Abstract

Purpose: Parkinson’s disease (PD), the fastest-growing neurodegenerative disease, is a movement disorder that manifests unilaterally. Clinical studies, neuroimaging studies, and longitudinal studies all indicate that the clinical features and progression of PD are asymmetric. The asymmetry of PD is thought to be an important clue in understanding the disease’s pathophysiology. The purpose of this study is to see how the concept of PD asymmetry evolved over time, to identify the different types of asymmetry that can be seen in PD, and to understand the clinical implications of the different types of asymmetry in PD.

Method: The following were our review questions. (1) How has PD asymmetry research evolved over time? (2) What types of asymmetry can be seen in PD? (3) What are the clinical implications of the various types of asymmetry seen in PD? To investigate such questions, we used the keywords “Parkinson” and (“symmetry” or “asymmetry”) in PubMed. Articles about idiopathic Parkinson’s disease (iPD) patients with a clear concept of symmetry or asymmetry that were peer-reviewed and written in English were included. The type of article, participants, three main keywords, and the type of symmetry concepts in the study were extracted. We excluded studies that did not include patients with idiopathic PD or that did not have a clear concept of symmetry.

Results: Based on a PubMed search, the number of published articles on iPD and symmetry gradually increased beginning in the 1980s. Of the 563 articles that were initially searched, 333 articles were related to both iPD and symmetry or asymmetry concepts. There were 171 articles on nervous system asymmetry, 133 on motor symptoms and gait asymmetry, 24 on disease presentation asymmetry, and 5 on anatomical or histological structures asymmetry. The majority (n = 70) of the 171 studies on nervous system asymmetry dealt with lateralization of brain function and the resulting asymmetries in motor symptoms and disease manifestations in iPD patients.

Conclusion: Asymmetry in iPD patients has mainly been studied based on nervous system asymmetry, motor symptoms, and overall disease presentation. Other types of asymmetry, such as asymmetry in anatomical and histological structures, have been studied in some studies. Asymmetry in iPD is not only an inherent feature of the disease; it also appears to be related to the disease’s various symptoms and signs. As a result, more research is needed to better understand the pathophysiology of iPD and to provide iPD patients with a prognosis and advice for disease management.

Keywords: Parkinson’s Disease, Neurodegenerative Disease, Motor Symptoms, Asymmetry, Scoping Review

1. Introduction

Parkinson’s disease (PD) is the fastest-growing neurodegenerative disease [1], and its prevalence is rising especially in aging countries. According to a study based on sample cohort data from the Korean National Health Insurance Corporation, the prevalence of PD in Korea increased from 41.4 in 2004 to 142.5 in 2013 per 100,000 people [2]. The gender and age-standardized
prevalence of the disease also increased from 115.9 in 2010 to 139.8 in 2015 per 100,000 people[3]. As the global population ages, the prevalence of degenerative brain diseases such as PD will rise, necessitating the development of appropriate countermeasures.

PD is a movement disorder with clinical features of bradykinesia, postural instability, resting tremor, and rigidity due to dopaminergic neurodegeneration in the midbrain substantia nigra. These motor symptoms of PD typically begin unilaterally and later become bilateral as the disease progresses[4][5]. Neuroimaging studies, such as diffusion magnetic resonance imaging(MRI) and positron emission tomography/computed tomography(PET/CT) studies, also suggest that dopaminergic neurodegeneration in the substantia nigra begins unilaterally in PD[6][7]. Furthermore, a longitudinal study in PD patients using high-density electroencephalography(HD-EEG) found asymmetry in the disconnected brain networks, which was associated with the lateralization of motor symptoms[8].

Unlike other parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, and diffuse Lewy body disease, unilateral symptoms are so prominent in PD that they serve as a clinical parameter to differentiate it from other disorders. Although the specific cause of the asymmetry of PD has not been elucidated, researchers believe that it will be an important clue in understanding the pathophysiology of the disease[9]. Therefore, in this brief scoping review, the authors aimed to identify the areas studied for PD asymmetry and organize specific asymmetry types. We believe that the findings of this review will help us better understand the pathophysiology of PD.

2. Methods

2.1. Review questions

i. How has research on PD asymmetry developed over time?

ii. What kinds of asymmetry can be seen in PD?

iii. What are the clinical implications of the different types of asymmetry seen in PD?

