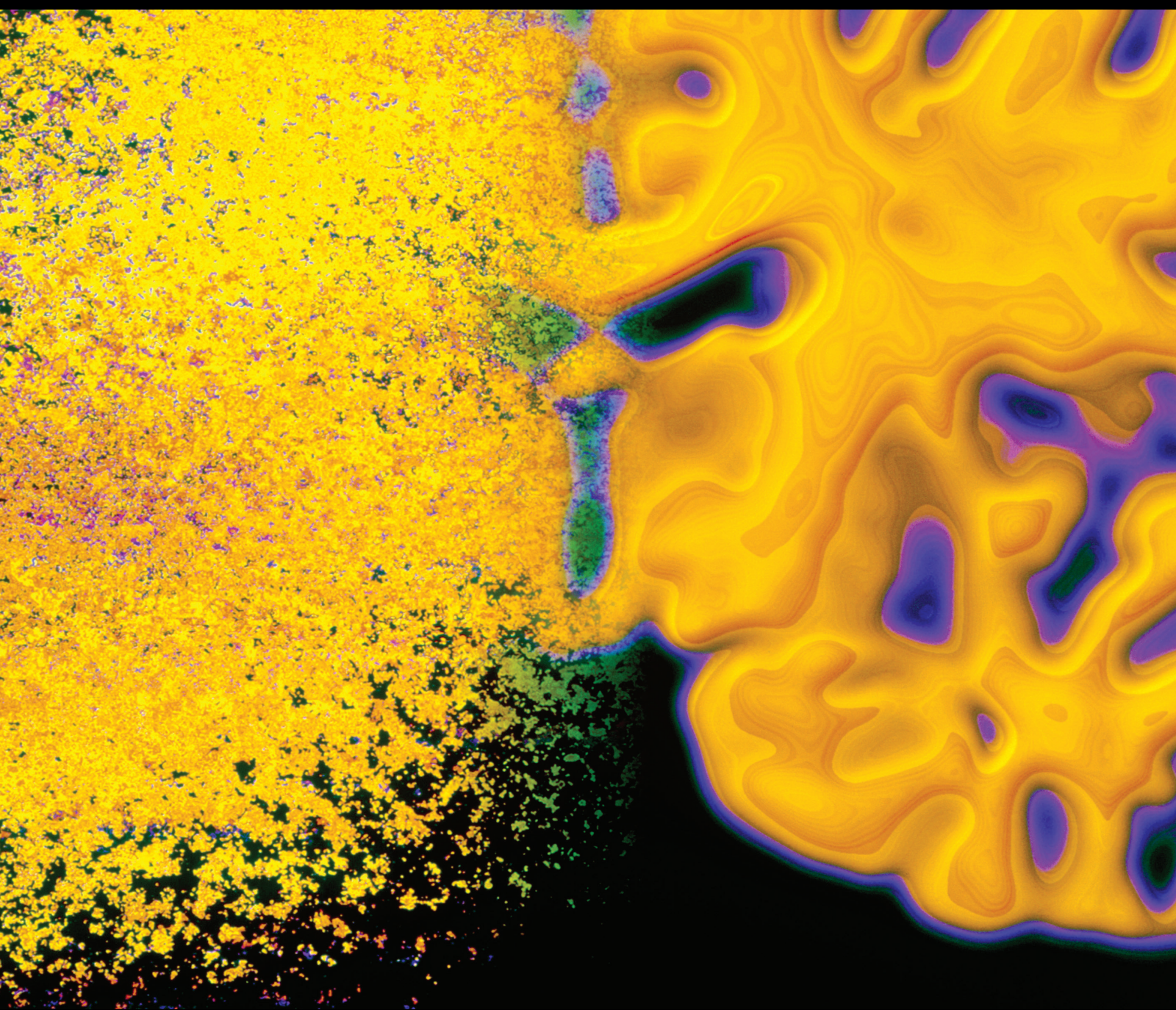
Behavioural Neurology

Behavioural and Cognitive Changes in Lewy Body Dementias

Lead Guest Editor: Woon-Man Kung
Guest Editors: Ying-Jui Ho, Hiroshi Yoshizawa, Shinro Matsuo, and Cheng-Yu Wei



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Editorial

Behavioural and Cognitive Changes in Lewy Body Dementias

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Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) share many clinical and pathological features. They are therefore discussed together and referred to as Lewy body dementias (LBD).

Incidence of DLB seems low. It is plausible that a systematic review of population and clinical studies is more appropriate to estimate prevalence A recent interesting study addressed the mean prevalence of DLB to be 4.2% and 7.5% in community and healthcare unit, respectively [1]. Another epidemiological article showed the incidence rate of DLB in the United States to be 3.5 per 100,000 person-years but increased steeply to 31.6 per 100,000 person-years among people older than 65 years [2].

After rigorous peer review, we decided to include 10 manuscripts in this special issue, including both research studies and reviews. S.-K. Yang et al. reported the incidence of DLB in Taiwan to be 7.1 per 100,000 person-years while the comorbidity rates of hypertension and hyperlipidemia in DLB patients were higher in females than in males.

Another retrospective longitudinal study conducted by P.-H. Chen et al. implied that 17.2% of patients with mild cognitive impairment progressed to LBD, while older age and higher Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) were the associated risk factors of progression.

An extensive meta-analysis study conducted by Y.-C. Wang et al. evaluated and clarified the correlation between antidepressants and dementias.

Advanced age, male sex, and a family history of dementia are risk factors of DLB [3]. C.-K. Cheng et al. further discovered evidence demonstrating that metabolic risk factors are important to DLB, and DLB might have higher risk of ischemic stroke, basing on large-scale nationwide, population-based information obtained from the Taiwan National Health Insurance Research Database.

C.-Y. Lee et al. reported the first review article to date focusing on the quality of life in DLB patients.

Psychotic symptoms with recurrent visual hallucination and altered sleep and arousal behaviour are both important features of DLB [4]. In a retrospective registry study, R.-C. Tzeng et al. proposed a high incidence of 51.2% of DLB patients with delusional feature.

P.-C. Chan et al. further did a systemic review on this important issue. They summarized and reviewed the history, clinical manifestations, possible pathophysiologies, and treatment of DLB and REM sleep behaviour disorder (RBD).

Basic science inevitably is the cornerstone of clinical practice. Occipital hypometabolism is a hallmark feature in DLB [5]. By comparing FDG-PET images between DLB

patients and healthy subjects, D. Chen et al.'s laboratory investigated brain metabolism patterns in DLB patients.

Treatment of LBD is challenging in everyday practice. Ceftriaxone is a β-lactam antibiotic and was suggested to have a potential role in neurodegenerative diseases. By using manganese-enhanced magnetic resonance imaging (MEMRI) and immunohistochemistry, Professor Y.-J. Ho et al. found that ceftriaxone treated DLB rat with improved neuronal density and activity in the hippocampal CA1 area, suppressed hyperactivity in the subthalamic nucleus, and reduced α-synuclein accumulation.

Hericium erinaceus is an edible mushroom with medicinal and some important physiological components [6]. I.-C. Li et al.'s laboratory reviewed the properties of the mycelia and suggested further research into its therapeutic role.

In this special issue, the authors aim to bring a multidisciplinary perspective and updated insight into the most recent advances in the field of LBD. We hope the efforts should progress our further understanding of the disease.

Conflicts of Interest

I declare that we have no conflict of interest or private agreements with companies concerning the manuscripts in this Special Issue.

Acknowledgments

The editors would like to express their deepest regards to all the featured authors for their informative high-quality contributions. Moreover, our most sincere appreciation is given to all the reviewers for their endless support yet valuable inputs. We are also deeply grateful to the journal for hosting and assisting in all aspects to make this special issue possible.

Woon-Man Kung
Ying-Jui Ho
Hiroshi Yoshizawa
Shinro Matsuo
Cheng-Yu Wei

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Research Article

Ceftriaxone Treatment for Neuronal Deficits: A Histological and MEMRI Study in a Rat Model of Dementia with Lewy Bodies

Ying-Jui Ho,[1] **Jun-Cheng Weng**,[2,3] **Chih-Li Lin**,[4] **Mei-Shiuan Shen**,[1] **Hsin-Hua Li**,[4] **Wen-Chieh Liao**,[5,6] **Nu-Man Tsai**,[7] **Ching-Sui Hung**,[8] **Te-Jen Lai**,[4,9] **and I-Yen Lee**[10]

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Dementia with Lewy bodies (DLB) is characterized by neuronal deficits and α-synuclein inclusions in the brain. Ceftriaxone (CEF), a β-lactam antibiotic, has been suggested as a therapeutic agent in several neurodegenerative disorders for its abilities to counteract glutamate-mediated toxicity and to block α-synuclein polymerization. By using manganese-enhanced magnetic resonance imaging (MEMRI) and immunohistochemistry, we measured the effects of CEF on neuronal activity and α-synuclein accumulation in the brain in a DLB rat model. The data showed that CEF corrected neuronal density and activity in the hippocampal CA1 area, suppressed hyperactivity in the subthalamic nucleus, and reduced α-synuclein accumulation, indicating that CEF is a potential agent in the treatment of DLB.

1. Introduction

Dementia with Lewy bodies (DLB) is a common neurodegenerative dementia, accounting for approximately 10%–25% of the dementia population. DLB patients show progressive cognitive decline and motor dysfunction. Psychiatric symptoms are reported in 99.2% of patients with DLB. DLB patients show higher subscores in the items of delusions, hallucinations, agitation, anxiety, irritation, and aberrant motor behavior, compared to the patients with Parkinson's disease dementia, which seriously affects their quality of life and social activities [1]. There is currently no rat model suitable for searching for more effective medications. In addition to the symptoms of progressive dementia and parkinsonism, accumulation of Lewy bodies in the central nervous system is the hallmark of DLB [2, 3]. Lewy bodies are cytoplasmic eosinophilic protein inclusions of α-synuclein (α-syn) [4–6]. β-Amyloid (Aβ) suppresses the clearance of α-syn [7, 8] and accelerates oligomerization of α-syn and its toxicity, leading to the deterioration caused by α-syn [9]. Moreover, direct or indirect interactions of α-syn and Aβ promote their mutual aggregation and accumulation, disturb the function

of mitochondria, cause excessive glutamate release in the synapse, and eventually result in excitotoxicity and cell death in the brain [8]. That is, Aβ aggravates the neurotoxicity of α-syn in the brain [10].

Viral vectors carrying the *SNCA* gene can constantly express α-syn in the host. Some studies have injected these vectors into the hippocampus, cortex, and striatum of rats to model the pathological changes seen in DLB [9, 11]. The advantages of using viral vectors are low cost, fast model establishment, and high expression of genes. Additionally, specific regions of the brain that are of research interest may be targeted [12]. Although viral vectors can deliver specific genes to the brain tissues of the host, the use of the method to transfer genes to larger brain regions, such as the cortex, remains a challenge [13, 14]. In the present study, the α-syn gene vector was injected into the lateral ventricle of rats, which diffused with the flow of the cerebrospinal fluid, facilitated α-syn expression throughout the regions of the brain, and contributed to the establishment of a rat model for DLB.

There is currently no specific medicine for treating DLB. Because of the cognitive dysfunction in patients with DLB, memantine, an antagonist of N-methyl-D-aspartate (NMDA) receptors, is used to alleviate this symptom. This indicates the involvement of glutamatergic hyperactivity in the disease. Rothstein and colleagues found that ceftriaxone (CEF) increases the expression of glutamate transporter-1 (GLT-1), which can remove excessive glutamate released in the synaptic cleft, reduce excitotoxicity, and yield neuroprotective effects [15]. We have demonstrated that CEF treatment prevents the decrease of neuronal activity [16] and loss of neuronal density in the nigrostriatal system and in the hippocampus in a Parkinson's disease (PD) rat model [17, 18]. Moreover, an *in vitro* model of PD revealed that CEF binds with high affinity to α-syn and blocks its polymerization [19].

Manganese-enhanced magnetic resonance imaging (MEMRI) is a valuable imaging tool for directly measuring activity-dependent neuronal events in a living animal [20]. Manganese ion (Mn^{2+}) may enter neurons through voltage-gated calcium (Ca^{2+}) channels [21] where it is retained there with a biological half-life of 51–74 days according to a study of adult rats' brains [22]. Before MR imaging, the animal was injected intraperitoneally (i.p.) with $MnCl_2$, and its neurons took up Mn^{2+} when activated. A quantitative analysis indicated that Mn^{2+} accumulates in neurons according to their activity, because Ca^{2+} elevation is related to the firing activity in excitatory neurons [23]. In addition, its paramagnetic feature enables Mn^{2+} to shorten the longitudinal relaxation time (T1) of water protons and thus enhance the T1-weighted MR signal that is specific to the tissues where Mn^{2+} has accumulated [24], thus rendering it an excellent MRI-detectable contrast agent [25]. Therefore, tissue contrast in Mn^{2+}-induced T1 signal intensity in MEMRI may be contingent upon the differential accumulation of Mn^{2+} in active and silent brain regions in which topography can be absolutely quantified by measuring the absolute T1 (or $R1 = T1^{-1}$) value [23, 26].

When combined with pharmacological manipulation, MEMRI can be used to detect changes in neuronal activities that are produced by the treatment. However, whether changes of neuronal activity are accompanied by a loss of neurons in the DLB rat model remains unclear. The purpose of this study was to elucidate the effects of CEF (100 mg/kg/day) on neuronal density and activity in the brain of the DLB rat model using immunohistochemistry and MEMRI.

2. Materials and Methods

2.1. Animals. Twelve-week-old male Wistar rats (420 ± 30 g; $n = 25$; BioLASCO Taiwan Co Ltd., ROC) were randomly assigned to groups of 3 or 4 and housed in acrylic cages ($35 \times 56 \times 19$ cm^3) in a temperature-controlled animal room (21–25°C) with free access to food and water. Photoperiods in rodent rooms were controlled using an automatic timer set to provide 12 h of light (from 7:00 to 19:00) and 12 h of dark (from 19:00 to 7:00). To minimize defensive behaviors and stress response to the experimenter, prior to the start of the experiment, all animals were handled for 5 min/day on 2 consecutive days. All experimental procedures were performed according to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care Committee of Chung Shan Medical University (IACUC approval number 1455). All efforts were made to minimize animal suffering and to reduce the number of animals used [27].

2.2. General Procedures. For inducing DLB in the rat model, rats were randomly divided into three groups and underwent stereotaxic brain surgery on day 0 as described in our previous reports [8, 27]. Briefly, the rats were anesthetized by an i.p. injection of Zoletil (20 mg/kg; Virbac, Carros, France) and mounted in a stereotaxic frame. To overexpress α-syn, recombinant adeno-associated viral (rAAV) vector containing human α-syn gene, *SNCA*, (10 μg/10 μL/rat) was injected into the left lateral cerebral ventricle using the following coordinates adapted from the rat brain atlas: AP: −0.8 mm, ML: −1.5 mm, and DV: −3.6 mm from the bregma, midline, and skull surface, respectively. The $A\beta_{1-42}$ solution (5 μg/2.5 μL/side × 2 sides/rat) was bilaterally infused in the prefrontal cortex using the following stereotaxic coordinates: AP: 1.6 mm, ML: ±2.0 mm, and DV: −2 mm from the bregma, midline, and skull surface, respectively. During the 5 days after surgery, the rats were housed individually in plastic cages and 10% sucrose solution was provided ad libitum to prevent weight loss after surgery and reduce mortality.

Starting from the next day after the surgery (day 1), the animals received the following treatments: the "sham + saline" group ($n = 5$) and "DLB + saline" group ($n = 7$) were injected with saline (1 mL/kg/day, i.p.), and the "DLB + CEF" group ($n = 6$) was injected with ceftriaxone (CEF) (100 mg/kg/day, i.p.) (Roche, Kaiseraugst, Switzerland) for 27 days.

Hydrated manganese chloride ($MnCl_2 \cdot 4H_2O$, Sigma Aldrich, UK) was dissolved in saline at a concentration of 100 μmol/mL (20 mg/mL). On day 26, all rats received two 1 mL/kg i.p. injections of $MnCl_2$ solution separated by 1 h (total dose 40 mg/kg) [28]. Twenty-four hours later

(day 27), when Mn^{2+}-induced signal enhancement reached a stable asymptotic level [28], the rats were transported to the MR center for MR imaging, anesthetized during imaging, and transported back to the animal room.

On day 28, rats were euthanized by exposure to CO_2, transcardially perfused with phosphate-buffered saline (PBS) followed by 4% paraformaldehyde in PBS. The brain was then immediately removed and postfixed in PBS containing 30% sucrose and 4% paraformaldehyde at 4°C until use.

2.3. MEMRI Data Acquisition. Brain images were acquired on a 7T MRI system (Bruker BioSpec, Karlsruhe, Germany), as described in our previous paper [16]. Briefly, rats were initially anesthetized with 5% isoflurane vapor in oxygen at a flow rate of 500 mL/min. T2-weighted contrast of anatomical images was acquired using the turbo rapid acquisition with relaxation enhancement sequence. T1-weighted images were acquired using a multislice spin-echo sequence. To improve detection sensitivity over the full extent of Mn^{2+} concentrations, R1 images were acquired using a rapid acquisition with relaxation enhancement with variable time of repetition. Six sets of images corresponding to six TRs (ranging from 500 to 3500 ms) were taken during the recovery of the longitudinal magnetization to perform R1 mapping. The R1 maps shown in the paper are representations of the distribution of Mn^{2+} uptake in the region of interest (ROI) that were manually defined in the hippocampus and subthalamic nucleus (STN) in the coronal images. The mean signal intensity for all voxels in the ROIs, averaged for both hemispheres, was used to compare R1 differences between the groups.

2.4. Histological Assessment. For histological assessment, frozen coronal sections of the brain (25 μm thick) were cut and mounted on gelatinized slides and maintained in PBS until staining. The regions seen in the stained brain sections were identified according to the rat brain atlas [29] and used for image analysis to measure histological changes, as described previously [17, 28, 30–34]. The ROI was defined in the hippocampus (bregma −2.76 mm to −4.20 mm).

Nissl staining, which is used to identify pyramidal cells in the hippocampus, was performed as described in our previous reports [16, 17, 32]. α-Syn staining was used to evaluate the density of α-syn immune-positive cells in the brain sections [8, 35]. The coronal sections were rinsed (3×5 min each) with 0.05 M Tris buffer (TB), incubated for 20 min at room temperature with 0.3% hydrogen peroxide to block endogenous peroxidase activity, and blocked by incubation for 1 h at room temperature in 100% normal goat serum dissolved in TB containing 10% Triton-100. They were then incubated overnight at 4°C with polyclonal rabbit anti-α-syn antibody (1 : 100; GeneTex, USA) and incubated sequentially for 2 h at room temperature with HRP-conjugated goat anti-rabbit IgG (1 : 200; GeneTex, USA), followed by 5 min at room temperature with 3,3′-diaminobenzidine tetrachloride (DAB; Sigma, USA) before being dehydrated in ethanol and xylene. The stained sections of images were acquired using a microscope (ZEISS AXioskop 2, Germany). The density of neurons and α-syn-positive cells (number/mm^2) in the brain sections were counted using the Image Pro Plus Software 6.0 (Media Cybernetics, CA, USA) as described in our previous paper [16].

2.5. Data Analysis. SPSS 17.0 statistical software was used for data analysis. Analysis of variance (ANOVA) and the least-significant difference (LSD) post hoc test were used to analyze the data. All results are expressed as the mean ± standard error of the mean (SEM). The level of significance was defined as $P < 0.05$.

3. Results

3.1. Image Analysis. One-way ANOVA revealed significant differences in brain MRI images between the groups. Compared with the sham + saline group, the DLB + saline group showed decreased R1, Mn^{2+} uptake level in the hippocampal CA1 area ($F(2,17) = 3.79$, $P = 0.05$) (LSD post hoc test, P value = 0.03). However, normal Mn^{2+} uptake in the hippocampal CA1 area was seen after CEF treatment because no difference between the sham + saline and DLB + CEF groups was found (Figure 1). One-way ANOVA revealed significant differences in STN MRI images between the groups ($F(2,17) = 5.57$, $P = 0.016$). The LSD post hoc test revealed a higher Mn^{2+} uptake and neuronal activity in the DLB + saline group, compared with the sham + saline group ($P < 0.05$). The rats receiving CEF treatment showed the same neural activity in the STN as did the controls (Figure 2).

3.2. Histological Assay

3.2.1. Density of Pyramidal Neurons in the Hippocampal CA1. The ANOVA revealed that density of pyramidal neurons in the hippocampal CA1 showed a significant difference ($F(2,14) = 56.69$, $P < 0.001$), and post hoc analysis showed that rats in the DLB + saline group had a significantly lower neuronal density than did those in the sham + saline group ($P < 0.001$). The DLB + CEF group showed a higher neuronal density than the DLB + saline group ($P < 0.001$) (Figure 3).

3.2.2. Density of α-Syn in the Dentate Gyrus. The ANOVA revealed significant differences in the density of α-syn-positive cells in the hippocampal dentate gyrus (DG) ($F(2,14) = 3.91$, $P < 0.05$) (partial eta squared = 0.638), and post hoc analysis showed that rats in the DLB + saline group (152 ± 56 number/mm^2) had a significantly higher density of α-syn-positive cells compared with the sham + saline group (23 ± 10 number/mm^2) ($P < 0.05$). The DLB + CEF group (90 ± 32 number/mm^2) showed no difference in the density of α-syn-positive cells compared with the sham + saline group (Figure 4).

4. Discussion

In the DLB rat model, we found an accumulation of α-syn in the hippocampal DG and lowered neuronal density and activity in the hippocampal CA1 of the DLB + saline group compared with the sham + saline group. In addition, hyperactivity in the STN was also observed in DLB + saline rats. Treatment with CEF at a dose of 100 mg/kg corrected these

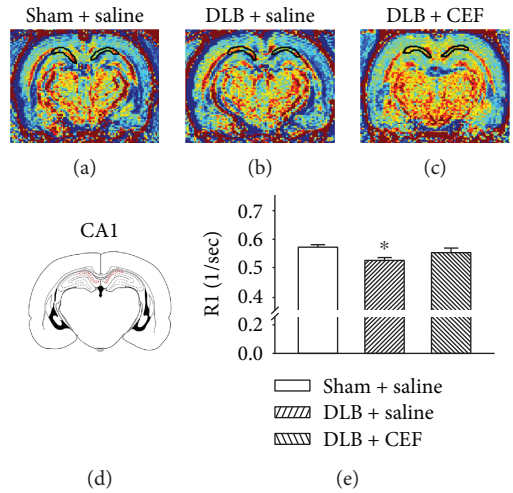

Figure 1: Effect of treatment with ceftriaxone (CEF) on neuronal activity in the hippocampal CA1 area of the DLB rat model. The rats were bilaterally infused with $A\beta_{1-42}$ in the prefrontal cortex and unilaterally infused with viral vectors with the *SNCA* gene in the left lateral ventricle to model DLB in rats. The sham + saline group and DLB + saline group were injected with saline (1 mL/kg/day, i.p.), and the DLB + CEF group was injected with CEF (100 mg/kg/day, i.p.) for 27 days. (a–c) Coronal R1 maps of the rat brain. The regions of interest used for quantitative analysis of Mn^{2+}-induced signal enhancement in the hippocampal CA1 area are indicated by the outlines on the schematic (d). (e) Quantitative results. Data are expressed as the mean ± SEM. $^{*}P < 0.05$, compared with the sham + saline group.

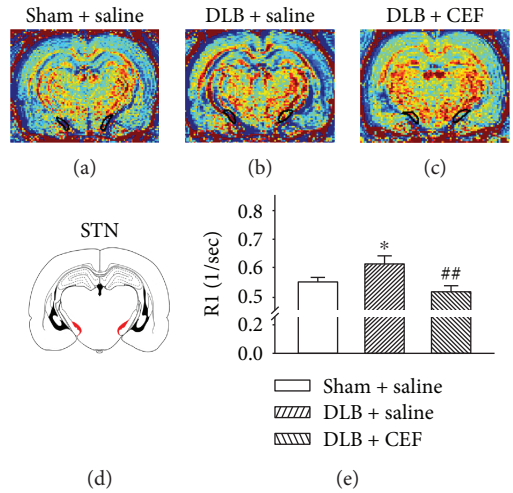

Figure 2: Effect of treatment with ceftriaxone (CEF) on neuronal activity in the subthalamic nucleus (STN) in the DLB rat model. The group names are the same as those in Figure 1. (a–c) Coronal R1 maps of the rat brain. The regions of interest used for quantitative analysis of Mn^{2+}-induced signal enhancement in the STN are indicated by the outlines on the schematic (d). (e) Quantitative results. Data are expressed as the mean ± SEM. $^{*}P < 0.05$, compared with the sham + saline group; $^{\#\#}P < 0.01$, compared with the DLB + saline group.

neuronal deficits. CEF was previously found to increase GLT-1 expression, resulting in sequestration of excess synaptic glutamate and protection of hippocampal neurons from excitotoxicity [36]. It has been reported that treatment with CEF prevented neurodegeneration in the hippocampus and nigrostriatal system, increasing neuronal activity [16] and improving cognitive function in an MPTP-induced PD rat model [17, 18]. We have previously reported that CEF, at the dosages of 100 and 200 mg/kg, per se did not affect motor function, cognitive behavior, and neuronal density in the hippocampus in healthy rats [17]. These results suggest that CEF can prevent DLB-related neuronal deficits in the brain.

The present study revealed that the injection of $A\beta$ and viral vectors with the *SNCA* gene into the brain caused an accumulation of α-syn, neuronal loss, and lowered neuronal activity in the hippocampus, suggesting that this method can induce a useful model of DLB. The pathophysiology of DLB is related to the aggregation of Lewy bodies and Lewy neurites that are formed by α-syn accumulation [37, 38], resulting in neurotoxicity and cell loss in the limbic system, brainstem, and cortical regions [5, 39, 40]. Although α-syn accumulation is the core pathological feature of DLB, the deposition of extracellular $A\beta$ is also observed in the brains of up to 80% of DLB patients [7]. Direct and indirect

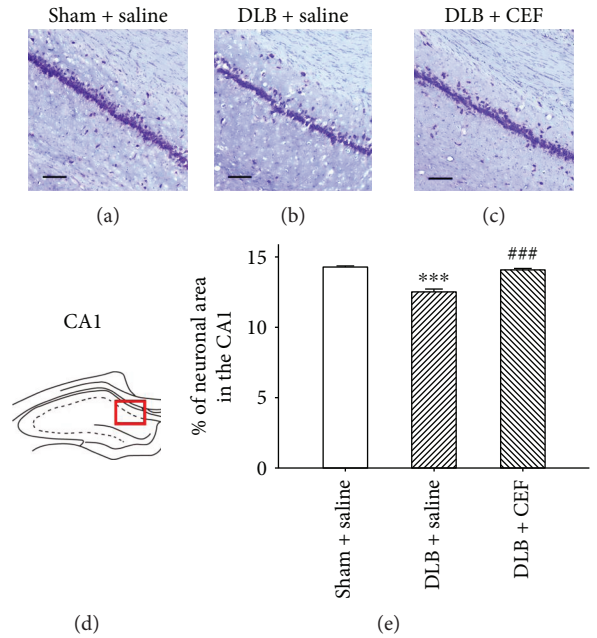

Figure 3: Effect of ceftriaxone (CEF) on the neuronal density in the hippocampal CA1 area of DLB rats. The treatment and group names are the same as those in Figure 1. (a–c) Coronal brain sections of the hippocampal CA1 area; pyramidal cells are revealed through Nissl staining. Magnification, 200x; bar, 100 μm. (d) CA1 region of the hippocampus. (e) Quantitative results. Data are expressed as mean ± SEM. $^{***}P < 0.001$, compared with the sham + saline group; $^{\#\#\#}P < 0.001$, compared with the DLB + saline group.

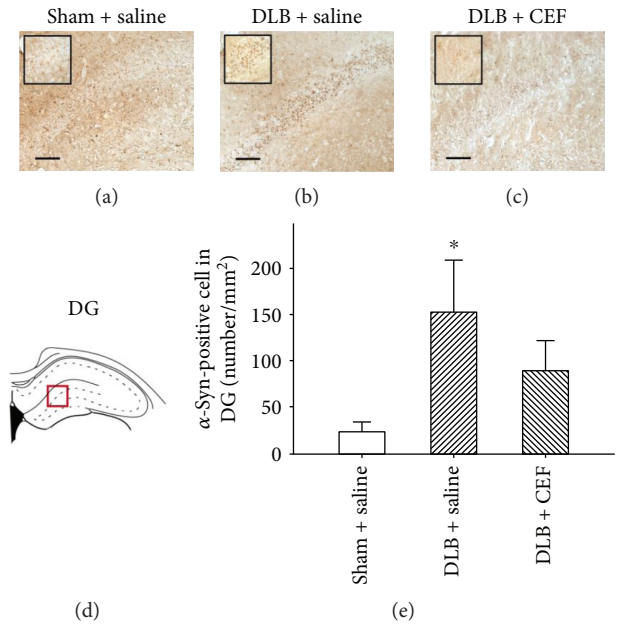

Figure 4: Effect of ceftriaxone (CEF) on the density of α-synuclein- (α-syn-) positive cells in the DG of DLB rats. The treatment and group names are the same as those in Figure 1. (a–c) Coronal sections in the DG. α-Syn-positive cells are indicated by anti-α-syn labeling in representative coronal sections. Magnification, 200x; bar, 100 μm. High magnification images (1000x) of α-syn-positive cells are shown in the insets. (d) The DG of the hippocampus. (e) Quantitative results. Data are expressed as the mean ± SEM. $^{*}P < 0.05$, compared with the sham + saline group.

interaction between α-syn and Aβ has been reported to promote α-syn aggregation [8]. Aβ increases the toxicity of α-syn [8] and aggravates the relevant defects triggered by α-syn, causing neurodegeneration [41]. Thus, in addition to injecting the α-syn gene vector into the rat's lateral ventricle, Aβ was also injected into the bilateral prefrontal cortex to more accurately model the pathological characteristics of DLB. In this study, the α-syn gene vector was injected into the lateral ventricle of rats, which diffused with the flow of the cerebrospinal fluid and facilitated the expression of

α-syn throughout the regions of the brain. A high level of α-syn accumulation was observed in the hippocampal DG area of DLB + saline rats, which may be involved in lower density of pyramidal neurons in the hippocampal CA1 because the abnormal accumulation of α-syn in the limbic system leads to cell loss and dysfunction in the hippocampus [42]. Reportedly, CEF binds to α-syn [19] and may thus block polymerization of α-syn and exert neuroprotective effects *in vitro* [19], which may underlie the effects of CEF on reducing α-syn accumulation and restoring neuronal density and activity in the hippocampus of DLB rats. The subject number in the study is relatively small. The level of α-syn in the DG of the hippocampus in the DLB + CEF group may be only partially reversed. To increase statistical power and to provide convincing treatment effect, further study using a larger number of subject is needed.

Aβ oligomers have been reported to play a pivotal role in synaptic impairment and neuronal degeneration [43]. Based on this amyloid hypothesis, the formation of soluble species of Aβ can directly interfere with memory formation and cause synaptic degradation, excitotoxicity, and cell death [44], leading to cognitive decline. Glutamate is one of the main excitatory neurotransmitters in the central nervous system, is involved in synaptic plasticity, memory, and learning, and plays a substantial role in the pathogenesis from the early stages of neurodegenerative diseases. To bind Aβ peptides, NMDA receptors have attracted considerable interest because of their toxic effects and involvement in neurodegeneration [45]. Aβ oligomers interfere with glutamatergic transmission. Under pathological conditions, elevation of Aβ levels blocks glutamate uptake at the synaptic cleft, leading to increased glutamate levels, stimulation of NMDA receptors [46], and activation of extrasynaptic NR2B-enriched NMDA receptors [45], causing an increase of intracellular calcium levels and the activation of metabolic pathways responsible for neuronal shrinkage, synaptic loss, and neurodegeneration [47]. Moreover, Aβ oligomers form complexes with alpha7-nicotinic receptors at presynaptic sites, causing increased levels of glutamate release, and they are involved in synaptic plasticity [48]. These factors indicate that Aβ is responsible for impairments of synaptic plasticity, cell loss, and neuronal death.

Glutamatergic hyperactivity can cause neurodegeneration [49, 50] and may thus be involved in the parkinsonism of DLB. STN neurons express glutamate, innervate the substantia nigra (SNc), and are hyperactivated in PD. Modulation of STN activity by deep brain stimulation improves parkinsonism, indicating that STN hyperactivity is associated with the development of parkinsonian features [51, 52]. STN hyperactivation increases glutamate release, causing excitotoxicity of dopaminergic neurons in the SNc [53]. In the present MEMRI-based study, we observed hyperactivity in the STN in the DLB + saline rats and found that this change was prevented with CEF treatment. This was consistent with our previous findings that CEF prevents dopaminergic and hippocampal degeneration in a PD rat model [17, 18]. We therefore suggest that CEF treatment reduced STN hyperactivity by increasing GLT-1 expression and glutamate reuptake and thus blocked neurodegeneration in the DLB rat model.

The risk of developing dementia in patients with DLB may increase with hippocampal cell loss, because the decline in cognitive function is associated with hippocampal degeneration [54]. Since that hippocampal CA1 is reported to be involved in working memory and cognition [55] and that neurogenesis is observed in the DG [56], dysfunction of the hippocampus may result in impairments of memory and recognition [57, 58]. The hippocampus shows vulnerability of excitotoxic damage due to rich of glutamatergic synapses [36]; excessive glutamate release and excitotoxicity-induced neurodegeneration in this region may lead to memory and recognition impairment, as seen in patients with DLB. The present study revealed hippocampal lesions in the CA1 of DLB rats, which was accompanied by lowered neuronal activity, as measured using MEMRI. Our another study found impairments in cognitive behaviors, for example, object recognition and avoidance learning, in the DLB rats, where deficits were improved after CEF treatment. (Data have been submitted for publication.) Regarding the clinical features of patients with DLB, in addition to cognitive dysfunction, motor impairment is also observed. However, in the experiment, the DLB rats did not exhibit motor dysfunction (data not shown). According to the "1-year rule," the consensus guidelines to distinguish DLB and PD dementia [59], if cognitive impairment occurs within 1 year following the onset of motor impairment or if cognitive impairment occurs earlier than motor impairment, DLB is diagnosed. Lack of motor impairment in the present study may be due to the short experimental period (only 28 days). The present histological findings showing increased α-syn-positive cells in the hippocampus of DLB rats are in line with that α-syn pathologies observed in the hippocampus of patients with DLB, which is associated with memory impairment [60]. Furthermore, increasing evidence supports that α-syn aggregates may be the real culprit, causing deficits in neurotransmission and neurogenesis in the hippocampus, which is considered to be involved in mechanisms for the hippocampal dysfunctions and associated neuropsychiatric manifestations in synucleinopathy [61]. CEF treatment prevented decreased neuronal density and activity in the area, indicating that CEF may have the potential for treating neurodegeneration and dementia in patients with DLB [17].

Increase of GLT-1 expression may be involved in the CEF-induced prevention of the loss of neuronal function in DLB rats. Excessive release of glutamate and hyperactivity of the glutamatergic system play a critical role in neuronal and behavioral symptoms in neurodegenerative diseases [62, 63]. GLT-1 is responsible for glutamate clearance [64–67] and thus prevents glutamate excitotoxicity [68–70]. In previous studies [17, 18], we found that CEF treatment caused a dose-dependent increase in GLT-1 expression in the brain, had a neuroprotective effect in the hippocampus and nigrostriatal dopaminergic system, and improved cognitive function. We thus suggest that upregulation of GLT-1 and reduction of excitotoxicity may underlie the neuronal protective effect of CEF. Further studies are needed to elucidate the downstream molecular pathway of CEF that modulates glutamate transmission and their neuroprotective effects.

MEMRI data associated with Mn^{2+} uptake are used to quantitatively evaluate neural activity, where R1 value represents the accumulation of Mn^{2+} in neurons [23]. Consistently, our data showed that MEMRI R1 values in the hippocampus reflect cell loss in the DLB rats and treatment effects of CEF against the disease [16]. Higher neuronal activities in the STN of the DLB + saline group indicated similar clinical and pathological characteristics associated with parkinsonism and neurodegeneration [71]. Elevation of STN activities (i.e., a burst pattern of neuronal firing) is also observed in patients with PD [72]. Our previous study found a significant positive correlation between MEMRI R1 and neuronal density in the hippocampus [16], indicating that R1 values in the hippocampus may serve as an indicator of neuronal density of the hippocampus in the DLB rat model. Although the present data revealed hippocampal lesions with abnormal neuronal activity 4 weeks after the surgery, it would be of interest to measure the changes long after the surgery, which would provide evidence to elucidate whether the DLB rat model shares the same progressive features as in patients with DLB.

