contains data on several polymorphisms of *SNCA*, most of them are of unknown functional significance. Only polymorphisms that fulfilled the following criteria were selected for analysis:

(i) Evidence of an association of the specific polymorphism with either the disorders being studied or with their clinical manifestations based on human genetic studies;
(ii) Availability of data for diverse populations across 15 or more countries.

On the basis of these criteria, the following functional single-nucleotide polymorphisms (SNPs) of *SNCA* were selected for analysis: *rs356220*, *rs2736990*, and *rs3775439*. Details of the functional significance of these polymorphisms and the availability of allele frequency data for each of them are shown in Table 1[62-66].

Table 1. Functional polymorphisms of the alpha-synuclein gene *SNCA* analyzed in the current study and their significance

Polymorphism	Functional significance	Data availability
rs356220 (C/T)	Known to be associated with an increased risk of Parkinson's disease in both European and Asian populations[67] and more severe cognitive decline in Parkinson's disease[68]	18 countries
rs2736990 (T/C)	Known to be associated with an increased risk of Parkinson's disease, especially in East Asian populations[69], and altered levels of specific *SNCA* transcripts[68]	32 countries
rs3775439 (G/A)	The minor allele (*A*) is known to be associated with an increased risk of Parkinson's disease in the elderly[70] and may interact with other genes to influence the risk of developing Parkinson's disease[71]	32 countries

Among the environmental risk factors linked to both PD and AlzD, air pollution and pesticide exposure have shown to be the most consistently replicated associations[67-69]. Environmental air pollution, particularly exposure to particulate matter with a diameter of ≤2.5 microns (PM2.5), has been associated with significantly increased risk for both PD and AlzD in studies across 26 countries[70] and increased rates of depression[71]. Cumulative exposure to pesticides is associated with an approximately 50% relative risk increase for both PD and AlzD[72]; there is also evidence of a link between pesticide exposure and depression[73]. Genetic factors may partially mediate the association between pesticide exposure and PD[74]. Therefore, the effect of these two environmental factors on the possible associations between depression, PD, and AlzD was also examined in the current study through epidemiological and population genetic analyses. Information on the PM2.5 levels of each of the 193 countries and regions under the WHO's Global Health Observatory[75] and data on the levels of pesticide exposure, measured in terms of average pesticide application (in kilograms) per unit of cropland (in hectares), were obtained from the Food and Agriculture Organization's FAOSTAT database[76].

2.2. Methods

The identification of a positive correlation between the prevalence of distinct disorders across populations is suggestive, but not confirmatory, of a significant association between them. Such an association may also arise by chance or may be related to confounding factors[77]. Similar concerns arise when attempting to correlate putative risk factors, either genetic or environmental, with the

prevalence of specific disorders. In the current study, it is possible that depression, PD, and AlzD share common risk factors and depression may predict the subsequent risk of developing PD or AlzD. To test these hypotheses and minimize the risk of false-positive findings, the analysis of the aforementioned data was carried out according to the following steps:

(i) Direct bivariate correlations were computed between the prevalence of depression, PD, and AlzD at both time points (1990 and 2019);
(ii) A cross-lagged regression analysis was carried out between the two time points (1990 and 2019); in this model, a significantly greater "cross-correlation" between depression in 1990 and PD/AlzD in 2019 than that between PD/AlzD in 1990 and depression in 2019 would strengthen the possibility of a causal relationship[78];
(iii) Bivariate correlations were computed to examine the association between the prevalence of depression in 1990 and the percentage of change in the prevalence of PD and AlzD between 1990 and 2019; a positive correlation between these variables would also suggest a causal relationship;
(iv) For population genetic data, estimated allele frequency distributions were correlated with both the prevalence of each disorder at each time point and the percentage of change in the prevalence of each disorder over time;
(v) A general linear model was used to examine the influence of *SNCA* gene polymorphisms and baseline prevalence of depression on changes in the prevalence of PD and AlzD over the study period (1990–2019);
(vi) All the aforementioned analyses were adjusted for PM2.5 levels and pesticide exposure.

2.3. Data analysis

All study variables were tested for normality prior to further analysis using the Shapiro-Wilk test. Paired-samples *t*-test was performed to determine if the changes in the prevalence of depression, PD, and AlzD over the study period (1990 – 2019) were statistically significant.

Bivariate correlations were computed using Pearson's coefficient (*r*) and Pearson's partial coefficient (partial *r*). Analyses of epidemiological data were corrected for multiple comparisons using Bonferroni's method. Analyses of genetic data were not subjected to this correction due to the small number of cases available for study. Adopting such a method would raise the possibility of a false-negative finding. The strength of bivariate correlations was quantified using standard guideline values for biomedical research[79].

Repeated measures analysis of variance was used to examine the influence of *SNCA* polymorphisms and the baseline levels of depression on changes in the prevalence of PD and AlzD across countries.

All analyses were carried out using Statistical Package for the Social Sciences, version 26.0 (SPSS 26.0). All tests were two-tailed, and a significance level of $P < 0.05$ was used for all analyses in this study.

3. Results

Epidemiological and genetic data analyses were carried out for 204 countries and 32 countries, respectively, while environmental data analyses in relevance to PM2.5 and pesticide were carried out for 193 countries and 155 countries, respectively. The estimated prevalence of depression, PD, and AlzD in 1990 was 3.46%, 0.07%, and 0.40%, respectively, while that in 2019 was 3.95%, 0.11%, and 0.69%, respectively. The mean increases in the prevalence of each disorder over this 30-year period were 15.95% for depression, 11.30% for PD, and 66.67% for AlzD. All these changes were statistically significant (depression: $t = 14.93$, $P < 0.001$; PD: $t = 14.06$, $P < 0.001$; AlzD: $t = 12.13$, $P < 0.001$), indicating substantial increases in the prevalence of all three disorders over this period.

