Coexistence of Parkinson's disease and myasthenia gravis: A case report and literature review

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Abstract. The coexistence of Parkinson's disease (PD) and myasthenia gravis (MG) is rare. When similar symptoms of both diseases overlap, it is challenging to make a concomitant diagnosis of PD and MG. The present study describes the case of a patient with concomitant PD and MG. In addition, a systematic literature review was conducted by searching PubMed and Embase for reports on all patients with concomitant PD and MG, which were then grouped and compared according to different preexisting diseases. Finally, a total of 47 cases of concomitant PD and MG (35 men; 12 women), including the present case, were analyzed. The median age of the patients at first diagnosis was 66.59±9.91 years. The interval between the two diseases varied from 2 months to 22 years. Based on the sequential occurrence of these two diseases, the patients were categorized into three groups: The prePD-MG (30 cases), preMG-PD (12 cases), and coPD-MG (5 cases) groups. In the prePD-MG group, the onset age of MG was older and head drop was more common. In the preMG-PD group, the patients were more likely to have comorbid immune diseases.

Introduction

Parkinson's disease (PD) is a chronic, progressive degenerative disease associated with dopaminergic neuron loss of the substantia nigra, striatum and other brain structures, in which the balance between dopamine and acetylcholine neurotransmitters is disrupted. It is most common in middle-aged and older adults, and is characterized by resting tremors, muscle rigidity, bradykinesia and postural instability (1,2). Myasthenia gravis (MG) is a B cell-mediated, acquired autoimmune disease associated with antibodies that are directed mainly against the acetylcholine receptor (AChR) in the postsynaptic membrane at the neuromuscular junction. It occurs in patients of all ages, and is associated with partial or whole skeletal muscle weakness and fatigue (3). The coexistence of PD and MG is an uncommon phenomenon since they differ in their etiological and pathological features. Moreover, they share some similar clinical symptoms, such as fatigue, ocular symptoms, dysphagia, dysarthria and head drop (4), which may overlap and lead to diagnostic ambiguity, making co-diagnosis of PD and MG more challenging.

It is currently unclear whether the coexistence of PD and MG is coincidental or etiologically related. The imbalance between cholinergic and dopamine systems may link PD and MG. Notably, trihexyphenidyl (THP), which can reduce acetylcholine levels in the treatment of PD, has been reported to induce MG symptoms (5,6), and pyridostigmine, which can increase acetylcholine levels in the treatment of MG, can exacerbate PD symptoms (6,7). However, most patients develop the diseases without the being treated with such drugs (8-13), suggesting other mechanisms are involved in the coexistence of the two diseases. Multiple lines of evidence have indicated that immune system dysfunction serves as a critical component in susceptibility to and progression of PD, including shared molecular pathways (such as NLRP3 inflammasome activation) and polygenic risk variants (such as LRRK2 and PRKN genes) with autoimmune diseases, increased risk of PD in patients with autoimmune diseases, impaired humoral and cellular immunity, activated microglia in the brain, altered gut microbiota and inflammatory markers in the feces, as well as a lower risk after treatment with anti-inflammatory drugs and immunosuppressants (14). MG is a classic mainly AChR antibody-mediated disorder at the neuromuscular junction, which is accompanied by an activated immune response with the support of autoreactive B cells (15-17). Therefore, some links, such as immune system dysfunction, might result in the coexistence of the two diseases, even though they initially appear quite different in terms of pathogenesis.

To the best of our knowledge, there are only a few studies on MG comorbidity in patients with PD (4-13,18-28), and fewer studies (9,13,18) have summarized the clinical features of PD

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Abbreviations: PD, Parkinson's disease; LD, levodopa; THP, trihexyphenidyl; MG, myasthenia gravis; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; IVIG, intravenous immunoglobulin

Key words: PD, MG, coexistence, immune dysfunction, case report

and MG coexistence. The present study describes the case of a patient with concomitant PD and MG, and a literature search was conducted to identify reports on all patients diagnosed with concomitant PD and MG in an attempt to analyze the clinical characteristics and explore the possible mechanisms of such comorbidity. The present study aims to alert clinicians to this potential overlap between PD and MG, with the purpose of improving diagnostic accuracy and optimizing the management of both diseases.