In conclusion, the results demonstrated that CEF treatment prevented the loss of neuronal density and activity in the hippocampus and also normalized the hyperactivity of the STN in the DLB rat model. Treatment with CEF prevented the accumulation of α-syn in the hippocampus. Moreover, the MEMRI R1 value may serve as a suitable indicator for DLB severity and treatment effect. Our data provide support for the use of CEF as a potential therapeutic agent to prevent dementia in patients with DLB.

Disclosure

Some of the data in this paper have been presented as conference posters.

Conflicts of Interest

The authors declare no conflicts of interest for the material in the manuscript.

Acknowledgments

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Research Article

Increased Risk of Dementia in Patients with Antidepressants: A Meta-Analysis of Observational Studies

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Antidepressants are the most commonly and widely used medication for its effectiveness in the treatment of anxiety and depression. A few epidemiological studies have documented that antidepressant is associated with increased risk of dementia so far. Here, our aim is to assess the association between antidepressant use and risk of dementia in elderly patients. We searched articles through MEDLINE, EMBASE, Google, and Google Scholar from inception to December 1, 2017, that reported on the association between antidepressant use and dementia risk. Data were collected from each study independently, and study duplication was checked by at least three senior researchers based on a standardized protocol. Summary relative risk (RR) with 95% CI was calculated by using a random-effects model. We selected 9 out of 754 unique abstracts for full-text review using our predetermined selection criteria, and 5 out of these 9 studies, comprising 53,955 participants, met all of our inclusion criteria. The overall pooled RR of dementia was 1.75 (95% CI: 1.033–2.964) for SSRIs whereas the overall pooled RR of dementia was 2.131 (95% CI: 1.427–3.184) for tricyclic use. Also, MAOIs showed a high rate of increase with significant heterogeneity. Our findings indicate that antidepressant use is significantly associated with an increased risk of developing dementia. Therefore, we suggest physicians to carefully prescribe antidepressants, especially in elder patients. Additionally, treatment should be stopped if any symptoms related to dementia are to be noticed.

1. Introduction

Dementia is a neurocognitive disorder characterized by cognitive impairment. As the life expectancy of people has been increasing, and the prevalence of dementia has been increasing dramatically [1], dementia, therefore, has appeared as a major cause of disability and dependence among older people which is triggering huge economic burdens around the world. In 2012, nearly 35.5 million of people had dementia, and this number is expected to be doubled by 2030 and approximately 115 million by 2050 [2, 3]. A few epidemiological studies have found the possible link between late-life depression and consistently an increased risk of dementia so far. These studies also mentioned that several factors like stroke, diabetes mellitus, hypertension, head trauma, and hyperlipidemia might be associated with dementia [4, 5].

Antidepressants are a commonly and widely used medication for its effectiveness in the treatment of anxiety and depression [6]. Despite their benefits in depression, concerns have emerged on their safety and the subsequent risk for dementia, but the results are still inconsistent. Previous studies have demonstrated that antidepressant drugs are responsible for adaptive process disruption. It is basically triggered by serotonin, reduces brain metabolism, and escalates the clinical conversion to dementia risk [7, 8]. Contrary, Schmitt et al. reported that treatment with an antidepressant like SSRIs may help to improve cognitive function in patients with Alzheimer's dementia [9].

Until now, there is no particular meta-analysis on the association between antidepressant use and the risk of dementia among the elderly patients. We therefore conducted a meta-analysis of observational studies to evaluate the relationship between antidepressant use and dementia risk. Finding from our present meta-analysis would assist healthcare providers to improve treatment outcome and improve the existing knowledge about antidepressant therapy. In this meta-analysis, we only included studies that reported patients having exposure to antidepressants for at least one month and included patients' mean age more than 50 years.

2. Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Supplementary Table S1) [10]. We have used similar methods in our previous published three literatures [1, 11, 12].

2.1. Database. In the initial stage, we developed in this study a search strategy by consulting with our senior researchers at the International Center for Health Information Technology lab. Our three senior pharmacists (MMI, TNP, and H-CY) are experts in systematic review and meta-analysis regarding drug-disease and disease-disease associations. We searched for articles on the electronic databases such as PubMed, EMBASE, and Scopus until December 1, 2017, which reported on the possible association between antidepressant use and dementia risk. We used the following search terms as medical subject headlines and keywords: ("Anti-depressant drugs" OR "SSRIs" OR "Tricyclics (TCAs)" OR "Monoamine oxidase inhibitors (MAOIs") And ("Dementia risk") (Supplementary Table S2). To find any missing article in our initial search, we conducted additional searches in the reference lists of all included full text. However, Google Scholar was used to finding academic articles citing eligible articles. After assembling all potential articles, we then used EndNote X7 (Thomson Reuters) to manage and remove the duplicates.

2.2. Eligibility Criteria. Firstly, our authors independently screened all titles and abstracts of all retrieved articles. At the initial stage, they considered all studies published only in English. Additionally, observational study designs such as case-control, cohort, and randomized control trials that reported on antidepressant use and the risk of dementia were considered in our primary search strategy. The following criteria were considered to exclude studies if (1) they published as a letter to the editor, editorial, case study, and short communications; (2) patients had less than 30 days' antidepressant use; and (3) studies had a less than one-year follow-up period.

2.3. Inclusion and Exclusion Criteria. In this stage, two authors (MMI and TNP) retrieved full-text articles and checked the duplication of included studies. We considered only those studies if they met the following criteria:

(1) were published in English

(2) reported an association between antidepressants and dementia risk

(3) having at least 50 participants in both treatment and control groups

(4) having results demonstrated on OR/HR with 95% CI.

(5) having a more than one-year follow-up period

(6) identified dementia patients with ICD-9/biochemical test or other standard procedure

However, they excluded those articles if they were not an observational study and if the participants are not patients with dementia due to antidepressants. If the study met all inclusion criteria at this stage, our two authors (MMI and TNP) further reviewed to ensure the quality of the final analysis. Any disagreements regarding quantitative information (number of participant, dementia identification, duration of therapy, etc.) between two authors (MMI and TNP) were resolved by our main supervisor (YCL) of this study. They also kept some studies for reference, if they provide valuable information regarding their associations.

2.4. Data Extraction and Risk Bias Assessment. We finally included four studies, and those two authors then garnered information from each of these four studies. They collected the following information from four included studies: (a) author name and publication years; (b) study duration, study location, and study design; (c) condition information (i.e., data source, condition definition, and the total number of participants); and (d) odds ratios/hazard ratios with 95% CI for summary calculation.

2.5. Methodological Quality Assessment. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality of included observational studies (Supplementary Table S3) [13]. We evaluated included studies in three categories: selection (4 stars) and comparability (2 stars) of study groups and assessment of the outcome of interest (3 stars). The star rating system was used to indicate the quality, with 0–6 stars defined as low-quality and 7–9 stars as high-quality.

2.6. Statistical Analysis. In the final analysis, we calculated risk ratios (RRs) with 95% CIs to assess the risk of dementia with antidepressants. Odds ratios are close approximations of RR. We therefore combined odds ratios with HRs, resulting in a common estimate of RR [14]. A risk rate greater than 1 indicates an increased risk of dementia, and a risk rate smaller than 1 indicates a decreased risk of dementia. Statistical significance was evaluated using the 95% CIs. If the 95% CI did not include the neural value 1, we consider the risk statistically significant. In our study, we calculated the risk ratio (RR) from both case-control and cohort studies and used the most adjusted estimate available in each study due to estimation of a valid result.

A random-effects model was used to reduce the heterogeneity among the studies. We used comprehensive

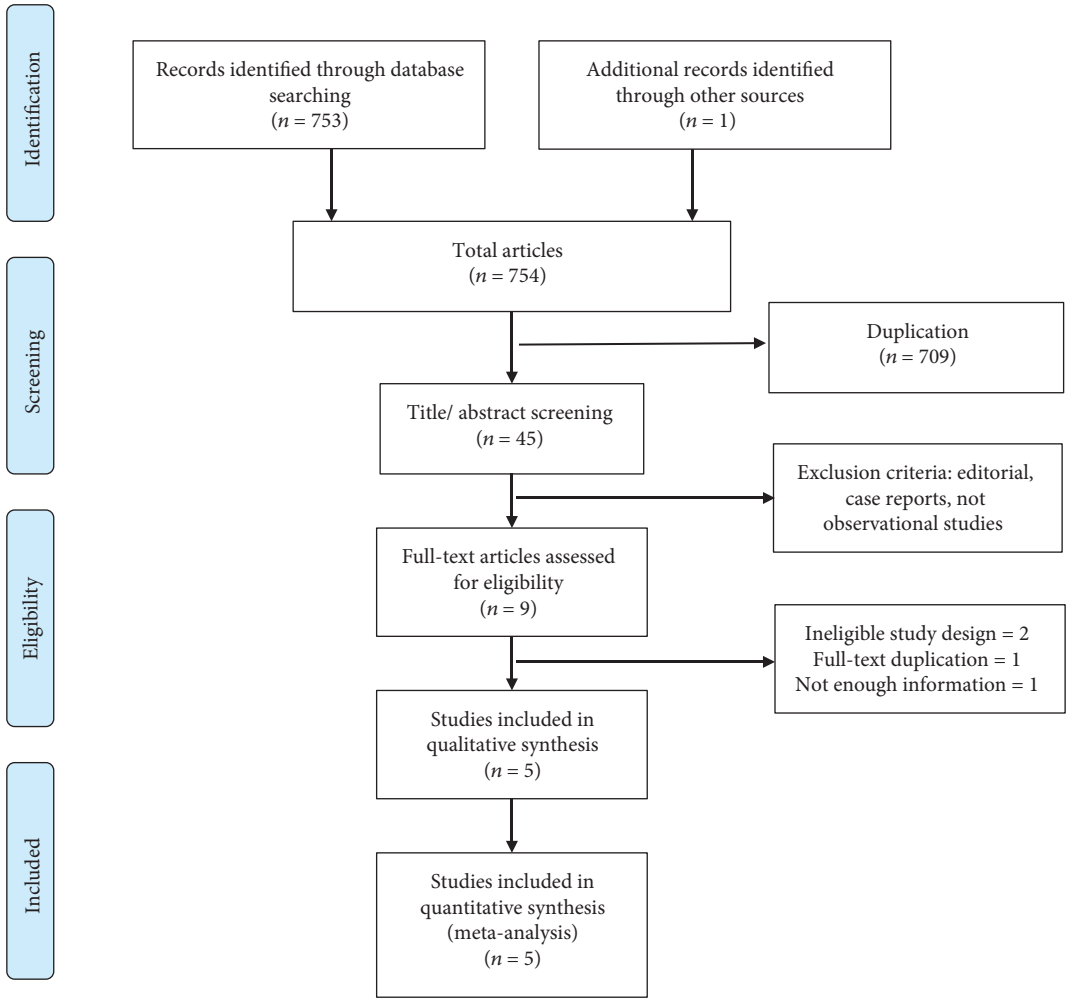

Figure 1: Flow chart of study selection. Diagram of study selection, adapted from the PRISMA group 2009 flow diagram.

meta-analysis package (Version 3) to draw forest plots and subgroup estimation. The meta-analysis of proportion uses the binominal distribution for analysis. We quantified heterogeneity of the studies using the I^2 statistic, and its significance was determined based on the accompanying P value in Cochran's Q test. If the I^2 value is 0%, it indicates no heterogeneity, and increasing values represent greater amounts of heterogeneity. The I^2 values of 25%, 50%, and 75% were considered as low, moderate, and high levels of heterogeneity. However, τ^2 values arising from the random-effects models were also used to quantify heterogeneity.

3. Results

3.1. Literature Search. A total of 754 records were identified through our initial database search. Of those, 745 studies were excluded based on our predetermined inclusion and exclusion criteria. We described full details in method parts. We reassessed the full text of the remaining 9 articles. Finally, 5 studies met all our inclusion criteria and were included in the final meta-analysis. A flow chart showing the study selection is presented in Figure 1.

3.2. Study Characteristics. The characteristics of the selected studies are presented in Table 1. The five included observational studies [15–19] were published between 2012 [19] and 2017 [18]. Among these studies, 3 were from Asia and 2 were from North America. Three studies were cohort studies [17–19], and two studies were case-control study designs [15, 16]. Two studies reported that the possible onset age of dementia was over 60 years [17, 19], and three studies reported an age of development of dementia which was below 60 years [15, 16, 18]. Almost every study mentioned antidepressant exposure, and they also evaluated the various classes of antidepressant use and dementia risk. A total of 53,955 study participants were included in our quantitative synthesis of which female patients were higher than male patients. The length of follow-up ranged from 3 to 11 years. All dementia patients were confirmed by checking the medical history, and all of the studies adjusted their results of potential confounding factors.

3.3. Methodological Quality of Included Studies. The Newcastle-Ottawa Scale (NOS) was used to assessed the methodological quality of included observational studies. The mean value for the five studies was 7.8 (Table 2).

Table 1: Characteristics of five included studies regarding antidepressants use and dementia risk.

Author/year	Country	Study duration	Study design	Adjustments	Results
Wei-Sheng Lee-2016 [15]	Taiwan	2005–2011	Case-control	1, 2, 3, 4, 5, 6, 7, 8, 9	For SSRIs, OR = 2.48 (95% CI: 2.27–2.71) For MAOIs, OR = 1.86 (95% CI: 1.47–2.36) For TCAs, OR = 1.44 (95% CI: 1.32–1.57),
Wei-Sheng Lee-2017 [16]	Taiwan	2005–2011	Case-control	1, 2, 3, 4, 5, 6, 7, 8, 9	For SSRIs, OR = 0.58 (95% CI: 0.50–0.69) For TCAs, OR = 1.02 (95% CI: 0.89, 1.17 For NGAs, OR = 4.23 (95% CI: 3.34, 5.37)
Wang 2016 [17]	USA	1991–2010	Cohort	1, 2, 3, 6, 9, 10 , 11, 12, 13, 14, 15, 16, 17, 18	For SSRIs, HR = 1.83 (95% CI) For non-SSRIs, HR = 1.50 (95% CI)
Then 2017 [18]	Taiwan	2003–2006	Cohort	1, 2, 3, 4, 8, 9, 19, 20	For SSRIs, HR = 3.66 (95% CI: 2.62–5.09) For SNRI, HR = 4.73 (95% CI: 2.54–8.80) For TCAs, HR = 3.26 (95% CI: 2.30–4.63) For MAOIs, HR = 4.94 (95% CI: 2.17–11.24)
Goveas 2012 [19]	USA	1996–2007	Cohort	1, 2, 3, 4, 6, 9, 10, 11, 21	For SSRIs, HR = 1.78 (95% CI: 1.01–3.10) For TCAs, HR = 1.78 (95% CI: 0.99–3.21).

(1) age, (2) gender, (3) diabetes, (4) hypertension, (5) stroke, (6) coronary artery disease, (7) head injury, (8) anxiety, (9) depression, (10) smoking, (11) body mass index, (12) cancer, (13) COPD, (14) liver disease, (15) hyperlipidemia, (16) renal disease, (17) thyroid disease, (18) cerebrovascular disease, (19) insomnia, (20) CCI, and (21) history of alcohol consumption.

3.4. Meta-Analysis. In the main analysis, a total of five studies evaluated the risk between selective serotonin reuptake inhibitor (SSRI) use and development of dementia. SSRI use is significantly associated with an increased risk of dementia when compared with nonuse. The overall pooled increase of dementia in patients with SSRI use was RR 1.75 (95% CI: 1.033–2.964) with significant heterogeneity present ($I^2 = 98.553$, $\text{tau}^2 = 0.34$) (Figure 2).

Four studies provided the risk estimation of tricyclic (TCA) use and dementia risk. The pooled RR for dementia risk was 2.131 (95% CI: 1.427–3.184) with the patients with TCAs (Figure 3). There was also significant heterogeneity ($I^2 = 96.393$, $\text{tau}^2 = 0.378$) among studies.

Two studies evaluated the impact of monoamine oxidase inhibitor (MAOI) therapy and risk of dementia. The overall pooled increase of dementia in patients with MAOI use was RR 2.791 (95% CI: 1.086–7.169) with significant heterogeneity present ($I^2 = 80.019$, $\text{tau}^2 = 0.382$) (Figure 4).

3.5. Sensitivity Analysis. Lee et al. [15] evaluated the risk of dementia according to cumulative dose of individual antidepressants. Patients with SSRIs had higher risk of dementia [(HR = 2.04, 95% CI: 1.80–2.31; HR = 2.10, 95% CI: 1.85–2.39; HR = 2.96, 95% CI: 2.60–3.37; and HR = 3.07, 95% CI: 2.69–3.51)] for <840 mg, 841–3000 mg, 3001–10,500 mg, and >10,500 mg. Contrarily, tricyclic was associated with a decreased risk of dementia [(HR = 0.44, 95% CI: 0.38–0.51, HR = 0.26, 95% CI: 0.22–0.30; HR = 0.20, 95% CI: 0.17–0.24; and HR = 0.13, 95% CI: 0.11–0.15)] for <840 mg, 841–3000 mg, 3001–10,500 mg, and >10,500 mg, respectively. Then et al. [18] investigated gender, different age groups, and dementia risk. Males had a higher risk of developing dementia (HR = 3.59, 95% CI: 2.64–4.88) than female patients (HR = 4.45, 95% CI: 3.11–6.37). Additionally, patients aged 45–65 had a higher risk (HR = 8.34, 95% CI: 4.45–15.61) than patients aged ≥65 years (HR = 3.84, 95% CI: 2.98–4.94). Goveas et al. [19] provided information about developing adverse effects such as mild cognitive impairment (HR = 1.70, 95% CI: 1.14–2.54) and probable dementia (HR = 1.24, 95% CI: 0.71–2.17).

3.6. Publication Bias. In our study, we showed the visual interpretation and test for asymmetry of the funnel plot of the publications. However, it is well established that the test of asymmetry will not be reliable when the included study number is not substantial [20]. Figure 5 depicts the funnel plot, indicating the presence of publication bias. Egger's regression test was used to present the funnel asymmetry, and it showed a highly significant publication bias (P value = 0.79).

Table 2: Methodological quality assessment of the observational studies using the NOS.

(a)

Case-control study	Selection				Comparability	Exposure			Total
	Definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	(0–9)
Wei-Sheng Lee-2017 [16]	*	*	*	*	**	*	*		8
Wei-Sheng Lee-2016 [17]	*	*	*	*	**	*	*		9

Note: a "star (*)" system of the Newcastle-Ottawa Scale (NOS) has been developed for the methodological quality assessment: each study can be awarded a maximum of one star for each numbered item within the selection and exposure categories, while a maximum of two stars can be given for the comparability category.

(b)

Cohort study	Selection			Comparability	Exposure			Total
	Selection of nonexposed cohort	Representativeness of the cohort	Ascertainment of exposure	Outcome of interest	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	(0–9)
Wang 2016 [17]	*	*	*	*	*	*	*		7
Then 2017 [18]	*	*	*	*	**	*	*	*	9
Goveas 2012 [19]	*	*		*	*	*	*		6

Note: a "star (*)" system of the Newcastle-Ottawa Scale (NOS) has been developed for the methodological quality assessment: each study can be awarded a maximum of one star for each numbered item within the selection and exposure categories, while a maximum of two stars can be given for the comparability category.

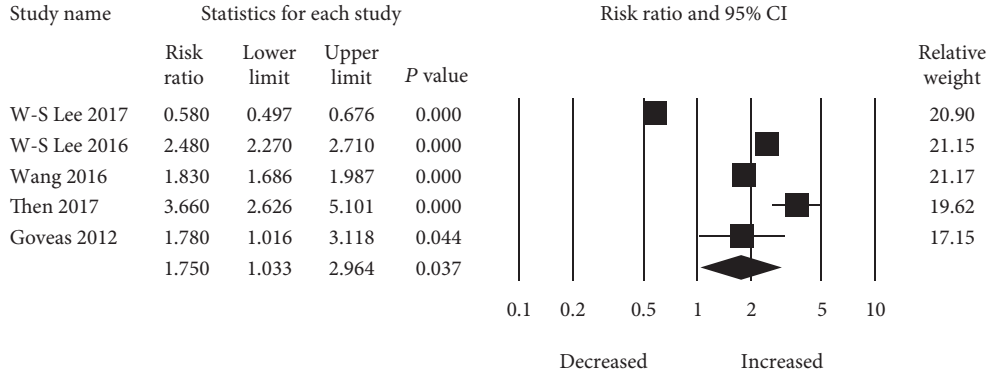

Figure 2: Forest plot of studies examining the association between SSRI use and dementia risk.

4. Discussion

4.1. Main Outcome. This current meta-analysis of observational epidemiological studies suggests that use of antidepressants increased a risk of developing dementia among the elderly population when compared with nonusers. Patients with monoamine oxidase inhibitor therapy had a higher risk of developing dementia than those with tricyclic and selective serotonin reuptake inhibitor therapy. Of importance, these findings would make physicians more cautious when they will consider an antidepressant treatment to their patients with depression. However, the

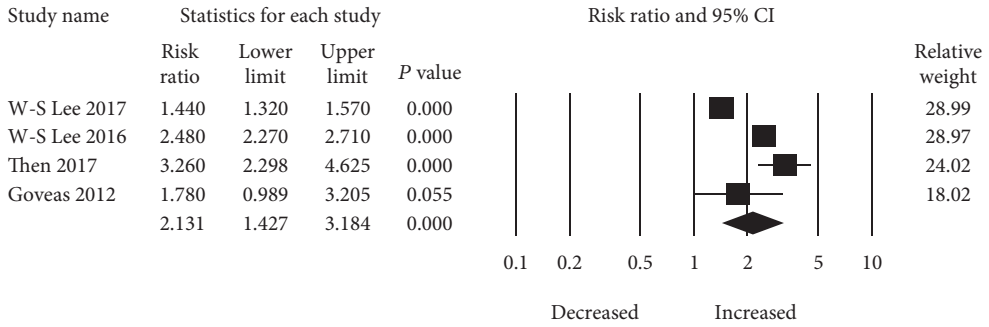

Figure 3: Forest plot of studies examining the association between TCA use and dementia risk.

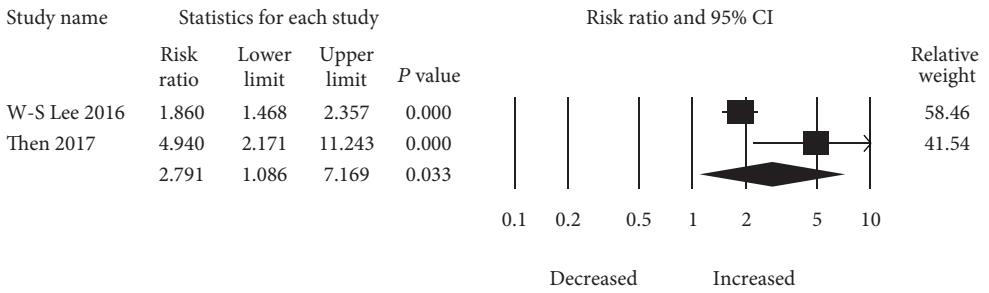

Figure 4: Forest plot of studies examining the association between MAOI use and dementia risk.

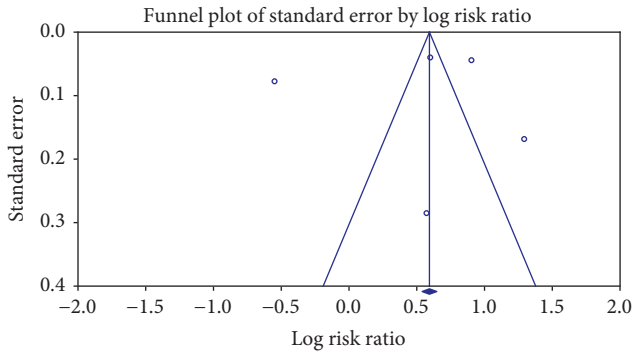

Figure 5: Funnel plot showing the association between antidepressant use and dementia risk.

decision to prescribe antidepressant therapy should be made in the light of the stringent clinical evaluation of benefits and risks, more particularly when physicians will prescribe antidepressants to a patient with depression. If antidepressant therapy is needed, it should be used judiciously and for the shorter period of time. Additionally, healthcare providers should routinely monitor the symptom of dementia risk factors such as memory loss, confusion, and disorientation while initiating or rewriting antidepressants to patients.

4.2. Biological Evidences. The biological mechanisms of the association between antidepressants and risk of developing dementia are still unclear. However, there are various possible ways of explanations for their association. First, the onset of depression before 65 years' age might be linked to the development of dementia and more recent depressive symptoms might link to the prodromal phase of dementia [7, 21]. Several biological studies reported that apolipoprotein (APOE) ε4 is a major known genetic risk factor that synergistically interacts with depression. Their interaction enhances the possibility of dementia risk, but it is not still well established [22, 23]. Second, use of antidepressants might prompt the imbalance of various neurobiological pathways. Therefore, it could help to elevate oxidative and nitrosamine stress as well as inflammation. Additionally, it might promote mitochondrial dysfunction, increased apoptosis, and finally diminished neurotrophic support [24]. Third, Steffens et al. reported that antidepressants increase subclinical cerebrovascular disease risk and promote cognitive decline by elevating potential oxidative stress [25]. Furthermore, to confirm the possible biological mechanism/link, more experimental and biological models are warranted.

4.3. Strengths and Limitations. Our study has several strengths. First, there is an enhanced statistical power to evaluate any association between antidepressant use and dementia risk. Second, this study evaluates the association in great detail and showed an association of different categories of antidepressants. However, our study has several limitations that need to be addressed. First, we included a small number of studies in our analysis. Second, a meta-analysis of epidemiological studies always has some unmeasured or uncontrolled confounding factors from the original studies. Our study findings had some degree of heterogeneity even though we used a random-effects model in our study analysis that helps to reduce publication bias. Third, we did not provide any information regarding dose differential and risk of dementia due to an insufficient amount of information. Fourth, duration of antidepressant and dementia risk were

not evaluated because of restrained data. Fifth, types of dementia risk with antidepressant use were not investigated due to lack of information. Sixth, females are more prevalent to depression and anxiety than males are, and females act differently in the metabolism and distribution of antidepressants [26, 27], but we could not categorize dementia risk on the basis of gender. Finally, we were unable to include randomized controlled trials due to the absence of data.

4.4. Recommendation. Till now, no particular treatments are available to improve cognitive and behavioral symptoms of dementia patients. Additionally, antidepressant prescription has been increasing and concerns have been increased due to antidepressant therapy. Therefore, treatment of depression patients with antidepressant therapy should be assessed on a timely basis to reduce any unfavorable effects. If any symptoms are observed, then physicians need to stop antidepressant therapy or treat patients with a low dosage or shorter period of time. It is also indispensable to inform patients or their family about the inauspicious consequence of antidepressant therapy and other treatment options available for their current physical condition. However, to ensure safe and effective treatment, it is high time to provide proper guidelines for patients and healthcare providers.

4.5. Unanswered Questions and Future Direction. Since our study summarized results from several epidemiological studies, this is why we acknowledge that findings from this study could not clarify whether the observed association between antidepressants and dementia risk is the causal effect or other unmeasured confounding variables [28]. Hence, larger long-term prospective randomized control trials and biological studies are warranted to justify a possible biological mechanism which links dementia risk or rebut their association.

5. Conclusion

To our knowledge, this meta-analysis shows the most rigorous and precise analysis regarding antidepressant use and the risk of dementia. Our findings showed a significantly increased risk of dementia with antidepressant therapy. Healthcare providers might preferentially avoid unnecessary prescription of antidepressants to the patients if any symptoms regarding dementia are noticed. Additionally, proper guidelines should be provided for quality and safety treatment.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Table S1: PRISMA 2009 checklist. Table S2: search strategy. Table S3: modified Newcastle-Ottawa Scale for risk of bias assessment. *(Supplementary Materials)*

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Review Article

Quality of Life in Patients with Dementia with Lewy Bodies

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Dementia with Lewy bodies (DLB) is a complex, multisymptom disorder. When making decisions regarding the treatment of DLB, the patient's quality of life (QoL) should always be the main consideration. To our knowledge, this is the first review article focusing on the QoL in DLB patients. We searched the PubMed database using the keywords "quality of life" and "dementia with Lewy bodies." Previously, no specific instrument had been developed for assessing the QoL in DLB patients. Patients with DLB have a decreased QoL compared to patients with Alzheimer's disease, which is reportedly caused by several factors including level of independence in instrumental activities of daily living, whether the patient is living with the caregiver, apathy, delusion, and dysautonomia. The direct effect of visual hallucination, sleep, and movement disorders on the QoL in DLB patients has not been previously studied. The role of cognitive function on the QoL is still controversial. In a randomized controlled study, memantine may improve the QoL in PDD or DLB patients. We concluded that it is important to develop a specific instrument to assess the QoL in DLB patients. Furthermore, there is an urgent need for large clinical trials to identify factors associated with the QoL and how they can be managed.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia after Alzheimer's disease (AD) in people over 65 years of age. A recent published population-based cohort study from the Taiwan National Health Insurance Research Database showed the incidence of DLB was 7.10 per 100,000 person-years [1]. DLB differs from AD as early cognitive symptoms include deficits in visuospatial and executive function, rather than memory. DLB is characterized by parkinsonism, fluctuations in mental status, visual hallucination, and hypersensitivity to neuroleptics. Therefore, it is difficult to discriminate between DLB and Parkinson's disease with dementia (PDD). Both diseases also share a similar pathologic finding, Lewy bodies. Generally, if cognitive impairments appear within a year of parkinsonism, DLB is diagnosed, while patients with parkinsonism for at least a year prior to cognitive impairment are classified as PDD. Early amyloid deposition in DLB relative to PDD may explain the difference in the timing of dementia and parkinsonism [2].

The quality of life (QoL) is a key outcome measure of health and social service interventions. Currently, patient-reported outcome measures are increasingly used in evaluating health and social care. Definitions of health-related QoL include physical, mental, social, and role functioning and health perceptions [3]. Because aging is a global issue, it is critical to identify QoL determinants in the elderly who suffer from chronic disease. A recent study from Southern Taiwan showed Alzheimer disease-8, a screening tool, had the strongest association with the total QoL score in 115 old-age adults suffering from chronic disease. It is important for geriatric

health care providers to realize that cognitive impairment among old age adults with chronic disease is a critical determining factor of poor QoL [4].

Assessing the QoL in people with dementia is crucial for evaluating their outcomes; however, it is challenging to interview patients who have a limited ability to express themselves and may lack insight. Meanwhile, there are questions concerning the validity of generic measures of QoL, which are not specific to dementia. Currently, evaluations of QoL largely focus on general dementia or AD. A systematic review [5] regarding the QoL in dementia strongly suggests that depression is consistently related to a decreased QoL. Surprisingly, there is no convincing evidence indicating that lower cognitive ability or greater limitations in the activity are associated with a lower QoL.

Evidence concerning the QoL in DLB patients is limited [6]. In a comparison study, the QoL was measured using the *Alzheimer Disease-Related Quality of Life* (ADRQL) evaluation, a proxy-rated, dementia-specific instrument. The authors concluded that DLB patients have a poorer QoL than AD patients [7]. Figari et al. compared the QoL in 46 AD, 23 DLB, and 39 Huntington's disease (HD) patients, all of whom had dementia for at least two years. Patients with DLB scored significantly lower on the SF-12 Physical and Mental Health Summary than patients with HD and AD. The authors concluded that, when adjusted for age, cognition, comorbidity, and depression, patients with DLB had the poorest QoL [8].

There is only one study whose primary aim was to compare the QoL in patients with DLB and AD [9]. 34 DLB patients and 34 cognitive-matched AD patients were evaluated using two QoL instruments: EQ-5D and QoL-AD. The results showed both patient-rated QoL and proxy-rated QoL were poorer in patients with DLB than those with AD. Due to many differences in clinical symptoms, it is reasonable to predict differences in the QOL between diseases. Herein, we elaborate on studies related to the QoL in DLB patients.

2. Methods

Studies were selected from the PubMed database using keywords "quality of life" and "dementia with Lewy bodies." All languages (with an English abstract) were included. Articles spanned the period between June 1986 and December 2017. Searches yielded 102 citations of which 21 were included as relevant. Other data were collected through references from selected articles and searching relevant journals offline.

2.1. Dementia-Specific QoL Measurement Scales. Unfortunately, there are no instruments available to specifically evaluate the QoL in DLB patients. Therefore, we herein discuss QOL measurement scales for dementia.

There is some debate regarding whether to use the patient's or caregiver's reported QoL as the measurement. Typically, the QoL is rated higher by patients than by caregiver proxy measures. The differences are associated with increased levels of caregiver burden and caregiver depression, rather than lower levels of patients' cognitive performance [10]. Therefore, it is reasonable to directly assess subjective QoL in patients with mild to moderate dementia. Interestingly, Karlawish et al. proposed a method to minimize the discrepancy between patient's and caregiver's QoL scores: caregivers should rate using substituted judgment as if they were the patients [11]. Issues regarding the exclusion of patients with severe dementia from self-reported questionnaires and weak reliability of proxy versions remain unresolved.

There is limited knowledge regarding the standard instruments used to evaluate the QoL in dementia patients. In a recently published review [12], the most frequently used dementia-specific instrument was the Quality of Life in Alzheimer's Disease (QOL-AD) and Dementia Quality of Life questionnaire (DEMQOL). As for generic measures, EuroQol 5-dimension (EQ-5D) and Short Form surveys (SF-36 or SF-12) were widely used. The authors recommended dementia-specific DEMQOL, generic SF-12, and health utility EQ-5D-5L, based on both self- and proxy-report [12]. In the following paragraphs, we will briefly introduce each widely-used measurement scale.

2.2. Quality of Life in Alzheimer's Disease (QOL-AD). The QOL-AD [13] is an instrument specifically developed for mild to severe dementia. It includes 13 items, including physical health, energy, mood, living situation, memory, family, marriage, friends, self, ability to do chores, ability to do things for fun, money, and life as a whole. Each domain is rated from 1 (poor) to 4 (excellent). As for the caregiver version, which contains 15 items, marriage and money are removed, while people who work here, ability to take care of oneself, ability to live with others, and ability to make choices in one's life are added.

2.3. Dementia Quality of Life Questionnaire (DEMQOL). The DEMQOL [14] aims to assess QoL in mild to moderate dementia. It includes 5 domains including daily activities and looking after self, health and well-being, cognitive functioning, social relationships, self-concept, and a total of 28 items. Each item is scored from 1 to 4. A proxy version has been developed for caregivers, DEMQOL-Proxy, which contains 31 items.

2.4. EuroQol 5-Dimension (EQ-5D-5L). The EQ-5D-5L [15] is a generic instrument. Respondents are asked to rate their current health status on 5 dimensions: mobility, hygiene, usual activities, pain/discomfort, and anxiety/depression. For each dimension, the respondent gives 1 of 5 possible ratings according to symptom severity. The questionnaire also includes a visual analog scale (VAS) as a secondary part, ranging from 0 (death) to 100 (perfect health). Thus, two QoL values are acquired with this instrument.

2.5. Short Form-36 and Short Form-12 (SF-36 and SF-12). The SF-36 [16] is a generic measurement containing 36 questions across 8 dimensions of health status: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. A shorter version, SF-12, was

Table 1: Characteristics of QoL measurement scales for dementia.

Instrument	Patient report	Proxy report	Domains	Items	Measurement	Brief summary
Quality of Life in Alzheimer's Disease (QOL-AD)	Yes	Yes	Physical health Mental health Social and functional domains	13 (15 for proxy version)	Four-point scale score Range 13–52 for patient report and range 15–60 for proxy report Higher scores equal to higher QoL	The best researched of all the dementia measurement scales Relatively brief Suitable for mild to severe dementia
Dementia Quality of Life questionnaire (DEMQOL)	Yes	Yes	Daily activities and looking after self Health and well-being Cognitive functioning Social relationships Self-concept	28 (31 for proxy version)	Four-point scale score Range 28–112 for patient report and range 31–124 for proxy report Higher scores equal to higher QoL	The conceptual framework is based on health-related QoL, with less social relevance The proxy version performed well in psychometric tests Suitable for mild to moderate dementia
EuroQol 5-dimension (EQ-5D-5L)	Yes	No	1st part: Mobility Hygiene Usual activities Pain/discomfort Anxiety/depression 2nd part: Visual analogue scale (VAS)	No	1st part: having no problems for 1, having slight problems for 2, having moderate problems for 3, having severe problems for 4, and being unable to do/having extreme problems for 5 2nd part: 0 for worst; 100 for best health status	A generic, preference-based instrument for health related QoL The 5-digit number for 5 domains can be converted into a single weighted index score Appropriate in people with mild to moderate dementia
Short Form-36 (SF-36)	Yes	No	Vitality Physical functioning Bodily pain General health perceptions Physical role functioning Emotional role functioning Social role functioning Mental health	36	One score in each domain, calculated by special software, representing weighted sums of the questions (0 equivalent to maximum disability; 100 equivalent to no disability)	A generic health status measure A shorter version, SF-12, was developed to minimize respondent burden if only physical and mental health summary scores are of interest

developed to minimize respondent burden if only physical and mental health summary scores are of interest.