3.1. Bivariate correlations between the prevalence of depression and both PD and AlzD

The results of direct correlations between the estimated prevalence of depression and both PD and AlzD in the years 1990 and 2019 are presented in Table 2. From these results, it can be seen that the prevalence of all forms of depression (major depression, dysthymia, and depressive

Table 2. Correlations between the prevalence of depression and both Parkinson's disease and Alzheimer's disease in 1990 and 2019

Year	Variable	Parkinson's disease	Alzheimer's disease
1990	Depression	0.49 (<0.001)[a]	0.53 (<0.001)[a]
	MDD	0.38 (<0.001)[a]	0.43 (<0.001)[a]
	Dysthymia	0.62 (<0.001)[a]	0.61 (<0.001)[a]
	Depression*	0.45 (<0.001)[a]	0.51 (<0.001)[a]
	MDD*	0.35 (<0.001)[a]	0.41 (<0.001)[a]
	Dysthymia*	0.59 (<0.001)[a]	0.56 (<0.001)[a]
2019	Depression	0.31 (<0.001)[a]	0.34 (<0.001)[a]
	MDD	0.19 (0.004)[b]	0.25 (<0.001)[a]
	Dysthymia	0.47 (<0.001)[a]	0.35 (<0.001)[a]
	Depression**	0.24 (0.004)[b]	0.22 (0.006)[b]
	MDD**	0.16 (0.054)	0.19 (0.022)[b]
	Dysthymia**	0.34 (<0.001)[a]	0.17 (0.037)[b]

MDD: Major depressive disorder. [a]Significant at $P < 0.05$ after applying Bonferroni's correction. [b]Significant at $P < 0.05$, uncorrected. *Adjusted for life expectancy. **Adjusted for life expectancy, particulate matter (PM2.5) pollution, and pesticide exposure

disorders as a whole) was significantly and positively correlated with the prevalence of both PD and AlzD at both time points, even after correction for multiple comparisons. The magnitude of these correlations was somewhat greater in 1990 (r = 0.38 – 0.61) than in 2019 (r = 0.19 – 0.47) and appeared to be slightly greater for dysthymia (r = 0.35 – 0.62) than for major depression (r = 0.19 – 0.38). When these associations were adjusted for life expectancy (in 1990 and 2019) and environmental risk factors (in 2019), their strength was somewhat attenuated (r = 0.16 – 0.59), but they remained statistically significant. This suggests that the link between these disorders cannot be entirely ascribed to shared environmental risk factors.

3.2. Cross-lagged regression analysis of depression, PD, and AlzD

The results of cross-lagged regression analysis are presented in Table 3. From these results, it can be seen that the cross-correlations between depressive disorders in 1990 and PD/AlzD in 2019 were greater (r = 0.34 – 0.60) than those between PD/AlzD in 1990 and depressive disorders in 2019 (r = 0.22 – 0.41). For depressive disorders as a whole and for major depression, this difference was not statistically significant (regression coefficient: 0.09 – 0.14, $P > 0.05$). However, for dysthymia, this difference was statistically significant (dysthymia/PD: 0.19, $P = 0.005$; and dysthymia/AlzD: 0.21, $P = 0.004$). These results support the possibility of a causal relationship; in other words, dysthymia appears to be prospectively associated with the subsequent risk of PD and AlzD.

3.3. Bivariate correlations between *SNCA* allele frequencies, depression, PD, and AlzD

The associations between population genetic data and the prevalence of each specific disorder are presented in Table 4. In these analyses, the frequencies of all three alleles included in this study (*rs356220*, *rs2736990*, and *rs3775439*) showed significant correlations with the estimated prevalence of depressive disorders at both time points. The *rs2736990* and *rs3775439* allele frequencies were significantly correlated with the prevalence of both PD and AlzD. After correcting for possible confounding factors (life expectancy, air pollution, and pesticide exposure), only the *rs3775439* allele frequency distribution remained significantly and negatively correlated with the prevalence of depression and PD (at both time points) as well as AlzD (in 1990). This suggests that the distribution of the *rs3775439 (A)* allele across populations may be associated with a lower prevalence of the aforementioned disorders.

To examine the possibility that the above association might be mediated by depression, partial correlation analyses of the associations between each allele frequency and both PD and AlzD were carried out, while adjusting for the prevalence of depression (Table 5). In these analyses, the association between *SNCA* variants and both PD and AlzD was not significant after adjusting for MDD but remained significant when adjusting for dysthymia. This suggests that while *SNCA* gene variants may influence the development of both MDD and neurological disorders, these variants may interact with dysthymia to influence the risk of subsequent PD or AlzD.

3.4. Bivariate correlations between depression, *SNCA* allele frequencies, and changes in PD and AlzD over time

The results of these analyses are presented in Tables 6 and 7. In both the unadjusted and unadjusted analyses, neither the baseline prevalence of depression nor the frequencies of specific *SNCA* alleles were significantly correlated with subsequent increases in the prevalence of PD or AlzD. There was a positive correlation between changes in the prevalence of depression and changes in the prevalence of PD or AlzD over the study period, but only the correlation with PD remained significant after adjusting for life

Table 3. Cross-lagged regression analyses of the associations between depression, Parkinson's disease, and Alzheimer's disease

Association	Cross-correlation (depression in 1990 to neurological disorder in 2019)	Cross-correlation (neurological disorder in 1990 to depression in 2019)	Regression coefficient	Interpretation
Depression and Parkinson's disease	0.46	0.32	0.14	Causal relationship not supported
Major depression and Parkinson's disease	0.34	0.22	0.12	Causal relationship not supported
Dysthymia and Parkinson's disease	0.60	0.41	0.19[a]	Causal relationship supported
Depression and Alzheimer's disease	0.47	0.37	0.10	Causal relationship not supported
Major depression and Alzheimer's disease	0.38	0.29	0.09	Causal relationship not supported
Dysthymia and Alzheimer's disease	0.54	0.33	0.21[a]	Causal relationship supported

[a]Significant at $P<0.05$

Table 4. Correlations between frequencies of *SNCA* gene polymorphisms and depression, Parkinson's disease, and Alzheimer's disease

SNCA variant	Major depression	Dysthymia	Depression	Parkinson's disease	Alzheimer's disease
			1990		
rs356220 (A)					
Unadjusted	0.58[a]	0.48[a]	0.62[a]	0.43	0.59[a]
Adjusted*	0.47	0.35	0.50[a]	0.11	0.35
rs2736990 (C)					
Unadjusted	−0.47[a]	−0.36[a]	−0.48[a]	−0.47[a]	−0.55[a]
Adjusted*	−0.31	−0.19	−0.31	−0.17	−0.28
rs3775439 (A)					
Unadjusted	−0.75[a]	−0.57[a]	−0.76[a]	−0.65[a]	−0.72[a]
Adjusted*	−0.69[a]	−0.48[a]	−0.70[a]	−0.52[a]	−0.64[a]
			2019		
rs356220 (A)					
Unadjusted	0.58[a]	0.21	0.62[a]	0.50[a]	0.46
Adjusted**	0.48	0.74[a]	0.63[a]	0.37	−0.11
rs2736990 (C)					
Unadjusted	−0.50[a]	−0.26	−0.53[a]	−0.49[a]	−0.45[a]
Adjusted**	−0.38	−0.32	−0.41	−0.07	−0.01
rs3775439 (A)					
Unadjusted	−0.71[a]	−0.24[a]	−0.72[a]	−0.51[a]	−0.45[a]
Adjusted**	−0.62[a]	−0.52[a]	−0.68[a]	−0.47[a]	−0.04

