Tzu Chi Medical Journal 2022; 34 (2): 169-181

Review Article

Epidemiology of atypical parkinsonian syndromes

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Abstract

Atypical parkinsonism or atypical parkinsonian syndromes (APS) refer to a group of neurodegenerative disorders which mimic typical Parkinson's disease but poorly respond to levodopa treatment and deteriorate faster. APS are very rare and among them, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD) are the three relatively better characterized entities. The prevalence estimates of PSP, MSA, or CBD are mostly $<10/10^5$, and the incidence estimates are around $1/10^5$ person-year; both estimates remain stable over the past few decades. The age at onset is relatively young for MSA at late 50s, followed by CBD at early 60s, and then PSP at late 60s. The gender difference is not significant in APS, although slight female predominance in CBD has been reported in literature. Little is known about genetic and environmental risk factors for PSP, MSA, and CBD; although the *COQ2* mutation has been identified as a genetic risk for MSA, familial cases are extremely rare. Survival after symptom onset is generally within 10 years, but cases with longer disease duration do exist. Respiratory infection remains the major cause of death for APS, but cardiac arrest should be particularly considered in MSA. In addition to disease rarity, the phenotype–pathology discrepancy in APS makes the epidemiological studies even more challenging. Including biomarkers in future diagnostic criteria and establishing disease registry for collecting sufficient number of APS cases may increase the likelihood of finding modifiable risk factors for prevention and intervention.

Keywords: *Atypical parkinsonism, Corticobasal degeneration, Epidemiology, Multiple system atrophy, Progressive supranuclear palsy*

Submission : 17-Aug-2020
Revision : 10-Sep-2020
Acceptance : 15-Sep-2020
Web Publication : 19-Jan-2021

Introduction

Parkinsonism is a general description for conditions like those seen in Parkinson's disease (PD), such as tremor, stiffness, and slowness. While idiopathic PD is the most common diagnosis in the context of parkinsonism, atypical parkinsonian syndromes (APS) are rare and underrecognized, comprising only 5%–7% of all types of parkinsonism [1,2]. APS are often indistinguishable with typical PD due to symptom overlap early in the disease course, leading to underdiagnosis, misdiagnosis, or diagnostic delay. The diagnosis of APS depends on how likely certain key features, or "red flags," can be identified. These red flags include early frequent falls, early cognitive impairment, more rapid progression, poor response to levodopa, severe autonomic dysfunction, and early bulbar symptoms such as dysphagia, dysphonia, and dysarthria [3]. These red flags also indicate generally worse clinical outcomes in APS, and there is currently indeed no effective treatment available to patients with APS.

To identify potential etiologies of APS and further prevent the disease occurrence, we need more comprehensive understanding of the distribution and risk factors of APS. In an ideal epidemiologic study for APS, cases and controls are sampled from a large, well-defined group of individuals representative of the general population, and evaluated by movement disorder specialists using established diagnostic criteria, together with medical records, imaging data, and even postmortem verification of clinical diagnosis. However, such rigorous approfaches are time consuming, labor intensive, and too expensive; therefore, most estimates of APS were derived from investigations focused on idiopathic PD or clinic-based case series of a rather small sample size. In this review article, we will start with the epidemiology of typical PD as a reference and then mainly focus on APS with primarily motor dysfunction,

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Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_218_20

How to cite this article: Lo RY. Epidemiology of atypical parkinsonian syndromes. Tzu Chi Med J 2022;34(2):169-81.

namely progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD), while excluding dementia with Lewy bodies, PD dementia, or other rare forms of parkinsonism such as the parkinsonism–dementia complex of Guam and Guadeloupean parkinsonism.

Parkinson's disease

PD is the second-most common neurodegenerative disease, after Alzheimer's disease, characterized by slowness, resting tremor, rigidity, and postural instability. The underlying pathology of typical PD is loss of dopaminergic cells in substantia nigra pars compacta in association with the formation of intraneuronal Lewy bodies, and patients with typical PD are usually responsive to levodopa treatment.

Prevalence and incidence of Parkinson's disease

The prevalence of PD has been recently updated based on data from North America, and estimated to be $572/10^5$ (95% confidence interval [CI]: 537–$614/10^5$) for people at age of 45 or above, suggesting its consistency and stability [4]. The incidence of PD for people at the age of 40 or above is estimated to be $37/10^5$ person-year for women and $61/10^5$ person-year for men; however, the onset of PD as a degenerative disease is hard to determine, and the incidence estimation is often based on the time when PD is first diagnosed, which varies across different studies [5]. The distribution of PD is not so much different in Asia than in North America as one representative report from Taiwan estimated the prevalence of PD to be $130.1/10^5$ and the incidence to be $10.4/10^5$ person-year across all age groups [6]; however, the study has been done for more than two decades and the demographics of older adults might have changed as the global population ages.

Genetic and environmental risk factors of Parkinson's disease

A handful of specific genes causing parkinsonism have been identified [7,8], and all of these are rare. First identified was the *SNCA* gene on chromosome 4q21.3, which encodes *α*-synuclein, responsible for a rare, dominantly inherited disorder limited to a few families worldwide [9]. The protein, *α*-synuclein, is a major component of Lewy bodies, the pathologic hallmark of PD. More common is the recessively inherited disorder caused by mutations in the *Parkin* gene on chromosome 6q25.2–27, accounting for most cases of parkinsonism beginning before the age of 30 [10]. Mutations in the *PINK1* and *DJ-1* genes are also limited to very few families worldwide. Most common are mutations in the leucine-rich repeat kinase 2 or *LRRK2* gene on chromosome 12q12 [11]. The G2019S mutation is the most common mutation of the *LRRK2* gene in North African and Jewish populations and is associated with an autosomal dominant inheritance pattern with incomplete penetrance and typical late-onset PD features. The glucocerebrosidase or *GBA* gene mutation, known to cause Gaucher's disease, has also been identified as a cause of PD [12]. In a meta-analysis of genetic associations with PD, only specific mutations in the *LRRK2* and *GBA* genes yielded odds ratios (ORs) above 2 in the PDGene database. In general, genetic contribution is only considered significant when PD begins before the age of 50 [13].