A summary of the four widely-used scales is provided in Table 1.

2.6. Reported Symptoms That May Affect QoL in DLB Patients. One study compared the QoL in patients with DLB and AD as its primary aim and demonstrated that the following are important determinants of the QoL in DLB patients: their Neuropsychiatric Inventory score and level of independency in instrumental activities of daily living (ADL), whether the patient lives with the caregiver, apathy, and delusion [9]. Similar to most findings in overall dementia, cognitive function has no strong relation to the QoL in this study.

Caregivers play an important role in affecting a patient's QoL. In a cross-sectional study [17] of 161 patients with dementia (including 13 DLB patients), the QoL was measured using the ADRQL. The results indicated that some predictors of a reduced QoL include behavioral and depressive symptoms, dependency in basic ADL, poorer cognitive function, use of antipsychotic medication, caregiver burden, and caregiver not being an adult child. The role of cognitive function on the QoL is still controversial. Here, we will discuss some reported causative factors for a poorer QoL in DLB patients.

2.7. Visual Hallucinations. Visual hallucinations occur in 60 to 70% of DLB patients, usually beginning in the first 2 or 3 years of the disease [18]. The presentation of visual hallucinations in the first 4 years following the onset of dementia has a positive and negative predictive value for DLB of 81% and 79%, respectively [19]. The most common visual hallucinations are fully formed persons (84%), animals or bugs (37%), and objects (39%) [20]. Early misperceptions and misidentification of family members are usually reported in

DLB. Capgras syndrome, a delusion where a person has been substituted by an imposter with a similar outward, is also common in DLB and is associated with higher rates of visual hallucinations and anxiety [21]. A recently published post-mortem study [22] showed DLB cases had reduced neuronal density in the intermediate gray layer of the superior colliculus tissue, a structure important for directing attention toward visual targets. This finding may provide pathologic evidence for visual hallucinations in DLB.

A cross-sectional and retrospective study of 1025 patients with dementia in Spain found that delusion and hallucinations were more prevalent in DLB patients than those with AD and PDD [23]. In a recent comparative study of 207 delusional and nondelusional patients with DLB, the authors concluded that the delusional patients had poorer cognitive function and more severe neuropsychiatric symptoms [24]. In a cross-sectional study, 21 DLB and 35 PDD patients with recurrent visual hallucinations were evaluated. Most patients had complex hallucinations daily, usually lasting minutes. The study showed that neuropsychiatric symptoms that coexist with hallucinations are apathy, sleep disturbance, and anxiety [25]. The direct effect of visual hallucination on the QoL in DLB patients has not been previously studied.

Treatment of psychosis is challenging in DLB, since many patients are hypersensitive to neuroleptic drugs; therefore, nonpharmacologic treatment approaches should be considered first. Typical antipsychotic agents should be avoided, while the evidence for atypical antipsychotics is controversial. At present, quetiapine and clozapine are usually prescribed. Pimavanserin, a selective serotonin 5-HT2A inverse agonist, has beneficial effects on treating psychosis in PDD [26], while similar results are expected in DLB patients.

2.8. Depression and Apathy. The presence of depression and other behavioral and psychological symptoms of dementia (BPSD) may worsen the QoL of dementia patients and their caregivers [27]. The BPSD can be classified into four clusters: depression, aggressive behaviors, psychosis, and euphoria. In AD and DLB patients, a cross-sectional analysis determined that depressive symptom in patients may be the most important BPSD symptom as it was the only one shown to cause depression in caregivers [28].

A previous literature revealed that DLB is associated with higher scores on the Geriatric Depression Scale compared to AD, and a higher rate of depression is found in the early stages of the disorder [29]. Kurisu et al. compared the QoL of 279 degenerative dementia patients with different subtypes by using the *QOL Questionnaire for Dementia* (QOL-D) as an evaluation scale. The QOL-D comprises six domains: positive affect, negative affect and actions, communication, restlessness, attachment to others, and spontaneity. Results showed that apathy in frontotemporal dementia (FTD) and DLB patients and depression in DLB patients might cause the reduced positive affect in FTD and DLB patients compared to AD patients [30]. Apathy also plays an important role in evaluating the QoL in DLB patients. In a DLB and AD comparison study, DLB patients are less able to complete the QoL questionnaire [6].

In DLB, the presence of Lewy bodies in limbic, paralimbic, and neocortical regions may account for the appearance of depressive symptoms [27]. Early detection of depression in DLB patients is important as these symptoms are treatable. In a recently published review, the authors concluded that neuropsychiatric symptoms, especially psychosis and depression, are priority targets for intervention to improve the outcome of patients with DLB [6].

2.9. Sleep Disorders. Sleep disorders are common in DLB patients, with both rapid eye movement sleep behavior disorder (RBD) and fluctuating cognition being part of the clinical diagnostic criteria. In a contemporary review in sleep medicine, the authors concluded that appropriate management of sleep-related symptoms can improve the QoL in patients with neurodegenerative disorders [31]. Orexins (also known as hypocretins) are secreted in neurons in the lateral hypothalamus that are related to sleep regulation and attention [32]. Lower levels of orexin-1 were detected in the cerebrospinal fluid of DLB patients compared to AD patients and control subjects [33].

76% of DLB patients had RBD [34], which is characterized by acting out dreams, resulting in vocalizations and even violent behavior. Other nocturnal symptoms such as anxiety, periodic leg movements, urinary dysfunction, and difficulty turning over in bed can contribute to sleep problems [31]. In a retrospective study of 78 patients with DLB and sleep disorders who underwent polysomnography, approximately three quarters experienced many arousals not accounted for by a movement or breathing disturbance. Among patients who did not show evidence of significantly disordered breathing, 62% of arousals were arousals for no apparent reason [35]. The direct effect of sleep disorders on the QoL in DLB patients has not been previously studied.

2.10. Dysautonomia. In a study [36] of the prevalence of autonomic symptoms in dementia, the authors concluded that total autonomic symptom scores [37], urinary symptoms, constipation, and postural dizziness were significantly higher in DLB patients than in AD patients. By using the SF-36 [38] as a measurement, higher autonomic symptom scores were related to a lower QoL. The authors proposed that the effect of autonomic symptoms upon the QoL may be due to the limitations in ADL.

A systematic review of autonomic dysfunction in α-synucleinopathies revealed that cardiovascular autonomic failure has a significant impact on daily activities and QoL. Cerebral white matter changes in image and cognitive decline may be related to altered cerebral perfusion, vascular pressure stress, and associated disruption of the blood-brain barrier [39]. In α-synucleinopathies, autonomic dysfunction is more severe in DLB than in PD patients [40].

Both preganglionic and postganglionic dysfunctions may be present in DLB patients [41]. In a retrospective examination of DLB patients, urinary incontinence and constipation were the most commonly presented autonomic symptoms, occurring in 97 and 83% of patients, respectively, while syncope occurred in 28% of patients [42]. Orthostatic hypotension (OH) has been reported in around 50% of DLB

patients [43]. OH is defined as the reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing from the lying position [44]. Patients may not present with classic postural dizziness, but instead nonspecific malaise or lethargy, which can markedly increase the risk of falls or syncope. Management may include salt supplementation, compression stockings, or oral medication such as midodrine or fludrocortisone [45]. Furthermore, a higher prevalence of carotid sinus syndrome, an altered arterial sinus response to baroceptive stimulation resulting in syncope, was found in 32% of DLB patients compared to 11.1% of AD patients [46].

2.11. Reported Management That May Improve QoL in DLB Patients. It can be helpful to divide the symptoms of DLB into five categories: cognitive, neuropsychiatric, movement, autonomic, and sleep. It is important to take a detailed history and form a comprehensive treatment strategy to improve a patient's QoL [47]. There is little published data regarding the effect of the management of symptoms on the QoL in DLB patients.

2.12. Armodafinil. Because armodafinil has a longer half-life than modafinil, we may predict its better effect at treating patients with excessive daytime sleepiness [48]. In a 12-week pilot trial of oral armodafinil therapy (120–250 mg daily), DLB patients with hypersomnia showed improved scores on the Epworth Sleepiness Scale, Maintenance of Wakefulness Test, and Clinical Global Impression of Change. Moreover, caregivers' overall QoL improved at week 12 [49]. It should be noted that the effect of armodafinil on patients' QoL was not analyzed in this trial.

2.13. Memantine. Memantine, an NMDA receptor antagonist, has been widely used in treating moderate to severe AD. A randomized controlled study was conducted on 70 patients with PDD or DLB over 24 weeks using caregiver-rated QOL-AD as a measurement. A secondary analysis of this study showed that memantine improved the total QoL, body function, physical health, energy, mood, and memory when compared to the placebo group [50]. Large-scale trials are required to confirm these preliminary findings. On the other hand, although cholinesterase inhibitors are widely prescribed for patients with DLB, we found no reported effect of cholinesterase inhibitors on the QoL in DLB patients.

2.14. Exercise. Exercise may improve functional outcomes in PD and AD patients. The multisymptom nature of the DLB (parkinsonism, cognitive, and psychiatric) results in these patients often being excluded from clinical trials to avoid confounding results. A recent systematic review confirms a scarcity of research investigating exercise as a potential therapy in DLB patients [51]. The authors concluded that the effect of exercise on cognitive, psychiatric, QoL, and physiological outcomes remains unclear in DLB patients. Further clinical trials in larger cohorts are necessary.

3. Conclusions

This is, to our knowledge, the first review article focusing on the QoL in patients with dementia with Lewy bodies. Our review may not be fully comprehensive due to the limited literature available regarding this topic. Physicians should keep the patient's QoL in the forefront when managing their symptoms. The following are reported factors leading to poorer QoL in DLB patients: independence in instrumental ADL, whether the patient is living with the caregiver, the presence of depression, apathy, delusion, and dysautonomia.

First, we concluded that it is important to develop a specific instrument to assess the QoL in DLB patients. Apathy is more common in DLB patients, causing them less able to complete the questionnaire [6]. Therefore, it is reasonable to design a scale with proxy version. Since DLB is a complex, multisymptom disorder, we recommend the following domains should be taken into account: health and well-being, daily activities, cognitive functioning, positive and negative affect, restless behavior, social interaction, and satisfaction (i.e., restful sleep). Second, we hope that with the advent of more diagnostic criteria and advances in biomarkers, there will be well-defined DLB cohorts for clinical trials. Further studies may be facilitated by international or multicenter cooperation. For example, a large longitudinal cohort of 5624 DLB patients has been developed recently in 135 dementia centers in Italy (the DLB-SINdem study group) [52]. There is an urgent need for large, cross-sectional, and longitudinal trials to determine other factors associated with the QoL, such as cognition, visual hallucination, sleep, and movement disorders. Finally, because of the poor prognosis and high socioeconomic burden of DBL, we should consider the health-related QoL as one of the outcome measurements when developing new drugs for DLB.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Review Article

REM Sleep Behavior Disorder (RBD) in Dementia with Lewy Bodies (DLB)

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Rapid eye movement sleep behavior disorder (RBD) is a parasomnia, with abnormal dream-enacting behavior during the rapid eye movement (REM) sleep. RBD is either idiopathic or secondary to other neurologic disorders and medications. Dementia with Lewy bodies (DLB) is the third most common cause of dementia, and the typical clinical presentation is rapidly progressive cognitive impairment. RBD is one of the core features of DLB and may occur either in advance or simultaneously with the onset of DLB. The association between RBD with DLB is widely studied. Evidences suggest that both DLB and RBD are possibly caused by the shared underlying synucleinopathy. This review article discusses history, clinical manifestations, possible pathophysiologies, and treatment of DLB and RBD and provides the latest updates.

1. Introduction

Lewy body dementia (LBD), including dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), is often discussed simultaneously because of the overlaps in pathological features, such as the presence of Lewy bodies and intracellular inclusions of α-synuclein and ubiquitin in the brain stem, limbic area, forebrain, and neocortex. It is still not clear whether DLB and PDD are distinct disorders or the same disease but at different stages. DLB is the third most common type of dementia in the world [1]. The annual incidence is 0.1% of the general population and 3.2% of all new dementia population [2]. The prevalence of DLB varied from 3.0% to 26.3% of patients who are above 65 years old [3, 4]. On the other hand, rapid eye movement sleep behavior disorder (RBD) is a disorder with abnormal behavior during the rapid eye movement (REM) sleep. RBD is acknowledged as a core clinical feature of DLB because the prevalence is up to 76% [5]. RBD not only precedes or coincides with the onset of DLB but also occurs during the course of the progression [6]. The cooccurrence of RBD, DLB, and Parkinson's disease is an important topic. In this review, we aimed to review the clinical features of DLB and its sleep manifestations. New advances in diagnosis, management, and underlying pathophysiology of DLB and RBD would also be discussed and summarized.

2. Dementia with Lewy Bodies

DLB was first clearly defined in 1996, at the First International Workshop of the Consortium on Dementia with Lewy Bodies [7]. The clinical diagnostic criteria include rapid progressive mental impairment to dementia as the central feature of DLB. Specific core features include fluctuated cognitive function, persistent well-formed visual hallucinations, and spontaneous motor features of parkinsonism. DLB is distinct from PDD, Alzheimer's disease (AD), and other types of dementia in several aspects, including clinical symptoms,

Table 1: Revised [7, 121] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB).

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.
Core clinical features (The first 3 typically occur early and may persist throughout the course.) (i) Fluctuating cognition with pronounced variations in attention and alertness (ii) Recurrent visual hallucinations that are typically well formed and detailed (iii) REM sleep behavior disorder, which may precede cognitive decline (iv) One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity
Supportive clinical features Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, for example, constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression
Indicative biomarkers (i) Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET (ii) Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy (iii) Polysomnographic confirmation of REM sleep without atonia
Supportive biomarkers (i) Relative preservation of medial temporal lobe structures on CT/MRI scan (ii) Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity 6 the cingulate island sign on FDG-PET imaging (iii) Prominent posterior slow-wave activity on EEG with periodic fluctuations in the prealpha/theta range
Probable DLB can be diagnosed if (a) Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or (b) Only one core clinical feature is present, but with one or more indicative biomarkers.
Probable DLB should not be diagnosed on the basis of biomarkers alone. *Possible DLB* can be diagnosed if (a) Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or (b) One or more indicative biomarkers is present but there are no core clinical features.
DLB is less likely (a) In the presence of any other physical illness or brain disorder including cerebrovascular disease sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or (b) If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.
DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting, the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

(Adapted from Ian G. McKeith et al., Neurology 89 July 4, 2017).

pathological findings, and nuclear imaging studies [8]. The extrapyramidal symptoms of DLB are extremely sensitive to neuroleptic medications [7]. Lower dopamine transporter uptake in the basal ganglia is demonstrated by SPECT or PET imaging. They are also the suggestive features of DLB [9]. The confirmation of DLB is based on pathology which shows Lewy bodies in the brain stem or cerebral cortex [10]. Lewy-related neurites, Alzheimer pathology, and spongiform change may also be presented, but they are not necessary features for diagnosis.

In 2017, the diagnostic criteria have been updated for the fourth time (Table 1) [5]. The revised criteria had made some changes and defined essential diagnosis of dementia in a more detailed way. Dementia, defined by progressive cognitive decline of sufficient magnitude, interferes with normal social or occupational functions, or usual daily activities are still essential for the diagnosis of DLB. Unlike AD, patients are not necessary to have prominent or persistent memory impairment in the early stages, instead of dysfunction of attention, executive function, and visuoperceptual ability [11]. Core clinical features may precede dementia including fluctuating cognition with pronounced variations in attention and alertness, recurrent well-formed and detailed visual hallucinations, and RBD [12]. One or more spontaneous cardinal features of parkinsonism may also present such as bradykinesia, rest tremor, and rigidity. Supportive

clinical features include severe sensitivity to antipsychotic agents, postural instability, repeated falls, syncope or other transient episodes of unresponsiveness, severe autonomic dysfunction, hyposmia, hallucinations in other modalities, delusions, apathy, anxiety, and depression and may exist in the early stage [13].

The revised DLB consensus criteria are now distinguished clearly between clinical features and diagnostic biomarkers. If one or more of the indicative biomarkers are identified and are associated with one or more core clinical features, then probable DLB should be diagnosed. Dementia without any core clinical features, but with one or more indicative biomarkers, may be classified as possible DLB. For the supportive biomarkers, these are biomarkers consistent with DLB that help the diagnostic evaluation, but without clear diagnostic specificity.

3. Recommended Management of DLB

With few randomized controlled trials in DLB, recommendations about clinical management are largely based upon expert opinions. Management of DLB is complex, and the approach with a multidisciplinary team is helpful. It is recommended that the combination of pharmacologic and nonpharmacologic approaches might result in an optimal outcome. Among others, exercise [14], cognitive training [15], and caregiver-oriented education and training are promising nonpharmacologic managements for DLB patients [16, 17]. For the pharmacologic therapy, there are four clinical aspects that should be considered:

(1) Cognitive functions

It is well established that the involvement of cholinergic deficits in DLB and cholinesterase inhibitors (ChEIs) is beneficial for better clinical courses by lowering the choline degradation [18]. Either rivastigmine or donepezil may improve cognition, global function, and activities of living [19, 20]. On the other hand, there are evidences of hyperactivity of glutamatergic neurons in both human and animal studies [21, 22]. It is likely that memantine, the N-methyl-D-aspartate receptor antagonist, may be effective by amelioration of glutamatergic neurotransmission for cognitive improvement of DLB patients. However, memantine produced remarkable efficacy on global assessment, but the cognitive function, behavioral symptoms, and activities of daily living are based on current evidence [19].

(2) Psychiatric symptoms

ChEIs may reduce apathy, visual hallucinations, delusion, and associated anxiety and agitation [23]. The use of antipsychotics should be avoided because of the increased risk of mortality [24]. The second generation of antipsychotics, such as quetiapine, may be beneficial and safer based on a previous study [25]. However, efficacy and tolerability are not well established yet. On the other hand, the incidence of depression ranged from 22 to 53 per 100 person-years in atypical PD, including DLB, which is higher as compared to PD [26]. Regarding the management of depression in DLB patients, serotoninergic-targeted therapy would be an option based on individual response. Furthermore, selective serotonin reuptake inhibitor treatment may even be associated with increased hippocampal neurogenesis and preservation of cognition in DLB/PDD patients according to a recent study [27].

(3) Extrapyramidal symptoms

Previous studies mostly revealed no benefits or mild improvement with levodopa treatment in motor symptoms of DLB patients [28, 29]. The use of dopaminergic medications in DLB is often withheld by fears of aggravating psychosis and confusion. However, although the response to dopaminergic treatment in DLB for its motor symptoms is poor, a low dose of levodopa is still an alternative and should be titrated slowly in order to avoid psychiatric side effects [28, 30].

(4) Sleep disturbances

DLB patients frequently have several sleep problems, and they often occur simultaneously. Excessive daytime sleepiness can be managed by improving sleep hygiene. Previous studies regarding central nervous system stimulants such as modafinil and armodafinil revealed inconsistent results [31]. Armodafinil has been associated with increased wakefulness but may exacerbate agitation and hallucinations [32]. It is critical to prevent sleep-related injuries in DLB patients with RBD. Taking clonazepam before bedtime may reduce the RBD and consequent injuries. However, it may worsen the cognitive function and daytime sleepiness.

4. REM Sleep Behavior Disorder (RBD)

The first major classification of sleep disorders, the Diagnostic Classification of Sleep and Arousal Disorders, was published in 1979 [33]. In 2014, the International Classification of Sleep Disorders (ICSD) made the 3rd revised version of the American Academy of Sleep Medicine's manual of sleep disorders nosology [34]. A parasomnia involves undesired events that happen during sleeping. It also involves three different classifications: nonrapid eye movement- (NREM-) related parasomnias, REM-related parasomnias, and other parasomnias. RBD is one of the REM-related parasomnias.

RBD was first described in 1986 by Schenck et al. [35]. In this 2-year study, 5 patients were found to have similar behavioral disturbances during REM sleep. They were associated with loss of chin and limb electromyography atonia [12, 36, 37]. RBD is either idiopathic or secondary [34]. Idiopathic RBD is cryptogenic since Lewy bodies were demonstrated by autopsy in two cases of presumptive idiopathic

RBD [38, 39]. Idiopathic RBD is also found to have α-synuclein accumulation and thought to be the prodromal stage of many neurodegenerative disorders, such as PD and DLB, multiple system atrophy (MSA), and a pure autonomic failure [40]. Secondary RBD is defined to be caused by other diseases, most commonly in neurodegenerative or other neurologic disorders, sleep disorders, medications, and withdrawal states. Known causes of secondary RBD up to date are spinocerebellar ataxia [41], limbic encephalitis [42], brain tumors [42], multiple sclerosis [43], stroke [44], different antidepressants [45–47], alcohol [48], and barbiturate withdrawal [49].

5. Clinical Presentation of RBD

RBD has special clinical dream-enacting behavior symptoms such as repeated episodes of sleep-related vocalization and/or complex motor behaviors during REM sleep, correlating with dreams [50]. Patients with RBD act out their dreams and commonly have violent or injurious behavior during sleep [35, 51, 52]. The behavior includes purposeful movements of short duration and can be really violent thrashing, punching, kicking, and even falling out of the bed [53]. The patients also have loud vocalizations, screaming, and talking. Under normal conditions, the skeletal muscles lose muscle tone physiologically when dreaming [54]. In RBD, a loss of atonia causes self-injury and injury to their bed partners. Diagnosing RBD needs a careful and detailed history taking [55]. Males are much more than females in RBD patient groups. The median age at diagnosis is between 60 and 70 years [56]. The symptoms progress gradually; they can occur daily or once per year [57]. Dream contents of RBD patients are different from the normal population. Their dreams are mostly unpleasant and more violent. Patients do not usually consider this a problem, until themselves or their bed partners get hurt [58].

6. Clinical Implications of RBD and Its Relationship to DLB

RBD can be either idiopathic and a marker of prodromal neurodegeneration or secondary to neurodegeneration [59]. Longitudinal studies of idiopathic RBD had shown evidence of a strong association with eventual phenoconversion to a neurodegenerative disease. Phenoconversion risk between two and five years is about 15% to 35%, and the risk may increase to 41% to 90.9% if extending the follow-up period up to 12 to 25 years. When patients have RBD, compared to those without RBD, the accompanied neurodegenerative disease tends to be worse, such as more severe parkinsonian symptoms, autonomic dysfunction, and cognitive impairment [37].

Overall, idiopathic RBD patients convert to PD eventually and accomplish with 5 years. Those PD patients converted from RBD were faster motor progression, less response to levodopa therapy, and more severe postural instability [60, 61]. RBD appears to be associated with the α-synucleinopathies [62]. Previous studies showed that 38%–65% of RBD patients have developed α-synucleinopathy from 10 to 20 years after RBD presentation; it could be most likely PD, DLB, or multiple system atrophy [63, 64]. Other cohort studies have provided evidence that patients with idiopathic RBD will eventually develop a synucleinopathy, such as PD, DLB, or MSA [37, 40, 65–68].

Prevalence of RBD in the general population is between 0.38 and 0.5%, but RBD has been found in 70% of patients with MSA, 40% of patients with DLB, and between 15% and 33% of patients with PD [69–71]. Another study even showed that 74% of the DLB population had RBD [72, 73]. By using diffusion magnetic resonance imaging (MRI), PD patients with RBD showed microstructural white matter changes in the bilateral cingulum, inferior front occipital fasciculus, bilateral corticospinal tracts, and middle cerebellar peduncles. However, PD patients without RBD do not have such signal changes [74]. A series of autopsies of RBD patients shows underlying synucleinopathy up to 94% of patients [65, 75–77]. Furthermore, peripheral tissues such as submandibular glands and the enteric nervous system from living patients with idiopathic RBD also show abnormal α-synuclein immunoreactivity [78, 79]. The implication from these evidences aforementioned is that RBD onset in older adults is associated with underlying synucleinopathy in pathology.

7. Diagnoses and Treatment of RBD

The diagnosis of RBD is based on clinical features and polysomnography (PSG) findings. Firstly, the patients must have repeated episodes of complex motor behaviors or vocalization during REM sleep, and they can be documented by PSG or reports of dream enactment. Secondly, it must have evidence of REM sleep without atonia on PSG, namely, REM sleep without atonia (RSWA). Other clinical findings are strongly suggested by the diagnosis of RBD, but RSWA is not observed, yet the diagnosis can still be given. RBD can be secondary to several medications, most of which are antidepressants [80, 81]. When RBD is believed as a secondary cause of medication use, a diagnosis of RBD is still applicable.

The management of RBD should be applied carefully because around 33% to 65% RBD patients have sleep-related injuries that are caused by the patients themselves [82]. Sleep disruption usually happens because of abnormal or disruptive, or even violent, behavior during REM sleep [83]. So, modifying the sleep environment is necessary for RBD patients to prevent from getting sleep-related injuries. Under certain circumstances, separating bedrooms may be necessary to prevent bed partners from getting injuries. Pharmacologic therapy includes clonazepam and melatonin [82, 84]. Both are modestly effective in preventing sleep-related injuries. Clonazepam is a long-acting benzodiazepine with increased risks of falls and cognitive impairment. It should be used with caution in RBD patients with dementia, gait disorders, or concomitant obstructive sleep apnea. Melatonin is a hormone releasing from the pineal gland with favorable safety and tolerability. Thus, RBD patients not suitable for clonazepam should consider melatonin as their first-line treatment [85]. Other dopaminergic medications, such

as pramipexole, paroxetine, or levodopa, show no therapeutic effect, sometimes even worsen RBD [86]. Only few studies have discussed about the drug effect of ChEIs [87]. They are considered to treat RBD patients with a concomitant synucleinopathy. Other medications are used for RBD treatment, with less evidence, such as zopiclone, benzodiazepines, desipramine, clozapine, carbamazepine, and sodium oxybate [88–91].

8. Pathophysiology of RBD

Sleep is a physiological state, which is defined by consciousness loss, reduced responsiveness to the environment, and decreased body movement [66]. Two different states with different biochemical, neuronal, and metabolic properties are involved in sleep: non-REM sleep and REM sleep. REM sleep was named because of its most obvious behavior—rapid eye movements during sleep [92, 93]. Besides rapid eye movement, one of the features of REM is muscle atonia, which means the muscle activity is inhibited, except middle ear muscle activity and eye movement. A recent study has proved that the modulation of dorsal medulla GABAergic neurons control the REM phenomenon in rodents [94]. The atonia is believed to be controlled by nuclei in the lower pons and medulla, particularly the perilocus ceruleus area. This area directly innervates the spinal interneurons and induces REM atonia via a flip-flop switch [32]. During REM sleep, excitatory sublateral dorsal/subcoeruleus nucleus glutamatergic neurons activate spinal cord inhibitory interneurons to hyperpolarize and thereby inhibit the spinal motoneuron pool and cause REM sleep atonia. It is proposed that hypocretin neurons, located in the posterior hypothalamus, may further stabilize the REM-active and REM-inactive centers [95].

The key structure for modulating REM sleep is the brain stem, particularly the pons and adjacent portions of the midbrain. During REM sleep, cholinergic neurons in the pontine tegmentum of the reticular formation are active. GABAergic neurons and orexin/hypocretin neurons also regulate REM sleep [96]. REM sleep has special EEG characteristics with low-amplitude desynchronized theta activity with the presence of saw-tooth waves, the presence of pontine–geniculate–occipital (PGO) waves, and hippocampal theta activity. PGO waves occur during the transition from non-REM sleep to REM sleep or during REM sleep itself. REM sleep is the sleep state with the highest physiological arousal.

Currently, the loss of REM sleep atonia control is well accepted in RBD patients. However, the underlying mechanisms for RBD or RSWA are far from clear. Motor circuits involve afferent, integrative, and efferent systems in the spinal cord, the brain stem, the basal ganglia, the cerebellum, and the limbic/cerebral cortex. Abnormal activation and disinhibition of these motor circuits may explain this sleep-related motor manifestation. During REM sleep, there are physiologic intermittent muscle twitches that could be originated from the red nucleus, pedunculopontine nucleus, and lateral dorsal tegmental nucleus. Dysfunction of sublateral dorsal/subcoeruleus nucleus from brain lesions in the dorsal pons was proved to cause RSWA and may cause clinical RBD [97, 98]. It is proposed that the accumulation of Lewy bodies in the pontine and medullary structures, which is in advance to the degeneration of the substantia nigra according to the Braak stage [99], will result in RSWA and RBD. With the ascending of Lewy bodies to the substantia nigra and cortex, the motor symptoms and dementia evolved [100]. On the other hand, regarding DLB, before the development of parkinsonism and other features, RBD typically begins many years before cognitive dysfunction. It can be explained that the nigrostriatal system is later or less involved in DLB as compared to PD and PDD, and the neocortex is involved in an earlier phase.

Animal experiments can help understand the biological mechanism, pathogenesis, and treatment of RBD. In 1965, Jouvet and Delorme first reported a cat model of loss of REM atonia, which was induced by bilateral, symmetrical, and mediodorsal pontine tegmental electrolytic injury [101]. These 35 pontine-impaired cats have de novo "hallucinatory-type" behavior during REM sleep. During non-REM sleep, the hallmark phasic REM sleep PGO waves were frequently seen [102]. Jouvet's group then discovered that bilateral lesions of the caudal and ventral pons were descending pathways for REM atonia [103]. Morrison's group designed an idiopathic RBD cat and dog animal model and discovered clonazepam as an effective therapeutic medication [35, 104]. Valenica Garcia et al. developed the RBD rat model for pharmacotherapies of clonazepam and melatonin [82]. Also, the rat model can be used for studying other medication effects, such as antidepressants [105]. Currently, Lyon's group developed a novel rat model of RBD with precision techniques that deepen the understanding of the human RBD basic and clinical research [106].

The specific neuronal networks and neuropathology involved in human RBD pathogenesis have not been identified with certainty; more work is needed for determination. RBD shares similar pathological changes with PD and DLB in sleep-related brainstem nuclei, specifically those in the rostral pontine tegmentum. In PD and DLB, α-synuclein immunoreactive Lewy-related pathology and neuronal loss are discovered in the same area [107–109]. But DLB with or without RBD differs clinically or pathologically. DLB without RBD has early involvement of corticolimbic areas and later extension to brainstem nuclei. DLB with RBD has early brainstem involvement then extends to forebrain structures [110–112]. AD-type neuropathology is frequent in DLB. Some of the DLB and PD patients, especially those with PD with later developing dementia, can have β-amyloid plaques and tau-positive neurofibrillary degeneration, which belongs to AD. RBD is uncommon in AD, but when RBD occurred, α-synuclein deposition is discovered [113]. Another study showed that probable RBD is associated with DLB and less severe AD-related pathology in the medial temporal lobes. If the absence of probable RBD, AD-like atrophy patterns on MRI and increased phospho-tau burden are noted [114, 115]. The cholinergic mechanism is an important modulatory role of RBD. Cholinergic depletion is also known to be severe in DLB, even in the early beginning of the dementia [116]. Loss of neurons in the locus coeruleus

and substantia nigra in DLB with subsequent dysregulation of cholinergic neurons in the pedunculopontine nucleus increased REM sleep drive and RBD [116, 117]. The pedunculopontine/laterodorsal tegmental nuclei (PPN/LDT) are active during REM sleep which contain cholinergic neurons. In an animal study, damage in PPN/LDT leads to RBD-like behavior. Cholinergic neurons decrease, and α-synuclein accumulation in the PPN/LDT is seen in DLB with and without RBD, also in PD and AD. But different from AD, significant neuronal loss was only detected in these nuclei in DLB [69, 77, 118–120]. With the help of these innovative research methodologies and materials, further insight of mechanisms of pathogenesis can be expected in the near future.

9. Conclusions

Compelling evidence has suggested that both DLB and RBD are possibly caused by underlying synucleinopathy, and RBD often precedes DLB. Currently, the mainstay of pharmacological treatment of RBD is clonazepam and melatonin, which may reduce the possibility of sleep-related injuries. As a sentinel of possible DLB and other synucleinopathy, RBD may be the beginning of degenerative diseases and provide opportunities for preemptive treatment for earlier disease-modifying therapy, targeting α-synuclein or its regulatory pathways. Further studies need to address factors that will determine its phenoconversion to different types of synucleinopathy. Early interventional strategies should be developed to prevent or at least delay the consequences of devastating dementia, parkinsonism, and autonomic failures.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Po-Chi Chan and Hsun-Hua Lee contributed equally to this study.

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Research Article

Risk Factors for the Progression of Mild Cognitive Impairment in Different Types of Neurodegenerative Disorders

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Objective. Mild cognitive impairment (MCI) is a transitional state between normal aging and early dementia. It has a heterogeneous etiology and clinical course. This study aimed to examine the factors associated with the progression of MCI in different types of dementia disorders. *Method*. A retrospective, longitudinal, observational study of outpatients with MCI was conducted at a medical center in northern Taiwan. Patient medical records were reviewed, and risk factors were analyzed by multivariate analysis. *Results*. Among 279 patients with MCI, 163 (58.4%), 68 (24.4%), and 48 (17.2%) were diagnosed with Alzheimer's disease, vascular cognitive impairment, and Lewy body diseases, respectively. During the observation period, 37.2% of patients progressed to dementia. Older age and a higher Clinical Dementia Rating Scale-Sum of Boxes were associated with the risk of progression. Hyperlipidemia was associated with a decreased risk. Converters were more likely to receive an antidementia prescription. *Conclusion*. Our study suggests the importance of comprehensive clinical profiling, risk factor assessment, and detailed drug history evaluations in improving our understanding and management of dementia subtypes.

1. Introduction

Dementia can result from several underlying diseases, including Alzheimer's disease (AD), cerebrovascular disease, Lewy body diseases (LBD), frontotemporal dementia, and other less common disorders such as Huntington's disease, supranuclear palsy, and others. Mild cognitive impairment (MCI) is considered an intermediate state between normal cognitive aging and very early dementia. Individuals diagnosed with MCI may remain stable, return to normal (14.4–55.6% of patients), or progress to dementia [1]. There is extensive literature on MCI in AD but limited to other types of dementia. Many epidemiological studies have reported that the presence of vascular risk factors (i.e., hypertension, diabetes, cerebrovascular disease, and hyperlipidemia) in midlife is associated with an increased risk of cognitive impairment and dementia, particularly AD and vascular dementia (VaD) [2, 3]. Previous studies have reported older age, lower education status, prestroke cognitive and functional status, and history of diseases as risk factors for poststroke dementia [4]. However, cardiovascular risk factors in the midlife increase the risk of dementia, but their roles in the late-life are less clear [5]. Apart from vascular risk factors, other clinical conditions have been reported to show associations with MCI and dementia, including chronic obstructive pulmonary disease [6], chronic heart disease [7], cirrhosis [8], and chronic kidney disease [9]. By contrast, there has been a limited focus on whether chronic

comorbid illnesses exhibit differential associations for different types of dementia. Cognitive impairment, seen with both delirium and dementia, has been associated with polypharmacy. Inappropriate use of benzodiazepine (BZD) in the elderly is also a major public health problem. The consequences of inappropriate BZD use include falls, delirium, other cognitive dysfunction, acute respiratory failure, car accidents, dependence, and withdrawal symptoms [10]. Studies on associations between sedative hypnotics and cognitive decline in elderly patients have yielded mixed findings [11]. Previous studies cannot yet determine whether the observed epidemiological association is a causal effect or the result of unmeasured confounding variables.

It is important to understand which clinical and medical factors might be associated with cognitive decline. Identifying these risk factors that hasten the onset of dementia is crucial for timely medical intervention and predicting prognoses. Improved knowledge of comorbidities in patients with MCI would facilitate the development of preventive strategies aimed at slowing rapid clinical and functional deterioration. This study aimed to examine the association between common clinical and neuropsychological factors in later life at the MCI stage and the risk of converting to dementia, with a particular focus on specific dementia disorders.

1.1. Specific

1.1.1. Study Design. This was a retrospective, longitudinal, observational study that used an unselected sample to test for associations between comorbidities in patients with MCI and the rate of cognitive decline or dementia.