Case report

A 68-year-old man developed right-hand resting tremor, bradykinesia, hypomimia, constipation and sleep disturbance in January 2015, showing decreased function of dopamine transporters in the bilateral caudate nuclei, and bilateral posterior and anterior putamen as revealed by ^{11}C-CFT PET/CT (Fig. 1). The patient was therefore diagnosed with PD. The patient responded well to levodopa (LD) (125 mg tid) and entacapone (100 mg tid). A total of 6 months before admission, the patient gradually developed fluctuating double eyelid drooping without diplopia or abnormality of ocular movements, and ophthalmic examination showed no abnormality. The patient experienced weakness in the neck muscles, with problems raising their head soon afterward, and the symptoms of muscle weakness gradually deteriorated. Furthermore, no improvement was observed after adjusting the anti-PD drugs (LD, 125 mg tid; pramipexole, 0.25 mg tid; entacapone, 200 mg tid). On admission to Tongji Hospital (Wuhan, China) in January 2021, besides ptosis and head drooping, the patient complained of symptoms of bulbar palsy (such as choking and dysphagia) and mild dyspnea. Considering the fluctuating and deteriorating muscle weakness, a neostigmine test was performed, which was positive. Repetitive nerve stimulation (RNS) revealed a progressive decrement in low-frequency RNS in both the accessory and facial nerves (Fig. 2). Nerve conduction studies were normal. Thymic hyperplasia and thymoma were not observed. There were no obvious abnormalities in thyroid function or serum creatine levels. Furthermore, tumors, autoimmune disorders (including rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome) or systemic autoimmune antibodies (such as antinuclear antibody) were not detected. The serum anti-AChR antibody was 30.9 nmol/l (normal range <0.40 nmol/l, enzyme-linked immunosorbent assay) and the anti-muscle specific tyrosine kinase (MuSK) antibody was negative. The patient was finally diagnosed with MG based on fluctuating weakness, positive neostigmine test results and the classical decrement in low-frequency RNS, as well as the positive anti-AChR antibody. Following treatment with intravenous immunoglobulin (IVIG, 0.4 g/kg/day for 5 days), cholinesterase inhibitors (pyridostigmine, 60 mg tid), steroids (prednisone, 20 mg qd) and immunosuppressant therapy (tacrolimus, 3 mg qd), the symptoms of MG improved, as evidenced by no drooping eyelids or drooping head, and an improvement in swallowing.

After a 3-year follow-up, both MG and PD symptoms remained stable. At this time point, the patient had discontinued the steroid treatment, whereas a low dosage of tacrolimus (1 mg daily) and pyridostigmine (60 mg, twice daily) was maintained to prevent MG relapse. For PD treatment, LD (125 mg tid), pramipexole (0.25 mg tid) and Stalevo (325 mg tid) were used as maintenance medications.

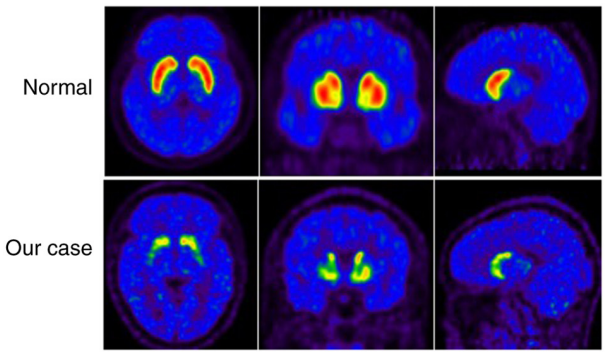

Figure 1. ^{11}C-CFT PET/CT. Decreased function of dopamine transporters in the bilateral heads of caudate nuclei, and bilateral anterior and posterior putamen. The normal images were obtained from healthy individuals at the medical examination center in Tongji Hospital, and individuals provided written informed consent for the publication of these images.