SNCA: Alpha-synuclein gene. *Adjusted for life expectancy. **Adjusted for life expectancy, particulate matter (PM2.5) pollution, and pesticide exposure. [a]Significant at $P < 0.05$

Table 5. Correlations between frequencies of *SNCA* gene polymorphisms and both Parkinson's disease and Alzheimer's disease, corrected for the prevalence of depressive disorders

SNCA variant	Parkinson's disease (1990)	Parkinson's disease (2019)	Alzheimer's disease (1990)	Alzheimer's disease (2019)
rs356220 (A)				
Adjusted for MDD	0.12	0.39	0.34	0.42
Adjusted for Dys	0.18	0.46	0.42	0.49[a]
Adjusted for Dep	0.01	0.34	0.26	0.45
rs2736990 (C)				
Adjusted for MDD	−0.23	−0.33	−0.34	−0.33
Adjusted for Dys	−0.34	−0.43[a]	−0.46[a]	−0.44[a]
Adjusted for Dep	−0.20	−0.29	−0.32	−0.32
rs3775439 (A)				
Adjusted for MDD	−0.25	−0.28	−0.37[a]	−0.27
Adjusted for Dys	−0.42[a]	−0.47[a]	−0.55[a]	−0.44[a]
Adjusted for Dep	−0.17	−0.22	−0.29	−0.27

All statistics are given as Pearson's partial *r*. Dep: Depression; Dys: Dysthymia; MDD: Major depressive disorder; SNCA, Alpha-synuclein gene. [a]Significant at $P < 0.05$

expectancy. These results do not support a prospective longitudinal association between depression, PD, and AlzD; instead, they are more suggestive of possible shared risk factors for all three conditions.

Table 6. Bivariate correlations between depression, *SNCA* allele frequencies, and changes in Parkinson's disease and Alzheimer's disease in the period 1990 – 2019

Variable	MDD, baseline prevalence	Dysthymia, baseline prevalence	Depression, baseline prevalence	*rs356220*	*rs2736990*	*rs3775439*
Parkinson's disease, change (%)						
Unadjusted	−0.13	0.07	−0.10	−0.01	−0.09	0.35
Adjusted*	−0.13	0.03	−0.11	0.01	−0.11	0.33
Alzheimer's disease, change (%)						
Unadjusted	−0.03	0.07	−0.01	0.09	−0.20	0.18
Adjusted*	−0.03	0.04	−0.02	0.09	−0.21	0.17

MDD: Major depressive disorder. *Adjusted for changes in life expectancy over the period 1990–2019

Table 7. Bivariate correlations between changes in the prevalence of depression and both Parkinson's disease and Alzheimer's disease in the period 1990 – 2019

Variable	MDD, change (%)	Dysthymia, change (%)	Depression, change (%)
Parkinson's disease, change (%)			
Unadjusted	0.12	0.11	0.26[a]
Adjusted*	0.08	0.10	0.23[a]
Alzheimer's disease, change (%)			
Unadjusted	0.09	0.06	0.17[a]
Adjusted*	0.05	0.05	0.13

MDD: Major depressive disorder. *Adjusted for changes in life expectancy over the period 1990–2019. [a]Significant at $P < 0.05$

3.5. General linear model analyses of changes in PD and AlzD over time

The results of repeated measures analyses of variance are presented in Table 8. As observed in the independent sample *t*-tests, there was a significant increase in the prevalence of both disorders (PD: $F = 197.78$, $P < 0.001$; AlzD: $F = 147.24$, $P < 0.001$) over time. There was a significant effect of the baseline prevalence of all forms of depression on this increase for both PD and AlzD over time. In contrast, no such effect was observed for the frequencies of *SNCA* polymorphisms included in this study. These results are suggestive of a prospective relationship between the baseline levels of depression in a population and the subsequent risk of both PD and AlzD.

4. Discussion

The current study was conducted to strengthen the evidence supporting the association between depressive disorders, AlzD, and PD as well as to investigate the potential effect of functional polymorphisms of the *SNCA* gene on these associations, while adjusting for confounding factors. Significant associations were found between the prevalence of depressive disorders and that of both PD and AlzD at a cross-national level. When longitudinal methods of analysis were adopted, two out of the three analyses (cross-lagged regression and general linear models) were suggestive of a prospective association between depression and the subsequent risk of both neurological disorders (Table 3 and Table 8). These results are consistent with existing evidence on the shared pathogenic mechanisms for these disorders[80-83] and the results of longitudinal research in community samples demonstrating a prospective link between depressive disorders and neurodegenerative disorders[84-87]. Prior evidence has suggested that the links between depression and both PD and AlzD are mediated by genetic vulnerability[88-90] and exposure to environmental risk factors, such as stress and environmental toxins[91-93]. These two sets of risk factors do not operate in isolation. There is preliminary evidence that the development of subsequent PD is influenced by gene-environment interactions between genetic risk and diabetes mellitus as well as between genetic variants and pesticide exposure[74,94].

In this study, the cross-sectional association between dysthymia and each neurological disorder was stronger than that observed for MDD (Table 2), and dysthymia was the only form of depression that showed evidence of a prospective link with both PD and AlzD in the cross-lagged analyses (Table 3). Dysthymia is defined as a chronic form of depression, characterized by mild but persistent depressive symptoms that remain below the diagnostic threshold for MDD[95]. Many patients with dysthymia have superimposed episodes of MDD, in which this is referred to as "double depression"[96]. Dysthymia has not been studied as extensively as MDD in relation to PD or AlzD. According to available data, at least 13% patients with established PD fulfill the diagnostic criteria for dysthymia[97]. Furthermore, a study has found that 28% of AlzD patients qualify for a diagnosis of dysthymia[98]. The presence of dysthymia has also been found to be associated with the occurrence of extrapyramidal features

Table 8. General linear model analyses of changes in Parkinson's disease and Alzheimer's disease over the period 1990 – 2019