The idea that environmental exposure might cause PD was triggered by the observation of a cluster of parkinsonism in narcotics addicts, and the causative agent was identified as 1-methyl-4-phenyl-1,2,4,6-tetrahydropyridine (MPTP) [14]. MPTP-induced parkinsonism is extremely rare, whereas the most frequently observed environmental risk is lack of cigarette smoking [15-17]. This pattern has been seen in nearly every population in which it has been investigated, independent of race, nationality, or time. Cigarette smoke contains hundreds of compounds, and identification of a causative agent is challenging. The causal relationship between smoking and PD cannot be verified directly because conducting a trial to test smoking on PD is not ethically feasible. Coffee intake is also associated with a decreased risk of PD in many large cohort studies [18-20]. Most believe that pharmacological properties of caffeine, an adenosine receptor antagonist, may have neuroprotective effects on dopaminergic neurons. PD risk is increased in association with farming or pesticide exposure in several large cohort studies [21-23]. Specific agents associated with mitochondrial complex I inhibition or oxidative stress, such as paraquat, rotenone, and certain organochlorines, have been associated with a 2–3 fold increased risk of PD in populations with good exposure information [24-26]. In addition to pesticides, metal (manganese and lead) and solvent (trichloroethylene) exposures also appear to increase the risk of PD [27-33].

Survival and cause of death in Parkinson's disease

In 1967, Hoehn and Yahr reported that mortality in paralysis agitans was nearly three times greater than expected [34]. Survival studies following the introduction of levodopa therapy have consistently reported an approximately two-fold increase in mortality risk in PD [6,35-51]. The aforementioned mortality risk was estimated from prevalent cases, and for newly diagnosed PD patients, the mortality risk may be no different from the general population during the first 3–5 years [37,40]. The median survival length after diagnosis of PD was 10.3 years in one incidence study from Olmsted County, MN, USA [40], and 61% of PD cases had died 10 years after diagnosis in another large incident cohort from California [49]. These incidence studies provide us a general picture of survival dynamics in PD. Clinical features such as postural instability, hallucinations, and cognitive impairment, when present early in the disease course, predict poor survival in PD [49].

Reporting of PD on death certificates is inconsistent, perhaps in part because PD *per se* is rarely the immediate cause of death. Based on death certificates from the Michigan Department of Public Health during 1970–1990, PD patients were almost four times more likely to die of pneumonia [52]. In community-based studies from Sweden and Norway, about two-fold or more PD patients than the control group died of pneumonia [41,53], which is in line with a 20-year follow-up study from Sydney that reported pneumonia as the major cause of death among PD patients [54]. The consistency of this finding across populations and time is compelling. The greater vulnerability to pneumonia among PD patients at advanced stages is likely multifactorial, reflecting the combined effects of dysphagia and ineffective cough with consequent aspiration risks.

Progressive supranuclear palsy

PSP, synonymous with Steele–Richardson–Olszewski syndrome, was recognized as a pathologic entity in 1964 [55]. The classical PSP is characterized by vertical gaze palsy, rigidity, akinesia, postural instability, and cognitive impairment, also known as Richardson's syndrome. Unlike typical PD, PSP is poorly responsive to levodopa treatment. The clinical diagnostic criteria were established and validated for Richardson's syndrome by the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) in 1996 [56]; however, there are other PSP subtypes identified in recent years, such as PSP–parkinsonism, PSP–corticobasal syndrome (CBS), and PSP–speech/language disorder, depending on the associated symptoms and, therefore, the criteria have been revised accordingly by the Movement Disorder Society in 2017 [57].

Prevalence of progressive supranuclear palsy

Golbe *et al*. conducted the first prevalence study of PSP in a combined population of 799,022 people in two New Jersey counties, finding 11 cases in total ($1.4/10^5$) [58]. The study adhered to its own diagnostic criteria, and all cases were assessed by neurologists in the nearby counties. It was assumed that nonneurologists would refer PSP patients and thus cases not referred may have been missed, and prevalence was likely underestimated. Schrag *et al*. later reported the adjusted PSP prevalence as $6.4/10^5$, based on six cases in a population of 121,608 people [59], from primary care sites with available computerized records and linked to the National Hospital for Neurology and Neurosurgery, London; the prevalence may be overestimated in this selected population. Nath *et al*. studied PSP prevalence study in the UK as well, using NINDS-SPSP criteria to define cases [60]. A total of 577 cases were identified nationwide (adjusted prevalence: $1.0/10^5$), while 80 regional cases and 17 community cases were found (adjusted prevalence: $2.4/10^5$ and $5.0/10^5$, respectively). Medical records were not available to confirm most cases at the national level, making the NINDS-SPSP criteria less applicable; more rigorous case ascertainment in the smaller populations may have increased the estimates.

Prevalence estimates of PSP from studies of PD ranged from 3.2 to $4.6/10^5$ [61-63]. Diagnostic criteria for PSP were not always described, and estimates were based on few cases. The Rotterdam door-to-door study identified only one case of PSP among 129 patients aged above 55 years with parkinsonism (prevalence estimate: $14.3/10^5$) [64], which is lower than the Nath *et al*. estimate ($25.6/10^5$) for the same age group. Estimates based on a single case are tenuous but suggestive of the rarity of PSP. There are a handful of subsequent prevalence studies from Japan (Yonago and Kochi) and Switzerland, and all had identified more cases and estimated higher prevalence [65-68], but generally the prevalence of PSP is a little less than $10/10^5$ [Table 1].