1.1.2. Setting. Data used for this present study were obtained from a dementia care database from January 2014 to June 2017.

1.1.3. Participants. Patients were enrolled and studied at the neurological department of the MacKay Memorial Hospital (Taiwan). We recruited patients by reviewing electronic medical records and documenting information related to clinical measurements, diagnoses, comorbidities, neuroimaging reports, biochemical tests, and neuropsychological assessments at the first visit. The medical records were reevaluated by a dementia expert who was not involved in the assessments of the patients. The rate of decline in cognition was measured based on changes in the Mini-Mental Status Exam (MMSE) scores [12] and Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) [13]. A previous study reported that the conversion to dementia from MCI stages could be predicted by MMSE changes over time instead of single measurements [14]. This approach is useful for the detection of AD and other dementias in people with MCI. The Clinical Dementia Rating Scale (CDR) was initially designed to stage clinical dementia in older persons [15]. It yields both a global score and CDR-SB score. The global score is used to stage dementia severity, whereas the CDR-SB score is a more detailed quantitative version of that scale [16]. Progression of MCI to dementia (converter) was defined as a change in the overall CDR score from 0.5 to ≥1.0. The inclusion criteria were as follows: (1) cognitive complaints not normal for the age of the individual, (2) no dementia (cut-off MMSE score > 23 in persons with at least 6 years of education or >13 in persons with less than 6 years of education and CDR = 0.5), (3) cognitive decline, and (4) essentially normal functional activities in everyday life at the first visit [17]. All participants were evaluated from the first visit and followed up at regular intervals for at least one year until a clinical diagnosis of specific dementia (converter) or MCI (nonconverter) was reached. We included patients who had received regular ambulatory care for 12 months or longer. The intervals between two cognitive assessments were greater than six months. Exclusion criteria were as follows: (1) inability to establish a definite diagnosis for converters at the end of the study; (2) clinical suspicion of frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, or other rare types of dementia; and (3) mixed dementia or mixed neurodegenerative diagnoses. In cases of atypical clinical manifestations, one optimal diagnosis for each patient was made under the consensus of neurologists. We excluded patients with uncertain dementia syndromes. Figure 1 provides a flowchart of the inclusion/exclusion criteria.

1.1.4. Classification of Dementia Syndromes. Diagnoses of dementia syndromes were confirmed by two study clinicians who reviewed clinical, neuropsychological, and brain imaging data and biochemical tests. Comprehensive neuropsychological testing was performed by an experienced clinical psychologist. Dementia subtypes were classified using international consensus clinical criteria. Dementia due to AD was diagnosed in patients who fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD [18]. Dementia or MCI due to vascular disease was diagnosed in patients who fulfilled the American Heart Association/American Stroke Association Statement on Vascular Contributions to Cognitive Impairment and Dementia criteria [19]. LBD is an umbrella term for two closely related clinical diagnoses: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). The third report of the DLB Consortium was used for probable DLB diagnoses [20]. The diagnosis of PDD was made based on recommendations of the movement disorder society task force [21]. The onset age of dementia was defined as the date on which the clinical symptoms and neuropsychological tests first allowed the diagnosis to be made. For nonconverters, MCI due to AD was diagnosed based on the National Institute on Aging and the Alzheimer's Association work group criteria [22]. Neuroimaging criteria for vascular cognitive disorders were based on the 2014 International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) statement [23]. Diagnostic criteria for MCI due to Parkinson's disease or DLB are based on international consensus clinical criteria [24, 25].

1.1.5. Comorbidities and Medication History. Comorbidities, including diabetes mellitus, hypertension, hypercholesterolemia, heart disease (history of coronary artery disease,

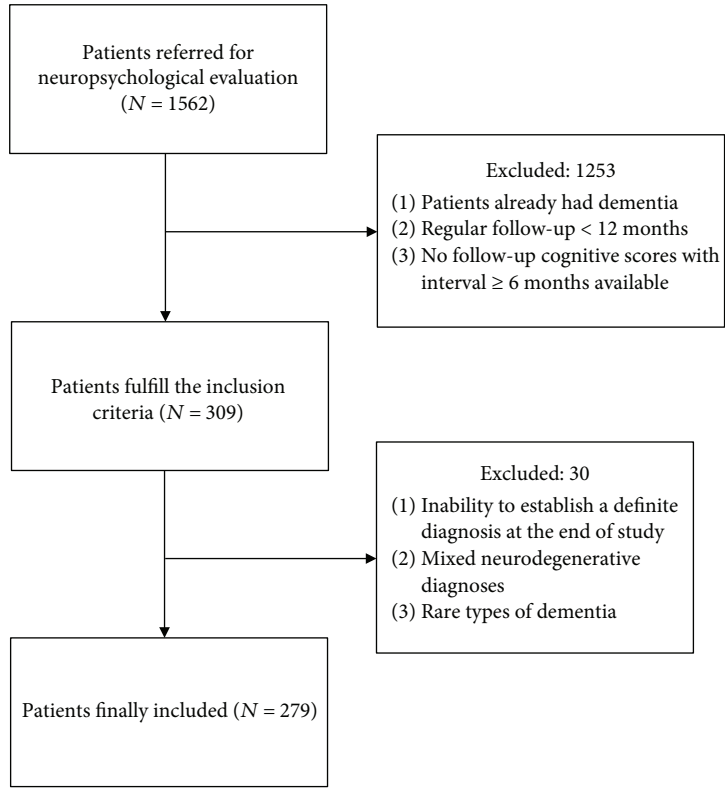

Figure 1: Flow diagram showing the patient exclusion criteria.

atrial fibrillations, heart failure, or valvular heart disease), gastrointestinal disorder, chronic kidney disease, liver function impairment, anemia, and depression, were documented by reviewing the medical records and laboratory documents in the hospital. Medication history of using antidementia agents (cholinesterase inhibitors or memantine) and hypnotic agents, including BZD or nonbenzodiazepine hypnotic agents ("Z drugs") during observational periods, were identified from the medical records and/or medical history interviews. Taking five or more regular medications prescribed >30 days at the time of diagnosis was defined as polypharmacy in our study.

1.1.6. Statistical Methods. We used a stepwise multiple logistic regression model to analyze the data. Each categorical variable was examined using χ^2 tests. The Student t-test was used to analyze continuous variables. Variables with a p value ≤ 0.1 were included in the multiple regression model. The effects of each variable were represented by odds ratios and corresponding 95% confidence intervals (CIs), which were calculated based on the exponential coefficient of the multiple logistic regression model. We also analyzed these factors in different etiologic subgroups. All statistical analyses were performed using R version 3.4.2 (2017-09-28).

1.1.7. Ethical Review. This present study was reviewed and approved by the MacKay Memorial Hospital Institutional Review Board (number 18MMHIS037).

2. Results

We recruited 279 patients with MCI from the database. A total of 163 patients were diagnosed with AD (female 64.4%), 68 had vascular cognitive impairment (female 30.9%), and 48 had Lewy body diseases (LBD) (female 45.8%). The distributions of age did not differ significantly among these groups. In this patient cohort, 58.7%, 31.8%, and 46.5% had hypertension, diabetes, and hypercholesterolemia, respectively, while 19.2% diagnosed as having depressive disorders. Additionally, 37.4% of our MCI patients progressed to dementia with a mean follow-up period of 27.09 ± 15.09 months. The proportion of conversion in the three dementia syndromes was 39.9% in AD, 38.2% in VaD, and 27.1% in LBD ($p = 0.2683$) (Figure 2). Univariate tests showed that the ages of onset, CDR-SB, and baseline MMSE were significant between stable MCI and converters (Table 1). Converters were more likely to receive antidementia agents (66.3% versus 34.9%, $p < 0.001$). The MMSE scores could be divided into subscores for orientation, memory, calculation, language, and perceptual motor function. The subscores of orientation were significantly different between MCI converters and nonconverters.

A multiple logistic regression model revealed that older age at onset, female sex, and a greater CDR-SB were significantly associated with a higher risk of converting from MCI to dementia. Receiving antidementia agents was strongly associated with a higher probability of this conversion

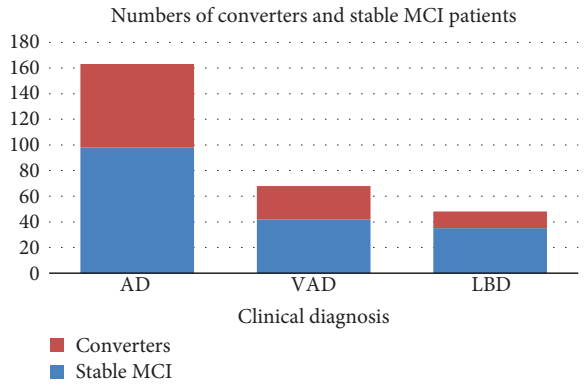

Figure 2: Proportions of conversion to dementia in patients with different clinical diagnoses. AD: Alzheimer's disease; VaD: vascular dementia; LBD: Lewy body diseases.

Table 1: Univariate analysis of clinical characteristics in 279 MCI patients who remained stationary course or progressed to dementia.

	Stable MCI $N = 175$ (percentage)	Dementia $N = 104$ (percentage)	p value
Etiology	AD 98 (56) VaD 42 (24) LBD 35 (20)	AD 65 (62.5) VaD 26 (25) LBD 13 (12.5)	0.268
Age of onset	70.9	74.7	<0.001
Female	100 (57.1)	48 (46.2)	0.098
Education	6.9	7.3	0.425
CDR-SB	2.20	2.96	<0.001
MMSE	24.5	23.3	0.004
Hypertension	101 (57.7)	63 (60.6)	0.954
DM	51 (29.1)	38 (36.5)	0.373
Dyslipidemia	90 (51.4)	39 (37.5)	0.021
Liver disease	24 (13.7)	19 (18.3)	0.279
Renal disease	20 (11.4)	14 (13.5)	0.844
Gastrointestinal disease	82 (46.9)	50 (48.1)	0.942
Anemia	10 (5.7)	7 (6.7)	0.918
Heart disease	73 (41.7)	47 (45.2)	0.894
Stroke	43 (24.6)	25 (24)	1.000
Depression	26 (14.9)	25 (24)	0.065
Antidementia agents	61 (34.9)	69 (66.3)	<0.001
Hypnotic agents	61 (34.9)	49 (47.1)	0.064
Polypharmacy	103 (58.9)	69 (67.0)	0.314

AD: Alzheimer's disease; VaD: vascular dementia; LBD: Lewy body diseases; MMSE: Mini-Mental State Examination; CDR-SB: Clinical Dementia Rating-Sum of Boxes; DM: diabetes mellitus. Remark: antidementia agents: acetylcholinesterase inhibitors and memantine. Hypnotic agents: benzodiazepines and nonbenzodiazepine hypnotics.

(Table 2). Hyperlipidemia was associated with a decreased risk of conversion. The interaction between hyperlipidemia and etiologies was nonsignificant. We also evaluated baseline MMSE scores (substituting CDR-SB in the model), and the results of the other risk factors were unaltered. We tested four interactions between etiologies and each one of DM, hypertension, stroke, and heart disease, respectively, in the multiple logistic regression model, and all were nonsignificant. These interactions were not reported. Selection of risk factors in the model was based on the previous studies and aforementioned statistical criteria.

Table 2: Logistic regression model of variables associated with conversion to dementia in the MCI cohort.

	OR	2.50%	97.50%	p value
(Intercept)	0.0014	$1.00E-04$	0.029	<0.001
VaD	2.082	0.910	4.909	0.089
LBD	0.536	0.225	1.223	0.146
Age	1.071	1.032	1.113	<0.001
Gender	0.540	0.293	0.980	0.044
CDR-SB	1.553	1.221	2.008	<0.001
Hyperlipidemia	0.554	0.310	0.980	0.044
Depression	1.624	0.730	3.623	0.233
Antidementia agents	5.162	2.663	10.522	<0.001
Hypnotic agents	1.346	0.719	2.517	0.352

VaD: vascular dementia; LBD: Lewy body diseases; CDR-SB: Clinical Dementia Rating-Sum of Boxes. Remark: antidementia agents: acetylcholinesterase inhibitors and memantine. Hypnotic agents: benzodiazepines and nonbenzodiazepine hypnotic agents.

We performed a subgroup analysis from the MCI cohort according to the etiology. Age of onset was a significant risk factor in AD and VaD. Female was associated with an increased risk in AD. CDR-SB was associated with higher risk in AD and VaD. Receiving antidementia agents was significantly associated with conversion in AD. The trend was mostly consistent with the finding in the main cohort (Table 3). The LBD and AD subgroups had very similar risk factor profiles of conversion from MCI to dementia.

3. Discussion

MCI is heterogeneous in its etiology and clinical course. Older age and higher CDR-SB are major important markers for the identification of patients at a higher risk of progression. In our present study, we found that CDR-SB is highly indicative both in the whole cohort and different subgroup analyses. Because of the scoring rule, a CDR global score of 0.5 was unable to detect the cognitive categories that were affected (i.e., memory, orientation, judgment/problem solving, community affairs, hobbies, and personal care). In contrast, CDR-SB includes all categories, and the sensitivity might differ from the CDR global score.

Cholesterol has been recently shown to be important for synaptic transmission, and many neurodegenerative diseases, including AD and PD, are characterized by impaired cholesterol turnover in the brain [26]. A population-based prospective cohort study from Denmark showed that subjects with objective cognitive impairment who were most likely to progress were older, physically inactive, had a higher level of total cholesterol, and had a history of depression [27]. Reviews and meta-analyses revealed that midlife high total serum

Table 3: Logistic regression model of variables associated with conversion to dementia in the AD (a), LBD (b), and VaD (c) cases of the MCI cohort.

(a) Subgroup of AD

	OR	2.50%	97.50%	p value
(Intercept)	0.008	$1.00E-04$	0.309	0.013
Age	1.058	1.010	1.112	0.021
Gender	0.424	0.202	0.874	0.021
CDR-SB	1.395	1.030	1.913	0.034
Hyperlipidemia	0.761	0.364	1.569	0.462
Depression	1.124	0.419	2.985	0.814
Antidementia agents	3.411	1.572	7.789	0.003
Hypnotic agents	1.800	0.808	4.051	0.151

(b) Subgroup of LBD

	OR	2.5%	97.50%	p value
(Intercept)	0	0	0.529	0.067
Age	1.186	1.021	1.446	0.051
Gender	0.143	0.012	1.009	0.080
CDR-SB	1.079	0.486	2.358	0.845
Dyslipidemia	0.321	0.045	1.825	0.218
Depression	7.221	0.720	106.364	0.109
Antidementia agents	66.025	7.839	1340.956	0.001
Hypnotic agents	0.410	0.057	2.3819	0.337

(c) Subgroup of VaD

	OR	2.50%	97.5%	p value
(Intercept)	0.000	0.000	0.068	0.009
Age	1.106	1.030	1.203	0.010
Gender	0.563	0.129	2.233	0.421
CDR-SB	2.172	1.229	4.309	0.015
Hyperlipidemia	0.459	0.131	1.550	0.211
Depression	8.786	1.059	101.545	0.057
Hypnotic agents	0.820	0.216	2.934	0.762

AD: Alzheimer's disease; VaD: vascular dementia; LBD: Lewy body diseases; CDR-SB: Clinical Dementia Rating-Sum of Boxes. Remark: hypnotic agents indicate benzodiazepines and nonbenzodiazepine hypnotic agents. Antidementia agents were not reimbursed for VaD patients in Taiwan health insurance system. They were not analyzed in the model due to sparsity.

cholesterol was associated with an increased risk of MCI, AD, and cognitive decline in late-life; however, high cholesterol in late-life was not associated with MCI, AD, VaD, any dementia, or cognitive decline [28]. Patients with late-life cardiovascular factors, including body mass index, atrial fibrillation, hypertension, hyperlipidemia, and diabetes, were more likely to have a diagnosis of VaD than the normal populations. However, there were no associations between AD and DLB with hypertension, hyperlipidemia, or diabetes [5]. In our study, we found that hypercholesterolemia was not a risk factor but had a nonsignificant protective effect on the progression of MCI. More than 70% of our patients used statins during the study period. However, we were not sure based on the prescription pattern, whether these patients received treatment from other hospitals or clinics. A previous study concluded that statins may slow the rate of cognitive decline and delay the onset of AD and all-cause dementia in cognitively healthy elderly individuals, whereas individuals with MCI may not have comparable cognitive protection from these agents [29]. A meta-analysis of two large trials, including a total of 26,340 patients aged ≥ 40 years with cardiovascular risk factors, reported that statins administered in later life do not prevent cognitive decline or dementia [30].

In Taiwan, cholinesterase inhibitors and memantine can be provided by the health insurance system under the following rules. AD or PDD was diagnosed by a neurologist or psychiatrist using the clinical diagnostic criteria. They had the latest MMSE scores of 10–26 and did not have contraindications. The authority required annual reevaluations of the initial prescription, and the reimbursement would be

discontinued in case there is too much deterioration in MMSE scores or CDR. In our study, 45.5% of patients received antidementia agents during the observation period. Prescribing these medicines was associated with the likelihood of converting to dementia. However, those who received antidementia treatments also had higher CDR-SB (significant) and lower baseline MMSE scores (not significant). A possible explanation is that the physicians more likely prescribed antidementia agents to improve the cognitive functions in patients who they found were more severe at baseline. The results did not imply that the clinical courses in MCI patients were changed by these treatments.

Risks of cognitive decline and delirium were known to be associated with polypharmacy. In a prospective cohort study of 294 elderly patients, 22% taking five or fewer medications were found to have impaired cognition when compared with 33% of patients taking 6–9 medications and 54% in patients taking 10 or more medications [31]. A previous study of patients with cognitive impairment found that 70.4% were on multiple medications and 42% took BZD [32]. In our study, 61.5% of patients took more than five types of medications and almost 40% of patients were prescribed sedative/hypnotic drugs for at least 30 days during the study. In a large cohort of postmenopausal women, all types of antidepressant use and different levels of depression severity were associated with subsequent cognitive impairment [33]. By contrast, MCI has reported being a risk factor for depressive and anxiety disorders, suggesting common pathological pathways for cognitive and psychiatric outcomes [34]. A recently published article found that executive dysfunction in elderly people with depression may be associated with the age effect [35]. The reciprocal effects of depression and MCI were inconclusive. Our data revealed a nonsignificant trend ($p = 0.06$) supporting a link between depression and cognitive decline.

The effects of hypnotic agents and risk of dementia remained a subject of debate. A recent study based on longitudinal data found a slight association, but no dose-effect, in elderly nondemented individuals [36]. We found that hypnotic agents were very commonly used in depressed patients in our cohort. Neither depression nor hypnotics use was associated with conversion from MCI to dementia. These findings are consistent with a recent study performed in Taiwan [37].

3.1. Limitations. In our study, the diagnosis of dementia syndromes was justified by two clinicians who were experienced in dementia care. Comprehensive neuropsychological testing was performed by an experienced clinical psychologist. We excluded MCI of uncertain etiology and mixed neurodegenerative diagnoses. Lack of pathological confirmation was a weakness of our study, similar to the majority of the previously published articles. The primary clinical etiologic diagnosis remained stable in more than 90% of our patients. Previous results from a multicenter longitudinal database suggested that hospital-based studies were more accurate in categorizing dementia subtypes because they involve a multidisciplinary diagnostic approach and an adequate diagnostic infrastructure compared with community-based studies [38]. Due to the Personal Data Protection Act of 2010 of Taiwan, medication history may not be perfectly completed. The small case numbers limited our capacity to analyze whether there were any differences among different dementia syndromes.

4. Conclusions

Our retrospective, longitudinal, observational study showed the distribution of dementia subtypes from MCI and described the clinical progression, comorbidity, and medication history associated with dementia subtypes. We believe that comprehensive clinical profiling, assessments of risk factors, and detailed drug history evaluations are helpful to better understand and manage dementia subtypes. Our study suggests the importance of early detection of individuals with MCI. In the future, prospective studies should establish which of these factors are the most influential to aid the development of treatment and prevention strategies. Polypharmacy and hypnotic sedatives should be avoided if they are not essential, especially in elderly patients with MCI.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Metabolic Risk Factors of Alzheimer's Disease, Dementia with Lewy Bodies, and Normal Elderly: A Population-Based Study

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Background. Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) share many risk factors. Evidence suggests that metabolic risk factors are important to AD; however, their association with DLB is unclear. The risk of cardiovascular diseases (CVD) associated with AD and DLB is also uncertain. Thus, this nationwide, population-based study was designed to evaluate the metabolic and CVD risks in AD and DLB. *Materials and Methods*. Data were obtained from the Taiwan National Health Insurance Research Database. AD patients, DLB patients, and normal control (NC) individuals from 1996 to 2013 were enrolled for risk assessment. *Results*. In total, 7544 NC individuals, 1324 AD patients, and 562 DLB patients were enrolled. Participants with one or more metabolic risk factors had significantly higher odds of AD or DLB. No significant differences in metabolic risk factors were observed between DLB and AD patients. AD patients had a lower risk of CVD (aHR = 0.67, 95% CI = 0.59–0.76, p value < 0.001) and coronary artery disease (CAD) (aHR = 0.59, 95% CI = 0.51–0.69, p value < 0.001) than NC. DLB patients had a higher risk of ischemic stroke (aHR = 2.27, 95% CI = 1.68–3.06, p value < 0.001) than NC. *Conclusion*. Metabolic risk factors are important in AD and DLB. Patients with AD might have a lower risk of CAD and ischemic strokes. Patients with DLB might have a higher risk of ischemic stroke.

1. Introduction

Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are leading causes of dementia [1]. AD is caused by progressive neurodegeneration in the medial temporal lobe, hippocampus formation, and other brain areas with synergistic amyloid and tau proteinopathy [1, 2]. The risk factors for sporadic AD are complex. Apolipoprotein E ε4 allele (APOE4) is one of best-known genetic risk factors. Additional risk factors include age, family history of AD, previous stroke, sleep apnea, traumatic brain injury (TBI), and limited education [1]. DLB is characterized by the propagation of aggregated intracellular α-synuclein (Lewy bodies) [3]. Risk factors of DLB overlap with that of AD to some extent; for

example, APOE4, previous stroke, and TBI are risk factors of both DLB and AD [1, 4–6].

Emerging evidence suggests that metabolic risk factors contribute not only to cardiovascular diseases (CVD) like coronary artery disease (CAD), and ischemic strokes, such as cerebrovascular accident (CVA), but also to dementia [7–9]. Hypertension, diabetes mellitus (DM), and hyperlipidemia are known risk factors for AD [9, 10]. Moreover, a history of CAD or CVA is associated with accelerated cognitive decline in AD patients [8, 11, 12].

However, it is unclear if metabolic risks are also important risk factors of DLB, and it is unclear if AD and DLB patients are more susceptible to CVD. Hence, we conducted a nationwide, population-based, normal control, risk-adjusted, retrospective cohort study in Taiwan to investigate the metabolic risks and the incidence of CVD in patients with AD and DLB. Our purpose is to determine the modifiable metabolic risk factors in DLB and the risk of CVD in AD and DLB to improve the prevention of dementia and CVD.

2. Materials and Methods

2.1. Study Design. We conducted a retrospective cohort study using health insurance data from the National Health Insurance Research Database (NHIRD), which contained medical information of over 99% of Taiwan citizens. The Longitudinal Health Insurance Database 2000 (LHID2000), a subdataset of the NHIRD, was applied for this study. The LHID2000 contains diagnostic data of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code, and treatment data from the outpatient visits and hospitalizations from 1996 to 2013 of 1 million random individuals. All participants were encrypted with a dummy number. This study was approved by the Institutional Review Board and the Ethics Committee of China Medical University Hospital, Taiwan (CMUH104-REC2-115 (CR-2)).

This study investigated AD patients, DLB patients, and normal control (NC) individuals who were enrolled. Both AD and DLB patients were identified using specific criteria. AD patients who met any of the following criteria were included: (1) the ICD-9-CM code 331.0 (AD diagnosis date defined as the index date), or (2) having a diagnosis record of dementia (ICD-9-CM: 290.0–290.4, 294.1, and 331.0–331.2) and receiving acetylcholinesterase inhibitors or memantine treatment (dementia diagnosis date defined as the index date). The exclusion criteria for the AD cohort were patients with (1) any records of cognitive impairment (ICD-9-CM: 331.8, 331.83, and 331.9), Huntington's disease (ICD-9-CM: 333.4), Creutzfeldt-Jakob disease (ICD-9-CM: 046.11 and 046.19), and hydrocephalus (ICD-9-CM: 331.3, 331.4, 331.5, 741.0, and 742.3), (2) a history of stroke (ICD-9-CM: 430–435) or CAD (ICD-9-CM: 410–414) before the index date, and (3) Parkinson's disease (PD) or Parkinsonism diagnosis recorded within 1 year after the index date. For DLB patients, the inclusion criteria were (1) the diagnosis of PD and Parkinsonism (ICD-9-CM: 332, 332.0, 332.1, 333, 333.0, and 333.9) 1 year after diagnosis of dementia (ICD-9-CM: 290.0–290.3, 294.1, and 331.0) (dementia diagnosis date defined as the index date), (2) diagnosis of dementia within 1 year after diagnosis of PD and Parkinsonism (dementia diagnosis date defined as the index date), and (3) ICD-9-CM code 331.82 (DLB diagnosis date defined as the index date). The exclusion criteria for DLB patients included a history of stroke, CAD, head injury (ICD-9-CM: 850–854 and 959.01), or hydrocephalus. Patients with the diagnosis of both AD and DLB were excluded from the study cohorts. The NC population was defined as patients without the diagnosis of AD, DLB, other dementias, or Parkinson's disease. The NC population excluded individuals with a history of stroke or CAD. The study population selection procedure is shown in Figure 1.

2.2. Statistical Analysis. The main outcomes of this study were stroke (ICD-9-CM: 430–435) and CAD (ICD-9-CM: 410–414) after the index date. Only inpatient records were used to identify patients with stroke. A history of hypertension (ICD-9-CM: 401–405), diabetes mellitus (ICD-9-CM: 250), and hyperlipidemia (ICD-9-CM: 272) were included as comorbidities. All comorbidities were considered to be significant after at least one inpatient visit or two outpatient visits. In addition, we investigated the use of aspirin, clopidogrel, and warfarin before the index date. Demographic characteristics of sex and age were considered as covariates. We combined the AD and DLB cohorts and matched them with the NC population according to sex and age in a 1 : 4 ratio by propensity score matching. This study compared the risk of the main outcomes, that is, CAD and stroke, among the three cohorts. The risk factors for AD and DLB were also evaluated. The baseline characteristics among the three groups were tested using the chi-square test and ANOVA. Logistic regression was used to evaluate the probable risk factors of AD and DLB. We examined whether the risk of stroke and CAD increases among AD and DLB patients using the Cox proportional hazard regression. A p value less than 0.05 was significant. All the statistical analyses were conducted using the statistical software package, SAS, version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

The final study population consisted of 7544 NC individuals, 1324 AD patients, and 562 DLB patients (Table 1). The number of female participants was higher than male participants in the AD cohort. Contrarily, the DLB cohort included a higher number of male participants. The difference in the average ages among the three cohorts was insignificant (p value = 0.26). Participants under 65 years were less than 20% in each cohort. The distributions of baseline comorbidities differed among the NC, AD, and DLB groups (p value < 0.001). The medication status was also significantly different (p value < 0.01) among the cohorts. The proportions of diabetes mellitus and hyperlipidemia were higher in AD patients than in DLB patients. There were 58.4% and 60.5% hypertensive individuals in the AD group and the DLB group, respectively.

Between AD and NC, compared to participants without any metabolic risk factors, the participants with one or more metabolic risk factors had significantly higher odds of AD

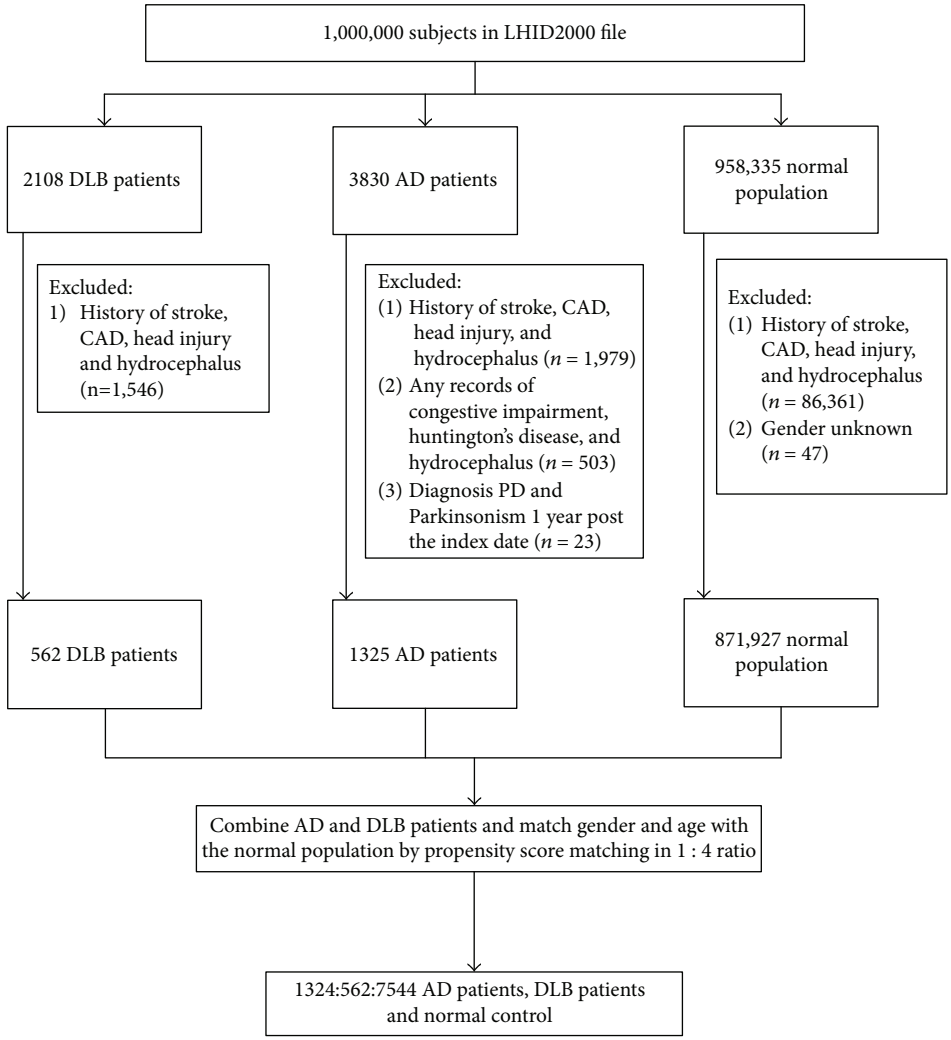

Figure 1: Enrollment flow chart for the study population.

Table 1: Demographic and background characteristics of NC, AD, and DLB patients.

	NC	AD	DLB	*p* value
N	7544	1324	562	
Sex, f/m	3758/3786	768/556	242/320	<0.001
Age				
<50	216 (2.9)	39 (2.9)	15 (2.7)	
50–64	939 (12.4)	188 (14.2)	50 (8.90)	
≥65	6389 (84.7)	1097 (82.9)	497 (88.4)	
Mean (SD)	74.5 (11.1)	74.2 (11.4)	75.1 (10.3)	0.26*
Comorbidity				
Hypertension	2777 (36.8)	773 (58.4)	340 (60.5)	<0.001
Diabetes mellitus	1132 (15.0)	387 (29.2)	142 (25.3)	<0.001
Hyperlipidemia	1201 (15.9)	466 (35.2)	146 (26.0)	<0.001
Drug				
Aspirin	1139 (15.1)	468 (35.3)	186 (33.1)	<0.001
Clopidogrel	21 (0.28)	18 (1.36)	7 (1.25)	<0.001
Warfarin	45 (0.6)	20 (1.51)	5 (0.89)	0.002

Chi-square test; *ANOVA. NC, normal control; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; SD, standard deviation.

Table 2: Risk factors for AD and DLB patients.

Risk factors	Multivariable ORs (95% CI)		
	AD versus NC	DLB versus NC	DLB versus AD
Sex			
Female	1 (reference)	1 (reference)	1 (reference)
Male	0.82 (0.72–0.92)**	1.42 (1.19–1.69)***	1.75 (1.43–2.15)***
Age, per year	1.0 (0.99–1.0)	1.0 (0.99–1.01)	1 (0.99–1.01)
Combination of metabolic risk factors (hypertension, diabetes, and hyperlipidemia)			
(− − −)	1 (reference)	1 (reference)	1 (reference)
(+ − −)	2.29 (1.95–2.69)***	2.74 (2.2–3.42)***	1.16 (0.89–1.52)
(− + −)	2.28 (1.64–3.18)***	2.23 (1.38–3.62)***	0.91 (0.52–1.6)
(− − +)	3.7 (2.78–4.93)***	2.66 (1.65–4.29)***	0.66 (0.39–1.11)
(+ + −)	3.08 (2.42–3.92)***	3.6 (2.6–4.99)***	1.18 (0.81–1.73)
(+ − +)	3.63 (2.94–4.49)***	3.25 (2.37–4.46)***	0.88 (0.62–1.26)
(− + +)	3.58 (2.48–5.17)***	2.14 (1.1–4.17)*	0.62 (0.3–1.28)
(+ + +)	4.9 (4.01–5.99)***	3.64 (2.65–5)***	0.7 (0.5–0.99)

+, presence; −, absence; CI, confidential interval; OR, odds ratio; NC, normal control; AD, Alzheimer's disease; DLB, dementia with Lewy bodies. Adjusted sex and age in logistic regression. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

(Table 2). The odds ratio of AD was 4.9 (95% CI = 4.01–5.99, p value < 0.001) in patients with three metabolic risk factors. For DLB and NC, the logistic regression showed an odds ratio of 3.64 for DLB (95% CI = 2.65–5, p value < 0.001) in patients with three metabolic risk factors. Between DLB and AD, there were no significant odds of DLB in patients with any metabolic risk factors. The male patients had low odds of AD (OR = 0.82, 95% CI = 0.72–0.92, p value < 0.01), but high odds of DLB (OR = 1.42, 95% CI = 1.19–1.69, p value < 0.001).

The results of the Cox model indicated that the AD patients had a lower risk of outcomes (aHR = 0.67, 95% CI = 0.59–0.76, p value < 0.001) than the NC population (Table 3). Separated, the risks of CAD and stroke were 0.59-fold (95% CI = 0.51–0.69, p value < 0.001) and 1.02-fold (95% CI = 0.8–1.3, p value > 0.05), respectively, in AD patients. Compared with the NC cohort, there was a higher stroke risk in the DLB group (aHR = 2.08, 95% CI = 1.58–2.73, p value < 0.001). The risk of both outcomes combined was also higher (aHR = 1.23, 95% CI = 1.06–1.44, p value < 0.01). However, the risk of CAD alone was negligible (aHR = 1.04, 95% CI = 0.86–1.24, p value > 0.05) among DLB patients. The risk of outcomes in males was higher than that in females (aHR = 1.14, 95% CI = 1.06–1.23, p value < 0.001). The risk of outcomes increased 1.03-fold per year with increasing age (95% CI = 1.03–1.04, p value < 0.001). The aHR outcomes of hypertension and diabetes mellitus were 1.39 (95% CI = 1.28–1.51, p value < 0.001) and 1.2 (95% CI = 1.09–1.34, p value < 0.001), respectively. Hyperlipidemia reduced the risk of stroke (aHR = 0.7, 95% CI = 0.55–0.9, p value < 0.01), but did not affect the risk of outcomes (aHR = 0.9, 95% CI = 0.81–1, p value > 0.05) and CAD (aHR = 0.96, 95% CI = 0.86–1.09, p value > 0.05). There was no significant effect on the risk of outcomes with aspirin (aHR = 0.98, 95% CI = 0.89–1.09, p value > 0.05), clopidogrel (aHR = 1.25, 95% CI = 0.72–2.16, p value > 0.05), and warfarin (aHR = 0.66, 95% CI = 0.38–1.13, p value > 0.05). Additionally, we divided stroke outcome into ischemic and hemorrhagic stroke. The ischemic stroke risk was insignificant among AD patients (aHR = 1.01, 95% CI = 0.77–1.33, p value > 0.05) when compared to the NC population (Table 4). In contrast, the DLB group had a higher ischemic stroke risk (aHR = 2.27, 95% CI = 1.68–3.06, p value < 0.001). The aHRs of hemorrhagic stroke among AD and DLB patients were insignificant (for AD: aHR = 1.04, 95% CI = 0.61–1.77, p value > 0.05; for DLB: aHR = 1.4, 95% CI = 0.7–2.8, p value > 0.05).