Variable	Time (1990 – 2019)	MDD	Dysthymia	Depression	*rs356220*	*rs2736990*	*rs3775439*
Parkinson's disease, change over time	197.78[a]	10.05[a]	47.30[a]	21.28[a]	3.89	3.69	0.66
Alzheimer's disease, change over time	147.24[a]	13.02[a]	30.98[a]	22.48[a]	1.21	2.47	0.68

MDD: Major depressive disorder. All test statistics were given as repeated measures analysis of variance (RMANOVA) or repeated measures analysis of covariance (RMANCOVA) test statistic (*F*). [a]Significant at $P<0.05$

in patients with AlzD[12]. Although no studies linking dysthymia to the levels of α-synuclein or *SNCA* gene have been done, a study of older adults with either depression or dysthymia has found evidence of abnormal dopamine transporter binding on single-photon emission computed tomography (SPECT), and these alterations are associated with prodromal features of PD[99]. In a similar imaging study comparing patients with MDD alone and those with MDD superimposed on dysthymia (double depression), ligand binding to striatal dopamine transporters was found to be inversely correlated with illness duration only in the double depression group[100]. These findings, although few in number, are consistent with the possibility of a shared "hypodopaminergic" phenotype, characterized by specific neuropsychological deficits, that can be identified in patients with depressive disorders, AlzD, and PD[80]. It is possible that some cases of dysthymia may reflect an early or prodromal stage of neurodegenerative disorders linked to dopaminergic deficit. This possibility is also supported by the overlap between some of the core symptoms of dysthymia, such as fatigue and apathy, and the non-motor symptoms of PD[101]. When adjusting for PM2.5 levels and pesticide exposure in the present study, the relationship between dysthymia and both PD and AlzD remained significant. This suggests that depressive disorders and environmental toxins may independently influence the risk of neurodegenerative disorders, similar to what earlier studies have discovered[102].

When examining the relationship between the allele frequencies of specific *SNCA* SNPs in the current study, it was found that the distributions of all three SNPs (*rs356220*, *rs2736990*, and *rs3775439*) were significantly correlated with the prevalence of depression, PD, and AlzD at both time points (Table 4). With the exception of dysthymia in 2019, the strengths of the observed correlations were almost identical in 1990 and 2019, which is consistent with the relatively "fixed" effect that would be expected from specific vulnerability loci. After adjustment for confounding factors, the *rs3775439 A→G* polymorphism remained significantly associated with depression, PD, and AlzD. These results should be interpreted with caution in view of the minimal number of countries for which data were available (n = 18–32). However, they are consistent with the hypothesis of a shared genetic vulnerability for these disorders. A large-scale analysis of genome-wide association data has found plausible evidence that the *SNCA* gene is involved in the shared genetic vulnerability for PD and AlzD[103], and recent evidence has implicated the *SNCA* gene in the pathogenesis of depressive disorders[59]. Although a definitive causal association cannot be established through the current results, they do provide some support to the growing body of evidence implicating α-synuclein in the pathophysiology of depression[47-49] and AlzD[16,104,105]. The links between *SNCA* and both PD and AlzD were not significant after correcting for the prevalence of MDD; however, they remained significant after adjusting for dysthymia. When taken in conjunction with the results of direct bivariate correlations between *SNCA* distributions and depression, the following tentative interpretation can be advanced: certain functional polymorphisms of *SNCA* may be a shared risk factor for MDD, PD, and AlzD, and they may interact with dysthymia to influence the subsequent risk of both neurological disorders. Although it is intriguing and consistent with recent clinical evidence[17], this association is purely ecological in nature and requires careful evaluation in clinical and community samples.

The analysis of gene-environment interactions based on ecological data has certain shortcomings, and such results should be interpreted with caution[106]. Therefore, these analyses were considered a secondary objective in the current study. After taking air pollution and pesticide exposure into account, two of the studied polymorphisms (*rs356220* and *rs2736990*) were no longer associated with either PD or AlzD, suggesting that if these genes do truly represent vulnerability factors for either disorder, they do so only in association with exposure to environmental toxins. However, this was not observed in the case of *rs3775439*, thus suggesting the absence of such an interaction (Table 4). An earlier case-control study of patients with PD has found that the gene-environment interaction between exposure to ambient nitrogen dioxide (NO_2) and the functional polymorphism of *IL1β* gene is significant associated with the risk of PD[107]. It is possible that similar effects may occur in the case of *SNCA* gene variations, but this cannot be conclusively deduced from the current results.

Certain key limitations of the current study should be borne in mind. First, as the study was based on cross-national estimates, there may be a certain level of

uncertainty or error in each parameter that could affect the certainty of any conclusions drawn from these results. Second, any conclusions regarding causation should be considered provisional: evidence of significant cross-sectional or cross-lagged correlations does not necessarily imply a causal chain linking genetic variations, depressive disorders, and neurodegenerative disorders. Third, as the estimates used in this study covered countries in whole, they cannot account for variations within a country, such as urban/rural differences in particulate matter pollution or pesticide exposure. Fourth, the number of cases available for population genetic analysis was relatively low, and it was based on a relatively small number of volunteers who were willing to participate in research on allele frequencies. Fifth, the results obtained at the national level cannot be extrapolated directly to individuals. Sixth, since the research focus was on α-synuclein, other genes that may be involved in mediating the link between depression, environmental toxins, and neurodegenerative disorders, such as those involved in dopaminergic transmission or inflammation, were not analyzed. Finally, the effects of other environmental factors that may be associated with both AlzD and PD, such as diet, smoking, and other occupational exposures, could not be assessed in a study of this sort due to a lack of large-scale, cross-national data.

It should also be noted that epidemiological findings, even if replicated, represent a starting point for further research and not an end in themselves. To translate these findings into improved diagnostic and early intervention strategies, a deeper understanding of the molecular links between depression and neurodegeneration as well as the gene-environment interactions mediating these links is required. Innovative approaches aimed at elucidating this association include studies of epigenome or transcriptome[108,109] and genome-wide association studies that identify shared genetic components across these disorders[110]. The associations between the normal processes involved in brain aging and those implicated in neurodegeneration also represent a fruitful line of inquiry, given that depression may be associated with both these phenomena[111]. Such research would build on the foundations laid by epidemiological and genetic association studies and lead to a precision medicine-based approach to early intervention in PD and AlzD.

5. Conclusion

Despite certain inherent methodological limitations, the current study provides some evidence of a significant association between depressive disorders, particularly dysthymia, and the subsequent risk of PD and AlzD. This relationship may be partly related to the functional variants of the α-synuclein gene *SNCA*, either alone or in combination with exposure to environmental toxins. Although these results cannot be taken as definitive, they highlight the need for further investigations into the molecular mechanisms underlying this relationship. These results may be of value to those examining the shared pathophysiological basis of these conditions and pave the way for early intervention or preventive strategies for both PD and AlzD.