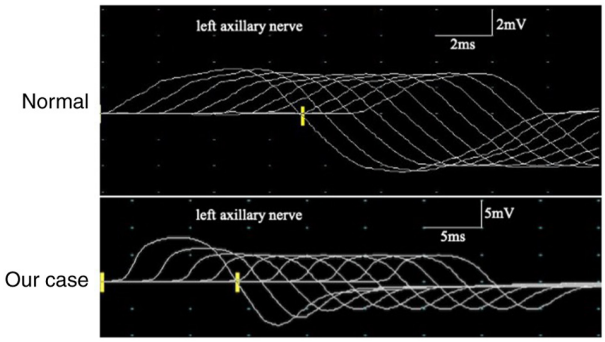

Figure 2. Repetitive nerve stimulation at 3 Hz showed a >10% decrease in the wave amplitudes of the left axillary nerve. The normal images were obtained from healthy individuals at the medical examination center in Tongji Hospital, and individuals provided written informed consent for the publication of these images.

Subsequently, a systematic literature review was conducted by searching the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Embase (http://www.embase.com). databases for reports on all patients with concomitant PD and MG up to October 31, 2023. Search terms included 'Parkinson's disease' or 'Parkinson's syndrome' or 'Parkinsonism' AND 'myasthenia gravis' or 'myasthenia'. The reference lists of the included articles were also reviewed. All cases of concomitant PD and MG were summarized and analyzed, then grouped and compared according to different preexisting diseases.

Finally, a total of 47 cases of concomitant PD and MG, including the current case, were analyzed. The patients were categorized into three groups based on the sequential occurrence of these two diseases. In the prePD-MG group, 30 patients were initially diagnosed with PD, followed by a subsequent diagnosis of MG (Table I). In the preMG-PD group, MG was diagnosed in 12 patients, followed by a subsequent PD diagnosis (Table II). The remaining 5 cases failed to note the order of diagnosis occurrence and were considered the coPD-MG group (Table III).

The overall median age of patients at first diagnosis was 66.59±9.91 years (range: 49-90 years), with 35 (74.47%) men

Table I. Demography and clinical characteristics of the prePD-MG group.

First author, year	Sex/Age, years	PD symptoms	PD treatment	Comorbidities	Interval	MG antibodies	Ocular symptoms	Dysphagia	Dysarthria	Head drop	MG treatment	(Refs.)
Ueno, 1987	M/55	RT + Hm	THP, LD	DM	5.5 years	AChR: P	Y	Y	N	Y	Pyd	(5)
Tasić, 1991	M/74	RT + R	THP, amantadine	Tuberculous lymphadenitis	3 years	NR	Y	Y	Y	N	Pyd	(21)
Kao, 1993	F/54	R + RT + Hm + BK	THP, Sinemet	NR	7 years	AChR: P	Y	Y	Y	Y	Pyd, CS	(6)
Levin, 2003	M/76	RT + R	LD	NR	5 years	AChR: P	N	N	N	Y	Pyd, AZA	(8)
Levin, 2003	M/62	R + RT	LD, pergolide, selegiline, amantadine	NR	4 years	AChR: P	Y	N	N	N	Pyd	(8)
Levin, 2003	M/61	R	LD	GD, hyperthyroidism	NR	NR	Y	N	N	N	Pyd	(8)
Fasano, 2008	F/53	RT + R + BK	NR	NR	5 years	AChR: Ne; MuSK: Ne	N	N	N	Y	Pyd, CS, AZA, PE	(19)
Unal-Cevik, 2009	M/80	RT + R + BK	NR	Hypothyroidism, HPT	4 years	AChR: Ne	N	N	N	Y	Pyd	(22)
Uludag, 2011	M/66	RT + R	LD, benserazide	HPT, COPD, hyperlipidemia	9 years	AChR: P	N	N	N	Y	IVIG, Pyd	(10)
Lanfranconi, 2011	M/70	RT + BK + R + Hm	LD	NR	3 years	AChR:Ne; MuSK: P	Y	Y	Y	N	CS	(11)
Zis, 2014	M/64	R	NR	HPT, RA	5 years	AChR: P; Musk: Ne	N	N	N	Y	Pyd, CS	(20)
Neuman, 2014	F/68	RT + R + BK	LD	NR	7 years	AChR: P	N	N	N	Y	Pyd, AZA, IVIG	(12)
Sciacca, 2016	F/57	NR	NR	NR	9 years	NR	Y	N	N	N	Pyd	(18)
Sciacca, 2016	M/60	NR	NR	NR	3 years	NR	Y	N	N	Y	Pyd	(18)
Sciacca, 2016	M/67	NR	NR	NR	3 years	AChR: P	Y	N	N	N	Pyd	(18)
Tung-Chen, 2016	F/71	BK + Hm + R + RT	LD	Anemia	19 years	AChR: Ne	Y	Y	Y	N	Pyd, CS, AZA, IVIG	(13)
Aiba, 2016	F/71	R + BK	LD	NR	5 years	AChR: P	N	N	N	Y	Pyd, CS	(23)
Hogg, 2017	M/75	BK + Hm + R	NR	Myopathy	3-4 months	AChR: P	Y	Y	Y	Y	Pyd	(24)
Urban, 2018	M/76	NR	NR	NR	6 years	AChR: P	N	Y	N	N	Pyd, CS, IVIG, AZA	(25)
Urban, 2018	M/90	NR	NR	NR	5 years	AChR: P	N	Y	N	N	Pyd, CS	(25)
Urban, 2018	M/78	NR	NR	NR	5 years	AChR: P	N	Y	N	N	Pyd, CS. AZA	(25)
Urban, 2018	M/74	NR	NR	NR	7 years	AChR: P	N	Y	Y	N	Pyd, IVIG, CS, AZA	(25)