2.2. Study selection

In this review, we included studies involving patients with idiopathic Parkinson’s disease(iPD). Studies involving other parkinsonian syndromes or neurodegenerative disorders were excluded from the review. We used the keywords “Parkinson” and (“symmetry” or “asymmetry”) to search the PubMed database. The article titles and abstracts were screened. Peer-reviewed, English-written articles about iPD patients with a clear concept of symmetry or asymmetry were included. The type of article, participants, three key concepts, and the type of symmetry concepts in the study were extracted and charted using Microsoft Excel(Microsoft, Redmond, WA, USA). During the process, studies that did not include iPD patients or did not have a clear implication of symmetry or asymmetry concepts were excluded.

2.3. Data analysis and presentation

The quality of the included articles will not be evaluated, in accordance with scoping review standards. Instead, we will provide an overview of current asymmetry concepts seen in iPD patients. We will include all eligible literature covering the entire period to identify the research trends. Following that, we will include recent articles from 2010 to the present to analyze each concept in detail. However, if significant concepts were only discovered in the literature prior to 2010, we will include them in the analysis as well.
3. Results

3.1. Parkinson’s disease asymmetry research trends

From 563 initially searched articles, n = 333 articles were related to both iPD and symmetry or asymmetry concepts. Among those, 171 articles dealt with nervous system asymmetry, 133 with motor symptoms and gait asymmetry, 24 with disease presentation asymmetry, and 5 with anatomical or histological structures asymmetry. There were 317 original articles and 16 review articles. Among the 230 excluded articles, 112 were excluded because they were not directly related to iPD, 75 were excluded because they lacked a clear concept of symmetry or asymmetry, 41 were excluded because they were in-vivo or in-vitro studies on animals and cells, and 2 were excluded because they lacked an abstract. The detailed study selection process is shown in Figure 1.

Figure 1. Flow chart of the study selection process.

The number of published articles on iPD and symmetry, based on a PubMed search, gradually increased beginning in the 1980s, as shown in Figure 2. 2 articles from the 1980s dealt with nervous system asymmetry while 1 dealt with motor symptom asymmetry. 22 articles published in the 1990s dealt primarily (n = 17) with nervous system asymmetry. During the 1990s, only three articles dealt with asymmetry in motor symptoms, one with disease presentation-related asymmetry and one with structural asymmetry. In the 2000s, research on gait asymmetry began to emerge (8 out of 83 articles). During the 2000s, 51 studies reported nervous system asymmetry, 12 studies reported motor symptoms asymmetry, and 12 studies reported disease presentation asymmetry. Finally, there were 225 studies from 2010 to the present. Among the articles, 101 dealt with nervous system asymmetry, 76 with gait asymmetry, 33 with motor symptoms asymmetry, 11 with disease presentation asymmetry, and 4 with structural asymmetry. We will only include articles published after 2010 for further analysis. However, if important concepts were only found in the literature prior to 2010, then we will additionally include them in the analysis as well.

3.2. Asymmetry in the nervous system

The most studied area of asymmetry in iPD patients, according to a PubMed search, was asymmetry in the nervous system. Among the 101 studies on the topic, the majority (n = 48)
dealt with lateralization of brain function and resulting differences in disease manifestations in iPD patients. Neuronal damage typically begins asymmetrically in iPD, and corresponding parkinsonian symptoms appear first on the side of the body opposite the neuronal damage.

**Figure 2.** The number of articles published each year on idiopathic Parkinson’s disease and asymmetry research, based on a PubMed search.

Many studies have reported asymmetric neurodegeneration in brain regions such as the nigrostriatal system[9][10][11][12] in iPD patients. Asymmetric nigrostriatal degeneration in the brain results in the onset of motor symptoms on the contralateral side of the body[9][10]. According to magnetic resonance imaging(MRI) studies, substantia nigra pars compacta has lateral asymmetry and asymmetrical microstructural degeneration[9][13]. According to neuroimaging studies using single-photon emission computed tomography(SPECT) and positron emission tomography(PET), neurodegeneration and dopamine receptor changes in the substantia nigra and striatum also occur asymmetrically[14][15]. Furthermore, a transcranial sonography study in iPD patients revealed asymmetry in substantia nigra hyperechogenicity[16].