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Conflict of interest

The author declares that he has no competing interests.

Author contributions

This is a single-authored manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All the data used in this study were obtained from public domain databases that have been cited in the paper. A complete data sheet is available from the author, without undue reservation, on request.

Further disclosure

This paper has been uploaded to or deposited in a preprint server at *Preprints* (doi: 10.20944/preprints202209.0197.v1). However, the current paper is a substantial revision of the preprint and contains new results (longitudinal analyses) that were not included in the original preprint.

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ACCSCIENCE PUBLISHING

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CASE REPORT

Choreoathetosis of the upper limb with contralateral substantia nigra lacunar infarction: A case report and literature review

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Abstract

Choreoathetosis of the upper limb as the first manifestation of contralateral substantia nigra (SN) lacunar infarction is extremely rare. We report a case of choreoathetosis of the right upper limb in a 60-year-old man with SN infarction. Emergency brain magnetic resonance imaging showed discrete lacunar infarction localized in the left SN. Magnetic resonance angiography showed atherosclerotic stenosis of the basilar artery and the left posterior cerebral artery. He was diagnosed with contralateral SN infarction and then treated with antiplatelet, loading-dose statins, and allopathic therapy to achieve a positive outcome. During the follow-up period, there was no recurrence of stroke, and his symptom of choreoathetosis resolved. More cases alike should be studied to achieve satisfactory outcomes through early diagnosis and appropriate treatments.

Keywords: Substantia nigra; Dance-like movements; Ischemic stroke

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1. Introduction

Substantia nigra (SN), a dopaminergic nucleus located in the midbrain, plays a key role in regulating motor movements. The previous studies have indicated that ischemia in distal brain regions may cause delayed neurodegenerative changes, such as hyperkinetic and hypokinetic syndromes (especially vascular parkinsonism)[1]. However, the previous literature has suggested an inconsistency in the incidence of cerebrovascular disease-related movement disorders due to the different perception of its scope. According to Alarcón *et al*., the incidence of post-stroke dyskinesia in 2004 was 3.7%[2]. Tater *et al.* have suggested that 1 –4% of all stroke patients may present with movement disorders[3]. In particular, there have been several reports of choreoathetosis associated with lacunar infarction involving the SN. In this article, we report an unusual case of the right upper limb choreoathetosis with primary SN infarction and review the relevant literature.

2. Case presentation

We report an interesting case of acute choreoathetosis as the presenting symptom of acute ischemic stroke in a 60-year-old man, which lasted for 5 days. It was characterized by involuntary, irregular, and continuous circular movement of the right upper limb, with the shoulder joint as the axis. The frequency and the duration were uncertain. According

to the patient, grasping the affected limb with his left hand prevented the attack. Although there was no disturbance of consciousness, slurred speech, clenched teeth, and salivation at the corners of his mouth, he experienced numbness. The aforementioned symptoms affected his daily life. The patient had no significant medical history. A physical examination on admission revealed that he had a temperature of 36.4°C, a heart rate of 80 beats/min, a respiratory rate of 18 breaths/min, and a blood pressure reading of 140/80 mmHg. Cardiopulmonary and abdominal examination showed no obvious abnormalities. Neurological examination indicated that he was fully conscious and oriented. Bilateral pupils, about 3 mm in diameter, were sensitive to light reflex. Except for the involuntary dance-like movements of the right upper limb, there were no positive signs.

A high-intensity lesion in the left SN was revealed by diffusion-weighted magnetic resonance imaging (MRI), as shown in Figure 1. Magnetic resonance angiography (MRA) showed basilar artery (BA) and posterior cerebral artery (PCA) stenoses, as shown in Figure 2. No atherosclerotic changes were observed via carotid ultrasound. Electrocardiogram was normal, and there was no potential cardiac source of embolism or right-to-left shunt detected by transthoracic and transesophageal echocardiography.

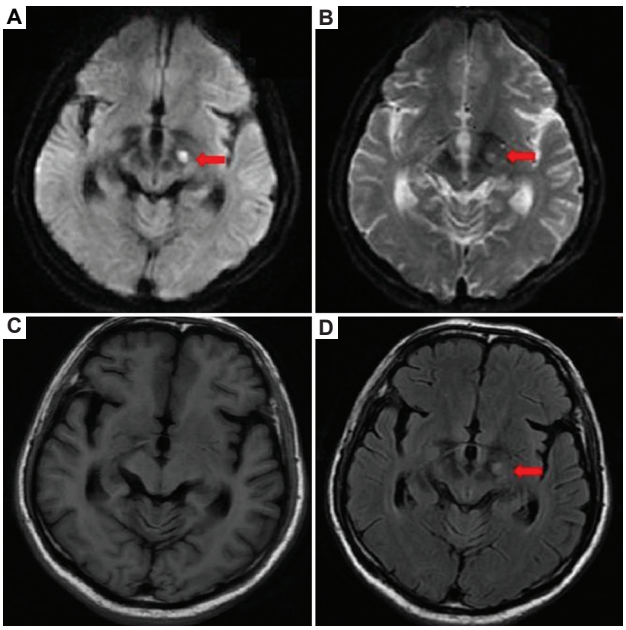


Figure 1. Magnetic resonance imaging indicating a discrete lacunar infarction in the left substantia nigra (SN). (A) Diffusion-weighted imaging (DWI) showing a new infarct in the SN of the left cerebrum. (B) An image of DWI sequence (b0), which is similar to a fast-scan T2WI sequence. (C) No abnormal signals in T1-weighted image. (D) T2-weighted image/fluid-attenuated inversion-recovery (FLAIR) showing a high-signal lesion located in the left SN.