Table I. Continued.

First author, year	Sex/Age, years	PD symptoms	PD treatment	Comorbidities	Interval	MG antibodies	Ocular symptoms	Dysphagia	Dysarthria	Head drop	MG treatment	(Refs.)
Marano, 2019	M/65	RT + BK + R	LD	NR	8 years	AChR: P	Y	Y	N	Y	Pyd, CS, AZA	(26)
Odajiu, 2019	M/49	BK + R + Hm	*Stalevo*, ropinirole rasagiline	Crohn's disease	11 years	AChR: P	Y	N	N	N	Pyd	(9)
Odajiu, 2019	F/64	BK + RBD + Hm + R	*Stalevo*, pramipexole, rasagiline	HPT	4 years	AChR: Ne	Y	Y	Y	N	Pyd	(9)
Odajiu, 2019	M/52	RT + BK + R	*Stalevo*, rasagiline, THP	DM, HPT	3 years	AChR:Ne; MuSK: Ne	Y	N	N	N	Pyd	(9)
Alshaikh, 2021	M/61	NR	NR	Vitamin B12 deficiency	6 years	AChR: P	Y	Y	Y	N	NR	(4)
Alshaikh, 2021	M/61	NR	NR	Neuropathy, vitamin B12 deficiency	1 year	AChR: P	Y	Y	Y	Y	NR	(4)
Alshaikh, 2021	M/82	NR	NR	NR	NR	AChR: P	NR	Y	Y	N	NR	(4)
Current case	M/62	RT + BK	LD, entacapone	None	6 years	AChR: P; MuSK: Ne	Y	Y	N	Y	Pyd, CS, IVIG, tacrolimus (FK506)	

F, female; M, male; PD, Parkinson's disease; Hm, hypomimia; R, rigidity; RT, resting tremor; BK, bradykinesia; LD, levodopa; THP, trihexyphenidyl; RBD, rapid eye movement sleep behavior disorder; DM, diabetes mellitus; GD, Graves' disease; HPT, hypertension; RA, rheumatoid arthritis; COPD, chronic obstructive lung disease; MG, myasthenia gravis; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; AZA, azathioprine; CS, prednisone/methylprednisolone; Pyd, pyridostigmine; IVIG, intravenous immunoglobulin; NR, not reported; P, positive; Ne, negative; Y, yes; N, No.

Table II. Demography and clinical characteristics of the preMG-PD group.