4. Discussion

In this retrospective cohort study, female patients were more likely to have AD, while male patients were more likely to have DLB. Patients with any one of the metabolic risk factors considered, had an increased risk of having AD or DLB. Patients who had three comorbid risk factors (hypertension, diabetes mellitus, and hyperlipidemia) simultaneously were at higher risk of having AD or DLB than patients with a single risk factor. The consequences of metabolic risk factors for AD are similar to those for DLB. Patients with AD had a lower risk, while patients with DLB had a higher risk of all CVD outcomes than the NC population. When outcomes were separated, patients with AD had a lower risk of CAD, and patients with DLB had a higher risk of ischemic stroke than the NC population. Patients with AD or DLB had no increased risk of hemorrhagic stroke.

We found that AD was more prevalent among female patients, while DLB was more prevalent among male patients. Sex differences between AD and DLB have been reported [13]. The age at onset of AD may be lower in women than in men with the same copies of the APOE $\varepsilon 4$ allele [14]. Male sex is a known risk factor for DLB [3, 5].

Table 3: Multivariable analysis of risk of CAD and stroke in Cox proportional hazard regression.

Risk factors	All outcomes Adjusted HR (95% CI)	CAD Adjusted HR (95% CI)	Stroke Adjusted HR (95% CI)
NC	1 (reference)	1 (reference)	1 (reference)
AD	0.67 (0.59–0.76)***	0.59 (0.51–0.69)***	1.02 (0.8–1.3)
DLB	1.23 (1.06–1.44)**	1.04 (0.86–1.24)	2.08 (1.58–2.73)***
Sex			
Female	1 (reference)	1 (reference)	1 (reference)
Male	1.14 (1.06–1.23)***	1.11 (1.02–1.21)*	1.26 (1.07–1.49)**
Age, per year	1.03 (1.03–1.04)***	1.03 (1.02–1.03)***	1.05 (1.04–1.06)***
Hypertension (yes versus no)	1.39 (1.28–1.51)***	1.39 (1.27–1.53)***	1.37 (1.14–1.64)***
Diabetes mellitus (yes versus no)	1.2 (1.09–1.34)***	1.15 (1.02–1.29)*	1.43 (1.15–1.78)**
Hyperlipidemia (yes versus no)	0.9 (0.81–1)	0.96 (0.86–1.09)	0.7 (0.55–0.9)**
Aspirin (yes versus no)	0.98 (0.89–1.09)	0.95 (0.85–1.07)	1.1 (0.89–1.37)
Clopidogrel (yes versus no)	1.25 (0.72–2.16)	1.29 (0.69–2.41)	1.14 (0.36–3.58)
Warfarin (yes versus no)	0.66 (0.38–1.13)	0.6 (0.31–1.15)	0.84 (0.31–2.27)

HR, hazard ratio; CI, confidence interval; NC, normal control; AD, Alzheimer's disease; DLB, dementia with Lewy bodies. Adjusted sex, age, hypertension, diabetes mellitus, hyperlipidemia, aspirin, clopidogrel, and warfarin in Cox proportional hazards regression. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

Table 4: Multivariable analysis of the risk of ischemic stroke and hemorrhagic stroke in Cox proportional hazard regression.

Risk factors	Ischemic stroke Adjusted HR (95% CI)	Hemorrhage stroke Adjusted HR (95% CI)
NC	1 (reference)	1 (reference)
AD	1.01 (0.77–1.33)	1.04 (0.61–1.77)
DLB	2.27 (1.68–3.06)***	1.4 (0.7–2.8)
Sex		
Female	1 (reference)	1 (reference)
Male	1.16 (0.97–1.4)	1.74 (1.21–2.49)**
Age, per year	1.05 (1.04–1.06)***	1.05 (1.03–1.07)***
Hypertension (yes versus no)	1.34 (1.09–1.64)**	1.5 (1.03–2.19)*
Diabetes mellitus (yes versus no)	1.48 (1.16–1.88)**	1.25 (0.76–2.06)
Hyperlipidemia (yes versus no)	0.75 (0.57–0.98)*	0.52 (0.29–0.95)*
Aspirin (yes versus no)	1.21 (0.95–1.53)	0.76 (0.46–1.27)
Clopidogrel (yes versus no)	0.91 (0.22–3.68)	2.36 (0.32–17.36)
Warfarin (yes versus no)	1.05 (0.39–2.82)	

HR, hazard ratio; CI, confidence interval; NC, normal control; AD, Alzheimer's disease; DLB, dementia with Lewy bodies. Adjusted sex, age, hypertension, diabetes mellitus, hyperlipidemia, aspirin, clopidogrel, and warfarin in Cox proportional hazards regression. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

The cause of these sex differences remains uncertain and need to be clarified.

We found that hypertension significantly increased the risk of both AD (OR = 2.29, 95% CI = 1.95–2.69) and DLB (OR = 2.74, 95% CI = 2.20–3.42). Hypertension is a risk factor for dementia [9]. Studies have shown that hypertension increases the risk of AD, and that antihypertensive treatment can reduce the risk of AD [10]. The relationship between hypertension and DLB is less understood. In a neuropathological study, patients with DLB pathology were found to have a significantly higher incidence of hypertension [15].

We also found that diabetes mellitus increased the risk of AD (OR = 2.28, 95% CI = 1.64–3.18) and DLB (OR = 2.23, 95% CI = 1.38–3.62). Diabetes mellitus is a risk factor for cognitive decline [10]. Insulin insufficiency increases the risk of AD [10]. Either an excessive glucose level or an insulin dysfunction may play a role in AD [10]. There is limited information about the effect of diabetes on DLB. Although diabetes was a risk factor for DLB in our study, it did not alter the risk of DLB in another study [5]. This conflicting result may have arisen because of the different diagnostic criteria for diabetes in different populations, and further studies are warranted to clarify if diabetes causes DLB.

Hyperlipidemia was another risk factor that increased AD (OR = 3.70, 95% CI = 2.78–4.93) and DLB (OR = 2.66, 95% CI = 1.65–4.29). Dysfunction of lipid metabolism plays an important role in dementia. High total serum cholesterol levels are associated with dementia and AD [10]. APOE is an important class of lipoprotein in lipid metabolism, and APOE4, an allele of APOE, is implicated in AD. APOE4 is also more frequent in DLB patients than in controls [5]. Nevertheless, the mechanism by which lipid disorders affect DLB is obscure. Considering its close association with dementia and that it is a modifiable risk factor, we suggest that studies focus more on lipid disorders in future DLB studies.

Having three metabolic risk factors simultaneously further increased the risk of AD (OR = 4.90, 95% CI = 4.01–5.99) and DLB (OR = 3.64, 95% CI = 2.65–5.00). The hazard of metabolic risk factors is similar in AD and DLB. AD and DLB share many similar risk factors such as depression, smoking, and the APOE $\varepsilon 4$ allele [5]. Cerebrovascular lesions are also frequent in both AD and DLB [16, 17]. AD and DLB show clinical and pathological similarity, and metabolic risk factors may have similar roles in the risk of developing AD and DLB. Summarizing, better lifestyle modifications and medication for the treatment of metabolic risk factors may not only prevent stroke and CAD but also AD and DLB.

In a risk-adjusted long-term follow-up, we found that AD had a decreasing risk of CAD (aHR = 0.59, 95% CI = 0.51–0.69), while DLB had an increasing risk of ischemic stroke (aHR = 2.27, 95% CI = 1.68–3.06). AD is associated with atherosclerosis [18]. Evidence has shown that cerebral atherosclerosis, involving extracranial or intracranial arteries, contributes to the cognitive decline in AD [19, 20]. Coronary atherosclerosis also worsens cognitive function in AD [11]. These facts reflect the hemodynamic compromise or hypoperfusion of the brain which correlates with AD deterioration [21–23]. However, AD itself does not necessarily increase the risk of CAD. In fact, a recent study showed that APOE $\varepsilon 4$ does not interact with CAD [24]. Interestingly, our results implied that patients with AD might have protective factors to CAD, with the underdiagnosis of CAD or ischemic stroke in AD having been one possible explanation. However, we did not find a similar effect in DLB, making it less likely. A change in eating behaviour in AD was another possible explanation. Anorexia and weight loss, which are common in advanced AD [25], may reduce blood sugar or lipid level and decrease the risk of atherosclerosis. A change in amyloid β (Aβ) metabolism may affect the risk of CAD in AD. Extracellular deposition of Aβ in the brain is the pathological hallmark of AD [26]. A dysfunction of Aβ production and clearance in the central nervous system may contribute to the accumulation of cerebral Aβ in late onset AD [27, 28]. Higher plasma Aβ also correlates with cerebral white matter lesions and ischemic heart disease [29]. In short, the change in the Aβ metabolic pathway in AD may be associated with cerebrovascular and cardiovascular risks, and further investigations are warranted.

A history of stroke is more frequently observed in patients with DLB [5]. White matter hyperintensities on cerebral T2-weighted magnetic resonance imaging are higher in DLB than in AD patients [17]. DLB usually shows hypoperfusion in the striatum and the visual cortex [3]. All these studies suggest that DLB correlates with the function of cerebral small vessels. Postural hypotension is commonly seen in DLB [3], and is also a potential risk factor for ischemic stroke. Intracellular α-synuclein aggregation is characteristic of DLB [1]. Studies also show a potential role for α-synuclein in ischemic stroke modulation [30]. Further studies are required to determine the mechanism of stroke in DLB.

Cerebral microbleeds are small hemosiderin deposits in the brain and are not unusual in AD or DLB [31, 32]. The gradual spreading of the intracellular aggregation of hyperphosphorylated tau (P-tau) in the brain is associated with AD progression [1]. Studies also reveal the association between cerebral microbleeds and P-tau [33, 34]. Interestingly, our data did not reveal increased hemorrhagic stroke in both AD and DLB patients when compared to NC individuals. This may imply that the pathological processes for intracerebral hemorrhage and cerebral microbleeds may differ in AD and DLB.

Limitations were inevitable in this study. First, subjects were classified based on the main clinical diagnosis and bias from misclassification was possible. Dementia is a complex syndrome and accurate diagnosis is challenging because of the overlapping clinical presentation. Although we used multiple methods during the inclusion process to identify the diagnosis and to minimize misclassification, a few atypical cases may still present difficulties in classification. Second, the severity of metabolic risk factors and their different treatment methods can potentially affect the risk of CAD or stroke. Third, this was a Taiwan-based study, and the influence of risk may vary among different racial groups. Fourth, this was a retrospective study, and selection and information biases cannot be completely excluded.

5. Conclusions

Hypertension, diabetes mellitus, and hyperlipidemia are risk factors of AD and DLB. Multiple metabolic risk factors, when simultaneously present, might aggravate the risk of AD and DLB. The control of metabolic risk factors is crucial for the prevention of AD and DLB. Patients with AD might have a lower risk of CAD, while patients with DLB might have a higher risk of ischemic stroke. Our study suggests that better lifestyle modifications and medications for the treatment of metabolic risk factors may lower the risk of AD and DLB. Furthermore, stroke prevention is important in patients with DLB. Further studies to understand the mechanism of stroke in DLB are warranted.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Incidence and Comorbidity of Dementia with Lewy Bodies: A Population-Based Cohort Study

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Background and Aims. Dementia with Lewy bodies (DLB) is the third most common form of dementia. Epidemiological studies of DLB in Taiwan are scarce. In this study, we estimated the incidence of DLB and comorbidity in the population of Taiwan. *Methods*. Data were obtained from the Taiwan National Health Insurance Research Database (NHIRD). DLB patients between 2000 and 2013 were enrolled in assessments of incidence and comorbidity. *Results*. The incidence of DLB was shown to be 7.10 per 100,000 person-years (95% CI = 6.63–7.59), which increased with age. The average age at diagnosis was 76.3, and this was higher for males than for females. The comorbidity rates of hypertension and hyperlipidemia in DLB patients were higher in females than in males. *Conclusions*. Epidemiologic data from large-scale retrospective studies is crucial to the prevention of DLB.

1. Introduction

Dementia is a major health issue around the globe. Affected individuals can have considerable difficulty in their daily functioning, due to an inability to maintain cogent thought processes or keep their memories in order [1]. Dementia with Lewy bodies (DLB) is the third most common form of dementia after Alzheimer's disease and vascular dementia [2]. In America, DLB has been shown to influence 10–25% of cases of dementia, affecting 1%-2% of the population aged over 65 years [3]. The comedian Robin Williams suffered from DLB at the time of his suicide in 2014 [4]. Lewy bodies are abnormal microscopic deposits that consist primarily of alpha-synuclein (a protein found widely in the brain). They were discovered by Frederick H. Lewy, M.D., in the early 1900s [5]. These abnormal aggregations lead to the gradual destruction of certain brain cells over time, resulting in a progressive decline in reasoning capacity and the ability to function independently.

The fact that DLB is a degenerative dementia with alpha-synuclein pathology makes it clinically different from other types of dementia [6]. The distinctive clinical features include visual hallucinations, Parkinsonism, cognitive impairment with fluctuations, autonomic dysfunction, rapid eye movement sleep behavior disorder (RBD), and neuroleptic sensitivity. Parkinson's disease with dementia (PDD) is another major neurocognitive disorder with Lewy bodies. DLB and PDD share many clinical and neuropathological features. It is always a challenge for physicians to differentiate DLB from PDD. Clinically, patients with DLB present with less tremor but more orthostatic hypotension, delusion, attention fluctuation, and visual hallucination. Poor balance and early onset of dementia are more frequent in DLB. However, patients with DLB vary in the severity of these symptoms, and many individuals lack standard signs in the early stages of the disease. Furthermore, because of the morphological heterogeneity of the DLB/PDD group within synucleinopathies, it would be difficult to differentiate DLB from PDD simply from

neuropathological findings without sufficient clinical data [7]. This means that no single test or combination of tests can conclusively diagnose DLB in a living patient. As a result, DLB is often misdiagnosed or progresses unrecognized, according to the criteria last revised in 2015 [2, 8, 9]. Palmqvist et al. found that more than 50% of cases with DLB go undiagnosed [10]. This led to the establishment of new criteria at the 2017 International Dementia with Lewy Bodies (DLB) Conference [11]. The new criteria feature sensitivity of 83% and specificity of 95%, based on research confirmed by postmortem autopsy [12]. So far, there is no clear or objective distinction between the two entities established, except the arbitrary timing of the appearance of cognitive impairments and Parkinsonism (1-year rule) [13].

One population-based prospective cohort study estimated the incidence of suspected DLB at 112/100,000 person-years among individuals aged 65 and over [14]. A systemic review revealed that DLB incidence ranges from 50 to 160 per 100,000 person-years [15]. Currently, very few studies focused on comorbidities of DLB. There was one linkage study indicating a worse comorbidity profile in DLB patients, with a higher prevalence of depression, stroke, and migraine, compared with the AD population [16]. Awareness of DLB has increased following the adoption of revised diagnostic criteria and the publishing of new studies reporting primary data; however, epidemiological and comorbidity studies of DLB in Taiwan remain scarce. In this study, we investigated the incidence and comorbidity of DLB in a national retrospective study.

2. Data Source

The Taiwanese government established the National Health Insurance (NHI) in 1995, and more than 99% of the population of Taiwan is currently enrolled [17]. Research institutes under the NHI have released databases to promote research as subsets of the National Health Insurance Research Database (NHIRD). The Longitudinal Health Insurance Database 2000 (LHID2000) includes a random selection of 1 million patients from the NHIRD. From this database, we were able to obtain registration and claim information of patients. To ensure the privacy of patients, personal ID numbers were reencoded prior to the release of information. This study was approved by the International Review Board, China Medical University and Hospital Research Ethics Committee (IRB permit number: CMUH-104-REC2-115).

3. Sampled Participant, Relevant Variables, and Comorbidities

In this study, DLB was defined as having been diagnosed based on ICD-9-CM code 331.82 or following the 1-year rule or having been diagnosed with Parkinson's disease (PD) or Parkinsonism (ICD-9-CM codes 332 and 333, excluding 333.1–333.8) within 1 year before or after the development of dementia (ICD-9-CM codes 290.0, 290.1, 290.2, 290.3, 294.1, and 331.0) [11]. The index date was the date of diagnosis according to ICD-9-CM code 331.82 or diagnosis with dementia. Patients who had been diagnosed with stroke (430–435), head injury (850–854, 959.01), or hydrocephalus (331.3, 331.4, 331.5, 741.0, and 742.3) prior index date were excluded.

The comorbidities discussed for DLB patients were diabetes mellitus (DM) (ICD-9-CM code 250), hypertension (HTN) (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (CAD) (ICD-9-CM codes 410–414), congestive heart failure (CHF) (ICD-9-CM code 428), and chronic kidney disease (CKD) (ICD-9-CM code 585). According to the location of insurance coverage, the patients were classified within Northern, Central, Southern, or Eastern Taiwan.

4. Statistical Analysis

We began by calculating the incidence of DLB between 2000 and 2013 according to the number of patients diagnosed with DLB during that period divided by the number of individuals in the LHID2000 in each year of the study period. We assembled 95% confidence intervals of incidence according to Poisson distribution. We compared the demographics of male and female DLB patients using the chi-squared test for categorical variables and the t-test for continuous variables. Data analysis in this study was performed using SAS statistical software (Version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA), with statistical significance set at a p value < 0.05.

5. Results

Between 2000 and 2013, 872 patients were newly diagnosed with DLB, which translated to an incidence rate of 7.10 per 100,000 person-years (95% CI = 6.63–7.59). The incidence rates among males and females were 7.06 and 7.14, respectively, per 100,000 person-years. The incidence rate increased with age regardless of sex. The incidence was higher in Southern and Eastern Taiwan than in other areas.

Then patients were divided into four groups according to the type of DLB with which they had been diagnosed as shown in Figure 1. Patients in Group A were diagnosed with PD within 1 year following diagnosis with dementia, whereas those in Group B were diagnosed with Parkinsonism within 1 year prior to the onset of dementia. Patients in Group C were diagnosed with DLB according to ICD-9-CM code 331.82. Patients in Group D were diagnosed with dementia and PD and/or Parkinsonism on the same day. We identified no patients diagnosed with DLB using ICD-9-CM code 331.82. Most of the patients belonged to Group A or B, regardless of gender, age, area, or the level of hospital. We also identified many patients in Group D. As shown in Table 1, the mean age of patients diagnosed with DLB was 76.3, and the average age was higher for males than for females. The mean age at the time of death was 83.3. Among patients with a history of HTN, 74.9% were diagnosed with DLB. We observed no significant differences between male and female patients with regard to the comorbidities DM, CAD, CHF, or CKD. A higher proportion of female patients presented HTN or hyperlipidemia.

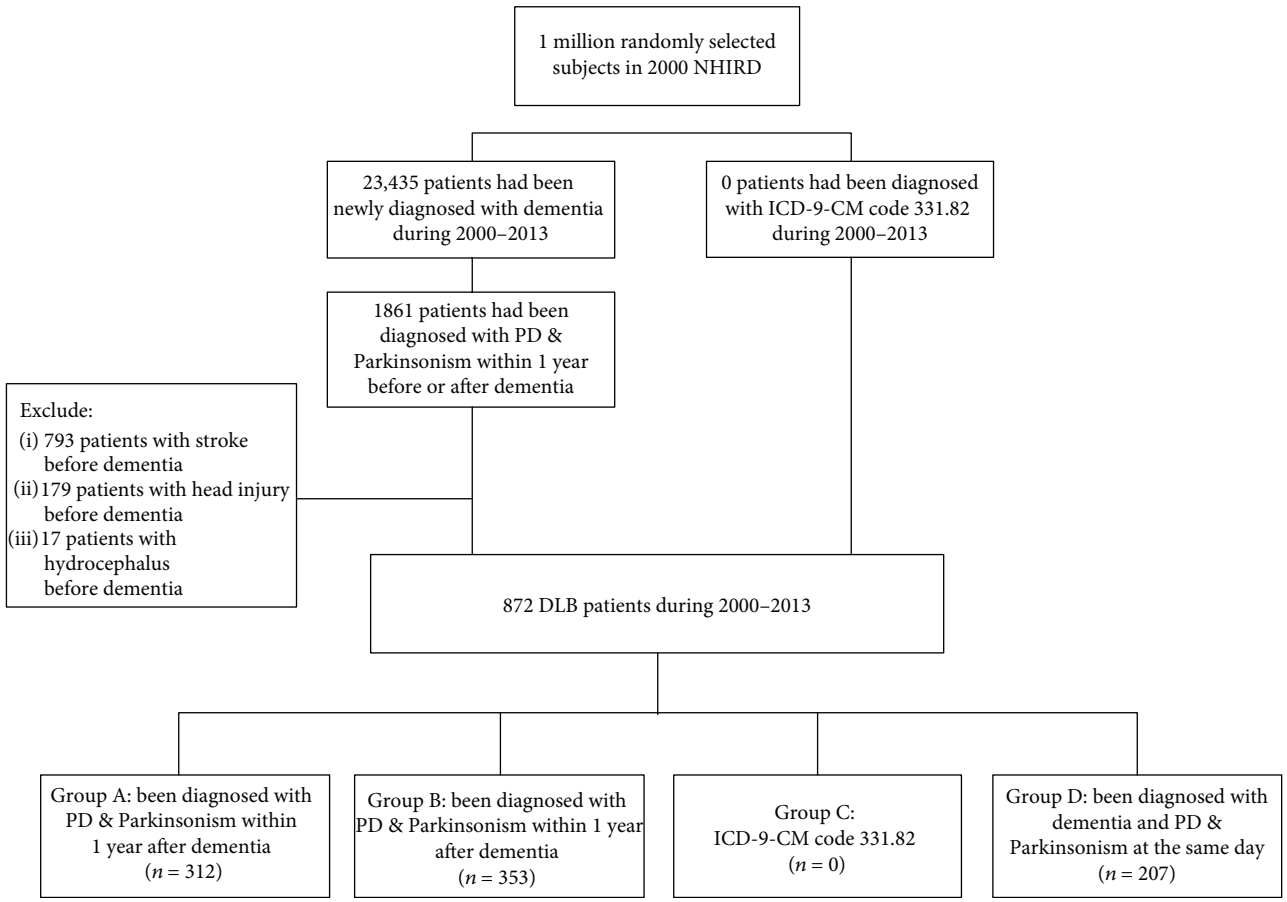

Figure 1: Flowchart of DLB patient selection from the National Health Insurance Research Database in Taiwan.

Table 1: Characteristics of DLB.

	Total (n = 872)	Male (n = 438)	Female (n = 434)	p value
Age				
<65	89 (10.2)	40 (9.13)	49 (11.3)	0.27
65–74	246 (28.2)	117 (26.7)	129 (29.7)	
75–84	397 (45.5)	202 (46.1)	195 (44.9)	
≥85	140 (16.1)	79 (18.0)	61 (14.1)	
Mean (SD)	76.3 (9.84)	77.1 (9.48)	75.6 (10.1)	0.03
Death	176 (20.2)	95 (21.7)	81 (18.7)	0.27
Mean age at death (SD)	83.3 (6.56)	83.5 (6.24)	83.1 (6.95)	0.70
Comorbidity				
Diabetes mellitus	230 (26.4)	104 (23.7)	126 (29.0)	0.08
Hypertension	653 (74.9)	313 (71.5)	340 (78.3)	0.02
Hyperlipidemia	340 (39.0)	148 (33.8)	192 (44.2)	0.002
CAD	420 (48.2)	201 (45.9)	219 (50.5)	0.18
CHF	148 (17.0)	66 (15.1)	82 (18.9)	0.13
CKD	70 (8.03)	40 (9.13)	30 (6.91)	0.23

CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease.

Table 2: Incidence rate of DLB.

			2000–2013	
	n	Cases	Incidence per 100,000 person-years	(95% CI)
Total	12,284,820	872	7.10	(6.63–7.59)
Sex				
Male	6,202,935	438	7.06	(6.42–7.75)
Female	6,081,806	434	7.14	(6.48–7.84)
Age				
<65	10,968,984	89	0.81	(0.65–1.00)
65–74	760,233	246	32.4	(28.4–36.7)
75–84	440,724	397	90.1	(81.4–99.4)
≥85	114,879	140	122	(103–144)
Area				
Northern	5,602,310	309	5.52	(4.92–6.17)
Central	2,531,483	169	6.68	(5.71–7.76)
Southern	3,140,566	302	9.62	(8.56–10.8)
Eastern & island	1,010,198	92	9.11	(7.34–11.2)

6. Discussion

DLB is the second most common cause of degenerative dementia; however, there has been a dearth of research into the incidence of DLB in Taiwan. Rongve and Aarsland found its incidence at 0.7–1.4 new cases/100,000 person-years [18]. Another geographically defined population in Olmsted County, Minnesota (MN), reported an overall DLB incidence of 3.5 per 100,000 person-years, which increased sharply with age [19]. Table 2 lists the age-, sex-, and area-specific incidence rates (new cases per 100,000 person-years) of DLB in Taiwan. Between 2000 and 2013, the overall incidence of DLB in Taiwan was 7.10 per 100,000 person-years (95% CI = 6.63–7.59), and the incidence was slightly lower among men than among women (7.06 versus 7.14, resp.). The incidence of DLB increased with age, ranging from 0.81 among those <65 years old and peaking at 122 among those >85 years old, with an overall DLB incidence of 244.5 cases per 100,000 person-years among subjects aged 65 and older. The overall incidence of DLB was shown to increase consistently with age. In Southern Taiwan, the overall incidence of DLB was 9.62 per 100,000 person-years (95% CI = 8.56–10.8), which was higher than in other regions of Taiwan. The incidence values in this study may have been influenced by ascertainment bias. Rather than adopting a clinical or pathological diagnosis of DLB, we defined DLB based on ICD-9 and diagnoses of Parkinsonism as well as dementia within 1 year. It is therefore possible that cases of early onset DLB without Parkinsonism or dementia may have been missed. It is also possible that we failed to exclude other non-DLB diseases presenting both Parkinsonism and dementia. Thus, our estimates pertaining to the incidence of DLB must be regarded as imprecise. Nonetheless, these are currently the only large-population estimates in Taiwan. One previous study found that among patients with DLB, the median age at the time of death was 78 years [20]. In the present study, the mean age at death was 83.3 years (Table 2).

DLB is difficult to differentiate from Alzheimer's disease (AD) or PD with dementia due to similarities in cognitive and motor symptoms. Table 3 shows that no patients were diagnosed with DLB using ICD-9-CM code 331.82 in Taiwan. This cannot be attributed to an inability to diagnose patients with DLB. Other explanations are at work. First, ICD-9-CM codes 294.20 (dementia without behavioral disturbance) and 294.21 (dementia with behavioral disturbance) were widely used as an alternative to definite diagnostic codes. Second, cholinesterase inhibitors and memantine are the only medications currently available for patients with dementia. Unfortunately, those medications are not covered by the NHI, even after DLB is clinically diagnosed. It is for this reason that ICD-9-CM code 331.82 is not used for DLB in Taiwan. This left us no alternative but to select Groups A, B, and D in order to form a cohort of DLB patients for subsequent investigations.

HTN is a major risk factor for cerebrovascular disorders; however, it increases the risk of cognitive decline and dementia. A growing body of evidence indicates that chronic HTN is an important factor associated with the microstructural damage of brain white matter and cognitive decline [21]. Control of HTN is a key intervention in the prevention of dementia, and the effects are similar to those obtained from most antihypertensive agents [22, 23]. Nonetheless, a very limited number of studies have investigated the association between HTN and DLB. One nationwide, population-based, cross-sectional study of dementia among individuals aged 65 years and over in Taiwan revealed that 52.94% of patients with dementia presented HTN levels exceeding those in the population with normal cognition [24]. As shown in Table 1, there is a high rate of HTN as a comorbidity of DLB (74.9%), and the proportion of HTN is higher among males versus among females (71.5% versus 78.3%, resp.). These results imply that the proportion of HTN in patients with DLB is higher among females However, there is little evidence concerning the association between DLB and NTN and the underlying mechanisms.

Table 3: Classified DLB patients.

		2000–2013			
		Group			
	Cases	A	B	C	D
		n (%)	*n* (%)	*n* (%)	*n* (%)
Total	872	312 (35.8)	353 (40.5)	0 (0)	207 (23.7)
Sex					
Male	438	155 (35.4)	179 (40.9)	0 (0)	104 (23.7)
Female	434	157 (36.2)	174 (40.1)	0 (0)	103 (23.7)
Age					
<65	89	41 (46.1)	26 (29.2)	0 (0)	22 (24.7)
65–74	246	98 (39.8)	97 (39.4)	0 (0)	51 (20.7)
75–84	397	132 (33.2)	167 (42.1)	0 (0)	98 (24.7)
≥85	140	41 (29.3)	63 (45.0)	0 (0)	36 (25.7)
Area					
Northern	309	112 (36.2)	112 (36.2)	0 (0)	85 (27.5)
Central	169	51 (30.2)	80 (47.3)	0 (0)	38 (22.5)
Southern	302	115 (38.1)	123 (40.7)	0 (0)	64 (21.2)
Eastern & island	92	34 (37.0)	38 (41.3)	0 (0)	20 (21.7)
Accreditation level of hospital					
Medical center	217	77 (35.5)	83 (38.2)	0 (0)	57 (26.3)
District hospital	343	116 (33.8)	139 (40.5)	0 (0)	88 (25.7)
Local hospital	197	69 (35.0)	87 (44.2)	0 (0)	41 (20.8)
Other	114	50 (43.9)	44 (38.6)	0 (0)	20 (17.5)

Group A: been diagnosed with PD & Parkinsonism within 1 year after dementia. Group B: been diagnosed of PD & Parkinsonism within 1 year before dementia. Group C: ICD-9-CM code 331.82. Group D: been diagnosed with dementia, PD, & Parkinsonism at the same day

Lewy bodies composed of alpha-synuclein fibrils are abundant in the cortical neurons of patients with DLB. Evidence suggests that the interaction between alpha-synuclein and lipids on the cell membrane can trigger alpha-synuclein aggregation [25]. However, the relationship between hyperlipidemia and cognition remains an issue of controversy. One large study of older adults identified a correlation between higher low-density lipoproteins and better cognitive performance [26]. A longitudinal study of 1159 elderly Chinese people found that higher amounts of low-density lipoproteins are associated with accelerated cognitive decline [27]. However, a meta-analysis of four large randomized trials among patients diagnosed with AD revealed that lipid-lowering therapy using statins had no effect on cognition in the treatment or prevention of dementia [28]. One study of dementia among a population aged 65 years and over in Taiwan revealed that the proportions of patients with hyperlipidemia comorbidity are similar among those with dementia and among those with normal cognition (16.79% and 18.71%, resp.). In this study, we found that 39.0% of DLB patients also presented with hyperlipidemia and that the rates were higher among females. Interestingly, no previous studies have focused on the association between hyperlipidemia and DLB.

This study was subject to a number of limitations that warrant consideration. First, diagnosing DLB is difficult, and the definition of DLB in this study inevitably leads to the identification of non-DLB patients and patients in the early stages of DLB. Second, we were unable to obtain information on factors that could affect the results, such as duration of the comorbidity and use of medication.

This is the first large-population retrospective study on the incidence of DLB and cardiovascular comorbidities in Taiwan. Our results showed the incidence of DLB and higher comorbidity HTN and hyperlipidemia in female DLB patients in Taiwan. In the future, more generalizable studies concerning the association between DLB and vascular risk factors and cardiovascular disease are warranted.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Acknowledgments

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Review Article

Neurohealth Properties of *Hericium erinaceus* Mycelia Enriched with Erinacines

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Hericium erinaceus, an ideal culinary-medicinal mushroom, has become a well-established candidate in promoting positive brain and nerve health-related activities by inducing the nerve growth factor from its bioactive ingredient. Among its active compounds, only erinacine A has confirmed pharmacological actions in the central nervous system in rats. Hence, this review has summarized the available information on the neurohealth properties of *H. erinaceus* mycelia enriched with erinacines, which may contribute to further research on the therapeutic roles of these mycelia. The safety of this mushroom has also been discussed. Although it has been difficult to extrapolate the *in vivo* studies to clinical situations, preclinical studies have shown that there can be improvements in ischemic stroke, Parkinson's disease, Alzheimer's disease, and depression if *H. erinaceus* mycelia enriched with erinacines are included in daily meals.

1. Introduction

Diseases of the aging nervous system, such as Parkinson's disease, Alzheimer's disease, and stroke, are serious global public health crises as there is no cure for them currently. These lucrative markets have thus attracted the interest of a majority of large pharmaceutical companies which have put a tremendous effort into seeking medications to relieve the symptoms. However, despite successful preclinical testing, clinical trials for novel drugs have a poor track record of success.

In stroke and traumatic brain injuries, a variety of N-methyl-D-aspartate receptor antagonists have halted the progression of secondary damages in rodent models [1, 2], yet they have failed in human clinical trials due to unwanted side effects of the drugs [3, 4]. Likewise, levodopa is the primary treatment for Parkinson's disease that passes through the blood-brain barrier and gets converted into dopamine, but its long-term use can elicit additional clinical symptoms such as psychosis, mood fluctuations, increased cognitive impairment, or drug-induced dyskinesias [5]. Similarly, despite one new drug out of 244 compounds tested in 413 Alzheimer's disease clinical trials between 2002 and 2012 being approved for use, it cannot stop Alzheimer's from progressing [6]. Even though several other studies are underway, huge disappointment from the largest pharmaceutical companies, such as Axovant Sciences Ltd., Merck & Co Inc., Biogen Inc., Prana Biotechnology Ltd., and Pfizer Inc., was observed during recent times [7]. With a significant number of failed clinical trials and without a clear understanding of the potential mechanism of these diseases, dementia specialists have therefore turned their focus from treatment to prevention to stop further disease progression [8].

It is time to stop dementia before it starts. Recently, the search for small preventative neurotrophic compounds that

can cross the brain-blood and are responsible for the maintenance, survival, and regeneration of neurons has attracted much attention [9]. In particular, compounds derived from natural sources with fewer side effects that can be part of everyday nutrition may help with dementia prevention. Mushrooms, which are considered nutritionally functional foods and sources of physiologically beneficial medicines, can be excellent candidates for this cause.

Among all culinary mushrooms, *Hericium erinaceus* (most commonly known as lion's mane) has been widely reported to have therapeutic activities related to the promotion of nerve and brain health. Different compounds isolated from this mushroom inducing the expression of neurotrophic factors such as nerve growth factors (NGF) have been actively studied and reported [10–15]. Hericenones were typically found in the fruiting bodies while erinacines were derived from the mycelia of the mushroom (Figure 1).

A previous double-blinded clinical study has shown that oral administration of *H. erinaceus* fruiting body was effective in improving mild cognitive impairment in 50- to 80-year-old Japanese patients [16]. However, when examining the constituents of this effect, hericenones failed to stimulate NGF gene expression in primary cultured rat astroglial cells and 1321N1 human astrocytoma cells [17], suggesting that hericenones were not the key components responsible for the neuroprotective activities of this mushroom. On the other hand, the prominent beneficial effect of erinacine A was confirmed in the central nervous system in rats [18]. It is essential to know the concentrations of the bioactive compounds present in the functional ingredients to better assess their effects on the quality and bioactivity. For food industries, it is even critical that strict specifications of their ingredients are complied with. Therefore, this review will summarize the recent advances on the neurohealth properties of *H. erinaceus* mycelia enriched with erinacines (≥3 mg/g) and discuss the potential mechanisms of action responsible for these medicinal properties.

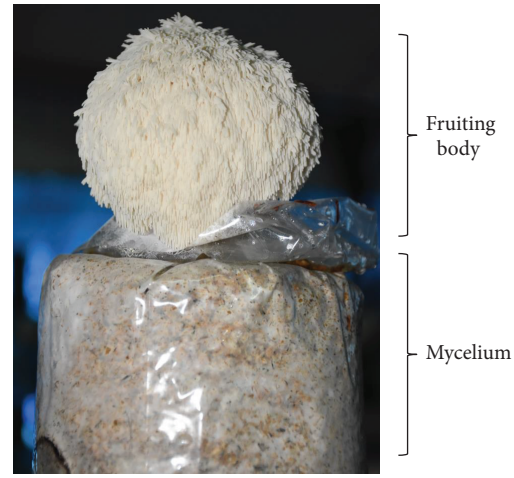

Figure 1: Fruiting body and mycelium of *H. erinaceus.*

2. Erinacines

Erinacines are groups of cyathin diterpenoids that show biological activities as stimulators of NGF synthesis and could be useful as a treatment for neurodegenerative disorders and peripheral neuropathy [19]. To date, 15 erinacines (erinacines A–K and P–S) have been identified (Figure 2) and further investigations have demonstrated that eight of them have various neuroprotective properties, such as enhancing NGF release (erinacines A–I), reducing amyloid-β deposition, increasing insulin-degrading enzyme (IDE) expression (erinacines A and S), or managing neuropathic pain (erinacine E), while others are either being currently discovered or have other pharmacological activities (Table 1). However, no direct evidence has yet shown that these compounds could pass through the blood-brain barrier. While other bioactive agents are still being explored, erinacine A has currently been the only one designed specifically to correlate results from *in vitro* studies with outcomes observed from *in vivo* studies [18], which could bring scientists a step closer to developing a better treatment option for neurodegenerative disorders.