Incidence of progressive supranuclear palsy

Mastaglia *et al*. reported the first incidence study of PSP in 1973 but included only eight cases during a 2-year period in a population of 1,000,000 in Perth, Australia, giving a crude incidence estimate of $0.4/10^5$ person-years [69]; the underlying population and the methods of case definition were unclear. Radhakrishnan *et al*. found six incident cases during a 4-year period of observation in Benghazi, Libya ($0.3/10^5$ person-years) [70], but all of the cases were ascertained at one center, and the number of patients not referred is unknown. Rajput *et al*. identified two incident PSP cases in Olmsted County (crude incidence: $0.3/10^5$ person-years) from 1967 to 1979, when the diagnostic criteria for PSP were not yet specified [1]. Bower *et al*. later conducted the first focused incidence study of PSP in the same population and observed a nearly four-fold increase ($1.1/10^5$ person-year) [2], following an extensive search for all types of parkinsonism, neurodegenerative disorders, and tremor. The reported PSP incidence in Moscow by Winter *et al*. is by far the lowest estimate ($0.14/10^5$ person-year) though which is based on only five cases. Although some subsequent studies from Sweden and Olmsted County, USA, showed similar estimates [71,72], the more recent studies from the UK and Switzerland reported higher incidence up to $1.9/10^5$ person-year [68,73], suggesting that PSP signs and symptoms might have been better known by physicians and more likely to be diagnosed and documented. However, even with high-quality medical records and expert review in a well-characterized population, PSP may be misdiagnosed or underdiagnosed. Overall, the reported incidence of PSP is at least as high as other more widely known neurological disorders such as amyotrophic lateral sclerosis ($1.5–1.9/10^5$ person-year) [74] and Guillain–Barre syndrome ($1.7–1.8/10^5$ person-year) [75] [Table 2].

Age at onset and gender difference in progressive supranuclear palsy

The age at disease onset and a temporal relationship to risk factors may provide important etiologic clues; however, nonmotor features may predominate initially and mask other symptoms for years before PSP diagnosis. The mean age at onset was 62.9 years (range: 44–75 years) in the first PSP prevalence study by Golbe *et al*. [58] Schrag *et al*. reported a mean onset age of 68 years in six prevalent PSP cases, also with considerable age variability (53–84 years) [59]. Nath *et al*. found that the median age at onset was similar around 65–69 years in national, regional, and community studies [60] and significantly younger for patients referred to neurologists. Bower *et al*. reported that the median age at onset was 72.5 years (56–88 years) in an incidence study, older than the average from prevalence studies [2]. Considering that patients with late-onset PSP may have a shorter survival and are more likely to be identified in an incidence study, this number may be accurate. Cosseddu *et al*. described the natural history of a series of 100 consecutive PSP patients from one single center in Italy and reported the mean age at onset to be 69.6 years [77]. Although the number of cases was limited, the quality of medical records was not consistent across studies, and diagnostic criteria excluded patients with onset before age 40, which might increase the variability of estimates. The onset age of PSP is generally around late 60s.

Bower *et al*. reported more men than women (9:7) to be affected with PSP annually [2]. In the member survey of the Society for PSP (n = 437), the gender ratio of men: women

Table 1: Prevalence studies of progressive supranuclear palsy

Published studies	Study region (point/period)	Number of cases (male:female)	Crude prevalence (per 10^5)
Golbe *et al*., 1988 [58]	New Jersey, USA (5/1/1986)	11 (6:5)	1.4
De Rijk *et al*., 1995 [64]	Rotterdam, Netherlands (1990- 1993)	1 (N/A)	14.3 (>55 years old)
Wermuth *et al*., 1997 [61]	Faroe Islands (7/1/1995)	2 (N/A)	4.6
Chiò *et al*., 1998 [62]	Socio-Sanitary District, Italy (10/20/1991)	2 (N/A)	3.2
Schrag *et al*., 1999 [59]	London and Kent, UK (7/1/1997)	6 (3:3)	4.9
Nath *et al*., 2001 [60]	National study, UK (1/1/1999)	187 (91:96)	0.3
Nath *et al*., 2001 [60]	Northern England, UK (1/1/1999)	80 (31:49)	3.1
Nath *et al*., 2001 [60]	Newcastle upon Tyne, UK (1/1/1999)	17 (8:9)	6.5
Kawashima *et al*., 2004 [65]	Yonago, Japan (4/1/1999)	8 (6:2)	5.8
Wermuth *et al*., 2008 [63]	Faroe Islands (7/1/2005)	2 (N/A)	4.1
Osaki *et al*., 2011 [66]	Kochi, Japan (11/1/2007)	12 (8:4)	18
Takigawa *et al*., 2016 [67]	Yonago, Japan (10/1/2010)	25 (12:13)	17.9
Fleury *et al*., 2018 [68]	Canton, Switzerland (1/1/2013)	39 (22:17)	8.3

N/A: Not available

Table 2: Incidence studies of progressive supranuclear palsy

Published studies	Study region (point/period)	Number of cases (male:female)	Adjusted incidence (per 10^5 person-years)
Mastaglia *et al*., 1973 [69]	Perth, Australia	8 (N/A)	0.4
Rajput *et al*., 1984 [1]	Olmsted County, USA (1967- 1979)	3 (N/A)	0.3
Radhakrishnan *et al*., 1988 [70]	Benghazi, Lybia (1983- 1986)	6 (5:1)	0.3
Bower *et al*., 1997 [2]	Olmsted County, USA (1976- 1990)	16 (9:7)	1.1
Linder *et al*., 2010 [72]	Umea, Sweden (2008- 2009)	6 (3:3)	1.1
Winter *et al*., 2010 [76]	Moscow, Russia (2006- 2008)	5 (3:2)	0.14
Savica *et al*., 2013 [71]	Olmsted County, USA (1991- 2005)	16 (10:6)	0.9
Caslake *et al*., 2014 [73]	Northeast Scotland, UK (2006- 2008)	20 (10:10)	1.7
Fleury *et al*., 2018 [68]	Canton, Switzerland (2009- 2012)	35 (22:13)	1.9

N/A: Not available

was nearly 1:1 [78]; while the data might represent a larger sample of patients, selection bias is inevitable. There is an inconsistency with regard to sex ratio in different population studies, such that Golbe *et al*. (USA) [58] and Kawashima *et al*. (Japan) [65] found more male patients with PSP, but Schrag *et al*. and Nath *et al*. observed a near-equal frequency or even a slight female propensity (UK) [59,60]. In a large clinical cohort (n = 121), Baba *et al*. found similarities between men and women in a broad range of clinical characteristics such as age at onset, disease duration, initial motor symptoms, and mean score on the Unified Parkinson's Disease Rating Scale [79]. Methods of case recruitment and accessibility to specialty care vary across different regions, which would contribute to the inconsistency. Overall, there is little or no evidence showing gender differences in disease occurrence, expression, and progression of PSP.