Asymmetry in symptoms and neurodegeneration is prominent in iPD, but the exact cause of this phenomenon is unknown. Among the 48 studies, some(n = 7) attempted to link handedness and lateralization of iPD symptoms. Some studies suggest that there is a link between handedness and the side of symptom onset. According to a systematic review and meta-analysis by van der Hoorn et al., there are more cases where the dominant hand and the side of the initial motor symptom are the same than the other way around, with an overall odds ratio of 2.13[17]. A similar pattern was observed in a more recent study between the dominant hand’s side and the side of initial motor onset. The study also displayed that according to neuromelanin-sensitive imaging, neurodegeneration was more pronounced on the contralateral side of handedness[18]. Another study using dopamine transporter(DAT)-SPECT and transcranial sonography revealed a similar pattern of asymmetrical neurodegeneration to the contralateral side of hand dominance[19]. There is evidence, however, that increased physical activity on the dominant side of handedness protects the contralateral motor cortex[20]. Such compensation in the cerebral cortex may explain some of the inconsistency in the proportion between the side of initial motor onset and contralateral neurodegeneration observed in Prasad et al.'s study[18].

Neurodegeneration asymmetry in iPD can occur in either the right or left hemisphere of the brain. Because the functions of the left and right hemispheres of the brain are not identical, researchers have attempted to compare the symptoms of patients with iPD, with the left onset of motor symptoms(LP), and with the right onset of motor symptoms(RPD). There were 20 studies that tried to compare LPD and RPD patients in terms of cognitive function and perception. In general, LPD patients had worse visuospatial performance[21], poorer spatial
memory[22], rightward bias and pseudo-neglect on the left side[23], impaired feedback-based associative learning[24], faster cognitive decline[25], problems with spatial attention and visuospatial orienting[26], decreased access to religious cognition[27], reduced linguistic complexity such as producing fewer verbs and function words[28], and increased harm avoidance[29]. On the other hand, RPD patients had impaired estimates of body-scaled aperture width[30], leftward bias and pseudo-neglect on the right side[23], more pronounced verbal memory problems[26], and decreased novelty seeking[29], but better prognosis in terms of cognition[25].

There have also been attempts to characterize the LPD and RPD patients’ neuropsychiatric characteristics. However, there are contradicting results as some studies suggest that a higher prevalence of hypomania and conversion profile could be found in LPD patients[31], as well as nocturnal hallucinations and daytime sleepiness[32], while other studies suggest that a higher prevalence of hallucinations and sleep behavior disorder are more frequent in RPD patients[33], and a higher degree of Parkinson-related psychosis[34]. It might be that those neuropsychiatric symptoms are related to Lewy-body pathophysiology rather than lateralization of PD manifestation[35], and the manifestation of Lewy-body pathology may not be as lateralized as that in iPD[36]. Meanwhile, there were some other interesting studies that suggest that LPD may be related to some obsessive-compulsive symptoms[37], and alteration in detecting and processing emotional salience in voices such as disgust, anger, and happiness[38][39].

Furthermore, many studies(n=41) indicate that there is marked asymmetry in neurodegeneration in iPD patients, which can be used as a tool for differential diagnosis of vascular parkinsonism[40][41][42], and Parkinsonism plus syndromes such as multiple system atrophy(MSA), dementia with Lewy bodies(LBD), and progressive nuclear palsy(PSP)[36][43]. However, unlike other non-idiopathic parkinsonian syndromes, corticobasal degeneration(CBD) patients have neurodegeneration asymmetry similar to iPD[44]. The rest(n = 12) of the studies suggest that there are asymmetries in visually guided saccades[45], blinking reflex[46], and optokinetic nystagmus[47]. Besides neurodegeneration, there were also accompanying changes in cerebral blood flow and hemodynamics[48], brain metabolic network[49], and neural activities[50][51] which were all less or more asymmetric.

3.3. Asymmetry in the motor symptoms and gait

Asymmetry in motor symptoms and gait in iPD patients was the second most studied area after the nervous system. Among the 109 studies, 76 were related to gait and 33 to motor symptom asymmetry. Gait parameters, such as step time and length[52][53][54][55], arm swing asymmetry, and reduced interlimb coordination[56][57] are all characteristics of iPD patients[58][59][60]. Especially, arm swing asymmetry is prominent from the early stage of iPD and it is suggested as one of the biomarkers for early detection of iPD[58][59]. Another characteristic of iPD is the freezing of gait(FOG). Studies suggest a possible relationship between FOG, turn bias, and gait asymmetry in iPD patients[57][61]. Gait is found to be less rhythmic and more asymmetric in patients with FOG[62]. In addition to reduced rhythmicity, reduced step length is suggested to be another factor that affects FOG[57].