First author, year	Sex/Age, years	MG antibodies	Ocular symptoms	Dysphagia	Dysarthria	Head drop	MG treatment	Comorbidities	Interval	PD symptoms	PD treatment	(Refs.)
Iwasaki, 1988	F/62	AChR: P	Y	N	N	N	Pyd	NR	2 months	R + RT + BK	None	(7)
Levin, 2003	F/68	AChR: P	Y	N	N	N	Pyd, AZA	NR	3 years	R + restlessness	LD	(8)
Neuman, 2014	M/72	AChR: P	Y	N	N	N	Pyd	NR	4 years	RT + R + BK	NO	(12)
Ozer, 2016	M/67	NR	N	N	Y	N	Pyd	Chronic subdural hematoma	16 months	BK	LD, benserazide	(27)
Alshaikh, 2021	M/70	AChR: P	Y	N	N	Y	NR	Thyroid disease	8 years	NR	NR	(4)
Alshaikh, 2021	M/66	AChR: P	Y	Y	Y	N	NR	Neuropathy, thyroid disease, vitamin B12 deficiency, childhood polio	1 year	NR	NR	(4)
Alshaikh, 2021	M/66	AChR: P	Y	Y	Y	Y	NR	Neuropathy, thyroid disease, vitamin B12 deficiency	8 years	NR	NR	(4)
Alshaikh, 2021	F/85	AChR: P	Y	Y	Y	Y	NR	Neuropathy	4 years	NR	NR	(4)
Alshaikh, 2021	M/49	SN	Y	Y	Y	N	NR	Thyroid disease	22 years	NR	NR	(4)
Alshaikh, 2021	F/55	NR	Y	Y	N	N	NR	Neuropathy	19 years	NR	NR	(4)
Alshaikh, 2021	M/59	SN	N	Y	N	N	NR	Neuropathy, thyroid disease, Lyme disease	10 years	NR	NR	(4)
Alshaikh, 2021	M/52	NR	Y	N	N	N	NR	Thyroid disease, vitamin B12 deficiency	20 years	NR	NR	(4)

F, female; M, male; PD, Parkinson's disease; R, rigidity; RT, resting tremor; BK, bradykinesia; LD, levodopa; SN, seronegative; MG, myasthenia gravis; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; NR, not reported; P, positive; Y, yes; N, No.

Table III. Demography and clinical characteristics of the co MG-PD group.

First author, year	Sex	Age at diagnosis of PD/MG, years	Comorbidities	MG antibodies	Ocular symptoms	Dysphagia	Dysarthria	Head drop	(Refs.)
Albassam, 2021	F	72/72	HPT, DM, dyslipidemia	AChR: N; MuSK: P	Y	Y	N	N	(28)
Alshaikh, 2021	M	78/-	Thyroid disease	AChR: P	Y	N	N	N	(4)
Alshaikh, 2021	M	60/-	Neuropathy, vitamin B12 deficiency, CVID	AChR: P	Y	Y	Y	N	(4)
Alshaikh, 2021	M	-/-	Thyroid disease, hemophilia A	AChR: P	Y	Y	Y	N	(4)
Alshaikh, 2021	M	84/-	Thyroid disease	AChR: P	NR	NR	NR	NR	(4)

F, female; M, male; PD, Parkinson's disease; MG, myasthenia gravis; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; NR, not reported; CVID, common variable immunodeficiency; -, unknown; P, positive; NeY, yes; N, No.

and 12 (25.53%) women (Table IV). Notably, some of the cases counted in the present study did not report detailed clinical information; therefore, proportions were calculated as the percentage of individuals reporting on that indicator. Various comorbidities were observed, particularly autoimmune diseases, with hypertension present in 6 patients (21.43%) of 28 patients, thyroid disease in 12 patients (42.86%), neuropathy in 7 patients (25.00%), and rheumatoid arthritis, Crohn's disease or myopathy in 1 patient each (3.58%).

The initial symptoms of PD included rigidity (88.00%), resting tremors (64.00%), bradykinesia (64.00%) and hypomimia (32.00%), which could be present in any combination with other symptoms. The anti-PD therapy was mainly LD (85.71%), THP (19.05%), dopamine receptor agonists (14.29%), monoamine oxidase-B inhibitors (19.05%), catechol-O-methyltransferase inhibitors (19.05%), and amantadine (9.52%).

In terms of MG clinical signs, 32 patients (69.57%) had ocular symptoms, including ptosis and diplopia, 26 (55.32%) had dysphagia, 18 (38.30%) had dysarthria, 18 (54.54%) had head drop and 12 (36.36%) had limb weakness. Among the 40 patients who underwent antibody detection, 31 (77.50%) were positive for AChR antibodies and 2 (5.00%) were positive for MuSK antibodies. None of the patients had thymoma or thymic hyperplasia (data not shown). Anti-MG therapy was mainly pyridostigmine (96.88%), and some patients were treated with prednisone/methylprednisolone (40.63%), azathioprine (31.25%) or IVIG (6 cases, 12.8%).