Genetic and environmental risk factors of progressive supranuclear palsy

Studies in familial clusters of patients with PSP may help identify related candidate genes, but only a handful of such cases with compatible clinical history and pathological findings have been reported [80-82]. De Yébenes *et al*. described one pedigree with at least seven individuals and five generations affected, showing that autosomal dominance with low penetrance was likely the hereditary pattern [83]; similar patterns of genetic transmission were also found later in 12 pedigrees of familial PSP collected from 5 countries [84].

Fujioka *et al*. reviewed literature of familial PSP and did not find a major genetic cause for PSP [85]. Nevertheless, genome-wide association studies (GWAS) revealed that *MAPT* common variants and duplication might play a role in PSP tauopathy [86,87].

Davis *et al*. conducted the first case–control study to investigate risk factors for PSP [88]. Smoking was less frequent in cases than in controls, though not significantly; however, the recruitment of controls excluded those with illnesses linked to smoking, and possibly biasing potential differences between the groups. Vanacore *et al*. conducted another case–control study to evaluate smoking in various parkinsonian disorders and confirmed an inverse association between smoking and PD, but found no differences in the smoking habits of PSP patients (average disease duration: 4.4 years) and healthy controls [89]. Cognitive impairment is a common feature of PSP and thus recall bias in a group with late-stage disease may influence the results.

In addition to smoking, a number of other environmental risk factors have also been investigated in the seminal study by Davis *et al*., but there was no significant association with respect to occupation, toxicant exposure, alcohol intake, contact sports, head trauma, hypertension, medical or surgical comorbid illness, or potential sources of viral transmission [88]. In a follow-up study in the same New Jersey population, Golbe *et al*. found that PSP cases were less likely than controls to complete 12 years of education, an opposite

result to the earlier Davis *et al*.'s study [90]. Golbe *et al*. chose control patients who visited an outpatient neurology clinic in the same hospital as cases, excluding those with PD, Huntington's disease, amyotrophic lateral sclerosis, or other degenerative dementias; it is not clear what neurological illnesses the controls had.

Exposure to pesticides or organic solvents has been suggested as a causative factor for PSP [91], but this is simply based on clinical observation and not supported by the existing case–control literature [88,90].

Survival and cause of death in progressive supranuclear palsy

The annual mortality of PSP was estimated as 1.8 per million persons in the UK, using the International Classification of Diseases versions 9 and 10 from the death certificates [92]. Though this strategy might underestimate the rate, it increased from 1993 to 2000 ($1.1–2.7/10^6$), possibly due to increased physician awareness, changes in diagnostic criteria, less mortality from competing illnesses due to improved care, or an actual increase in PSP mortality.

Many studies of the natural history of PSP included cases from neuropathology files [93-96]. Although this ensured a definitive PSP diagnosis, only those with autopsy results were studied. Studying consecutive patients with PSP at tertiary referral centers is another strategy [97-99], but may yield a group with select demographic features [100]. Santacruz *et al*. published a systematic survey of disease course for patient members of the Society for PSP; the mean disease duration was 6.0 years for 119 deceased members and 5.0 years for 318 living members [78]. Potential differences in demographic features of members from the entire PSP population and the average disease duration for living members are not known. Golbe *et al*. reported the mean disease duration to be 6.9 years (range: 2–17 years) in 15 patients [58], but this population was limited by a small sample size. Nath *et al*. described the natural history of PSP from those in a prevalence cohort and reported the mean disease duration to be 5.7 years for deceased cases [101]. Both the above studies tended to miss incident cases with shorter survival. Bower *et al*. reported the median survival from onset to be 5.3 years in an incidence study [2], which is slightly lower as PSP patients with shorter survival are less likely missed.

Glasmacher *et al*. conducted a meta-analysis and described the median survival of PSP to be 5–8 years after diagnosis based on a total of 1911 patients with PSP [102]. Poor prognostic predictors included typical Richardson's phenotype, early dysphagia, early fall, and cognitive impairment. These findings were corroborated by a clinic-based study from Italy that the mean survival was 8.3 years after symptom onset, and dementia at the time of diagnosis almost doubled the mortality risk [77]. Papapetropoulos *et al*. systematically studied the cause of death among patients with PSP and found that pneumonia (respiratory infection, respiratory failure, and aspiration pneumonia) was the most common proximate cause of death and significantly more frequent than in PD [103]. Somehow, cancer is less likely to be the cause of death for PSP and PD when compared with controls, but more hypertension as a comorbidity is reported. Overall, the survival of PSP may be largely dependent on the care for swallowing difficulty and thus prevention of aspiration is much warranted.

Multiple system atrophy

MSA is composed of different diagnostic terms including olivopontocerebellar atrophy, Shy–Drager syndrome (SDS), striatonigral degeneration, and first assembled into a single entity by Graham and Oppenheimer in 1969 [104]. MSA is characterized by autonomic failure, slowness, postural instability, cerebellar ataxia, or parkinsonism. Glial cytoplasmic inclusions are considered the underlying pathology of MSA, and alpha-synuclein protein is the major component of the inclusions. There are two subtypes of MSA: MSA-P when parkinsonism is the predominant feature and MSA-C when cerebellar ataxia is the predominant feature. MSA-P appears to be more common than MSA-C in many European and US studies, and both subtypes respond to levodopa treatment poorly. Quinn was the first to propose diagnostic criteria for MSA in 1989 [105]; a decade later, an international consensus statement was published [106], which were updated in 2008 as the second consensus criteria [107]. The concordance between Quinn's criteria and new criteria was moderate (k = 0.59) for possible MSA and substantial (k = 0.64) for probable MSA [108]. Even by the second consensus criteria, only 62% met the pathological criteria for MSA, suggesting its diagnostic heterogeneity and challenges [109].