Meanwhile, studies suggest that cueing and increasing step length can assist iPD patients in restoring gait symmetry. Brodie et al. found that auditory cues tailored to each patient’s habitual gait symmetry and cadence could improve gait steadiness[63]. Virtual reality visual cueing combined with treadmill training could also improve step length and gait symmetry[64]. Another study discovered that swing time asymmetry worsens when stride length is reduced, so increasing stride length during gait training may improve gait symmetry[65]. These factors can be used to improve gait symmetry in iPD patients during rehabilitation training <Figure 3>.

Motor symptoms such as tremor[66][67][68], rigidity[69][70], bradykinesia[70], and posture instability[71][72] were all found to be asymmetric in iPD. Asymmetry in tremors in iPD can be
used as a tool for differential diagnosis against essential tremor (ET) patients. In parkinsonian tremors, waveform, as well as tremor frequency and frequency dispersion were more asymmetric compared to essential tremors[66][67][68]. Whether increased postural asymmetry increases fall risk in iPD patients is controversial[71][72]. It can be noted that in general, asymmetry of motor symptoms begins unilaterally and progresses bilaterally in many cases of iPD, and posture asymmetry may appear more pronounced in some early-stage patients. Meanwhile, a specific type of posture abnormality in iPD patients called Pisa syndrome appears in the late stage of disease progression and is considered to be related to verticality misperception and basal ganglia output asymmetry[73][74].

3.4. Asymmetry in the general disease presentation

As previously stated, in many cases, the symptoms and signs of iPD begin unilaterally. Although some patients have abnormal asymmetrical features such as a different side of disease onset and progression, a different source of resting and action tremor, different rates of disease progression on different sides, and less pronounced tremor as the disease progresses[75], the majority of patients have unilateral disease onset, and the laterality may decrease but can also persist for the most part throughout the disease course[76]. On the other hand, atypical parkinsonism often manifests bilaterally from the start and then progresses rapidly[77]. Symmetrical disease presentation can be used to differentiate iPD patients from other types of parkinsonism, but it can also be used to predict PD patient survival. In iPD patients, symmetry in disease presentation was a sign of poor prognosis and survival, as suggested by a long-term follow-up study[78].

3.5. Asymmetry in the anatomical structure

Lastly, there were 4 articles that dealt with anatomical or histological asymmetry in iPD patients. Baek et al. recently suggested interocular asymmetry of retinal thickness in iPD patients and there was a correlation between temporal macular retinal thickness asymmetry and motor symptom laterality[79]. There are dopamine neurons in the retina and there was a strong inverse correlation between the peripapillary retinal nerve fiber layer(RNFL) thickness and the PD severity, measured by Unified Parkinson's Disease Rating Scale(UPDRS)[80]. Other studies dealt with asymmetry in muscles such as paraspinal muscles[81], gastrocnemius muscles, and tibialis anterior muscles[82]. In addition, one study suggested that there are occlusal contact asymmetry and a high prevalence of temporomandibular disorder[83], as well as asymmetry in the foveal pit in iPD patients[84].
4. Conclusion

PD, the fastest-growing neurodegenerative disease, is a movement disorder with unilateral onset. Although the asymmetry of iPD is thought to be an important clue in understanding the disease’s pathophysiology, the cause of such asymmetry is unknown. To better understand the characteristics and types of asymmetry in iPD, we conducted a PubMed search and classified the studies based on the different types of asymmetries. Asymmetry in iPD patients has primarily been studied in terms of asymmetry in the nervous system, gait, motor symptoms, and disease presentation. Visual and auditory cueing, as well as increasing stride length, could help patients with iPD improve their symmetry during rehabilitation training. Other types of asymmetry such as asymmetry in anatomical and histological structures were also investigated in some studies. The asymmetry in PD is not only an intrinsic feature of the disease, but it also appears to be related to various symptoms associated with the disease. As a result, more research is needed to better understand the pathophysiology of iPD and explain the prognosis to patients with iPD.

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5.1. Journal articles


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6. Appendix

6.1. Author’s contribution

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