In the prePD-MG group, the average age at diagnosis with MG was 71.91±9.92 years, which was older than that in the preMG-PD group. GraphPad Prism (v8.0.2; Dotmatics) was applied for the statistical analysis. P-values were calculated using independent t-tests or Fisher's exact test. The interval between PD and MG diagnosis ranged from 3-4 months to 20 years (median, 5 years). These patients were more prone to comorbidities, such as hypertension. Most patients had typical PD symptoms and anti-PD therapy was diverse. As for MG clinical signs, head drop was more common in this group than in the preMG-PD group. However, due to limited information, the present study could not determine which stage of PD was prone to MG and which type of MG was more likely to occur.

Patients in the preMG-PD group were more prone to immune disease comorbidities, such as thyroid disease and neuropathy, and there were higher proportion of women in this group than in the prePD-MG group. The interval from MG to PD diagnosis ranged from 2 months to 22 years (median, 5 years). Moreover, in this group, although there was no statistical difference, the proportion of ocular symptoms and limb weakness seemed higher, whereas PD symptoms were relatively fewer than those in the prePD-MG group and anti-PD therapy was relatively single (only LD) The present study attempted to analyze which type of MG was more prone to PD; however, due to limited information, conclusions could not be drawn.

Although the number of CoPD-MG cases was relatively low, their clinical characteristics was similar to that of the prePD-MG group. Both the basic treatment of MG and PD were effective in the three groups.

Discussion

The coexistence of neurodegenerative diseases and autoimmune diseases is not uncommon. However, as a rare disease, the incidence rate of MG worldwide was only 10-29 per million person-years based on data from the past decade (29), which makes the coexistence of PD and MG relatively rare. In clinical practice, the overlap of some indicators, such as ocular symptoms, limb weakness and head drop, leads to a misdiagnosis or delayed diagnosis; therefore, the actual reported cases of PD and MG comorbidity may be less. The present study described the case of a patient co-diagnosed as having PD and MG with positive anti-AChR antibodies. After searching the literature, 47 cases of PD and MG comorbidity, including the current case, were identified. Similar to previous studies (9,13,18), in order to better present the cases, the clinical data of each patient were listed in tables. In contrast to other studies, the present study added newly reported cases, summarized their

demographic and clinical characteristics, and categorized and compared them based on different preexisting diseases. Overall, the average age of the three groups was relatively old. The interval between the two diseases varied from 2 months to 22 years. In addition to MG, autoimmune diseases, such as thyroid disease and rheumatoid arthritis, were also observed in these patients. AChR antibodies were the most common among those who underwent antibody testing. Consistent with recent studies, the present study revealed that most of the cases were male patients (30,31), and most patients were diagnosed with PD before being diagnosed with MG (30).

With varying initial diseases, each of the three groups exhibited distinct characteristics. The mean age at diagnosis of MG was older in the prePD-MG group than that in the preMG-PD group. One possible explanation for this phenomenon is the varying initial diseases, as PD tends to manifest in the older population. Moreover, hypertension was most frequently observed in this group, which may be due to the same reason as that aforementioned. Another possibility is the increase in the incidence of MG in older adults (32). The main clinical features of MG, such as ocular symptoms and limb weakness, were easily masked by bradykinesia and rigidity in the prePD-MG group, which challenged the diagnosis of MG in such a group. Moreover, the sign of head drop was more prominent in the prePD-MG group, which was consistent with a previous finding that the proportion of head drop in PD was higher than that in MG (33). Since the head drop was less affected by bradykinesia and rigidity, the comorbidity of MG should be considered once a fluctuation in head drop has been observed in patients with PD. In the preMG-PD group, it may be easier to make a certain diagnosis of both diseases because the symptoms related to MG are more clearly discernible in this pattern. Moreover, ophthalmoplegia and limb weakness appeared to be more common, as they were not masked by PD symptoms. Patients in this group were more prone to comorbid autoimmune diseases, with female patients being more susceptible to the preMG-PD pattern, which could be related to the fact that they were more prone to autoimmune diseases (34).