Prevalence of multiple system atrophy

The prevalence of MSA has been studied by several investigators. Many studies were focused on parkinsonism or PD; thus MSA-C may not have been included, and the prevalence may have been underestimated. The remaining were focused on MSA using different diagnostic criteria, which may miss individual cases without previous diagnosis of MSA. de Rijk *et al*. identified two MSA cases in 6969 participants (68% of eligible participants) in Rotterdam, a population-based, door-to-door study in persons ≥55 years, yielding an estimated prevalence of $28.7/10^5$ [64]. In a door-to-door survey of inhabitants >65 years in rural villages in Bavaria, Germany, the prevalence of MSA by Quinn's criteria was reported to be $300/10^5$ [110]. Although their case identification involved in-person examination by movement disorder specialists, the estimate was based on only 3 cases in 982 participants and caution should be taken when making comparisons with other studies. Other studies conducted in the Faroe Islands and Italy reported one SDS and three MSA cases, respectively [61,62]. Both found cases from different resources (clinical records or general practitioners) with a diagnosis of PD, which might miss cases diagnosed as MSA or its subtypes, though all cases were identified by neurologists.

A cross-sectional study in London, UK, by Schrag *et al*. reported an age-adjusted prevalence of MSA to be $4.4/10^5$ (n = 4) using Quinn's criteria [59]. This was the first prevalence study specific to MSA in a large population (121,608 people) and all cases were examined by movement disorder experts; however, it was based on hospital and general practices, which might miss underdiagnosed

cases or those who did not have the access to specialty care. Chrysostome *et al*. employed the first consensus criteria and reported the age-adjusted prevalence to be $1.9/10^5$ in France with 25 cases of MSA in total, which is the largest case number yet reported [111]. Barbosa *et al*. reported only one case of MSA in the community-based survey for parkinsonism in Brazil, within which 1186 inhabitants aged over 64 years were examined, yielding a prevalence estimate of $6.7/10^5$ [112]. Osaki *et al*. also used the first consensus criteria and estimated the age-adjusted prevalence of MSA to be $13/10^5$ in a rural Japanese district in 2007, and among 11 cases identified, 6 were MSA-C, suggesting that MSA-C might be the predominant subtype in Japan [66]. Sakushima *et al*. later found the frequency of MSA-C subtype to be 62% in a sample of 839 MSA cases from a national registry system in Japan and confirmed the race/ethnicity difference [113]. In a more recent nationwide study from Iceland, Bjornsdottir *et al*. used the second consensus criteria and estimated the adjusted prevalence of MSA to be $3.4/10^5$ in 2009 with MSA-P predominance [114]. Similarly, Fleury *et al*. reported the prevalence of MSA to be $4.0/10^5$ in 2012, using an extensive case-finding approach in Switzerland [68], showing that the prevalence estimate of MSA is quite stable below $10/10^5$ over the past two decades and across different regions [Table 3].

Incidence of multiple system atrophy

Rajput *et al*. reported only three cases of MSA in an incidence study of parkinsonism in Rochester, Minnesota, from 1967 to 1979, and thus the incidence was estimated to be $0.4/10^5$ person-year [1]. Given that parkinsonism was the primary syndrome for investigation, MSA with a predominance of cerebellar ataxia might not have been included. Later, in an incidence study specific to MSA in the same region during 1976–1999, a total of nine cases of MSA were identified, and the incidence was estimated to be $0.6/10^5$ person-year [2]. In a cross-sectional study from the UK, Schrag *et al*. identified four MSA cases using Quinn's criteria and derived the incidence to be $0.5/10^5$ person-year by existing prevalence and median survival data from other studies [59]. Linder *et al*. identified 12 MSA-P cases in an incidence study for parkinsonism in Northern Sweden and calculated the age-adjusted incidence to be $2.4/10^5$ person-year, among the highest reported ever [72]. The study was based on referrals to one single institution without competing groups and therefore more inclusive with respect to patient recruitment. However, another similar referral-based case finding approach by Winter *et al*. identified only four incident cases of MSA in Moscow, Russia, rendering the incidence estimate to be $0.1/10^5$ person-year [76]. Whether the more than 10-fold difference reflects variability across race/ethnicity is not known. Subsequent studies from the USA, UK, Iceland, and Switzerland during the last decade all reported incidence estimates of MSA around $0.7–1.4/10^5$ person-year, confirming that MSA is considered a rare disease [68,71,73,114] [Table 4].

Age at onset and gender difference in multiple system atrophy

The incidence study is supposed to detect all potential cases with full description of age at onset, but in fact, the reported age at onset varied with a wide range, mainly due to smaller sample size. Bower *et al*. first reported nine incident cases of MSA with a median age of 66 years at symptom onset (range: 51–82) [2], and another incidence study from Iceland reported 19 cases with a mean age of 65 years at disease onset (range: 46–85) [114]. The subsequent MSA incidence studies reported mainly age at diagnosis and which were mostly above 70 (Linder *et al*. in Sweden: 72.5 years [72]; Caslake *et al*. in Scotland: 76.9 years [73]) except the one from Moscow (Winter *et al*. in Russia: 58.3 years [76]). There might be a diagnostic delay between the symptom onset and diagnosis date, depending on the accessibility to specialty care and the detection of atypical features of MSA. Ben-Shlomo *et al*. did a systematic review of the neurologic literature with 433 cases of pathologically proven MSA cases over a 100-year period in 1997 and reported the mean age of onset to be 54.2 years (range 31–78) [115], which is younger than the onset in the incidence study. Watanabe *et al*. reviewed medical records for 230 Japanese patients, and reported a mean age at onset of 55.4 years [116]. Although MSA-C is the more common subtype in Japan, there is no difference between MSA-C and MSA-P regarding age at onset. Two recent large clinical studies of MSA from Europe and the USA reported the mean age at onset around late 50s [117,118], but the data from prevalence studies were likely susceptible to recall bias. Overall, age at onset varies considerably across studies but is generally between late 50s and the early 60s.