2.1. Erinacine A. Erinacine A, the main representative of the erinacine group, not only has an enhancing effect on NGF synthesis *in vitro* [12] but also can increase NGF and catecholamine content in the locus coeruleus and hippocampus of rats after administration (8 mg/kg body weight) [18]. This enhanced amount of NGF appears to markedly increase neuronal survival in different brain areas and substantially improve behavioral outcomes in various animal models. In the experimental model of stroke, 1 mg/kg erinacine A administered intraperitoneally in rats for 90 min significantly increased cell survival, attenuated the expression of proinflammatory mediators, and reduced infarct volume after transient focal cerebral ischemia [24]. In another study, it was shown that oral treatment with erinacine A could reduce amyloid-β plaque burden by increasing Aβ degradation by elevating the level of IDE in 5-month-old APPswe/PS1ΔE9 double transgenic mice [20]. These preclinical studies are very encouraging and suggest that erinacine A is effective in reducing neurodegenerative disease-induced cell death. However, no studies have shown that erinacine A could be absorbed into the blood capillaries, cross the blood-brain barrier, and be localized in the brain. Hence, future studies measuring the concentration of erinacine A in the brain and blood could be performed to clarify these mechanisms in detail.

Interestingly, neuroprotective compounds may also be effective in cancer therapy. Given the increasing evidence showing that genes are upregulated in central nervous system disorders and downregulated in cancers and *vice versa* [25], it suggests a bright future for developing common therapeutic approaches in the treatment of these diseases. In line with this finding, treatments with erinacine A have been found to inhibit the proliferation of DLD-1 colorectal adenocarcinoma cells *in vitro* as well as the growth of DLD-1 tumors *in vivo* [21] (Table 1). Despite the promising results, erinacines in *H. erinaceus* mycelia are usually present in microquantities and minor variations in the environment can

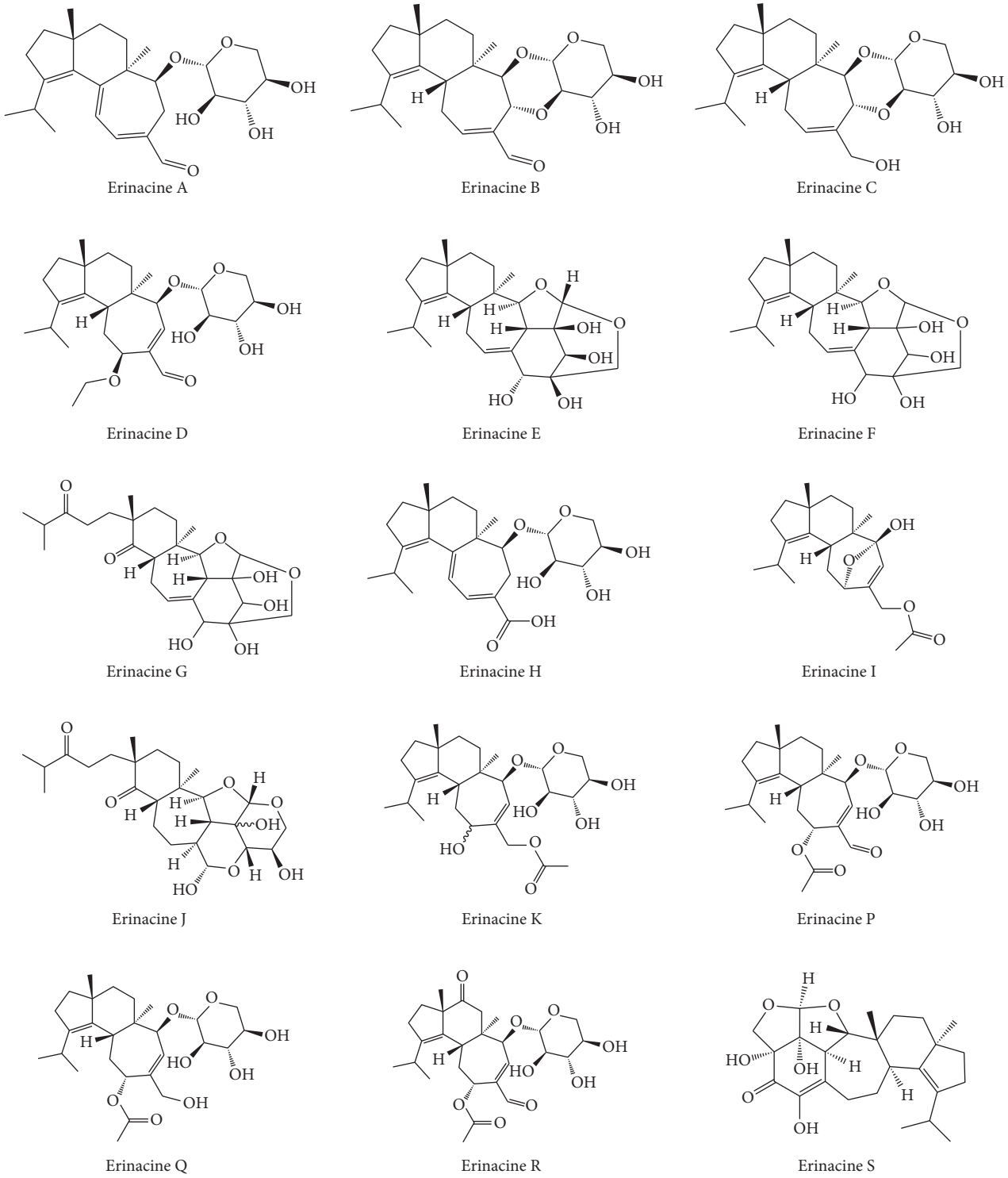

Figure 2: Chemical structures of 15 erinacines.

have huge impacts on the quantity, quality, and diversity of the metabolic products.

3. Production of Erinacines

As the fruiting body was reported to contain no erinacines [26], the best option would be to enhance erinacine production in *H. erinaceus* mycelia via submerged fermentation under constantly controlled culture parameters. Although chemical syntheses of cyathane-type diterpenoids are not impossible, they are complex, multistep processes that result in low yields and low purity levels [27]. Therefore, it seems highly desirable to biosynthesize erinacines using bioreactors to obtain a high yield of mycelia with high

Table 1: Erinacines with biological activities demonstrated *in vitro* and *in vivo*.

Erinacines	Tests	Concentration	Biological activities	Reference
Erinacine A	*In vitro*	1 mM	Induced 250.1 ± 36.2 pg/ml NGF synthesis	[12]
	In vivo	30 mg/kg body weight/day	(1) Reduced amyloid burden by 38.1 ± 19.7% (2) Increased IDE levels by 141.1 ± 63.7%	[20]
	In vivo	1 mg/kg body weight/day	Inhibited DLD-1 tumor growth by 66%	[21]
	In vivo	30 mg/kg body weight/day	(1) Reduced both the size and number of amyloid plaques (2) Increased IDE levels by 303.5% (3) Recovered from impairments in burrowing, nesting, and Morris water maze tasks	[22]
Erinacine B	*In vitro*	1 mM	Induced 129.7 ± 6.5 pg/ml NGF synthesis	[12]
Erinacine C	*In vitro*	1 mM	Induced 299.1 ± 59.6 pg/ml NGF synthesis	[12]
Erinacine D	*In vitro*	1.67 mM	Induced 141.5 ± 18.2 pg/ml NGF synthesis	[14]
Erinacine E	*In vitro*	5 mM	Induced 105.0 ± 5.2 pg/ml NGF synthesis	[13]
	In vitro	IC_{50}	Binding inhibitor for κ-opioid receptor at 0.8 μM	[23]
Erinacine F	*In vitro*	5 mM	Induced 175.0 ± 5.2 pg/ml NGF synthesis	[13]
Erinacine H	*In vitro*	70.8 mM	Induced 31.5 ± 1.7 pg/ml NGF synthesis	[15]
Erinacine S	*In vivo*	30 mg/kg body weight/day	(1) Reduced amyloid burden by 40.2 ± 15.2% (2) Increased IDE levels by 130.5 ± 68.9%	[20]
	In vivo	30 mg/kg body weight/day	(1) Reduced the size of amyloid plaques (2) Increased IDE levels by 269.8% (3) Recovered from impairments in burrowing, nesting, and Morris water maze tasks	[22]

concentrations of bioactive metabolites, which can expand mushroom potentialities for the development of functional foods, nutraceuticals, and novel drugs [28].

While there may have been various strategies developed over the past few decades for erinacine accumulation, it appeared, however, that only three reports concerning erinacines A and C have been published. In a 10 l bioreactor, a medium comprised of glucose 69.87 g/l, casein peptone 11.17 g/l, NaCl 1.45 g/l, $ZnSO_4$ 55.24 mg/l, and KH_2PO_4 1.0 g/l with a pH of 4.5 has produced 192 ± 42 mg/l of erinacine A after 8 days of cultivation [29]. With the monitoring of the temperature and ventilation during the processing, the highest yield of 206 ± 7 mg/l (17.34 mg/g) of erinacine A could be obtained after 14 days of cultivation using a 100 l bioreactor with the medium containing 0.5% yeast extract, 4% glucose, 0.5% soybean powder, 0.25% peptone, 1% oat, and 0.05% KH_2PO_4 at pH 5 [30]. These results suggest that a carbon-to-nitrogen (C/N) ratio of 6 and a pH value of 4 to 5 in a medium may be important parameters in promoting the biosynthesis of erinacine A in *H. erinaceus* mycelia.

Scale-up of pilot plant fermentors to large-scale bioreactors to enhance the biomass as well as erinacine production could also be an attractive proposal. Although various factors such as improper distribution of oxygen, uneven distribution of the media, or insufficient agitation environment could cause negative impacts on product formation and quality at a higher scale of operation [31], there has been one successful example of commercial exploitation. In this case, the medium was optimized for a C/N ratio of 10, temperature of 26°C, pH of 4.5, and agitation of 120 rpm. The highest accumulation of erinacine A (5 mg/g) was observed with 20-ton fermentors after 12 days [32]. This preliminary result was satisfactory, showing that implementation and successful commercial exploitation of research results in large-scale bioreactors are possible.

For erinacine C production, the optimal medium was found to include 5 g/l oatmeal, 1.5 g/l calcium carbonate, and 0.5 g/l Edamin® K at pH 7.5, which can generate concentrations up to 2.73 g/l after six days of cultivation [33]. However, it is noteworthy that this process was accomplished in a two-step course. The fungal pellets were concentrated by centrifugation to remove preculture medium components before inoculation of the main culture. Although an inoculation ratio of 5 : 10 volume/volume (*v*/*v*) is beneficial in producing erinacine C, it is only reproducible at a small laboratory scale and not feasible in industrial operations as the concentrated biomass is not easily adapted for the aseptic handling of large volumes.

These findings are extremely important as they could be used as references to enhance the production of useful secondary metabolites for industrial applications. Moreover, it should be noted that the presence of erinacines in *H. erinaceus* mycelia can also achieve pharmacological benefits. In this regard, isolation of erinacines from *H. erinaceus* mycelia is particularly important, as they could serve as quality controls in assuring the efficacy, quality, and safety of this mushroom in future markets.

4. *In Vivo* Preclinical Studies of *Hericium erinaceus* Mycelia Enriched with Erinacines

While 1/5 of dementia cases can be reversible in some cases when caused by drugs, alcohol, hormone imbalances, or depression, a significant proportion of individuals suffer

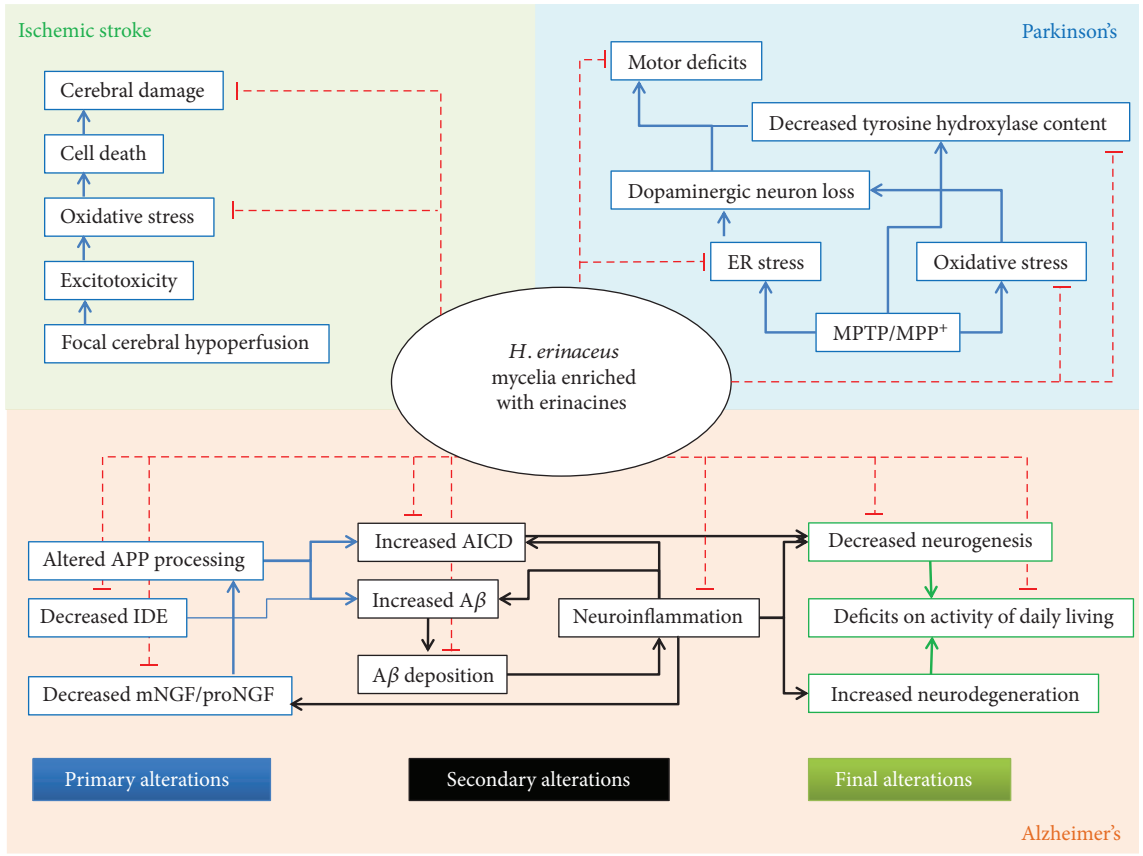

Figure 3: Summary of mechanisms of action of *H. erinaceus* mycelia enriched with erinacines in dementia. Primary alterations are possible contributors and drivers in the pathogenesis of Alzheimer's disease. Secondary alterations include increased amyloid precursor protein intracellular domain (AICD) and accumulation of Aβ, leading to neuroinflammation. Finally, decreased neurogenesis and increased neurodegeneration can cause deficits in activities of daily living. The red dashed lines indicate potential mechanisms of *H. erinaceus* mycelia-attenuated pathological and behavioral changes in stroke, Parkinson's disease, and Alzheimer's disease.

from dementias that are irreversible [34]. The most common irreversible dementia types include Alzheimer's disease, vascular dementia, Lewy body dementia, Parkinson's disease, and frontotemporal dementia [35]. Luckily, growing preclinical studies have demonstrated that the risk of dementia and cognitive impairment could be reduced in the early stages by erinacine-enriched *H. erinaceus* mycelium consumption. Figure 3 illustrates the overall therapeutic mechanism of action of *H. erinaceus* mycelia enriched with erinacine in dementia.

4.1. Protection against Ischemic Stroke. In a rat model of transient focal cerebral ischemia via the middle cerebral artery occlusion method, pretreatment with 3 mg/g erinacine A-enriched *H. erinaceus* mycelia orally at concentrations of 50 and 300 mg/kg for 5 days could reduce the total infarcted volumes by 22% and 44%, respectively [24]. Moreover, immunohistochemistry for neuronal nuclei (NeuN) revealed the presence of significantly more neurons after brain injuries in rats which were treated with erinacine A-enriched *H. erinaceus* mycelia. Excessive reactive oxygen species and oxidative stress have been strongly implicated in the pathogenesis of ischemic brain injury [36]. Decreased levels of proinflammatory cytokines and inducible NO synthase (iNOS), however, have been detected in ischemic neurons after mycelia exposure. These findings suggested that erinacine A-enriched *H. erinaceus* mycelia may be a promising agent for stroke injury as these have the ability to decrease neuronal apoptosis and reduce stroke cavity size in the rat brains by targeting iNOS/reactive nitrogen species (RNS) and p38 mitogen-activated protein kinase (MAPK)/CCAAT enhancer-binding protein homologous protein (CHOP) pathways.

4.2. Protection against Parkinson's Disease. Parkinson's disease (PD) is the second most common neurodegenerative disorder that is characterized by the progressive loss of dopaminergic cells in the substantia nigra pars compacta region of the brain, which results in motor problems including resting tremor, rigidity, bradykinesia, and postural instability [37]. Among models of PD, the involvement of the drug 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is most widely used. Once inside the brain, MPTP is metabolized into the toxic cation 1-methyl-4-phenylpyridinium (MPP^+) by the enzyme monoamine oxidase B, resulting in nigral dopaminergic neuronal death and mitochondrial damage, which can mimic the clinical and pathological features of PD [38]. In one study, the neuroprotective effect of erinacine

A-enriched *H. erinaceus* mycelia was assessed in the MPTP-induced PD model. Results showed that dopaminergic lesions and oxidative stress in the stratum and substantia nigra were significantly improved after pretreatment with 3 mg/g erinacine A-enriched *H. erinaceus* mycelia for 25 days [39]. Furthermore, the mycelia could reverse MPTP-associated motor deficits, as revealed by the analysis of the rotarod assessment. The mechanisms underlying the neuroprotective effect of erinacine A-enriched *H. erinaceus* mycelia were associated with the inhibition on the endoplasmic reticulum stress by lowering the expression of Fas and Bax via inositol-requiring enzyme 1α (IRE1α)/tumor necrosis factor receptor-associated factor 2 (TRAF2) complex formation and phosphorylation of c-Jun N-terminal protein kinase (JNK) 1/2, p38 and nuclear factor kappa light chain enhancer of activated B cell (NF-κB) pathways. Taken together, these results have demonstrated that erinacine A-enriched *H. erinaceus* mycelia have the potential to be a new therapeutic agent for the prevention and treatment of PD.

4.3. Protection against Alzheimer's Disease. There has been growing evidence which suggested that Alzheimer's disease progression becomes a runaway chain reaction after a certain point. In the presence of amyloid-β plaques, secondary injuries such as inflammation, excitotoxicity, and apoptosis may trigger the deposition of hyperphosphorylated tau proteins [40]. Once the process starts, the tau tangles are unabated even after the removal of amyloid-β plaques. Moreover, studies in transgenic amyloid precursor protein (APP) mice have shown that therapies are most effective when administered before plaque formation [41, 42]. Therefore, amyloid-β has become an ideal therapeutic target for primary prevention.

In one study, APPswe/PS1dE9 transgenic mice were utilized to evaluate the therapeutic effect of *H. erinaceus* mycelia containing 19 mg/g erinacine A on Alzheimer's disease. After 30 days of oral administration to 5-month-old transgenic mice, these mycelia were able to attenuate cerebral Aβ plaque burden, prevent recruitment and activation of plaque-associated microglia and astrocytes, promote the expression of IDE, increase the NGF-to-NGF precursor (proNGF) ratio, and enhance the proliferation of neuron progenitors and the number of newly born neurons in the dentate gyrus region [43]. Additionally, improvements in the impairment of other multiple brain regions were also shown when APP/PS1 transgenic mice treated with *H. erinaceus* mycelia could recover behavioral deficits after 81 days of administration. Collectively, these findings raise the possibility that prevention with erinacine A-enriched *H. erinaceus* mycelia could be an effective therapeutic strategy for managing Alzheimer's disease.

4.4. Protection against Depressive Symptoms. Depression is the most frequently occurring psychiatric comorbidity, with prevalence in Alzheimer's, Parkinson's, and stroke as high as 87%, 75%, and 79%, respectively [44]. Prior data has shown that levels of NGF are significantly lower in patients with major depressive disorder than in healthy subjects [45]. *H. erinaceus* mycelia enriched with erinacines, which are involved in the creation of the neurotrophic factors, are thereby hypothesized to play a role in depression.

In animal models, chronic restraint stress is known to cause decreased BDNF expression in the hippocampus and depression-like behaviors [46]. Hence, alleviation of *H. erinaceus* mycelia enriched with erinacines in animals subjected to repeated chronic stress was examined [47]. Two weeks of treatment with *H. erinaceus* mycelia have reduced the immobility time in the tail suspension test and forced swimming test as well as decreased the number of entries and the time spent in the open arm. In addition, restraint-induced low levels of norepinephrine, dopamine, serotonin, high interleukin-6, and tumor necrosis factor-α in the hippocampus were completely reversed by *H. erinaceus* mycelium administration. Furthermore, *H. erinaceus* mycelium was shown to activate the BDNF pathways and block NF-κB signals in mice. Hence, these results indicate that *H. erinaceus* mycelia could be an attractive agent for the treatment of depressive disorders through the modulation of monoamine neurotransmitters and proinflammatory cytokines as well as the regulation of brain-derived neurotrophic factor (BDNF) pathways.

4.5. Protection against Neuropathic Pain. Currently, there is a growing realization that lesions to the peripheral or central nervous system could lead to neuropathic pain [48]. Currently, both ionotropic P2X receptors and metabotropic P2Y receptors have been identified as key receptors in mediating neuropathic pain [49]. As *H. erinaceus* mycelium has a crucial role in nerve regeneration via the stimulation of neurotrophic factors, the analgesic potential of this mycelium using both a P2 purinergic receptor-coupled Ca^{2+} signaling platform and an *in vivo* model was investigated. The results indicated that the extracts of *H. erinaceus* mycelium could completely block ATP-induced Ca^{2+} signaling in human HOS cells, suggesting its inhibitory potential as a modulator of pain-related P2X receptors [50]. In addition, administration of the extracts of *H. erinaceus* mycelium in heat-induced mice could significantly postpone the tail-flick response to heat stimulation as well as the paw-lifting response to a hot plate, indicating that it has an excellent potential for pain relief.

4.6. Protection against Presbycusis. Recent research has highlighted that presbycusis may precede the onset of clinical dementia and may present as an early manifestation of probable Alzheimer's disease [51]. Exogenous application of NGF has been the first to promote nerve fiber regrowth or sprouting in deafened guinea pigs caused by neomycin [52]. Moreover, clinical studies in patients with sensorineural hearing defects have revealed that the amount of circulating NGF is relatively lower compared to the level found in normal patients [53]. Therefore, the otoprotective effect of *H. erinaceus* mycelia enriched with erinacines in rapidly aging mice has been observed [54]. The results indicated that the *H. erinaceus* mycelium-treated group had significantly lower hearing thresholds according to auditory brainstem responses measured using click sounds and 8 kHz and 16 kHz tone burst sound stimulation when compared with the control group. These findings suggested that *H. erinaceus*

Table 2: The beneficial activities of *H. erinaceus* mycelium and its active components on age-associated cognitive change and early dementia.

Material studied (dose used)	*In vivo* models	Effects	Reference
Erinacine A	Normal Wistar rats	Enhanced NGF and catecholamine secretion in the LC and hippocampus after intragastric dosing erinacine A at 8 mg/kg body weight	[18]
Erinacine A-enriched mycelia and erinacine A	Ischemic stroke in Sprague-Dawley rats	(1) Mycelia at 50 and 300 mg/kg body weight reduced infarcted volume in cortex and subcortex of transient stroke rats (2) Erinacine A at 1, 5, and 10 mg/kg body weight reduced levels of proinflammatory cytokines such as iNOS, IL-1β, IL-6, and TNF-α in the serum of transient stroke rats	[24]
Erinacine A-enriched mycelia	APPswe/PS1dE9 transgenic mice	(1) Mycelia at 300 mg/kg body weight reduced amyloid plaque burden in the area including the cerebral cortex and hippocampus (2) Increased NGF/proNGF ratio and promoted hippocampal neurogenesis (3) Restored nesting behavior	[43]
Erinacine A Erinacine S	APPswe/PS1dE9 transgenic mice	(1) Both compounds at 30 mg/kg body weight reduced amyloid plaque burden in the cerebral cortex (2) Increased the level of IDE in the cortex by $130.5 \pm 68.9\%$ and $141.1 \pm 63.7\%$, respectively	[20]
Erinacine A-enriched mycelia	MPTP-induced neurotoxicity in C57BL/6 mice	(1) Treatment at 10.76 and 21.52 mg/day elevated dopamine, NGF, and GSH levels (2) Reduced motor dysfunction (3) Reduced dopaminergic neurons apoptosis in the striatum and substantia nigra	[39]
Mycelia ethanolic extract	C57BL/6 mice	(1) Treatment at 2000 mg/kg body weight blocked the rise in $[Ca^{2+}]$ induced by ATP (2) Increased the latency in tail-flick and paw-lifting times exposed to a thermal stimulus	[50]
Erinacine A-enriched mycelium	Restraint stress induced depression in ICR mice	(1) Treatment at 200 and 400 mg/kg body weight increased dopamine and serotonin levels (2) Increased BDNF, TrκB, and PI3K expressions in the hippocampus (3) Reduced IL-6 and TNF-α levels (4) Reduced the immobility time in the tail suspension test and forced swimming test, as well as decreased the number of entries and the time spent in the open arm	[47]

mycelium diet supplementation was effective in slowing hearing threshold deterioration.

The beneficial activities of *H. erinaceus* mycelia on age-associated cognitive change and early dementia are summarized in Table 2. Given the fact that all seven of these studies have provided very encouraging findings, it is also of paramount importance that the daily intake of *H. erinaceus* mycelia in the context of the entire diet is established before the treatment is administered.

5. Toxicology Studies

To date, all experimental studies have suggested that *H. erinaceus* mycelium is safe and devoid of adverse effects (Table 3). In an animal study, the acute oral LD_{50} of *H. erinaceus* mycelia enriched with its active compounds was found to be higher than 5 g/kg in rats [55], indicating that the mycelium is reasonably safe in cases of overdose. Repeated daily doses of *H. erinaceus* mycelium enriched with its active compounds up to 3 g/kg have also been used without any adverse effects in rats [32]. Moreover, *H. erinaceus* mycelium was found not to be mutagenic in the bacterial reverse mutation test (Ames test), *in vitro* chromosome aberration test, and *in vivo* erythrocyte micronucleus test, with and without metabolic activation [56]. Further investigations also showed that erinacine-enriched *H. erinaceus* mycelium was not teratogenic in Sprague-Dawley rats with doses up to 2625 mg/kg [55]. In a well-designed clinical trial, erinacine-enriched *H. erinaceus* mycelia demonstrated significant clinical efficacy and had good safety and tolerability in 36 patients with Alzheimer's disease (unpublished data).

6. Conclusion

The evidence so far has shown that *H. erinaceus* mycelium enriched with its active compounds is capable of delaying neuronal cell death in rats with neurodegenerative diseases, such as ischemic stroke, Parkinson's disease, Alzheimer's disease, and depression. Moreover, results have indicated that administration of *H. erinaceus* mycelia enriched with its active compounds can promote functional recovery and enhance nerve regeneration in rats with neuropathic pain or presbycusis. Despite that more clinical research is needed to fully understand the potential applications of erinacine-

Table 3: The safety of *H. erinaceus* mycelia.

Material studied (dose used)	*In vivo* models	Effects	Reference
Erinacine A-enriched mycelia	Normal ICR mice	No adverse effects in (1) Bacterial reverse mutation test (Ames test) up to 5 mg/plate (2) *In vitro* chromosome aberration test up to 2.5 mg/ml (3) *In vivo* erythrocyte micronucleus test up to 5 mg/kg body weight	[56]
Erinacine A-enriched mycelia	Normal Sprague-Dawley rats	(1) Ethanolic extract induced neuritogenesis in postnatal cortical neurons (2) No adverse effect up to 5 g/kg body weight/day after acute exposure (3) No adverse effect up to 2625 mg/kg body weight/day for prenatal developmental study	[55]
Erinacine A-enriched mycelia	Normal Sprague-Dawley rats	No adverse effect up to 3 g/kg body weight/day for 28 days	[32]

Based on these results, the toxicity profile of *H. erinaceus* mycelium enriched with its active compound is extremely low and therefore has the potential to be developed into a functional ingredient or food associated with improved brain and nerve health. With this idea in mind, the first erinacine A-enriched *H. erinaceus* mycelium product was introduced to the market in 2015 in Taiwan [57].

enriched *Hericium erinaceus* mycelium, the majority of preclinical data strongly suggests that it is safe and offers much-needed neuroprotective applications.

Abbreviations

AICD: Amyloid precursor protein intracellular domain
APP: Amyloid precursor protein
BDNF: Brain-derived neurotrophic factor
CHOP: CCAAT enhancer-binding protein homologous protein
C/N: Carbon to nitrogen
ERK: Extracellular-signal-regulated kinase
IDE: Insulin-degrading enzyme
iNOS: Inducible NO synthase
IRE1α: Inositol-requiring enzyme 1α
JNK: c-Jun N-terminal protein kinase
MAPK: Mitogen-activated protein kinase
MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP^+: 1-Methyl-4-phenylpyridinium
NeuN: Neuronal nuclei
NF-κB: Nuclear factor kappa light chain enhancer of activated B cells
NGF: Nerve growth factor
PD: Parkinson's disease
proNGF: NGF precursor
RNS: Reactive nitrogen species
TRAF2: Tumor necrosis factor receptor-associated factor 2
v/*v*: Volume/volume.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Research Article

Glucose Metabolic Brain Network Differences between Chinese Patients with Lewy Body Dementia and Healthy Control

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Dementia with Lewy bodies (DLB) is the second most common degenerative dementia of the central nervous system. The technique ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F FDG PET) was used to investigate brain metabolism patterns in DLB patients. Conventional statistical methods did not consider intern metabolism transforming connections between various brain regions; therefore, most physicians do not understand the underlying neuropathology of DLB patients. In this study, ^{18}F FDG-PET images and graph-theoretical methods were used to investigate alterations in whole-brain intrinsic functional connectivity in a Chinese DLB group and healthy control (HC) group. This experimental study was performed on 22 DLB patients and 22 HC subjects in Huashan Hospital, Shanghai, China. Experimental results indicate that compared with the HC group, the DLB group has severely impaired small-world network. Compared to those of the HC group, the clustering coefficients of the DLB group were higher and characteristic path lengths were longer, and in terms of global efficiencies, those of the DLB group was also lower. Moreover, four significantly altered regions were observed in the DLB group: Inferior frontal gyrus, opercular part (IFG.R), olfactory cortex (OLF.R), hippocampus (HIP.R), and fusiform gyrus (FFG.L). Amongst them, in the DLB group, betweenness centrality became strong in OLF.R, HIP.R, and FFG.L, whereas betweenness centrality became weaker in IFG.R. Finally, IFGoperc.R was selected as a seed and a voxel-wise correlation analysis was performed. Compared to the HC group, the DLB group showed several regions of strengthened connection with IFGoperc.R; these regions were located in the prefrontal cortex and regions of weakened connection were located in the occipital cortex. The results of this paper may help physicians to better understand and characterize DLB patients.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common degenerative dementia of the central nervous system. Its clinical symptoms include fluctuating levels of cognition, cognitive impairment, parkinsonism, and visual hallucination [1]. Because clinical, neuropsychological, and pathological features of DLB are similar to those of Parkinson's disease (PD) and other dementia subtypes, such as Alzheimer's disease (AD), the rate of misdiagnosis has increased despite the publication of refined clinical criteria for DLB [2]. In clinical practice, it is necessary to have an exact diagnosis and identification of DLB.

In recent years, in order to better understand and characterize DLB patients, few scholars have used functional imaging techniques to elucidate brain metabolism patterns in DLB patients. Amongst them, ^{18}F fluorodeoxyglucose positron emission tomography (^{18}F- FDG PET) is considered as the gold standard [3] due to its high accuracy. Recently, ^{18}F-FDG PET imaging has been used to identify different

disease-specific patterns [4] that disrupt metabolic connectivity (MC). Moreover, it is being increasingly used in routine clinical practice [5].

Many research studies have described the advantages of ^{18}F-FDG PET technique. O'Brien et al. conducted an experimental research study to compare the accuracy with which ^{18}F-FDG PET and (hexamethylpropyleneamine oxime (HMPAO)) SPECT cerebral perfusion could diagnose DLB. They found that both modalities showed broadly similar patterns: parietal and temporal lobes of dementia patients showed reduced levels of activity. Moreover, DLB patients showed reduced uptake in the occipital lobe. Nevertheless, ^{18}F-FDG PET was significantly superior to cerebral blood flow SPECT [6]. There is consistent evidence to prove that DLB patients develop a specific dysfunctional pattern, characterized by significant hypometabolism in the occipital and parietotemporal lobes. In the frontal cortex of DLB patients, metabolism is reduced to a lesser extent [2]. For instance, DLB patients showed posterior brain hypometabolism primarily involving parietooccipital regions [7]. In particular, cingulate island sign (CIS), which refers to sparing of the posterior cingulate relative to the precuneus and cuneus, has been proposed as an FDG-PET imaging biomarker of DLB [8].

Although some initial findings can be found in previous research, more evidences are needed to validate these findings. As a complex integrative system in which billions of neurons are connected with each other, the human brain continuously processes and transmits information between spatially distributed but functionally linked regions [9]. However, such connections between functionally linked regions are not considered in traditional statistical methods. Therefore, scholars seed a new method to optimize current findings.

Brain network analysis may be a good alternative for addressing such issues. Presently, abnormal topology of different diseases can be determined with this method. Thus, the pathological mechanism of different diseases, such as Alzheimer's disease or schizophrenia, may be understood by a new perspective. Thus, it is possible to have an early diagnosis and evaluation of diseases with brain network imaging biomarkers [10]. For instance, using resting-state functional magnetic resonance imaging (rs-fMRI), researchers performed brain network analysis to assess brain network organization in patients diagnosed with DLB (22 patients) and Alzheimer's disease (24 patients). They found that global brain network measures of DLB patients were significantly different from those of Alzheimer's patients and healthy controls. By studying the metabolic network of DLB patients, researchers gained important insights into the link between local vulnerabilities, long-range disconnection, and neuropathological differences. For instance, Caminiti et al. studied fMRI images of 42 DLB patients and 42 healthy controls (HC) using sparse inverse covariance estimation method and graph theory. These methods revealed substantial alterations in connectivity indexes, brain modularity, and hub configuration. Compared to healthy controls, local metabolic connectivity was significantly decreased within the occipital cortex, thalamus, and cerebellum of DLB patients. However, local metabolic connectivity was significantly increased in the frontal, temporal, parietal, and basal ganglia regions of DLB patients. There were also long-range disconnections between these brain regions. This implies that the functional hierarchy of a normal brain was disrupted in DLB patients [11]. However, these studies were mainly conducted on Western subjects. These results may not be applicable to Chinese subjects.

Table 1: Statistical information of all participants.

Info	HC ($n = 22$)	DLB ($n = 22$)	p value
Male : female	5 : 17	21 : 1	$p < 0.001$[a]
Age	63.5 ± 5.6	66.9 ± 8.4	$p = 0.126$[b]
MMSE	28.9 ± 1.3	20.0 ± 5.0	$p < 0.001$[b]

Age and MMSE are given as mean ± standard deviation. [a]χ^2 test, HC, and DLB. [b]Analysis of variance, HC, and DLB.

The two main objectives of this study are therefore as follows: (1) to explore the differences in glucose metabolism of Chinese patients with DLB and to compare related parameters with HC and (2) to identify altered hubs of brain networks and to locate regions significantly correlated with altered hubs of brain networks in DLB patients. Finally, clear evidences on the differences between ^{18}F-FDG PET images of DLB and HC subjects are expected to be presented from the aspect of brain connectome.

