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REVIEW

Prevalence of pain in atypical parkinsonism: a systematic review and meta-analysis

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Abstract

Pain is common in atypical parkinsonism such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and dementia with Lewy bodies (LBD). In this study, a systematic review and meta-analysis was conducted and peer-reviewed literature was searched to determine the prevalence and types of pain in four atypical parkinsonism syndromes: MSA, PSP, CBD and LBD. The results show that pain was prevalent mainly in MSA patients in comparison to PSP and CBD patients. Pain was reported at an early stage and was found in females, with limb pain being the most common, followed by neck and back pain. In comparison to PSP, pain locations were similar to MSA patients. CBD patients experienced pain the least in comparison to MSA, PSP and LBD patients.

Keywords Pain · Atypical parkinsonism · Multiple system atrophy · Progressive supranuclear palsy · Corticobasal degeneration · Dementia with Lewy bodies

Introduction

Pain is a common non-motor symptom present in PD and in atypical parkinsonism [1–3]. However, no systematic studies summarizing the published data on pain in atypical parkinsonism have been performed. In PD, pain is often related to the illness itself or wearing off of a dopaminergic medication [4]. Chronic pain is reported by more than two-thirds of PD patients; yet it is still unclear whether the characteristics of pain in atypical parkinsonism such as progressive supranucealr palsy, multiple system atrophy and corticobasal degeneration are the same as idiopathic PD [5]. Although many non-motor symptoms occurring in PD are also present in atypical parkinsonism, there are some differences in frequency, intensity and response to treatment in idiopathic PD and atypical parkinsonism. Atypical parkinsonism is a group of sporadic, neurodegenerative diseases of the central nervous system, less common and usually more severe than PD [2]. The most common forms are multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and dementia with Lewy bodies (LBD). This meta-analysis will focus on evaluating the prevalence of pain in atypical parkinsonism and explore differences in characteristics of pain as well as its various causes. We performed analysis of peer reviewed literature to study the prevalence and types of pain in atypical parkinsonism such as MSA, PSP, CBD and LBD, the impact and significance of pain on quality of life of the atypical parkinsonism patient and the challenges inherent in

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the diagnosis and management of pain in these patients. The findings of articles indexed in the literature database were compared to the assessed symptoms reported by large cohorts of atypical parkinsonism patients [6]. These articles all reported the incidence, nature and quality of pain in these patients and described the effects of pain on quality of life and generally were cross-sectional, retrospective or case–control studies. Patients who reported pain were more likely to report associated depression and a decreased quality of life [6]. Many atypical parkinsonism patients also reported poor management of pain and lower analgesic use than expected [6]. We discuss some approaches towards the management of pain in atypical parkinsonism which hopefully would improve the patient's quality of life.

Methods

Search strategy

A systematic review of the research-based literature was performed within MEDLINE, PsycINFO, Embase and CINAHL from inception of the databases to October 20, 2016. The article search was conducted with one or more of the following key terms: pain, prevalence, atypical parkinsonism, CBD, corticobasal degeneration, MSA, multiple system atrophy, MSA-P, parkinsonian, PSP, progressive supranuclear palsy, DLB, LBD, DLBD, dementia with Lewy bodies, and Lewy body dementia. Published or unpublished articles, articles in press, and conference proceedings available in English had their title and abstracts screened.

Quality assessment

The quality of the studies was assessed using the modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS), (Table 1). The modified QUADAS was modified by LeBoeuf-Yde and co-workers, and was previously used to determine the prevalence of pain in PD [7, 8]. The modified QUADAS is a criterion by which the reliability of the prevalence retrieved from studies is evaluated. The score ranges from a minimum of 0 points to a maximum of 19 points, with the cut-off for methodological acceptability being set to greater than 13 points, which is 75% of the total amount of points achieved. All of the articles undergoing modified QUADAS evaluation were independently reviewed by two researchers (A.R.Q and O.S) for eligibility, and when there was a difference in opinion for scoring, a consensus was achieved after discussion.

Data extraction

The extracted data from eligible studies included first author name, publication year, country, ethnicity, study design, type of atypical parkinsonism, pain prevalence, assessment tool for pain prevalence, age, gender, disease duration, ethnicity, study design, and pain treatments. Pain descriptors were also extracted, and measurements of a pain descriptor from multiple studies for a particular form of atypical parkinsonism were combined together using weighted averages. If any of the aforementioned data was unclear or not reported, we attempted to contact the study authors to retrieve this information.