Previous epidemiological studies of MSA showed slight female preponderance, but their case numbers were too small to define gender difference [2,59]. Most of the following prevalence and incidence studies, however, found more men than women with MSA, with M: F ratio ranging from 1.7 to 4.6, except the most recent one from Switzerland in which a female preponderance was shown [68]. In general, there is no significant gender difference in terms of disease occurrence of MSA.

Genetic and environmental risk factors of multiple system atrophy

MSA has long been considered a sporadic disease, and positive family history was even included in the exclusion criteria for diagnosing MSA as a way to keep it separated from spinocerebellar ataxia. Based on the idea that abnormally phosphorylated α-synuclein is the shared underlying pathology for PD and MSA, Scholz *et al*. tested 384 single-nucleotide polymorphisms (SNPs) known to increase the risk of PD from GWAS and found *SNCA* SNPs rs11931074 and rs3857059 to be associated with MSA [119]. In another extensive genetic linkage analysis and whole-genome sequencing study, *COQ2* mutation and functionally impaired variants, essential for the biosynthesis of coenzyme Q10, were associated with both familial and sporadic cases of MSA, suggesting a genetic basis of MSA pathogenesis [120]. Furthermore, a common variant (V393A) was detected in Japanese MSA and other Asian countries including Taiwan but not European or North American MSA, and whether this can explain the predominance of MSA-C in Japan remains to be determined [121]. However, a GWAS conducted in larger sample of 918 MSA patients of European ancestry showed that neither *SNCA* nor *COQ2* was associated with MSA [122]. Therefore, positive

Table 3: Prevalence studies of multiple system atrophy

Published studies	Study region (point/period)	Number of cases (male:female)	Crude prevalence (per 10^5)
De Rijk *et al*., 1995 [64]	Rotterdam, Netherlands (1990- 1993)	2 (N/A)	28.7 (>55 years old)
Trenkwalder *et al*., 1995 [110]	Bavaria, Germany (5/1/1992)	3 (2:1)	300 (>65 years old)
Wermuth *et al*., 1997 [61]	Faroe Islands (7/1/1995)	1 (N/A)	2.3
Chiò *et al*., 1998 [62]	Socio-Sanitary District, Italy (10/20/1991)	3 (N/A)	4.8
Schrag *et al*., 1999 [59]	London and Kent, UK (7/1/1997)	4 (1:3)	3.3
Chrysostome *et al*., 2004 [111]	Gironde, France (11/1/1998)	25 (17:8)	1.9
Barbosa *et al*., 2006 [112]	Bambui, Brazil (1997- 2001)	1 (N/A)	83.7 (>64 years old)
Wermuth *et al*., 2008 [63]	Faroe Islands (7/1/2005)	3 (N/A)	6.2
Osaki *et al*., 2011 [66]	Kochi, Japan (11/1/2007)	11 (9:2)	17
Bjornsdottir *et al*., 2013 [114]	Iceland (4/1/2009)	10 (N/A)	3.1
Fleury *et al*., 2018 [68]	Canton, Switzerland (1/1/2013)	19 (8:11)	4.0

N/A: Not available

Table 4: Incidence studies of multiple system atrophy

Published studies	Study region (point/period)	Number of cases (male:female)	Adjusted incidence (per 10^5 person-years)
Rajput *et al*., 1984 [1]	Olmsted County, USA (1967- 1979)	3 (N/A)	0.4
Bower *et al*., 1997 [2]	Olmsted County, USA (1976- 1990)	9 (3:6)	0.6
Linder *et al*., 2010 [72]	Umea, Sweden (2008- 2009)	12 (8:4)	2.4 (MSA-P)
Winter *et al*., 2010 [76]	Moscow, Russia (2006- 2008)	4 (1:3)	0.11
Savica *et al*., 2013 [71]	Olmsted County, USA (1991- 2005)	15 (11:4)	0.8
Bjornsdottir *et al*., 2013 [114]	Iceland (1999- 2009)	19 (12:7)	0.7
Caslake *et al*., 2014 [73]	Northeast Scotland, UK (2002- 2009)	17 (14:3)	1.4 (MSA-P)
Fleury *et al*., 2018 [68]	Canton, Switzerland (2009- 2012)	14 (5:9)	0.7

MSA: Multiple system atrophy, N/A: Not available, MSA-P: MSA when parkinsonism is the predominant feature

family history of MSA is extremely rare but not necessarily considered an exclusion criterion, whereas for most patients with MSA, the genetic contribution may be inappreciable.

Environmental risks such as toxic and occupational exposures may provide clues for the etiology of MSA. Nee *et al*. conducted the first case–control study of MSA in 1991 with sixty clinically diagnosed MSA cases and sixty age-, sex-, and race-matched controls [123]. Significant differences between cases and controls were found in occupational exposure to organic solvents (OR = 2.4), plastic monomers and additives (OR = 5.3), pesticides (OR = 5.8), and metals (OR = 14.8). Chrysostome *et al*. conducted another case–control study with fifty MSA cases and fifty age- and gender-matched controls and found a trend of but nonsignificantly increased risk of disease with occupational (OR = 1.4, 95% CI: 0.4–4.5) and domestic (OR = 1.3, 95% CI: 0.5–3.5) exposure to pesticides [110], and the lack of association with occupational exposures was replicated in another case–control study [124]. Smoking has been inversely associated with PD, but this does not seem to be the case for MSA. Vanacore *et al*. focused on the smoking issue and reported a nonsignificantly decreased risk of MSA among smokers (OR = 0.3, 95% CI: 0.3–1.1) [89]. Other studies also reported findings of no statistical significance and thus whether smoking was inversely associated with MSA remains controversial [111,124]. With respect to dietary intake, alcohol consumption was not linked to MSA, but fish and seafood were more common in the diet of the control group (OR = 0.3, 95% CI: 0.1–0.8, P = 0.01), and meat and poultry intake were taken more frequently in MSA cases (OR = 4.8, 95% CI: 1.9–12.0) [124]. The study ran into an issue of multiple comparisons without correcting P values in the analysis and thus future dietary investigation is warranted. Although sharing underlying pathology with PD, the known genetic and environmental risk factors of PD do not appear to be associated with MSA.