2. Experimental Procedure

2.1. Subjects. In this study, the experimental data were obtained from the PET Center of Huashan Hospital in Shanghai, China. All participants were right-handed, including 22 normal subjects and 22 DLB patients. Standardized uptake value ratios (SUVR) of FDG were calculated by dividing the cerebellar cortex-standardized uptake values. Three days before or after PET image acquisition, we obtained basic information of these subjects, including age, gender, and Mini-Mental State Examination (MMSE) values. Table 1 displays statistical information of all participants.

2.2. PET Image Acquisition and Preprocessing. Whole brain PET images of 44 participants were acquired using Siemens Biograph 64 PET/CT machine, which was present in the PET Center of Huashan Hospital in Shanghai, China. The spatial resolution of the PET scanner was 5.9 mm full width at half maximum (FWHM) in the transaxial plane and 5.5 mm FWHM in axial plane. All subjects were intravenously injected with 185 MBq FDG in a dimly lit, quiet room. They were asked to keep their eyes closed for 60 min in order to minimize the confounding effects of any activity. Thereafter, static emission scans were continued for 10 min. Using a Shepp–Logan filter, we implemented a filtered back projection algorithm to reconstruct transaxial images of the following dimensions: $168 \times 168 \times 148$ matrices and a size of $2.0 \times 2.0 \times 1.5$ mm. The institutional review board of Huashan Hospital approved the acquisition of PET images

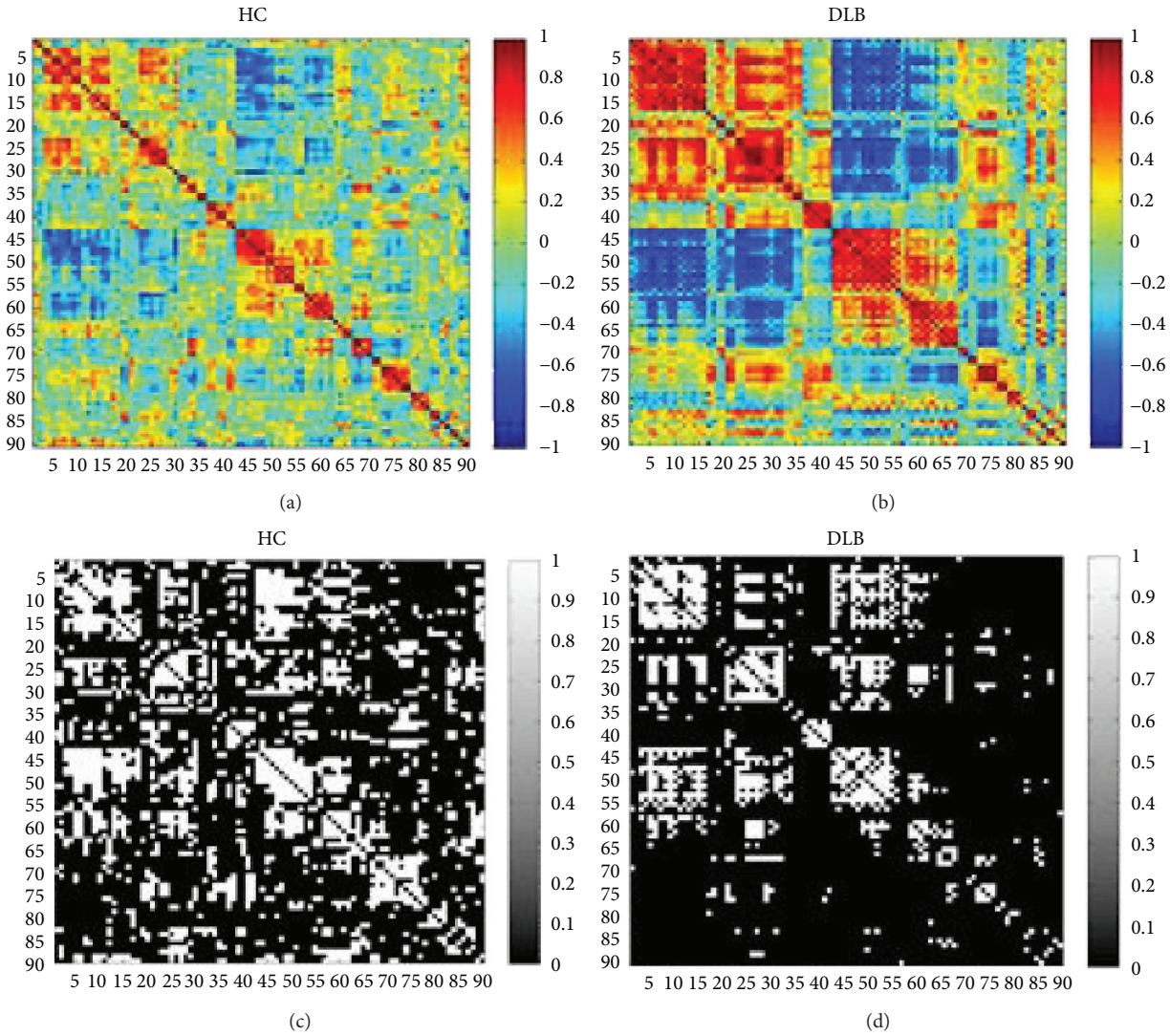


Figure 1: The partial correlation coefficient matrices and the binary matrices of the two groups. (a) The partial correlation coefficient matrix of the HC group. (b) The partial correlation coefficient matrix of the DLB group. (c) The binary matrix of the HC group in sparsity 21%. (d) The binary matrix of the DLB group in sparsity 21%.

[11]. The informed consent form was signed by all participants of this study.

All the original images were obtained in Digital Imaging and Communications in Medicine (DICOM) format. They were converted to NIfTI format using DCM2NII software (https://www.nitrc.org/projects/dcm2nii/). For preprocessing converted images, Statistical Parametric Mapping 8 (SPM8) software was implemented in MATLAB 2014a. Firstly, PET images were spatially normalized to the Montreal Neurological Institute (MNI, McGill University, Montreal, Canada) space. In this step, individual images were spatially warped to a reference PET template using SPM software. Spatial warping is a completely automated procedure based on 12-parameter affine transformation. Then, normalized images were smoothed by convolution using an isotropic Gaussian kernel with $10 \times 10 \times 10$ mm*3 FWHM. Finally, these images were transformed into gray level images with a grayscale of [0,255].

2.3. Brain Network Construction. Two networks of the HC and DLB groups were built based on two datasets, based on the definition of the network in graph theory [12]. The standardized AAL template contains 90 brain regions and 45 hemispheres, all of which are used to divide brain regions [13]. This AAL template was used to split all FDG-PET images into 90 nodes; each node implied a brain region. To further calculate the value of the node in the network, the average value of the intensity of each brain area was estimated. Then, we considered the value of each node as a whole and normalized it as a whole. Each node was normalized to zero-mean and unit-variance. It was obtained by subtracting the average value of the individual's whole brain and then dividing it by the standard deviation of the individual's whole brain. In previous studies, the partial correlation coefficient between each group of nodes was calculated, generating a partial correlation matrix of (90×90) samples. Figures 1(a) and 1(b)

illustrate the partial correlation matrix of the HC and DLB groups, respectively.

In this study, a sparse threshold method was used [12]. The covariance correlation matrix represents an undirected weighted graph. Then, the partial correlation coefficient values of each two brain regions were calculated, which represented the connection strengths of the two brain regions. A larger partial correlation coefficient value indicated a stronger correlation between these two brain regions, which meant that the transform of glucose metabolism in these brain regions was more obvious. Furthermore, in this study, a binary comparison-weighted graph was used. A strategy was used to get the binary matrix and to set the sparsity of the connection matrix. In particular, the data was sorted in the connection matrix in terms of absolute value. Then, the sparsity was set to 21%, implying that the first 21% of the sequence was converted to 1. This indicates that a connection exists between two regions, vice versa, behind which the value would be converted to 0. This implies that there was no connection. With increasing sparsity, the connection matrix becomes sparser. Conversely, the greater the sparsity, the higher would be the density of the connected graph. Network topology is significantly impacted by the choice of sparse threshold. Instead of selecting a single sparse value randomly and subjectively, sparse values from sparsity ($\min = 0.06$) to sparsity ($\max = 0.40$) are considered. The two groups of subjects are connected with the lower limit. The choice of cap satisfies the strongly suppressed contribution of pseudocorrelation, ensuring that the resulting graph has a small world. What needs to be clarified is the fact that in the academic community, it is difficult to deal with negative correlations at the time of binarization. In our experiment, the negative correlation was converted to 1 once the absolute value of the negative correlation was greater than sparsity 21% [10].

Subsequently, the binarized network matrix can be generated. As shown in Figures 1(c) and 1(d), an element of 1 and 0 stands for "connection" and "no connection" in the binary matrix.

2.4. Network Parameter Analysis. To further investigate the differences between two sets of network parameters, the following parameters were considered: clustering coefficient (C), characteristic path length (L), local E, global E, γ, lambda, sigma, and node agent center (BC). All parameters were obtained from open-source toolkit GRETNA (https://www.nitrc.org/projects/gretna/) [14] and Brain Connectivity Toolkit (BCT, http://www.nitrc.org/projects/bct/) [15].

Based on graph theory, clustering coefficient C (i) was defined as the network that expressed a local connection probability, that is, the probability of connecting any two nodes around the node i [16]. The clustering coefficient C of the entire network was defined as the average of clustering coefficients of all nodes in the network, and it was a measure of the degree to which nodes in the graph tend to be clustered together [17]. In topology, the shortest path length was defined as the shortest path distance from node i to node j. In practice, it represents the minimum number of points connecting node i with node j. The shortest path lengths of all the nodes was calculated. The characteristic path length L was defined as the average of these path lengths. A network was formed with high global network efficiency [18]. If there was no connection between two points, then, path lengths between them was infinite.

If the network satisfies the clustering coefficient, then, it also satisfies the corresponding random network clustering coefficient ratio, $\gamma = C/C\_r$. Moreover, it was determined using the characteristic path length; the clustering coefficient $\gg 1$ satisfies the characteristic path length and the corresponding stochastic network. The average path length was greater than $\lambda = L/L\_\text{rand} = 1$. For the comprehensive parameter $\sigma = \gamma/\lambda > 1$, it can be explained that the network had all the characteristics of a small world [16]. Random networks were obtained by randomly reattaching the original brain network between node edges. Meanwhile, the same number of nodes, edges, and degrees was preserved. To achieve statistical significances, we repeated 200 times random networks.

Global efficiency (global E) and local sales (local E) were also worked out to intuitively express transmission efficiency of the network at global and local levels. Global E is the average of shortest paths between nodes, reflecting the efficiency of the global network [19]. Local E is the average of the shortest paths between different connecting nodes, reflecting the efficiency of information exchange between subgraphs [20].

To further explore the nodes of this network, the concept of betweenness centrality was used. Betweenness centrality Bi of node i was defined as the number of shortest paths from all vertices to all others passing through node i. The betweenness centrality of the entire network was defined as the average of Bi from each node. In general, the Bi value was standardized while the normalized betweenness centrality of node i was defined by the expression: $\text{bi} = \text{Bi}/B$. From this definition, it can be inferred that the bi value was influenced by node i that transmits information in the entire network. Higher the bi value, stronger would be the regional centrality of the node. According to Seo et al. [21], hub regions of brain networks were proposed as nodes who have high bi values ($\text{bi} > 1.5$). To identify the hub region significantly altered, the results of the DLB group were compared with those of the HC group. A nonparametric permutation test was performed 1000 times. Statistical results were used to identify altered hubs ($p < 0.05$). Table 2 summarizes all the parameters defined in this study.

2.5. Seed Correlation Analysis. Once altered hubs were determined for each of the two groups, they were considered as seed points and the relationship between them and rest voxels of the individual's brain was calculated. This step was to validate the significances of altered hubs. Pearson correlation coefficient method was used firstly. Then, Fisher's r-to-z transformation was used to convert Pearson's correlation coefficients to z values. Thus, an

Table 2: The definitions of network parameters used in this study.

Parameters	Abbreviation	Equations	Meaning
Clustering coefficient	C	$C = (1/N)\sum_{i=1}^{N}((2E(i))/(k_i(k_i-1)))$ N: number of nodes K_i: number of nodes connected with node i $E(i)$: actual connection edges among k_i	A measure of the degree to nodes in a network which tend to cluster together
Characteristic path length	L	$L = 1/((1/N(N-1))(\Sigma_{i,j\in V,i\neq j}(1/d_{ij})))$ N: number of nodes in a network d_{ij}: the shortest path between node i and j	A measure of the efficiency of the information or mass transport on a network
Gamma	Gamma	Gamma = C/C_{rand} C_{rand}: clustering coefficient of the corresponding random network	A network could be defined as small-world network when gamma $\gg 1$, lambda~1, and sigma > 1
Lambda	Lambda	Lambda = L/L_{rand} L_{rand}: path length of the corresponding random network	
Small-world coefficient	Sigma	Sigma = gamma/lambda	
Global efficiency	Global E	Global E = $(1/N(N-1))\sum_{i,j\in V,i\neq j}(1/d_{ij})$	Measures how efficiently the network exchanges information
local efficiency	Local E	Local E = $(1/N)\sum_{k\in V}((1/(N_{vk}(N_{vk}-1)))\sum_{i,j\in V,i\neq j}(1/d_{ij}))$ N_{vk}: subgraph of node k	
Betweenness centrality	BC	$BC_k = \sum_{i,j\in V,i\neq j}((n_{ij}(k))/n_{ij})$ $n_{ij}(k)$: shortest path pass between nodes i and j through node k	An indicator of a node's centrality in a network

approximated Gaussian distribution was calculated using the following formula:

$$z_i = \frac{1}{2} \times \log\left[\frac{1+r_i}{1-r_i}\right]. \quad (1)$$

Here, r_i refers to correlation coefficients and z_i refers to the transformed z value. Finally, Z test was used to compare z values between groups, whose expression is mentioned as follows:

$$z = \frac{z_1 - z_2}{\sqrt{(1/(n_1-3)) + (1/(n_2-3))}}. \quad (2)$$

Here, n_1 and n_2 refer to samples of two groups [22]. To adjust variations associated with multiple comparison, a false discovery rate (FDR) method was performed at q value of 0.05.

2.6. Statistical Analysis. To confirm statistical significance of network parameters representing the DLB group and HC group, 2000 nonparametric permutation tests were performed [22].

To determine if the observed subject difference occurred accidentally (null hypothesis), we conducted further statistical analysis. The PET images of 44 participants were randomly assigned to the HC and DLB groups and then, the partial correlation matrix was calculated again according to Section 2.3. A set of binary matrices was obtained. The network parameters were also calculated for each network separately. The above process was repeated 1000 times, and the 95 percentile score for each differential distribution was considered as a cutoff ($p < 0.05$, one tailed). This meant that when the original results were within the first 5% of the random results, our results were considered to have significant differences.

3. Results

3.1. Network Parameters. As shown in Figures 1(a) and 1(b), partial correlation coefficient matrices of four groups were calculated using partial correlation analysis. Figure 1 illustrates that color distribution was not uniform for different groups; therefore, partial correlation coefficient was inconsistent. The DLB group exhibited a deep colored distribution; its partial correlation coefficient had the highest absolute value. As shown in Figures 1(c) and 1(d), the threshold for binary matrices of two groups was at a fixed sparsity of 21% (refer to Section 3.2 for threshold selection).

Figure 2 illustrates network parameters of gamma, lambda, and sigma for the DLB group and HC group. As shown in Figure 2, the entire threshold was ranging 6–40%. For both the DLB and HC groups, network parameters were as follows: gamma $\gg 1$, lambda ≈ 1, and sigma > 1. A small-world network was observed in this study. Compared to the DLB group, this property was more obvious and noticeable in the HC group. At sparsity 18%, the value of sigma was 1.625 and 1.244 for the HC group and DLB group, respectively. By performing further permutation tests, it was found that over the entire threshold range, the gamma and sigma values in the DLB group were significantly smaller than those in the HC group.

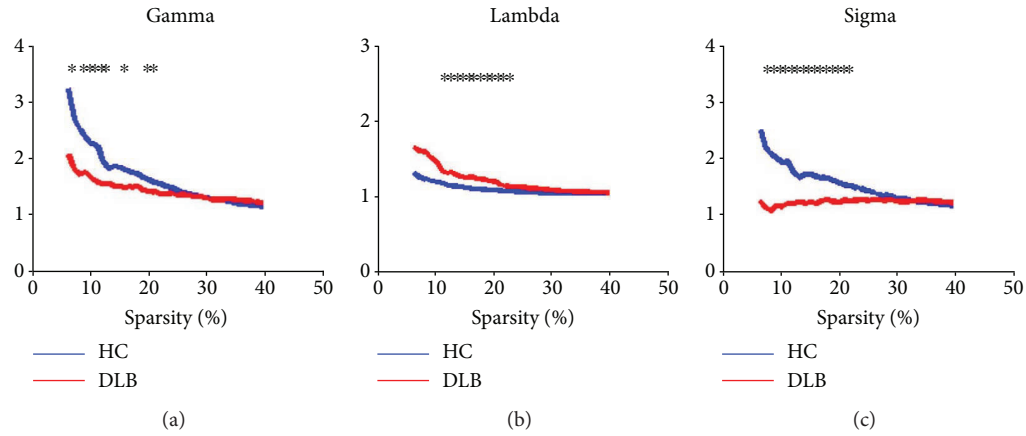


Figure 2: Gamma, lambda, and sigma values in the two groups. The asterisk refer to significant differences between the HC and DLB groups at the sparsity threshold ($p < 0.05$).

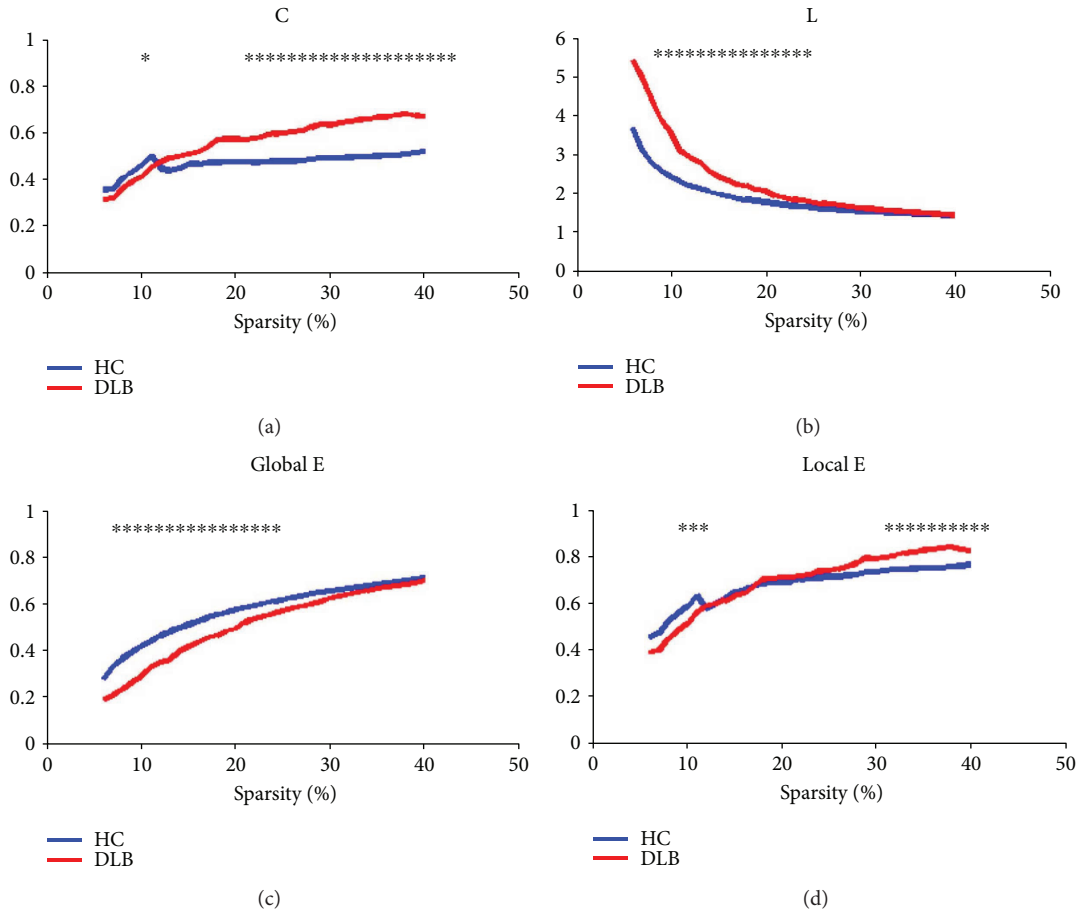


Figure 3: C, L, local E, and global E values in the two groups. The asterisk refer to significant differences between the HC and DLB groups at the sparsity threshold ($p < 0.05$).

On the other hand, the lambda value was higher in the DLB group than in the HC group ($p < 0.05$).

As shown in Figure 3, network parameters C, L, global E, and local E were completely different for both the two groups. To compare the DLB group with the HC group, a nonparametric permutation test was performed to display statistical significance of differences between the two groups ($p = 0.05$).

3.2. Hub Regions. In a complex network, the normalized betweenness centrality (bi) was an important indicator of regional characteristics. These characteristics were used

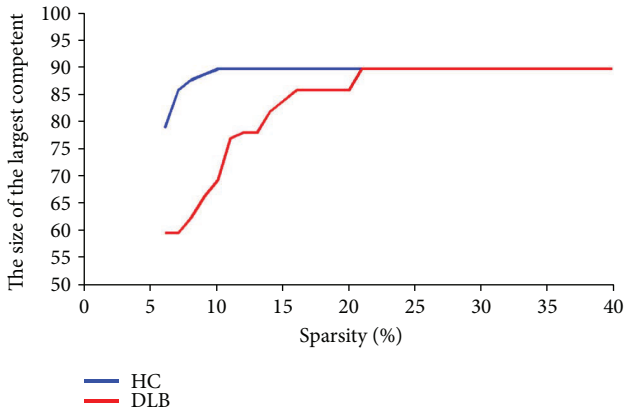


Figure 4: Different component of sizes of the two networks.

to determine the relative importance of network nodes and to identify key nodes in the network. These key nodes are defined as hubs in this study. To identify hubs in two groups, bi was calculated at a fixed sparsity of 21%. At the lowest sparsity of 21%, the component size was largest at 90. To guarantee >50 component size of the two networks, minimum sparsity thresholds were found to be 9% and 21% for the HC and DLB groups, respectively. At these thresholds, no node could be isolated from the remaining network. Figure 4 shows different component sizes of two networks with a different sparsity threshold. As a result, sparsity 21% was chosen as the threshold and bi values were calculated for each node in the two networks [21].

At sparsity of 21%, 16 hubs and 21 hubs were identified for the HC and DLB groups, respectively. bi values and functional classification of hub regions were also presented in Tables 3 and 4, respectively. Functionally, hubs were primarily located in association areas for HC and DLB groups. Figure 5 illustrates the results for hub nodes in the axial view. In the HC group, hubs are primarily located in the prefrontal and occipital cortices. In the DLB group, hubs are located in prefrontal, occipital, and subcortical cortices of the brain. (Figure 5 was drawn by BrainNet Viewer package [23]).

For comparing different groups, statistical analysis was done with permutation test. It was found that the DLB group showed significantly altered regions in the four brain regions ($p < 0.05$), including pars opercularis (IFGoperc.R), right lingual gyrus (LING.R), fusiform gyrus (FFG.L), and olfactory cortex (OLF.R). Amongst them, betweenness centrality in the DLB group became strong in OLF.R, HIP.R, and FFG.L compared to that in the HC group, whereas betweenness centrality became weak in IFG.R. Table 5 shows betweenness centrality values and p values of these four hubs.

3.3. Seed Correlation. To further investigate connectivity between hubs in two groups, the right inferior frontal gyrus and pars opercularis (IFGoperc.R) were selected as the seed. The region was selected because of two primary reasons: IFGoperc.R is the hub's node in the HC group (bi > 1.5), but it is not targeted for hubs in DLB groups. The values of normalized bi were 1.83 and 0.08 in the HC group and DLB group, which has the smallest bi value in the DLB

Table 3: The hub regions of the HC group.

Hubs	Anatomical classification	Bi (>1.5)	p with DLB value
IFGoperc.R	*Prefontal*	*1.83*	*0.0295*[a]
SMA.L	Frontal	1.70	0.058
SFGmed.L	Prefontal	2.09	0.218
SFGmed.R	Prefontal	1.69	0.059
ORBsupmed.R	Prefontal	1.61	0.3265
INS.L	Subcortical	1.51	0.109
INS.R	*Subcortical*	*2.50*	*0.037*[a]
DCG.R	Frontal	1.55	0.108
AMYG.L	Temporal	2.02	0.1035
CUN.L	Occipital	3.01	0.1065
CUN.R	*Occipital*	*2.62*	*0.041*[a]
LING.R	*Occipital*	*1.59*	*0.135*[a]
PUT.R	*Subcortical*	*2.71*	*0.138*[a]
PAL.R	Subcortical	2.62	0.2475
ITG.L	*Temporal*	*1.70*	*0.0155*[a]
ITG.R	*Temporal*	*2.18*	*0.0260*[a]

Hub is defined as the brain region with a bi value > 1.5; class represents the functional classification of the corresponding brain regions; bi represents the normalized betweenness centrality; and the p with DLB value represents the statistical p value of the permutation test between the DLB and HC groups. [a]Statistically significant difference ($p < 0.05$).

among hubs in the HC group. Compared with the HC group, IFGoperc.R status was different for DLB groups. Second, statistical analysis was conducted by conducting permutation test; it shows that for IFGoperc.R, bi values of DLB groups were significantly different from those of the HC group (p value = 0.0295). As shown in Figure 6, the results of voxel-wise correlation analysis were obtained with IFGoperc.R seed. Figure 6 illustrates the correlation coefficient map (R-map) associated with IFGoperc.R seed in the HC and DLB groups. (Figure 6 was drawn by the REST Slice Viewer [24]). In the HC group, the R-map shows that areas, which present positive connections with IFGoperc.R seed, were focused on the following components of parietal cortex: the bilateral postcentral gyrus (PoCG.R and PoCG.L), right middle frontal gyrus (MFG.R), and right angular gyrus (ANG.R). The weakened regions of the brain were mainly located in the following areas: the right and left cuneus (CUN.R and CUN.L), left insula (INS.L), and right parahippocampal gyrus (PHG.R).

In the DLB group, the prefrontal cortex showed enhanced brain activity in the following areas: the bilateral middle frontal gyrus (MFG.R and MFG.L), bilateral inferior frontal gyrus, pars triangularis (IFGtriang.R and IFGtriang.L), bilateral inferior frontal gyrus, and pars orbitalis (ORBinf.R and ORBinf.L). Weakened brain regions were mainly located in the occipital cortex, including the left calcarine sulcus (CAL.L), left middle occipital gyrus (MOG.L), parietal cortex left postcentral gyrus (PoCG.L), and right inferior parietal lobule (IPL.R).

Table 4: The hub regions of DLB group.

Hubs	Anatomical classification	Bi (>1.5)	p value
ORBsup.L	Prefontal	1.51	0.2185
ORBmid.L	Prefontal	1.73	0.23
ORBinf.R	Prefontal	1.92	0.0955
ROL.L	Frontal	2.59	0.173
OLF.L	Prefontal	3.83	0.134
OLF.R	*Prefontal*	*4.02*	*0.015*[a]
ORBsupmed.L	Prefontal	1.96	0.3045
REC.L	Prefontal	1.55	0.374
INS.L	Subcortical	3.67	0.109
HIP.R	*Temporal*	*5.19*	*0.008*[a]
CUN.L	Occipital	1.63	0.1065
SOG.R	Occipital	2.23	0.1375
MOG.R	Occipital	2.69	0.115
IOG.L	Occipital	1.68	0.2235
IOG.R	Occipital	2.04	0.204
FFG.L	*Temporal*	*2.65*	*0.0135*[a]
IPL.L	Parietal	2.26	0.128
ANG.R	Parietal	1.54	0.28
PCUN.L	Parietal	2.27	0.0895
PAL.R	Subcortical	1.82	0.2475
THA.R	Subcortical	3.88	0.0675

Hub is defined as the brain region with a bi value > 1.5; class represents the functional classification of the corresponding brain regions; bi represents the normalized betweenness centrality; and p value indicates statistic meaning. [a]Statistically significant difference ($p < 0.05$).

In this study, the DLB group was used as a reference for further analysis. Z-statistical mapping was performed in the IFGoperc.R region of the brain of the HC group. Figure 7 illustrates the results obtained by Z-statistical test (z-map).

Compared to the HC group, the results of Z-statistics indicated brain regions that had strengthened connections with IFGoperc.R in the DLB group. These regions were located in the prefrontal cortex, which included the right middle frontal gyrus (MFG.R), bilateral inferior frontal gyrus, pars triangularis (IFGtriang.R and IFGtriang.L), right middle frontal gyrus, orbital part (ORBmid.R), and right medial frontal gyrus (SFGmed.R) ($p < 0.05$, FDR corrected).

4. Discussion

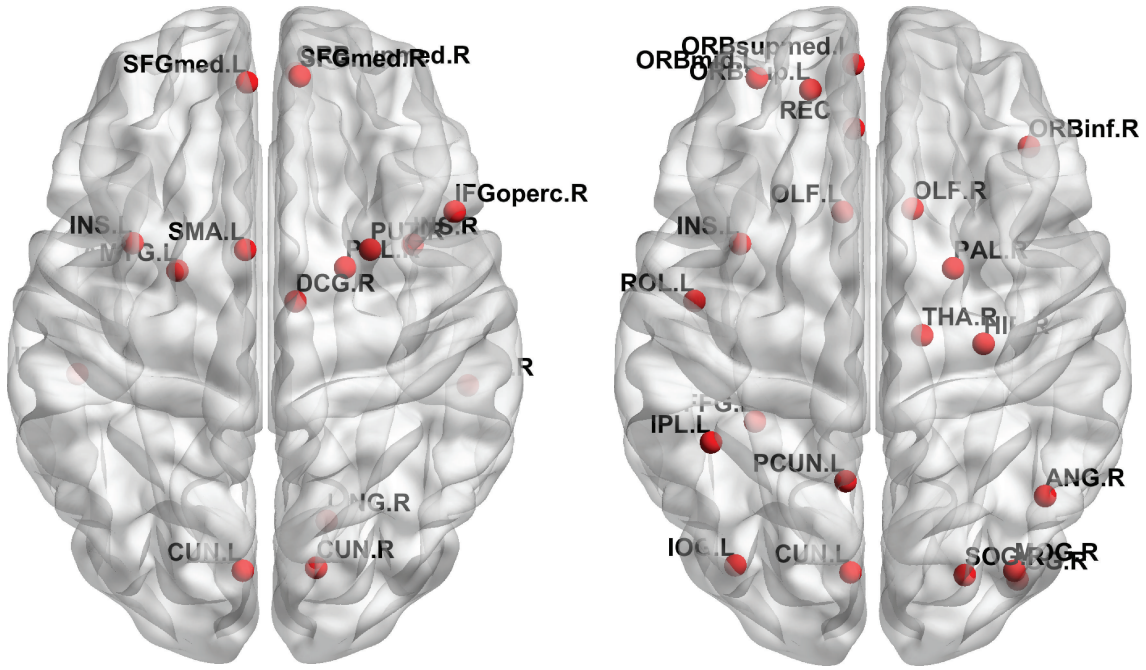
In this study, we found that the functional brain network of DLB patients was significantly different from that of healthy controls. Firstly, network alterations were broad in the DLB group. Secondly, divergent network alterations were manifested in the LDB group. Compared to the HC group, the DLB group suffered very severe dementia due to loss of characteristics of the small-world network. To perform seed correlation analysis, the brain region IFGoperc.R was selected as a seed in this study. Compared to the HC group, the results of z-map showed regions of strengthened connection with IFGoperc.R in the DLB group; these regions were located in the prefrontal cortex, and regions of weakened connection were located in the occipital cortex.

The physiological and pathological meanings of the above findings were discussed below.

4.1. Network Parameters. As shown in Figure 3, parameter C gradually becomes larger as the sparsity increases. When the HC group increases from 0.349 to 0.517, the DLB group increases from 0.305 to 0.668 over an entire threshold range. Statistical analysis based on permutation test showed that C was significantly higher in the DLB group than in the HC group at sparsity 10–14% and 21% ($p < 0.05$). Moreover, parameter L in the DLB group was significantly greater than that in the HC group when sparsity values were in the range of 21–40% ($p < 0.05$). At sparsity values of 31–40%, local E in the DLB group was significantly greater than that in the HC group. Global E in the DLB group was significantly lower than that in the HC group when sparsity values were in the range 7–22% ($p < 0.05$). Sigma in the DLB group was significantly smaller than that in the HC group when sparsity values were in the range 7–21% ($p < 0.05$). Finally, the local E values in the DLB group and HC group were approximately equal over the entire threshold range.

By accurately performing quantitative analysis, a small-world network was constructed. This network showed high global efficiency and optimal organizational structure, which better supported distributed information processing and extremely complex computation. In this study, small-world network was observed in both groups. The results of network parameters indicate that many changes were observed in the DLB group. Compared to the HC group, the characteristic path length was longer for the DLB group. Because characteristic path length was greater for observed points, the organization of the brain network was altered and network efficiency was lowered. In the DLB group brain network, the greater the clustering coefficient of the brain network, the longer would be the characteristic path length of the brain network in the DLB group. This network change tends to be a regular network, which has obvious shortcomings in communication and synchronization abilities of the signal when compared to a small-world network. Many diseases caused by disconnection of the nervous system were associated with loss of global characteristics of a small-world network, and they tend to form a regular network. A previous study had proved that in the DLB group [11], there was a significant loss in small-world network. This might be associated with presynaptic dysfunction, which is caused by α-synuclein aggregates present in the brain cortex, even at early stages of the disease. This finding was also confirmed in our research study.

4.2. Hubs of the Brain Network. Many studies have used fMRI and graph-based analysis method to investigate the functional network of the brain, revealing attributes such as small-world attributes [25, 26]. An important finding was that the networks governing the function of the human brain contained a small number of hubs, which were disproportionately associated with numerous connections. These hubs



(a) (b)

Figure 5: Hub nodes of two groups. (a) 16 hub nodes in the HC group. (b) 21 hub nodes in the DLB group.

Table 5: The significantly altered hubs in the DLB group compared to those in the HC group.

Hubs	Anatomical classification	Bi in HC	Bi in DLB	p value
IFGoperc.R	Prefontal	**1.83**	0.008	0.0295[a]
OLF.R	Prefontal	0.24	**4.02**	0.015[a]
HIP.R	Temporal	0.85	**5.19**	0.008[a]
FFG.L	Temporal	0.58	**2.65**	0.0135[a]

Compared with the HC group, the DLB group showed significantly different hubs. [a]Statistically significant difference ($p < 0.05$).

act as way stations for information processing by connecting distinct, functional specialized systems [27]. These brain hubs, which are mainly located in medial and lateral sections of frontal and parietal cortices, have higher rates of the following functions: cerebral blood flow, aerobic glycolysis, and oxidative glucose metabolism. They play vital roles in supporting fast communication across various brain regions [28]. In the present study, most brain hubs were located in the prefrontal and frontal cortices of the HC group. In the DLB group, brain hubs underwent significant changes, because normal hubs were attacked by dementia.

In present experiments, four significantly altered regions in the DLB groups were identified as hubs, including IFGoperc (IFG.R), olfactory cortex (OLF.R), hippocampus (HIP.R), and fusiform gyrus (FFG.L). This result could be proven in previous literature.

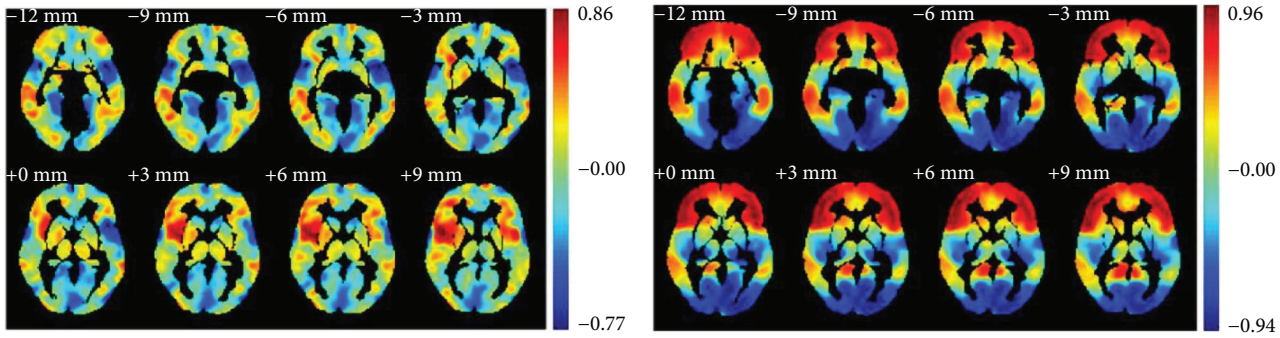
In a previous study conducted by Blanc et al., a significant variation in AAL brain regions was observed in the DLB group of patients. They found that in the DLB group, cortical thinning was found predominantly in the right temporoparietal junction, insula, cingulate, orbitofrontal, and lateral occipital cortices [29].