The mechanisms underlying concomitant PD and MG remain unknown. Whether it is a casual phenomenon or if there is a causative relationship between both diseases requires further clarification. Iatrogenic causes have been reported in some comorbidity cases (5-7). THP for treating PD has been reported to induce MG symptoms (5,6), and pyridostigmine for treating MG can exacerbate PD symptoms (6,7). Moreover, systematic immune dysfunction has been revealed in PD and MG comorbidity, with reports of thyroid disease, MG and PD (8), and rheumatoid arthritis, MG and PD comorbidities (20). However, it is currently unknown whether patients with PD and MG comorbidity share similar genetic associations, such as LRRK2 gene mutations, observed between PD and inflammatory bowel disease (35).

Some studies have detected autoantibodies to α-synuclein (36,37) and autoreactive T cells that recognize specific α-synuclein epitopes in patients with PD (38), thus indicating that immune reactions participate in the pathophysiology of PD. In addition, studies have revealed that B cells contribute to the pathogenesis of PD (39), including deposits of immunoglobulin G (IgG) found on dopaminergic neurons (40), Lewy bodies coated with IgG (41), and increased levels of anti-α-synuclein antibodies in the cerebrospinal fluid and the blood (36,37). Aberrant functioning of the immune system, as aforementioned, has been proposed as a critical component of susceptibility to and progression of PD (14). In addition, MG is a classic antibody-mediated disorder dependent on autoreactive B cells that require T-cell support (15,16), accompanied by an activated immune response in the neuromuscular junction from the early stage of the disease (17). Therefore, a common pathophysiological mechanism of immune dysfunction may result in PD and MG comorbidity.

Inflammatory mechanisms might also be involved in the process of concomitant PD and MG. An increase in cytokines, such as TNF-α, IL-1β and IL-6, in the peripheral blood has been detected and proven to have a significant role in the progression of PD (42). Adaptive immune components in the peripheral blood of patients with PD have also been observed, such as type 1 T-helper cells and interleukin-17-producing T-helper cells, contributing to high blood levels of interferon-γ and tumor necrosis factor (43). In a recent study, the neutrophil-to-lymphocyte ratio (NLR), a marker of peripheral inflammation, was used to detect peripheral inflammation in PD, and the NLR ratio was revealed to be higher in the PD group than that in the control group (44). Microglia, local innate immune cells in the brain, become activated in response to inflammation and are involved in dopaminergic neuron damage via various mechanisms in PD (14). Furthermore, different proinflammatory or inflammatory mediators have been reported to contribute to the pathogenesis of MG (45). The initial activation of peripheral immunocytes and cytokines in MG might infiltrate the brain parenchyma once the blood-brain barrier is compromised, thus leading to the subsequent activation of central inflammation, such as antigen-antibody reaction associated with α-synuclein, or the direct infiltration of the microglia, monocytes and dendritic cells (14).

Gut-derived inflammation may also be associated with the co-occurrence of PD and MG. The gut microbiota and its metabolites have been shown to be involved in the regulation of neuroinflammation, barrier function and neurotransmitter activity in PD (46). The microbiota-gut-brain axis, a form of bidirectional communication between the enteric nervous system and the central nervous system, may provide a pathway for the transmission of α-synuclein (46). Similarly, accumulating evidences has endorsed the key role of gut microbiota in the pathogenesis of MG (47,48), particularly the effects on T-helper 17/regulatory T cell balance, the imbalance of which can result in the progression of MG.

Taken together, it is plausible to assume that immune dysfunction and inflammatory mechanisms may contribute to the comorbidity of MG and PD, with the initial peripheral immune dysfunction or inflammation triggering neuroinflammation resulting in activation of the degenerative process. However, it is challenging to determine which mechanisms are involved in the different groups assessed in the present study.

The present study had some limitations. First, due to the small number of reported comorbidities and the lack of detailed patient-specific information, the analysis based on the existing data has a certain degree of bias, and it cannot be graded based on the severity of patients. However, the data of most patients were relatively detailed, and a small amount of unprovided data did not affect most results. Larger scale

Table IV. General characteristics of PD combined with MG.