Laboratory examinations showed no abnormalities besides hemoglobin A1c and glucose levels. The levels of C-reactive protein, erythrocyte sedimentation rate, liver and renal function, blood lipid, electrolytes, homocysteine, coagulation indices, including antithrombin III, prothrombin time, activated partial thromboplastin time, and D-dimer, were all within normal limits. Antinuclear antibody, anti-dsDNA antibody, anti-Smith (Sm) antibody, anti-SS-A/B antibody, proteinase 3 antineutrophil cytoplasmic antibody (PR3-ANCA), myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA), as well as beta-2-glycoprotein I, human immunodeficiency virus (HIV), and syphilis antibodies were all negative. The laboratory results are shown in Table 1. The patient was diagnosed with contralateral SN infarction and was started on antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg orally once daily for 21 days, followed by long-term maintenance of aspirin 100 mg. He was also given oral atorvastatin calcium tablets 20 mg once daily to the lower lipid levels and stabilize atherosclerotic plaques. The patient took oral metformin 500 mg twice/day and gliclazide 30 mg once a day for Type 2 diabetes. To control the involuntary movements of his right upper limb, he was given thiopride 50 mg thrice daily, and the dose was gradually increased to 100 mg; when his symptom was significantly alleviated, the dosage of thiopride was tapered until discontinuation. There were significant improvements in choreoathetosis and no recurrent strokes over a 6-month follow-up period post-discharge.

3. Discussion

Acute stroke is a common and prevalent clinical condition, which is characterized by sudden focal neurological deficit. Its clinical presentations vary depending on the site of involvement. The most common symptoms are facial weakness involving the mouth, slurred speech, paralysis, and sensory impairment, followed by dizziness, headache, choking after drinking, dysphagia, ataxia, and even loss of consciousness in severe cases. Movement disorders may be caused by small vessel disease in the middle or posterior cerebral artery territory supplying the basal ganglia[4,5].

Choreoathetosis of the right upper limb refers to the simultaneous occurrence of dance-like movements and athetosis, in which the latter is characterized by slow, twitchy, and peristaltic involuntary movements of the distal extremities, which may assume a variety of abnormal postures. However, the symptom usually resolves spontaneously over time. Despite specific anatomical and imaging evidence supporting its diagnosis, choreoathetosis, as a broad disease spectrum, is an uncommon manifestation of acute stroke. To better

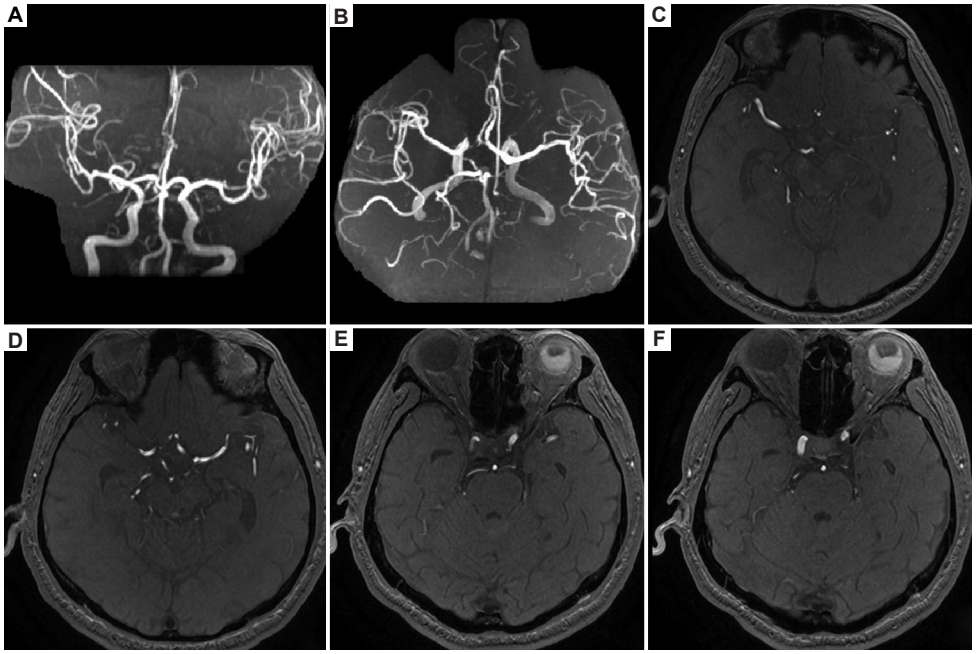


Figure 2. Cerebrovascular imaging of the patient. (A and B) Magnetic resonance angiography revealing atherosclerotic stenosis of the basilar artery and the left posterior cerebral artery (PCA). (C–F) Four images showing the cross-sectional images of BCA and PCA, with observable left PCA stenosis.

understand these conditions, we searched PubMed for reports using several keywords, such as "SN," "ischemic stroke," "dyskinesia," "movement disorders," "motor deficit," and so on. Table 2 is a summary of several patients with SN infarction presenting with movement disorders[6-14]. Nine patients were reviewed (excluding the present patient), including six male and three female patients, age ranging from 18 to 83. All patients exhibited symptoms similar to Parkinson's disease. Six patients presented with static tremor, four with bradykinesia, and three with rigidity. Besides these symptoms, other symptoms such as apathy, speech disorder, and panic gait also occurred. With regard to their previous medical history, there were six cases of hypertension, one case of diabetes, one case of hyperlipidemia, one case of myocardial infarction with atrial fibrillation, one case of cerebral infarction, and one case of subarachnoid hemorrhage.

However, the patient reported in this paper presented with choreoathetosis in contrast to the Parkinson's-like symptoms. This case caught out attention since there have not been any similar reports in the literature we reviewed. In this case, functional imaging examination was not performed to verify the motor dysfunction of the patient. However, the acute onset, rapid progress, and existence of risk factors for cerebrovascular disease suggested the different causes of choreoathetosis. Therefore, there is sufficient evidence to prove that the patient's clinical manifestation was in fact caused by the lacunar infarction located in the SN.

The pathogenesis of hyperactivity disorders may be related to elevated monoamine activity and/or relative cholinergic deficiency, or even the dysfunction in the cerebellum-thalamic or striatum-thalamic pathway[8]. The nucleus basalis is a group of grey matter nuclei under the cerebral cortex, consisting of the caudate nucleus, the shell nucleus, the pallidum, the subthalamic nucleus, and the SN[15]. It regulates motor function mainly through the cortico-basal ganglia-thalamo-cortical loop. In this loop, the neostriatum receives afferent fibers from the sensorimotor cortex of the brain, and its efferent fibers reach the basal ganglia output structures (globus pallidus internus [GPi]/substantia nigra reticularis [SNr]) through direct and indirect pathways. The direct pathway refers to the excitatory projection of glutaminergic nerve fibers from the cerebral cortex to the striatum, which, in turn, sends inhibitory projections of gamma-aminobutyric acid (GABA) nerve fibers to the GPi and SNr complexes. The GABA nerve fibers emanating from the latter can emit inhibitory projection to the ventrolateral thalamic nucleus[16]. When infarcts occur in the SN, the projection function of both the thalamus and the thalamic cortex is enhanced because of the reduced GPi-SNr complex activity. The motor impulses that generate in the cortex cannot be terminated, and it cannot receive impulses from the cerebellar-red nucleus-striatal pathway, thus leading to the development of choreoathetosis. From the perspective of neurotransmitters, the excitatory and inhibitory effects of neurotransmitters on neurons are in a coordinated

Table 1. Results of laboratory investigations.