Statistical analyses

Agreement for reviewers' assessment for eligible studies was calculated using Cohen's kappa coefficient. An adequate kappa value was considered to be 0.65 or higher [20]. The intraclass correlation coefficient (ICC) was used to calculate the agreement for assessments of risk of bias. A random-effects analysis of proportion was conducted across the four atypical parkinsonism groups (MSA, PSP, CBD and LBD) for pain prevalence. Pooled effect sizes were retrieved for group estimates of pain prevalence for MSA, PSP, CBD and LBD, as well as an overall estimate. For MSA, we pre-specified an a priori hypothesis to account for potential heterogeneity, which was ethnicity (Caucasian or White versus Asian). A second random-effects analysis of proportion was conducted to compare the pain prevalence in the parkinsonian subtype of MSA (MSA-P) to the cerebellar subtype of MSA (MSA-C) in eligible studies that had assessed MSA-P patients and MSA-C patients. All random-effects analyses underwent the χ^2 test for heterogeneity quantified by the I^2 statistic. I^2 values describe heterogeneity based on the range of values, in accordance to the Cochrane handbook as follows: unimportant (0–30%), moderate (30–60%), substantial (50–90%), and considerable (75–100%) [21]. Publication bias was examined using Egger's test. For analysis with at least ten studies a funnel plot was also used to assess publication bias. Statistical analysis was conducted using ProMeta (version 3.0, Internovi, Cesena, Italy). All tests of significance were two-tailed and used $p = 0.05$ as the cut-off for being considered significant.

Table 1 Characteristics of the studies included in the meta-analysis for pain prevalence

Article	Country	Ethnicity	Study type	Assessment of pain prevalence	Atypical parkinsonism type	Quality score	Age	Gender	Disease duration	Pain prevalence (%)	Pain descriptors
Sjostrom et al. [9]	Sweden	Caucasian	Prospective cross-sectional cohort study	Categorical pain scale	MSA	14	60 ± 11	43% M, 57% F	4.7 ± 2.2	68	Musculoskeletal (68%)
Schrag et al. [10]	UK, Austria, Italy, Spain, Sweden, Israël & Germany	Caucasian	Cross-sectional survey	EQ-5D	MSA	15	62 ± 8.8	NR	4.4 ± 0.97	76	NR
Schrag et al. [11]	UK, US & Canada	Caucasian	Cross-sectional survey	EQ-5D	MSA	15	65 ± 9.8	55% M, 45% F	6.3 ± 3.9	78	NR
					PSP	15	69 ± 6.9	58% M, 42% F	5.7 ± 7.8	56	NR
Colosimo et al. [2]	Italy	Caucasian	Longitudinal observational study	Categorical pain scale	MSA	16	64 ± 8.7	62% M, 38% F	4.4 ± 3.4	24	NR
					PSP	16	70 ± 6.3	53% M, 47% F	3.5 ± 3.1	12	NR
					CBD	16	70 ± 10	46% M, 54% F	2.5 ± 1.1	4	NR
					LBD	16	74 ± 6.5	86% M, 14% F	4.2 ± 3.1	50	NR
Higginson et al. [12]	UK	Caucasian	Longitudinal observational study	Categorical pain scale	MSA	15	67 ± 8.0	65% M, 35% F	5.9 ± 4.0	88	NR
					PSP	15	69 ± 11	47% M, 53% F	4.6 ± 2.7	60	NR
Rinne et al. [13]	UK	Caucasian	Longitudinal observational study	Direct observation of symptoms	CBD	14	61 ± 9.7	44% M, 56% F	5.9 ± 1.2	14	Dystonic (14%)
Kass-Iliyya et al. [14]	UK	Caucasian	Cross-sectional survey	MDS-UPDRS	MSA	16	64 ± 1.6	43% M, 57% F	3.2 ± 0.3	100	Neuropathic (18%)
					PSP	16	73 ± 1.7	44% M, 56% F	3.9 ± 0.6	25	Neuropathic (0%)
Zhang et al. [15]	China	Asian	Cross-sectional survey	NMSS	MSA	14	61 ± 7.5	58% M, 42% F	2.8 ± 1.7	51	NR
Calvert et al. [16]	UK	Caucasian	Cross-sectional survey	EQ-5D	MSA	15	67 ± 9.2	65% M, 35% F	7.3 ± 17	67	NR
					PSP	15	69 ± 7.1	50% M, 50% F	3.9 ± 10	88	NR
Onofrj et al. [17]	Italy	Caucasian	Prospective cross-sectional cohort study	Direct observation of symptoms	LBD	14	70 ± 8.3	52% M, 48% F	--	37	Multilocalized pain with GI symptoms (37%)
Stamelou et al. [6]	Germany	Caucasian	Cross-sectional case-control study	Categorical pain scale	PSP	14	67 ± 7.4	50% M, 50% F	3.4 ± 2.7	38	Musculoskeletal (38%)

Table 1 (continued)