In a study conducted by Laura et al., significant changes were observed in the olfactory cortex and Lewy body pathology. In future studies, the metamorphosis of the olfactory cortex must be investigated to further elucidate the pathophysiology of DLB patients [30].

In DLB patients, major changes occur in the hippocampus of the human brain. Many studies have recorded the unique response of hippocampal CA2/3 in patients with Lewy body disease. By characterizing dystrophy in HIC hippocampal CA2/3 neurites, one may clarify how lesions lead to the development of dementia in DLB patients [31].

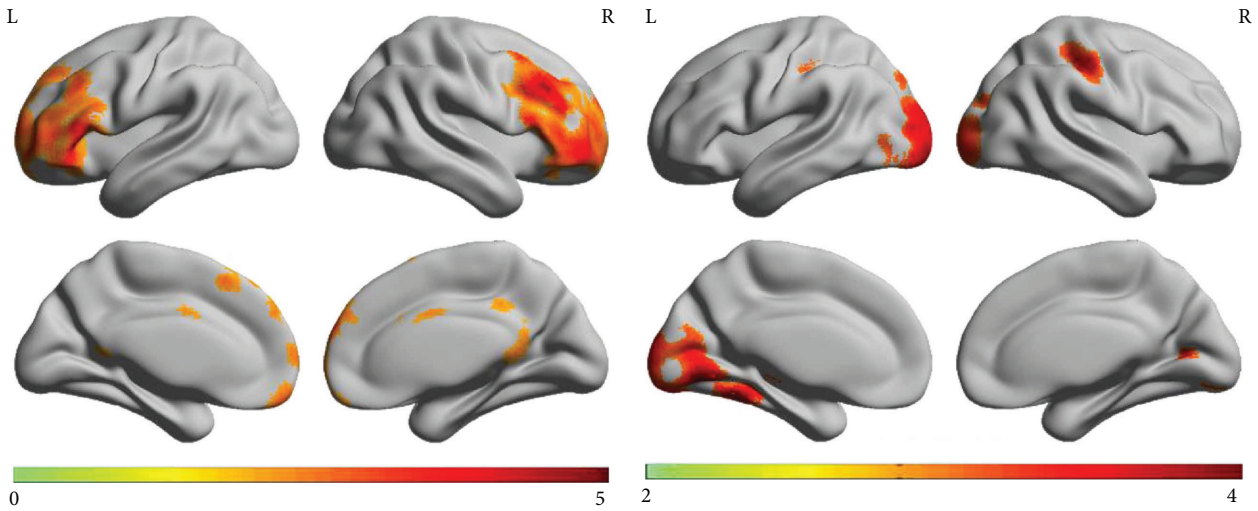
In a study conducted by Kosaka et al., a significant change was observed in the hippocampal gyri and fusiform gyri of a patient suffering from DLB. This disease was predominantly observed in the left region of the brain. This finding completely agrees with the conclusion of our current study [32, 33]. Thus, our experimental results have been validated with these findings.

4.3. Seed Correlation Analysis. The significantly altered region IFGoperc.R was selected as a seed. The results indicate that in the HC group, regions of strengthened connection were detected with IFGoperc.R seed. These regions were mainly located in the parietal cortex, including PoCG.R, PoCG.L, and MFG.R. Functional connection strength between prefrontal cortex and FGoperc.R seed was deep in the DLB group (its distribution was demarcated with a deep color.). In DLB patients, there were differences in the intrinsic functional connectivity of brains. Based on the



(a) (b)

Figure 6: Seed correlation associated with the IFGoperc.R seed. (a) Correlation coefficient map with IFGoperc.R in the HC group; (b) correlation coefficient map with IFGoperc.R in the DLB group.



(a) (b)

Figure 7: *Z*-statistics map. (a) *Z*-statistics map showing the brain regions that had strengthened connection with the IFGoperc.R region in the DLB group when compared to the HC group ($p < 0.05$, FDR corrected); (b) *Z*-statistics map showing the brain regions that had weakened connection with the IFGoperc.R region in the DLB group when compared to the HC group ($p < 0.1$, FDR corrected);

Table 6: Comparison of the DLB network parameters between the present study and Western studies.

	Experimental image	*N*	*C*	*L*	Sigma	*E*	Gamma
Our study	FDG-PET	22	0.59	1.95	1.23	0.55	1.36
Western study [34]	fMRI	22	~0.52	~1.9	~1.35	~0.6	—

N: the number of subjects participating in the experiment.

differences in this connectivity, a new biomarker, IFGoperc.R, was obtained for precisely diagnosing DLB. In the DLB group of patients, there was also a significant decrease in the functional connectivity between extraordinary regions (LING.L, PoCG.R, SMG.R, and SOG.R) and IFGoperc.R seed. These findings were useful for neuroscientists to further understand the pathology of DLB.

4.4. Comparison between Chinese and Western Patients with DLB. Not many studies have investigated the parameters of the brain function network on DLB patients. For the first time, Peraza et al. conducted a representative study on the brain function network parameters [34] to understand the impact of fMRI in 22 DLB patients; however, this study was conducted on Western subjects with DLB. To further explore similar treatment processes for DLB patients in China, the relationship between DLB brain network changes and race was explored. By comparing experimental results with current results in Table 6, broadly similar results were obtained. However, the differences between Chinese and Western DLB people were as follows: larger *C* and *L* values and smaller values would be sigma and global efficiencies.

This is an important point to consider because a change between these parameters was same as the difference between DLB and HC groups. To a certain extent, the parameter results of Chinese DLB patients were more serious than those of Western DLB patients. However, we cannot yet identify specific reasons for this difference. They also need to be studied further.

4.5. Limitations. In this study, there are still several limitations that need to be considered. Firstly, the gender distribution of the participants in the DLB group was extremely uneven (M : F = 21 : 1) in this study. The influences of gender for brain region analysis in the DLB group need be studied in the future. Secondly, the AAL template with 90 regions was used in this study. However, other templates with more regions could also be applied [35], and differences of brain region analysis amongst different templates need be studied. Thirdly, an unweighted and binary network was constructed in this study. Fourthly, partial correlation matrices were used to calculate network parameters and Pearson correlation was used for performing correlation analysis in this study. This may introduce bias in results. Differences of using various correlation matrices need be studied in the future.

5. Conclusion

By performing brain network analysis for FDG-PET images, this study systematically explored glucose metabolic brain network differences in HC and DLB groups in China. As a whole, a small-world topology was demonstrated by both groups. We found that the small-world network was severely impaired in the DLB group, implying that "small-world network" can be used as a biomarker for DLB. Based on seed ROI-based correlation analysis, the differences in brain functional connectivity were observed in DLB groups. One could obtain further insights into pathoetiological mechanisms of this condition. For better understanding and characterizing DLB patients and its triggering mechanisms, more relevant studies must be conducted. An accurate clinical diagnosis of DLB would then be possible.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Delusions in Patients with Dementia with Lewy Bodies and the Associated Factors

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Objective. Delusions are common neuropsychiatric symptoms in patients with dementia with Lewy bodies (DLB). The aim of this study was to investigate the associated factors of delusions in patients with DLB. *Method*. A retrospective study of outpatients with DLB registered in a regional hospital's database was performed. The associated factors including cognitive performance, clinical features, vascular risk factors, and neuropsychiatric symptoms between delusional and nondelusional patients with DLB were compared. *Results*. Among 207 patients with DLB, 106 (51.2%) were delusional and 101 (48.8%) were not. Delusion of other persons are stealing was the most common symptom (35.3%). The delusional group had a significantly higher diagnostic rate of probable than possible DLB, higher disease severity, poorer cognitive performance, more severe neuropsychiatric symptoms, and higher caregiver burden (all $p < 0.05$). In addition, the delusional group had a significantly lower frequency of diabetes compared to the nondelusional group (odds ratio = 0.28, $p < 0.001$). *Conclusion*. Delusion of other persons are stealing was the most common delusional symptom. The patients with DLB who presented with delusions had poorer cognitive function and more severe neuropsychiatric symptoms. A novel finding is that the DLB patients with diabetes had a lower frequency of delusions.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common degenerative dementia. According to the first consensus criteria for the diagnosis of DLB in 1996, it accounts for about 20% of all clinical and autopsy cases of degenerative dementia [1]. In a more recent systemic review of studies on the incidence and prevalence of DLB in 2005, it was reported to account for 0 to 30.5% of all dementia cases [2]. Delusions are among the most common neuropsychiatric features in patients with dementia, especially in those with DLB. Therefore, delusions become one of the supportive features for the clinical diagnosis of DLB [1, 3]. Studies on delusions in dementia have shown that delusions are seldom observed in the predementia stage; however, delusions increase in frequency from the early through the later stages of dementia [4–8].

Clinical studies of delusions in dementia have reported different frequencies and characteristics of delusions among different types of dementia [9]. Psychotic symptoms including delusions and hallucinations have been reported to be significantly more frequent in patients with DLB than in patients with Alzheimer's disease (AD) or other dementia [9–14]. Delusional misidentification is significantly more characteristic of DLB than AD, while paranoid delusions are not specifically associated with DLB [12]. Patients with DLB have more psychotic and mood symptoms; therefore, the carers of patients with DLB experience more stress than those caring for patients with AD and vascular dementia [9].

Pathophysiological studies of delusions in dementia have revealed specific neural substrates that may be associated with delusions in patients with DLB [12, 15–17]. In a study on correlations between cholinergic dysfunction and

neuropsychiatric symptoms of dementia, the authors found that defective cholinergic activity in patients with DLB was correlated with hallucinations and delusions [15]. An autopsy study revealed that delusions in DLB are associated with elevated M_1 binding in Brodmann area 36 [16]. Unlike AD, DLB has been reported to be significantly inversely associated with tangle burden and psychosis [12]. A genetic study reported that the 5-HTTLPR polymorphism is associated with delusions in Lewy body dementias including DLB and Parkinson's disease dementia (PDD) [17].

There is robust evidence of the contribution of vascular risk factors (VRFs) to the incidence and prevalence of AD and vascular dementia (VaD) [18–21]. Diabetes is among the most important VRFs, and a recent meta-analysis reviewed 28 studies and revealed that diabetes has a relative risk (RR) of 1.76 for developing all types of dementia [18]. A case-control study of the risk factors for AD, PD, and DLB by Boot et al. found no association of diabetes with DLB [22]. Some studies demonstrated that most of the risk factors appeared in midlife and that they may increase the risk of dementia later in life [21, 23]. However, associations of VRF with the clinical presentation of dementia have seldom been discussed, and studies on the relationship between VRF and the clinical presentation of DLB even less so [22].

The aim of this study was to investigate factors including clinical features, cognitive performance, neuropsychiatric symptoms, and vascular risk factors between delusional and nondelusional patients with DLB.

2. Methods

2.1. Database. This is a retrospective study of outpatients with DLB registered in a health system's dementia database. The following information from this database was used for this study:

(1) Diagnosis of dementia according to the criteria for primary degenerative dementia in the fourth edition of the Diagnostic and Statistic Manual of Mental Disorders (DSM-IV). Diagnosis of DLB according to the revised consensus criteria for probable or possible DLB developed by the third report of the DLB consortium [3]

(2) Age, gender, education, dementia severity, and medications at the time of entry

(3) Clinical DLB features including fluctuation, parkinsonism, visual hallucinations, REM sleep behavior disorder (RBD), and severe neuroleptic sensitivity

(4) Cognitive performance on the Cognitive Abilities Screening Instrument, Chinese version (CASI C-2.0) with the following domains: long-term memory, short-term memory, attention, mental manipulation, orientation, abstract thinking, language, drawing, and verbal fluency [24]

(5) Neuropsychiatric symptoms in the 12-item version of the Neuropsychiatric Inventory (NPI) including delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritation, aberrant motor behavior, night behavior, and eat/appetite behavior on the basis of observations within the past month [25]

(6) Clinically relevant vascular risk comorbidities including hypertension, arrhythmia, coronary artery disease, diabetes, hyperlipidemia, and cerebrovascular disease (history of stroke/transient ischemic attack or the diagnosis of vascular encephalopathy in brain imaging)

2.2. Assessment of Clinical Features and Diagnosis of DLB. In the dementia clinic, all of the patients and their main caregivers were interviewed by a behavioral neurologist for the assessment of core and suggestive features. Fluctuation was diagnosed when a clinical history of fluctuation in cognition and a Mayo Fluctuation Composite Score (MFCS) > 2 [26] were both present. Visual hallucinations (VHs) were diagnosed when a clinical history of recurrent complex VHs were present. Parkinsonism was diagnosed when at least two of the following were present: bradykinesia, tremor, rigidity, and postural instability. RBD was diagnosed when the minimal criteria for REM sleep behavior disorder according to the International Classification of Sleep Disorders (ICSD) [27] was met. Severe neuroleptic sensitivity was diagnosed when a clinical history was established for both the usage of neuroleptic drugs and an obvious association of adverse events with the neuroleptic drugs. Because dopamine transporter uptake imaging was not available in our hospital until 2010, the suggestive feature "low dopamine transporter uptake in basal ganglia" in the revised consensus criteria could not be evaluated and was thus not included in this study. This may have resulted in a lower diagnostic rate for probable DLB and a higher diagnostic rate for possible DLB.

2.3. Assessment of Delusions and Other Neuropsychiatric Symptoms. All of the patients and their main caregivers were interviewed by a trained neuropsychologist for assessment of the NPI domain of delusions, including ratings on eight individual forms of delusions for the past one month. The NPI is a validated, standardized, and widely used instrument that was developed specifically to evaluate the neuropsychiatric symptoms of dementia. All of the 12 NPI domains were rated for symptom frequency from 1 (occasionally) to 4 (very frequently), symptom severity from 1 (mild) to 3 (severe), and caregiver burden from 0 (none) to 5 (extremely) [25].

2.4. Assessment of Disease Severity and Cognitive Function. The global severity of dementia was assessed according to the Clinical Dementia Rating (CDR) scale and sum of boxes of the CDR (CDR-SB) [28]. Cognitive functions were assessed with the CASI and the Mini-Mental State Examination (MMSE) modified from the CASI [24]. Motor functions were assessed with motor score of the Unified Parkinson's Disease Rating Scale (UPDRS-m) [29], and all patients were rated under medication. Cognitive tests of all patients were performed by a trained neuropsychologist. Dementia and subtypes of dementia were diagnosed by a consensus meeting composed of three neurologists, one geriatric psychiatrist, and one neuropsychologist. All patients received

at least cerebral computed tomography or cerebral magnetic resonance imaging and also a set of blood screening tests for dementia.

2.5. Data Analysis. The Chinese version of SPSS 19.0 for Windows (IBM, SPSS Inc., Chicago) was used for statistical analyses. Comparisons between delusional and nondelusional DLB groups in demographic data, CASI, MMSE, motor score of the UPDRS, and composite scores (frequency × severity) of the NPI were analyzed using the independent t-test. Gender, CDR, clinical features, clinical history of VRFs, current use of antipsychotics, and current use of antiparkinsonian drugs were analyzed using the chi-square test. To compare the associations of clinical features, cognitive performance, neuropsychiatric symptoms, and VRFs between the delusional and nondelusional groups, we used both model 1 analysis (odds ratios (OR) adjusted for age and gender) and model 2 analysis (OR adjusted for age, gender, disease severity according to the CDR, antipsychotics, and antiparkinsonian drugs).

2.6. Ethical Considerations. The Committee for Medical Research Ethics of Show Chwan Memorial Hospital reviewed the project, and the Data Inspectorate approved it.

3. Results

From October 1, 2015, to June 21, 2017, a total of 207 patients who fulfilled the criteria for DLB and had complete data were analyzed. Among them, 106 (51.2%) were delusional and 101 (48.8%) were nondelusional (Figure 1). The delusion of other persons are stealing was the most common (35.3%), followed by delusions of self is in danger (21.3%), house is not his/her home (10.8%), spouse is having an affair (7.2%), family plans to abandon him/her (4.8%), an unwelcome guest is living in the house (2.9%), media persons are in the house (2.9%), and others are not who they claim (1.0%). The frequency of delusions increased as disease severity increased (28.6% in CDR 0.5, 47.5% in CDR 1, and 63.0% in CDR 2–3; $\chi^2 = 12.776$, $p = 0.002$). The severity of delusions among the delusional patients according to the composite score of delusion in the NPI was not different among the CDR groups (4.8 ± 3.7 in CDR 0.5, 4.6 ± 2.1 in CDR 1, and 4.9 ± 2.9 in CDR 2–3; $f = 0.481$, $p = 0.620$).

Comparisons of the demographic data are summarized in Table 1. The delusional group had a significantly higher diagnostic rate of probable DLB (74.5% in the delusional groups versus 60.4% in the nondelusional group, $p = 0.030$), higher disease severity according to CDR stage ($\chi^2 = 12.776$, $p = 0.002$) and CDR-SB ($t = 3.779$, $p = 0.002$), poorer cognitive performance according to the MMSE ($t = -2.623$, $p = 0.009$) and CASI ($t = -2.629$, $p = 0.009$), worse neuropsychiatric symptoms according to the NPI composite score ($t = 7.144$, $p < 0.001$), and higher caregiver burden scale in the NPI ($t = 10.113$, $p < 0.001$).

Comparisons of cognitive performance of each domain in the CASI are summarized in Table 2. The delusional group had poorer performance in the domains of mental manipulation (OR = 0.86, $p = 0.002$) and orientation (OR = 0.93, $p = 0.008$) in model 1 analysis, whereas no cognitive domain was associated with the delusional group in model 2 analysis.

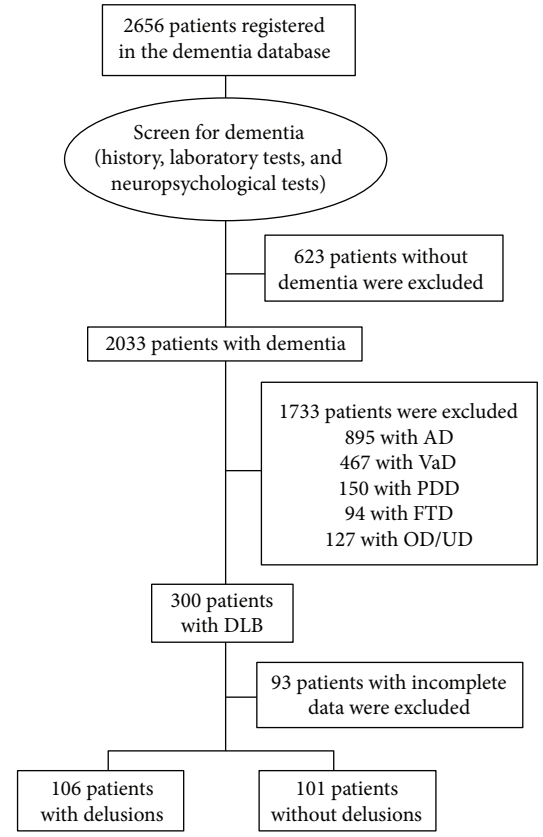

Figure 1

Comparisons of core and suggestive features are summarized in Table 3. The delusional group had a higher frequency of fluctuations (OR = 1.83, $p = 0.032$) and VH (OR = 2.99, $p < 0.001$) in model 1 analysis; however, only VH (OR = 2.31, $p = 0.019$) was significantly higher in the delusional group in model 2 analysis.

A comparison of a history of vascular risk factors demonstrated that the delusional group were significantly less associated with diabetes in both model 1 (OR = 0.36, $p = 0.002$) and model 2 (OR = 0.28, $p < 0.001$) analyses (Table 3). We further analyzed the delusional symptoms that were associated with diabetes after adjusting for age, gender, and disease severity according to the CDR and found that delusions of other persons are stealing (OR = 0.32, $p = 0.018$) and self is in danger (OR = 0.42, $p = 0.021$) were significantly lower in the patients with diabetes.

Comparisons of neuropsychiatric symptoms of each domain in the NPI are summarized in Table 4. The delusional group had higher frequencies of hallucinations (OR = 3.27, $p < 0.001$), agitation (OR = 2.40, $p = 0.003$), anxiety (OR = 2.49, $p = 0.002$), disinhibition (OR = 5.28, $p < 0.001$), irritation (OR = 4.85, $p < 0.001$), and aberrant motor behavior (OR = 2.93, $p = 0.001$) in model 1 analysis. In model 2 analysis, the delusional group had higher frequencies of hallucinations (OR = 2.59, $p = 0.003$), agitation

Table 1: Demographic and background characteristics between the delusional and nondelusional patients with DLB.

	Delusional	Nondelusional	t/χ^2	p
N	106	101		
Gender, male/female	53/53	62/39	2.716	NS
Age, years (SD, range)	78.9 (6.8, 62–91)	77.6 (6.8, 51–90)	−1.301	NS
Education, years (SD, range)	5.8 (5.2, 0–18)	6.6 (5.0, 0–19)	−1.047	NS
Duration, years (SD, range)				
Dementia	3.0 (3.0, 0–20)	2.8 (2.8, 0–15)	0.358	NS
Parkinsonism	3.0 (3.0, 0–20)	2.6 (2.3, 0–10)	1.019	NS
Psychiatric disorder	4.0 (5.1, 0–40)	3.2 (3.6, 0–25)	1.251	NS
RBD	5.0 (9.5, 0–50)	5.5 (11.0, 0–50)	−0.225	NS
DLB probable/possible	79/27	61/40	4.719	0.030
CDR 0.5/1/2–3	10/38/58	25/42/32	12.776	0.002
CDR-SB (SD, range)	9.3 (3.3, 1.5–17.0)	7.5 (3.8, 1.5–16.0)	3.779	<0.001
MMSE (SD, range)	14.0 (7.0, 0–29)	16.9 (8.0, 0–29)	−2.623	0.009
CASI (SD, range)	44.7 (23.1, 0–95)	53.7 (25.9, 0–94)	−2.629	0.009
NPI (SD, range)	34.3 (14.6, 3–77)	19.4 (15.4, 0–79)	7.144	<0.001
NPI burden (SD, range)	17.9 (6.7, 0–32)	9.1 (5.8, 0–25)	10.113	<0.001
UPDRS-m (SD, range)	17.7 (11.3, 0–63)	18.1 (11.4, 0–48)	−0.279	NS
Antipsychotics, *n* (%)	22 (20.8%)	12 (11.9%)	2.967	NS
Antiparkinsonian, *n* (%)	41 (38.7%)	42 (41.6%)	0.182	NS
LED (SD, range)	146 (237, 0–1050)	181 (276, 0–1158)	0.977	NS

NS: not significant; DLB: dementia with Lewy bodies; RBD: REM sleep behavior disorder; psychiatric disorder: psychosis or mood disorders; DLB probable/possible: diagnosis of probable DLB/possible DLB; CDR: Clinical Dementia Rating scale; CDR-SB: sum of boxes of CDR; MMSE: Mini-Mental State Examination; CASI: Cognitive Abilities Screening Instrument; NPI: total score of the 12-domain Neuropsychiatric Inventory; NPI burden: total caregiver burden scale in the NPI; UPDRS-m: motor score of the Unified Parkinson's Disease Rating Scale; antipsychotics: current using antipsychotics; antiparkinsonian: current use of antiparkinsonian agents; LED: levodopa equivalent dose, mg/day.

Table 2: Two models of risk estimates (odds ratios) for cognitive domains in CASI between the delusional and nondelusional patients with DLB.

Features	Mean (SD, range)		Model 1		Model 2	
	Delusional	Nondelusional	OR (95% CI)	p	OR (95% CI)	p
N	106	101				
Remote memory	6.6 (3.3, 0–10)	7.3 (3.2, 0–10)	0.95 (0.87–1.04)	NS	1.05 (0.94–1.17)	NS
Recent memory	4.2 (3.4, 0–12)	5.4 (3.7, 0–12)	0.92 (0.85–1.00)	NS	1.00 (0.90–1.10)	NS
Attention	5.2 (2.2, 0–8)	5.4 (2.2, 0–8)	0.98 (0.86–1.12)	NS	1.09 (0.94–1.27)	NS
Mental manipulation	2.5 (2.9, 0–10)	4.0 (3.5, 0–10)	**0.86 (0.77–0.95)**	**0.002**	0.91 (0.81–1.03)	NS
Orientation	6.7 (4.8, 0–18)	9.0 (6.0, 0–18)	**0.93 (0.88–0.98)**	**0.008**	0.99 (0.92–1.06)	NS
Abstract thinking	4.1 (2.8, 0–11)	4.8 (3.0, 0–12)	0.95 (0.85–1.05)	NS	1.04 (0.91–1.08)	NS
Language	6.8 (3.1, 0–10)	7.1 (3.0, 0–10)	0.98 (0.89–1.07)	NS	1.08 (0.96–1.20)	NS
Draw	4.8 (3.8, 0–10)	5.9 (3.9, 0–10)	0.94 (0.87–1.01)	NS	1.01 (0.92–1.10)	NS
Animal naming (verbal fluency)	4.0 (3.0, 0–10)	4.8 (3.3, 0–10)	0.94 (0.86–1.03)	NS	1.02 (0.92–1.14)	NS

DLB: dementia with Lewy bodies; CASI: Cognitive Abilities Screening Instrument; NS: not significant. The odds ratio (OR) and 95% confidence interval (CI) were calculated with the nondelusional group as reference. Model 1 ORs were adjusted for age, gender, and education; model 2 ORs were adjusted for age, gender, education, disease severity, antipsychotics, and antiparkinsonian agents.

(OR = 1.87, $p = 0.048$), anxiety (OR = 2.64, $p = 0.002$), disinhibition (OR = 4.81, $p = 0.003$), irritation (OR = 4.50, $p < 0.001$), and aberrant motor behavior (OR = 2.36, $p = 0.010$).

4. Discussion

In this study, about half (51.2%) of all patients had a delusion, and the delusion of other persons are stealing (35.3%) was the most common, followed by delusion of self is in danger (21.3%). These findings are consistent with the results from most of the previous studies on DLB [10–13] and also clinical study on AD [8]. The finding of higher frequency of delusions in more severe dementia is probably because delusions are highly associated with the ability of source memory monitoring, and this ability is gradually deteriorated as disease progresses [30]. In this study, although only a cognitive

Table 3: Two models of risk estimates (odds ratios) for core and suggestive features between the delusional and nondelusional patients with DLB.

Features	*N* (%)		Model 1		Model 2	
	Delusional	Nondelusional	OR (95% CI)	*p*	OR (95% CI)	*p*
N	106	101				
Clinical features						
Fluctuation	62 (58.5%)	44 (43.6%)	**1.83 (1.05–3.17)**	**0.032**	1.52 (0.84–2.73)	NS
Visual hallucinations	65 (61.3%)	35 (34.7%)	**2.99 (1.70–5.27)**	**<0.001**	**2.26 (1.21–4.21)**	**0.010**
Parkinsonism	96 (90.6%)	87 (86.1%)	1.54 (0.65–3.66)	NS	1.26 (0.49–3.25)	NS
RBD	44 (41.5%)	45 (44.6%)	0.88 (0.51–1.53)	NS	1.18 (0.66–2.12)	NS
Neuroleptic sensitivity*	12 (11.3%; 54.5%)	7 (6.9%; 58.3%)	1.71 (0.65–4.55)	NS	1.72 (0.61–4.83)	NS
Vascular risk factors						
Hypertension	52 (49.1%)	45 (44.6%)	1.10 (0.63–1.92)	NS	1.17 (0.65–2.09)	NS
Diabetes	21 (19.8%)	40 (39.6%)	**0.36 (0.19–0.68)**	**0.002**	**0.28 (0.14–0.56)**	**<0.001**
Coronary artery disease	7 (6.6%)	7 (6.9%)	0.93 (0.31–2.81)	NS	0.82 (0.26–2.60)	NS
Hyperlipidemia	4 (3.8%)	5 (5.0%)	0.84 (0.22–3.26)	NS	0.80 (0.20–3.21)	NS
Arrhythmia	9 (8.5%)	13 (12.9%)	0.67 (0.27–1.67)	NS	0.55 (0.21–1.46)	NS
Cerebrovascular disease	16 (15.1%)	19 (18.8%)	0.58 (0.33–1.02)	NS	0.63 (0.29–1.38)	NS

DLB: dementia with Lewy bodies; RBD: REM sleep behavior disorder; NS: not significant. The odds ratio (OR) and 95% confidence interval (CI) were calculated with the nondelusional group as reference. *Severe neuroleptic sensitivity (among all patients; among those who had ever used antipsychotics). Model 1 ORs were adjusted for age and gender. Model 2 ORs were adjusted for age, gender, disease severity, antipsychotics, and antiparkinsonian agents.

Table 4: Two models of risk estimates (odds ratios) for neuropsychiatric symptoms in the NPI between the delusional and nondelusional DLB groups.

Neuropsychiatric symptoms	Mean (SD, range)		Model 1		Model 2	
	Delusional	Nondelusional	OR (95% CI)	*p*	OR (95% CI)	*p*
N	106	101				
Hallucinations	71 (67.0%)	37 (36.6%)	**3.27 (1.83–5.85)**	**<0.001**	**2.59 (1.39–4.80)**	**0.003**
Agitation	52 (49.1%)	30 (29.7%)	**2.40 (1.34–4.30)**	**0.003**	**1.87 (1.01–3.48)**	**0.048**
Depression	76 (71.7%)	65 (64.4%)	1.31 (0.72–2.38)	NS	1.19 (0.64–2.22)	NS
Anxiety	72 (67.9%)	45 (44.6%)	**2.49 (1.40–4.43)**	**0.002**	**2.64 (1.45–4.81)**	**0.002**
Euphoria	2 (1.9%)	2 (2.0%)	1.22 (0.14–9.02)	NS	0.62 (0.77–4.96)	NS
Apathy	72 (67.9%)	59 (58.4%)	1.58 (0.88–2.82)	NS	1.26 (0.68–2.32)	NS
Disinhibition	24 (22.6%)	5 (5.0%)	**5.28 (1.91–14.44)**	**<0.001**	**4.81 (1.71–13.53)**	**0.003**
Irritation	62 (58.5%)	24 (23.8%)	**4.85 (2.62–8.99)**	**<0.001**	**4.50 (2.39–8.46)**	**<0.001**
Aberrant motor behavior	50 (47.2%)	23 (22.8%)	**2.93 (1.59–5.38)**	**0.001**	**2.36 (1.23–4.51)**	**0.01**
Sleep	91 (85.8%)	78 (77.2%)	1.72 (0.83–3.55)	NS	1.56 (0.74–3.30)	NS
Eat/appetite	47 (44.3%)	30 (29.7%)	1.54 (0.87–2.74)	NS	1.36 (0.75–2.46)	NS

DLB: dementia with Lewy bodies; NPI: Neuropsychiatric Inventory; NS: not significant. The odds ratio (OR) and 95% confidence interval (CI) were calculated with the nondelusional group as reference. Model 1 ORs were adjusted for age and gender; model 2 ORs were adjusted for age, gender, disease severity, antipsychotics, and antiparkinsonian agents.

screening tool was used to study the association of cognitive functions with delusions [24], our patients with DLB and delusions had poorer cognitive function, especially in the domain of mental manipulation, which is also regarded to be an executive function [31]. Studies on the mechanism and interaction of delusions with cognition had demonstrated that delusions are highly associated with cognitive impairment and especially with impairments in source monitoring [30] and are regarded to involve source memory and executive functions [30, 32]. A recent study on the interaction of cognitive functions and delusions in patients with AD also reported that psychosis is influenced by executive function [33]. In addition, relationships between behavioral syndromes and cognitive domains in patients with AD showed that psychosis was significantly associated with impaired working memory [33]. In previous studies of DLB and according to the consensus criteria, cognitive impairments in the domains of executive function, visuospatial function, and attention in patients with DLB have been noted in the early stage of disease [1, 3]. Therefore, it is reasonable to find a high frequency of delusions in patients with DLB.

Previous studies have shown that neuropsychiatric symptoms in patients with DLB are more severe and more frequent than in other types of dementia [9–14]. These symptoms are salient in the early stage of DLB, and they are manifested as delusions, visual hallucinations, REM sleep behavior disorder, and depression [1, 3]. Our patients with mild DLB had a high frequency of delusions (22.7% with CDR 0.5 and 39.5% with CDR 1), which is consistent with our previous study on delusions in different stages of AD [8]. The current study also demonstrated that the delusional patients generally had more severe neuropsychiatric symptoms and were associated with a higher frequency of hallucinations, agitation/aggression, anxiety, irritation, and aberrant motor behavior.

Previous studies on the association between vascular risk factors and degenerative and/or vascular disorders have focused on controlling risk factors in midlife to prevent morbidity and mortality in late life. In general, these factors are regarded to be important risk factors for both small and large vessel diseases, and most of the vascular risk factors, including diabetes, in midlife have been associated with increased neurodegenerative dementia and vascular dementia in late life [21, 23]. However, the association between the incidence of dementia or cognitive decline and diabetes in late life is still controversial. The contribution of vascular risk factors has seldom been studied in patients with DLB. A previous study on the risk factors for DLB compared to the risk factors for AD showed no differences in stroke or diabetes between the two groups [22]. A novel finding of the current study is that the patients with DLB comorbid with diabetes had a lower frequency of delusions. A possible explanation for this finding is that, similar to findings from a study of animals with diabetes, levels of muscarinic acetylcholine receptors (mAChRs) subtype M1 are decreased in the cerebral cortex of patients with diabetes [34]. The M1 subtype of mAChRs is the most abundant type in the human cerebral cortex and hippocampus [35]. In general, M1 immunoreactivity is markedly reduced in the brains of patients with AD and DLB [34]. However, in a study of autopsy cases, Ballard et al. reported that delusions in patients with DLB are associated with elevated M1 binding in Brodmann area 36 [12]. Another study found decreased levels of total muscarinic and muscarinic M1 receptors in animals with diabetes [34]. Based on these findings, we proposed that patients with DLB comorbid with diabetes may have decreased levels of M1 receptors in the brain, which may lead to a lower frequency of delusions. Further studies are warranted to clarify the pathophysiology and causal relationship among diabetes, antidiabetes drugs, and delusions in patients with DLB.

In conclusion, delusions and other neuropsychiatric symptoms were evaluated in a relatively large sample of patients with DLB in this study. We found that the frequency of delusions increased as the severity of dementia increased in patients with DLB. We use multidimensional analysis of the associated factors of delusions and found that the patients with DLB and delusions had a poorer cognitive function and more severe neuropsychiatric symptoms. The novel finding of this study is that the patients with DLB comorbid with diabetes had a lower frequency of delusions.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Additional Points

Significant Outcomes. (1) Neuropsychiatric symptoms were evaluated in a relatively large sample of patients with dementia with Lewy bodies (DLB). (2) We use multidimensional analysis of the associated factors of delusions in patients with DLB. (3) A novel finding is that patients with DLB comorbid with diabetes had fewer delusions. *Limitations*. (1) This study was conducted in 3 hospitals in Taiwan. Therefore, the findings may not be generalizable to all patients with DLB. (2) The comparison of associated factors between the delusional and nondelusional patients with DLB in this study was cross-sectional. Therefore, causal relationships of the factors and dementia could not be ascertained. (3) Because of a lack of measurable data including the glucose level, glycated hemoglobin level, blood pressures, and medications on vascular risk factors and the associated medications of the patients, further studies are needed to evaluate the contribution of these factors on the presentation of delusions in patients with DLB. (4) Because less than 20% of our participants had received dopamine transporter uptake imaging, this may have resulted in a lower diagnostic rate for probable DLB in this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ray-Chang Tzeng undertook the literature search and data analysis and edited the author contributions and was mainly responsible for revisions and drafts of the manuscript. Pai-Yi Chiu participated in the data analysis and contributed to revisions and the final draft of the manuscript. Tzu-Yuan Wang participated in data analysis and contributed to revisions of the manuscript. Ching-Fang Tsai contributed to revisions of the manuscript. Ching-Tsu Wang undertook the literature search and contributed to revisions.

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