Parameter	Result (Reference range)
CRP	<0.50 mg/L (0 – 10)
WBC	9.17×10^9/L (3.5 – 9.5)
RBC	4.62×10^{12}/L (4.3 – 5.8)
HGB	138 g/L (130 – 175)
PLT	236×10^9/L (125 – 350)
ESR	3.8 mm/h (0 – 15)
PT	9.6 s (9 – 14.5)
APTT	28.8 s (22.5 – 40.5)
TT	17.00 s (14 – 21)
D-dimer	0.320 mg/L (0 – 0.5)
INR	0.82 (0.8 – 1.5)
ALT	13.0 U/L (9 – 50)
AST	13.0 U/L (15 – 40)
GLU	12.28 mmol/L (3.8 – 6.1)
HbA1c	9.3% (4.2 – 6.2)
UA	134.0 μmol/L (135 – 425)
CREA	71.0 μmol/L (59 – 104)
CHOL	5.59 mmol/L (2.8 – 6.0)
TG	0.46 mmol/L (0.56 – 1.71)
HDL-C	1.73 mmol/L (1.2 – 1.68)
LDL-C	3.41 mmol/L (2.07 – 3.1)
Hcy	6.15 μmol/L (5 – 14)
HBsAg	Negative
HCVcAg	Negative
A-HCV	0.010 AU/mL (0 – 5)
HIV combi PT	0.010 AU/mL (0 – 1)
TP-CLIA	0.240 mIU/mL (0 – 10)
ANA	Negative (<1:100)
Anti-SSA	4.0 AU/mL (0 – 120)
Anti-SSB	23.0 AU/mL (0 – 120)
Anti-Sm	42.0 AU/mL (0 – 120)
Anti-dsDNA	70.0 AU/mL (0 – 120)
RF	1.2 IU/mL (<20)
ASO	18.0 IU/mL (<200)
Anti-PR3	3.0 AU/mL (<120)
Anti-MPO	3.0 AU/mL (<120)
Anti-GBM	1.0 AU/mL (<120)
AKA	Negative
Anti-CCP	1.1 AU/mL (< 120)

A-HCV: Hepatitis C antibody; AKA: Antikeratin antibody; ALT: Alanine transaminase; ANA: Antinuclear antibody; anti-CCP: Anti-citrullinated protein antibody; anti-MPO: Anti-myeloperoxidase antibody; anti-PR3: Anti-proteinase-3 antibody; APTT: Activated partial thromboplastin time; ASO: Antistreptolysin O; AST: Aspartate transaminase; CHOL: Cholesterol; CREA: Creatinine; CRP: C-reactive protein; anti-dsDNA: Anti-double stranded DNA antibody; ESR: Erythrocyte sedimentation rate; anti-GBM, anti-glomerular basement membrane antibody; GLU, glucose; HbA1c, hemoglobin A1c; HBsAg: Hepatitis B surface antigen; HCVcAg: Hepatitis C virus core antigen; Hcy: Homocysteine; HDL-C: High-density lipoprotein cholesterol; HGB: Hemoglobin; HIV: Human immunodeficiency virus; INR: International normalized ratio; LDL-C: Low-density lipoprotein cholesterol; PLT: Platelet; PT: Prothrombin time; RBC: Red blood cell; RF: Rheumatoid factor; anti-Sm: Anti-Smith antibody; anti-SSA: Anti-Sjögren's syndrome antigen A antibody; anti-SSB: Anti-Sjögren's syndrome antigen B antibody; TG: Triglyceride; TP-CLIA: Chemiluminescence immunoassay for *Treponema pallidum*; TT: Thrombin time; UA: Uric acid; WBC: White blood cell

and unified state. The motor function downstream of the basal ganglia circuit is regulated through two transmitters, dopamine (DA) and acetylcholine (Ach), which control the output of excitatory and inhibitory signals[17]. It is known that early ischemic stimulation of neurons increases the synthesis of neurotransmitters, while nerve terminal synapses practically lose their effect on the storage and reuptake of neurotransmitters, resulting in the release of large amounts of neurotransmitters into the synaptic gap. In a physiological state, the synthesis, release, degradation, and reuptake of DA are a dynamic equilibrium process, which depends on the adenosine triphosphate (ATP) energy supply. When cerebral ischemia occurs, neuronal energy metabolism is impaired, leading to decreased Na^+-K^+-ATPase activity. The automatic depolarization of neurons triggers a spontaneous release of DA from nerve terminal vesicles; a large amount of DA is thus released into the intercellular space. In addition, normal synaptic release is dependent on intracellular calcium ion (Ca^{2+}) levels. Since ischemia causes Ca^{2+} influx, it prompts the release of DA. The transmitters released into the synaptic gap are metabolized by two pathways: Reuptake and monoamine oxidase (MAO). During ischemia, there is reduced MAO activity, decreased degradation of DA, and inhibition of reuptake, resulting in increased DA and excitability. This is consistent with the research results of Brannan *et al.*[18]. In addition, acute cerebral ischemia/reperfusion experiments have demonstrated a significant reduction in hippocampal Ach levels during acute cerebral ischemia[19]. Nigrostriatal lesions can also impair the function of the striato-nigral-striatal loop, which may result in an imbalance between DA and Ach. The function of dopaminergic neurons becomes relatively hyperactive, whereas Ach levels are reduced due to decreased choline acetyltransferase activity. With the aggravation of ischemia, the neuronal damage is aggravated, and the synthesis and release of DA are inhibited. Therefore, movement disorders caused by stroke usually resolves spontaneously over time[20]. The above mechanisms play a joint role in the occurrence of the disease.

Although the diagnosis of this patient was apparent, this kind of infarction associated with choreoathetosis is extremely rare and varies greatly among individuals. It is difficult for clinicians to make this diagnosis through medical history, symptoms, signs, and ancillary examination results. The previous literature has indicated that there is an ongoing debate on the pathogenesis of choreoathetosis and whether or not it is an epileptic syndrome. In this case, the patient did not undergo electroencephalogram (EEG) examination or any experimental treatment with antiepileptic drugs. To summarize the clinical features of this type of disease, more case studies are needed.