Characteristic	Concomitant PD and MG (n=47)	PrePD-MG (n=30)	PreMG-PD (n=12)	CoPD-MG (n=5)	P-value[a]
Mean ± SD PD-onset age, years	68.76±9.44	66.60±9.81	72.58±6.72	73.50±10.25	0.061
Mean ± SD MG-onset age, years	69.67±10.25	71.91±9.92	64.25±9.78	-	0.030[b]
Sex, M/F	35/12	23/7	8/4	4/1	0.505
History diseases, %					
Hypertension	21.43	35.71	0	20.00	0.039[b]
Diabetes mellitus	10.71	14.29	0	20.00	0.360
Other immune diseases, %					
Thyroid disease	42.86	21.43	66.67	60.00	0.042[b]
Neuropathy	25.00	7.14	55.56	20.00	0.018[b]
RA	3.58	7.14	0	0	0.609
Crohn's disease	3.58	7.14	0	0	0.609
Myopathy	3.58	7.14	0	0	0.609
Median disease interval, years	5	5	5	-	
PD symptoms, %					
R	88.00	90.00	75.00	100.00	0.437
RT	64.00	70.00	50.00	0	0.407
BK	64.00	65.00	50.00	100.00	0.486
Hm	32.00	35.00	0	100.00	0.224
PD treatment, %					
Levodopa	85.71	93.75	50.00	100.00	0.088
THP	19.05	25.00	0	0	0.376
DA	14.29	18.75	0	0	0.491
MAO-B	19.05	25.00	0	0	0.376
COMT	19.05	25.00	0	0	0.376
Amantadine	9.52	12.50	0	0	0.632
MG symptoms, %					
Ocular symptoms	69.57	62.07	83.33	100.00	0.138
Head drop	54.54	71.43	25.00	0	0.013[b]
Dysphagia	55.32	54.84	50.00	75.00	0.521
Dysarthria	38.30	35.48	41.67	50.00	0.485
Limb weakness	36.36	32.14	50.00	100.00	0.427
MG-antibodies, %					
AChR-Ab	77.50	76.92	77.78	80.00	0.670
MuSK-Ab	5.00	3.85	0	20.00	0.743
MG-treatment, %					
Pyd	96.88	96.30	100.00	100.00	0.871
CS	40.63	44.44	0	100.00	0.123
IVIG	12.8	18.52	0	100.00	0.475
AZA	31.25	29.63	25.00	100.00	0.673

[a]P-value, PrePD-MG vs. PreMG-PD. [b]Significant P-values (P<0.05). P-values were calculated using independent t-tests or Fisher's exact test. F, female; M, male; PD, Parkinson's disease; MG, myasthenia gravis; Hm, hypomimia; R, rigidity; RT, resting tremor; BK, bradykinesia; RA, rheumatoid arthritis; THP, trihexyphenidyl; DA, dopamine receptor agonist; MAO-B, monoamine oxidase-B inhibitor; COMT, catechol-O-methyltransferase inhibitor; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; AZA, azathioprine; CS, prednisone/methylprednisolone; Pyd, pyridostigmine; IVIG, intravenous immunoglobulin.

studies are required to examine the co-occurrence of PD and MG, which may improve understanding of this complication. Second, all mechanisms of PD and MG comorbidity were speculative based on current reported studies, and more basic research is required to understand the pathogenesis of the comorbidity. New immune-based therapeutic options may

focus on eliminating circulating autoantibodies or inhibiting effector mechanisms by targeting B cells, B-cell growth factors or other immunosuppressive treatments in such comorbidities.

In conclusion, the coexistence of PD and MG is very rare. The overlapping symptoms of these two diseases can be challenging, especially when the initial disease is PD. Clinicians should pay attention to this potential overlap in order to improve the accuracy of PD and MG co-diagnosis, and to optimize the management of these two diseases. Immune dysfunction and inflammation may result in the coexistence of neurodegenerative and neuroimmune diseases due to interactions between the brain parenchyma and blood circulation. Further therapeutic interventions aimed at immune-associated mechanisms could be of great use to delay disease progression and pathological processes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZM and QN collected the data and confirm the authenticity of all the raw data. ZX processed the statistical data. ZM and ZL drafted and revised the manuscript. ZM and ZL designed and guided the study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval no. TJ-IRB20211273).

Patient consent for publication

The patient and healthy individuals providing normal images provided written informed consent for publication.

Competing interests

The authors declare that they have no competing interests.

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