Survival and cause of death in multiple system atrophy

The prognosis of MSA is generally poor. In an early observation of series of 59 MSA cases from Italy, the median survival time from symptom onset was approximately 7.5 years, with no difference between MSA-P and MSA-C [125]. A larger sample of 433 MSA cases from a systematic review showed the mean survival of 6.2 years, and there was no difference with respect to MSA-P or MSA-C subtype either [115]. Shrag *et al*. followed up 100 cases of MSA in the UK and reported the median survival time overall to be 8.3 years without significant predictors being identified [126]. In a Japanese MSA series of 230 cases (MSA-P: 75; MSA-C: 155), the median interval from onset was as follows: 3 years to aided walking; 5 years to confinement to a wheelchair; 8 years to a bedridden state; and 9 years to death [116]. The MSA-C predominated in the sample from Japan and thus the survival data might not be comparable with that of other regions. Wenning *et al*. studied 141 patients with MSA from Europe and reported the median survival to be 9.8 years and MSA-P appeared to have shorter survival [117]. From the USA, Low *et al*. recruited 175 patients with probable MSA and found almost the same median survival to be 9.8 years; there was no difference in survival between MSA-P and MSA-C, but those with significant autonomic dysfunction at diagnosis had worse prognosis [118]. In sum, the survival time of MSA from disease onset is <10 years, and MSA-C might have an earlier onset than MSA-P, but there is little

difference regarding survival. Falls within 3 years, bladder symptoms, urinary catheterization within 3 years, orthostatic intolerance within 1 year, and older age of onset all predict unfavorable outcomes [127].

Papapetropoulos *et al*. studied causes of death from 21 neuropathologically confirmed MSA cases in a brain bank and found that sudden death was reported in 8 cases; among them, 7 were due to cardiopulmonary arrest, which was more frequent than respiratory infection [128]. Zhang *et al*. studied 131 Chinese patients with MSA and found the most common cause of death to be respiratory infection (65.6%), followed by sudden death (14.5%); sudden death was more likely to occur in patients with nocturnal stridor [129]. In other words, autonomic dysfunction plays a major role in the prognosis of MSA, as it may be associated with sudden death of cardiopulmonary causes and increased mortality risks.

Corticobasal degeneration

CBD was first recognized as a disease entity by Rebeiz, Kolodny, and Richardson in 1968, and characterized by an asymmetric onset of slow, clumsy limb movement, accompanied by rigidity, dystonia, tremor, and disordered eye movement, leading to ultimately severe disability [130]. However, because of its clinical complexity and overlap with other parkinsonian disorders, CBD is often underdiagnosed [131]. The original description of clinical features of CBD has been shown to be sometimes due to other pathologies [132], rather than the typical hyperphosphorylated 4-repeat tau deposition in neurons and glia, and therefore the clinical phenotype is now called CBS. On the other hand, there are several clinical phenotypes other than CBS but associated with the pathology of CBD, such as frontal behavioral-spatial syndrome, nonfluent variant of primary progressive aphasia, and progressive supranuclear palsy syndrome. All the above add to the diagnostic challenge for CBD. Based on published literature and information from the available brain banks, together with movement disorder specialists and dementia experts, Armstrong *et al*. proposed the definition for CBS and the diagnostic criteria for CBD [133]. However, even with such great efforts to develop diagnostic criteria, the validation study revealed that the new criteria did not sufficiently improve the rate of accurate diagnosis of CBD pathology [134]. Tau-positron emission tomography imaging and cerebrospinal fluid/plasma levels of neurofilament light chain may serve as biomarkers to help differentiate CBD from PD, but are still not specific enough for CBD diagnosis [135]. Whether biomarkers can be incorporated for more effective CBD diagnosis requires further investigation.

Prevalence of corticobasal degeneration

Togasaki and Tanner first assumed that CBD might constitute ~1% of patients with parkinsonism seen by movement disorder specialists and that, accounting for underdiagnosis by physicians in nonspecialty clinics, CBD might be expected to be 4%–6% of those with parkinsonism in the community [136]. Extrapolating these results based on PD suggests that the prevalence of CBD would be 4.9–7.3/10^5. Morimatsu and Negoro conducted a survey of CBD from 29 neurological institutions in Japan and identified 164 CBD patients (probable n = 151; definite n = 13) and 391 PSP patients [137]. Given the ratio of clinical CBD/PSP to be 1/2.6, the authors used the only Japanese prevalence estimate of PSP (4.4/10^5 in 1999) to calculate the prevalence of CBD (1.7/10^5), which was revised later when new prevalence rates were reported in 2004 (PSP: 5.8/10^5, CBD: 2.2/10^5) [65]. In a Japanese epidemiological study of PD and APS, Osaki *et al*. identified six cases of CBD and estimated the prevalence to be 9/10^5, significantly higher than previous estimates [66]; nevertheless, the most recent epidemiological study of CBD from Switzerland reported the prevalence to be 3/10^5 [68]. Overall, CBD is less frequently seen than PSP and MSA, and the prevalence is generally less than 5/10^5 [Table 5].

Incidence of corticobasal degeneration

Fleury *et al*. identified 19 newly diagnosed cases of CBD in the Canton of Geneva, Switzerland, with about 470,000 residents during 2009–2012, and estimated the crude incidence to be 1.1/10^5 person-year [68]. This estimate is considered much higher than that of previous reports, and whether the result reflects increased awareness of CBD, improved diagnostic capacity, and thus higher case finding rate is not clear [Table 6].

Age at onset and gender difference in corticobasal degeneration

In a classic clinical study of 36 patients, Rinne *et al*. reported the mean age at symptom onset to be 60.9 years (40–76 years) and a slight female predominance (M: F = 16:20) [138]. Wenning *et al*. described the natural history of 14 CBD cases, whose age at onset was 63 years with a female predominance as well (M: F = 6:8) [139]. However, all these reported case series were limited by their small sample size and were not necessarily reflective of the general population. In a Japanese CBD survey (n = 164), by far the single largest clinical sample, Morimatsu and Negoro also reported a female predominance (M: F = 73: 91) [137].