Table 2. Previous reports of substantia nigra infarction.

Literature	Sex	Age	Clinical symptoms/manifestations	Medical history
Robles[6]	Female	68	Bilateral lower limb resting tremor	Hypertension and dyslipidemia
Ohta and Obara[7]	Male	61	Bradykinesia, cogwheel rigidity, and resting tremor of the left hand	Hypertension
Hunter *et al.*[8]	Male	62	Right-sided parkinsonism characterized by rigidity and flexion	Hypertension
Kim and You[9]	Female	71	Akinetic mutism and decreased speech, movement, and emotional reactions	Hypertension, diabetes, and old cerebral infarction
Orta Daniel and Ulises[10]	Female	45	Bradykinesia, hypomimia, hypophonia, dysarthria, hypokinesia, rigidity in the neck and all four limbs, resting tremor in the left arm, and festinating gait	Systemic lupus erythematosus
Gonzalez-Alegre[11]	Male	18	Parkinsonian tremor in the contralateral foot	Subarachnoid Hemorrhage
Akyol, Akyildiz , and Tataroglu[12]	Male	80	Bradykinesia, resting tremor of the left hand, and tremor of the lower limbs in an upright position, particularly in the left leg	–
Caparros-Lefebvre *et al.*[13]	Male	70	Biballism or paraballism	Hypertension
McKee *et al.*[14]	Male	83	Visual hallucinations, disordered sleep, and mild cognitive impairment	Myocardial infarction with atrial fibrillation

4. Conclusion

We present a case of choreoathetosis as the first manifestation of an ischemic lesion involving the contralateral SN. In our reported case, it is of concern that the localization of lesion shown by MRI, DWI, and MRA is associated with the sudden specific clinical symptom. This enlightening case suggests that clinicians should consider the possibility of ischemic stroke in the contralateral nigrostriatal pathway in patients presenting with sudden and rapidly progressive dance-like movements.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Yanqiang Wang
Investigation: Mengxin Li and Xiaojun Zhang
Supervision: Yanqiang Wang
Writing – original draft: Mengxin Li and Yanqiang Wang
Writing – review & editing: Mengxin Li and Yanqiang Wang

Ethics approval and consent to participate

Written consent was obtained from the patient. The Medical Ethics Committee of the Affiliated Hospital of Weifang Medical University approved the study. The approval number is wyfy-2022-ky-182.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of data

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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Type of file	File format	Requirements	Included items
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(2) Title page and back matter *	DOC or DOCX	- Use 1.5-spacing and format text in one column - Font and size: Times New Roman, 12	**<u>On the first page (title page):</u>** - Manuscript title - Authorship list (first and last names must be spelled out) - Author's affiliation, including department, institution, city, state, postal code, and country (indicated with superscript number) - Corresponding author information, including asterisk indication, mailing address and email - Indication of equally contributing authors (if any) with dagger symbol **<u>On the second page (back matter):</u>** - Acknowledgments - Funding - Conflict of interest (mandatory) - Author contributions (formatted as per CRediT) - Further disclosure about presentation of essential findings in conference(s) and/or upload of the paper to a preprint server
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A review article provides scholarly survey as well as balanced summarization and highlights of recent developments in a research field or emerging/future trends. Authors should ensure that all perspectives from different works are linked in balanced and cohesive manner, taking into consideration different schools of thought.

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An editorial piece is a solicited, concise commentary that highlights prominent topics in particular issue. Alternatively, an editorial represents the official opinions of the editors on the journal or special issue.

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Use sentence case capitalization in all aspects of the submission. In sentence case, most major and minor words are lowercase (proper nouns, including name of organizations and name of guidelines, are an exception in that they are always capitalized for the first letter of each word, except for minor words, such as conjunctions and short prepositions). The first letter of the first word should always be uppercase.

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The title should capture the conceptual significance for a broad audience. The title should not be more than 50 words and should be able to give readers an overall view of the paper's significance. Titles should avoid using uncommon jargons, abbreviations and punctuation.

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Write in italics. *Advanced Neurology* highly encourages the use the recommended names found in the gene nomenclature databases, for instance, **HUGO Gene Nomenclature Committee**.

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Younger P, 2004, Using the internet to conduct a literature search. *Nurs Stand*, 19(6): 45–51.

Journal article (print) with more than 3 authors:

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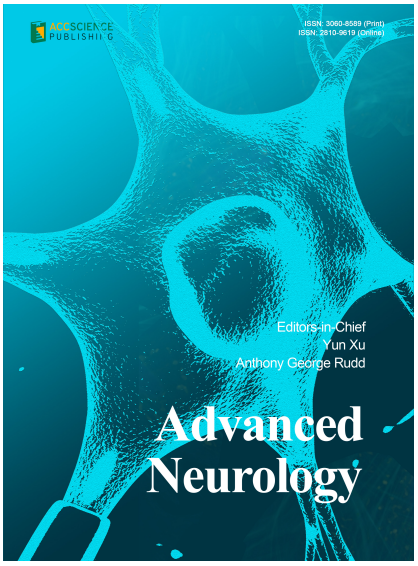
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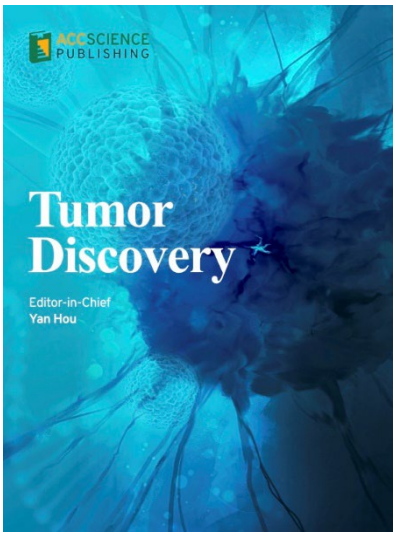
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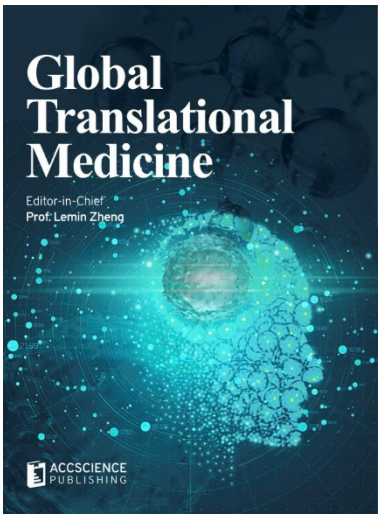


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