Furthermore, what could be defined in a clinical study was CBS at most, and not all patients with CBS had CBD as the underlying pathology. In an autopsy-defined case series, Lee *et al*. identified 14 CBS-CBD cases, whose age at onset was 62 years with a female predominance (M: F = 4:10) [132]. Although there is no sufficiently large sample of CBD to determine age at onset and gender difference, all these small-scale studies consistently reported the age at onset around the early 60s and slight female predominance with few reports of opposite findings [140,141].

Genetic and environmental risk factors of corticobasal degeneration

Little is known about etiology or risk factors for CBD. No familial clusters of typical CBDs have been reported, and it is largely considered a sporadic disease. A GWAS study based on 152 autopsy-proven CBD cases and 3311 controls identified risk variants shared with PSP, including MAPT H1c (17q21; rs242557) and MOBP (3p22; rs1768208), suggesting that certain genetic susceptibility does exist in CBD [142]. CBD may be studied retrospectively in a case–control design when

information about putative risk factors is available, but this is often difficult in those with diminished cognitive function.

Survival and cause of death in corticobasal degeneration

Of the 15 CBD cases reported by Riley *et al*., two had died during the study with a mean survival time of 8.5 years, and one of them died of pneumonia [140]. Ten out of 36 CBD cases in the clinical study by Rinne *et al*. had died during the follow-up and the mean disease duration was 5.9 years; however, their causes of death were not clearly reported [138]. Wenning *et al*. investigated the natural history of 14 autopsy-confirmed cases of CBD and calculated the mean disease duration to be 7.9 years or the mean age of 71.7 years at death, while bronchopneumonia was the reported cause of death for all cases [139]. However, only 50% of these cases received antemortem diagnosis of CBD, suggesting a considerable discrepancy between CBS phenotype and CBD pathology. Lee *et al*. reviewed 14 phenotype-pathology matched CBD cases and the mean survival time was 6.7 years, though with causes of death not being systematically collected [132]. Registry data are useful in studying rare diseases such as CBD. Valid diagnostic criteria are again needed to ensure accurate estimates of frequency and distribution in population studies.

Conclusion

APS are rare, heterogeneous, hard to diagnose, and poorly responsive to treatment, which all make epidemiological studies difficult. PSP, MSA, and CBD are relatively well-characterized atypical parkinsonism, and as opposed to typical PD, patients often present with, if not at the very beginning, red-flag features such as early dysphagia, dysphonia, dysarthria, unsteady gait, and cognitive impairment. Epidemiological features of typical PD and APS are briefly summarized in Table 7, which is not meant to be accurate in numbers but intended to present a larger picture of different types of parkinsonism. The prevalence estimates of PSP or MSA are generally <10/10^5, and even less for CBD, approximately below 5/10^5. MSA-P is once considered the predominant subtype, but it does not apply to some regions such as Japan, where MSA-C is more common. The incidence estimates of PSP or MSA are generally around 1/10^5 person-year, and a little lower for CBD. The age at onset is relatively young for MSA at late 50s, followed by CBD at early 60s, and then PSP at late 60s. Gender difference is inconsistent for PSP and MSA, while slight female predominance is observed in CBD. Compared to typical PD, genetic and environmental risk factors for PSA, MSA, and CBD are mainly unknown. Although the *COQ2* mutation has been identified as a genetic risk for MSA, familial cases are extremely rare. Risk variants of *MAPT* are associated with both PSP and CBD, consistent with the shared underlying 4-repeat tauopathy. Survival after symptom onset is within 10 years for all these APS, although it varies considerably in different care settings and may have to do with the underlying pathologies. Respiratory infection is the major cause of death for most APS, and it is worth noting that cardiac arrest or sudden death is one of the leading causes of death for patients with MSA. PSP, MSA, and CBD, all deteriorated relentlessly and there is no effective treatment yet. Disease registry for APS may be the feasible approach for further characterizing APS, identifying modifiable risk factors, and designing therapeutic trials.

Financial support and sponsorship

This study was financially supported by Tzu Chi Medical Foundation (TCMF-SP-109-1).

Table 5: Prevalence studies of corticobasal degeneration

Published studies	Study region (point/period)	Number of cases (male:female)	Crude prevalence (per 10^5)
Osaki *et al*., 2011 [66]	Kochi, Japan (11/1/2007)	6 (5:1)	9
Fleury *et al*., 2018 [68]	Canton, Switzerland (1/1/2013)	14 (6:8)	3.0

Table 6: Incidence studies of corticobasal degeneration

Published studies	Study region (point/period)	Number of cases (male:female)	Adjusted incidence (per 10^5 person-years)
Winter *et al*., 2010 [76]	Moscow, Russia (2006- 2008)	1 (0:1)	0.02
Savica *et al*., 2013 [71]	Olmsted County, USA (1991- 2005)	4 (1:3)	0.2 (crude)
Caslake *et al*., 2014 [73]	Northeast Scotland, UK (2002- 2009)	2 (0:2)	0.17
Fleury *et al*., 2018 [68]	Canton, Switzerland (2009- 2012)	19 (8:11)	1.0

Table 7: Brief summary of epidemiology of typical and atypical parkinsonism

Parkinsonism type	PD	PSP	MSA	CBD
Prevalence (per 10^5 persons)	100- 200	~10	~10	~5
Incidence (per 10^5 person-year)	10- 20	~1	~1	<1
Age at onset (10-year range)	60- 70	65- 75	55- 65	55- 65
Gender predilection	Male>female	Male ≒ female	Male ≒ female	Female >male
Genetic risk (example)	*PARK*	*MAPT*	*COQ2*	*MAPT*
Environmental risk (example)	Smoking and pesticide	Unknown	Unknown	Unknown
Median duration (years)	>10	5- 8	6- 10	6- 8
Cause of death	Pneumonia	Pneumonia	Pneumonia and sudden death	Pneumonia

MSA=Multiple system atrophy, PD=Parkinson's disease, PSP=Progressive supranuclear palsy, CBD=Corticobasal degeneration

Conflicts of interest

Dr. Raymond Y. Lo, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article.

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