Article	Country	Ethnicity	Study type	Assessment of pain prevalence	Atypical parkinsonism type	Quality score	Age	Gender	Disease duration	Pain prevalence (%)	Pain descriptors
Yust-Katz et al. [18]	Israël	Caucasian	Cross-sectional survey	Categorical pain scale	MSA	15	71 ± 9.7	58% M, 42% F	5.0 ± 3.4	64	Central (28%), Musculoskeletal (55%), Radicular (0%), Arteritic (14%), Neuropathic (5%)
					PSP	15	72 ± 6.6	68% M, 32% F	3.0 ± 2.8	42	Central (14%), Musculoskeletal (57%), Arteritic (14%), Neuropathic (14%)
					CBD	14	70 ± 11	63% M, 37% F	4.0 ± 2.5	38	Central (13%), Musculoskeletal (100%)
					LBD	14	70 ± 8.0	88% M, 12% F	3.5 ± 2.6	25	Musculoskeletal (100%)
Winter et al. [19]	Germany	Caucasian	Cross-sectional survey	EQ-5D	MSA	15	66 ± 6.0	46% M, 54% F	5.3 ± 2.3	86	NR
					PSP	16	68 ± 7.3	63% M, 37% F	4.7 ± 2.3	68	NR

MSA multiple system atrophy, *PSP* progressive supranuclear palsy, *CBD* corticobasal degeneration, *LBD* Lewy body dementia, *NMSS* Non-Motor Symptoms Scale, *EQ*-5D EurolQol-5D, *MDS-UPDRS* Movement Disorders Society—Unified Parkinson's Disease Rating Scale, *NR* not reported within the article, *EXC* Patients with pain treatments were excluded from the study; %M, % F = % Male, % Female

Results

Eligible and included studies

After removing the duplicates ($n = 125$), the remaining articles ($n = 1350$) had their titles and abstracts read, and studies reporting any form of pain or condition involving pain in atypical parkinsonism were subsequently read in full. All articles with a potential reference to the prevalence of pain ($n = 122$) were assessed for eligibility. After reading these articles, 100 articles were excluded due to the following reasons: there was no reference to the actual prevalence of pain ($n = 56$), the article was actually a literature review or a protocol ($n = 22$), the atypical parkinsonism groups of interest (MSA, PSP, LBD or CBD) were not studied ($n = 17$), or the article was a case-report or a non-original publication ($n = 5$). The remaining 22 studies were included in the qualitative synthesis. No additional articles in press, unpublished articles or conference proceedings were identified. The procedure is summarized in a Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow chart (Fig. 1). Agreement between the raters for study eligibility based on modified QUADAS scaled scoring was very high (kappa = 0.786, $p < 0.0001$), with strong reliability (ICC = 0.861, 95% CI 0.744–0.927; $p < 0.0001$).

Study characteristics

Of the 22 studies included in the qualitative synthesis, 13 met the cut-off criteria of 14 points on the QUADAS (59%), (Supplementary Table 1). From the 13 studies, a total of 24 datasets were obtained based on 3 for CBD ($n = 55$), 3 for LBD ($n = 95$), 10 for MSA ($n = 599$) and 8 for PSP ($n = 242$). All patients were diagnosed according to consensus criteria [22–24]. Five studies were longitudinal observational studies (38%), while the remaining eight studies were cross-sectional studies (62%). The mean age was 64.7 ± 3.27 years for MSA, 69.6 ± 2.00 years for PSP, 67.0 ± 5.20 years for CBD, and 71.3 ± 2.31 years for LBD. The mean percentage of males was 55% for MSA, 54% in PSP, 51% in CBD and 75% in LBD. The mean disease duration was 4.92 ± 1.36 years for MSA, 4.09 ± 0.871 years for PSP, 4.13 ± 1.70 years for CBD, and 3.85 ± 0.495 years for LBD. Pain was reported in four studies using the EuroQol-5D (EQ-5D), in one study using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), in one study using the Non-Motor Symptoms Scale (NMSS), in five studies using a categorical pain scale, and in two studies using direct observation of symptoms by the clinician. The ethnicity of patients was 100% Caucasian or White in all studied types of atypical parkinsonism except MSA, which had 87% Caucasian or White ($n = 523$ out of 599) and 8% Asian ($n = 76$ out of 599), (Supplementary Table 2).

Pain descriptors

Six out of the 13 eligible studies reported pain descriptors for patients with atypical parkinsonism. Pain types reported by MSA patients were musculoskeletal 59.5% [9, 18]; neuropathic 8.6% [14, 18]; central 28% [18]; radicular 0% [18]; and arthritic [18]. Types of pain reported by PSP patients were neuropathic 7.6% [14, 18]; musculoskeletal 51.4% [6, 18]; central 14% [18] and arthritic 14% [18]. Pain descriptors reported by CBD patients were dystonic 14% [13]; central 13% [18]; and musculoskeletal 13% [18]. Patients with LBD reported multilocalized pain with GI symptoms 37% [17] as well as musculoskeletal pain (Supplementary Table 2) [18].

Pain treatments

Two out of the 13 eligible studies reported pain treatments used by patients with atypical parkinsonism. One study reported 19% of MSA patients and 6% of PSP patients taking treatments for neuropathic pain [14]. The other study grouped all four groups of atypical parkinsonism together and reported usage of paracetamol in 47%, NSAID in 26%, pregabalin in 23%, tramadol hydrochloride in 9%, oxycodone in 3%, cannabis in 25%, and amitriptyline in 4% [18]. Another study excluded PSP patients taking analgesics or other pain-related medications [6].

Pain prevalence in MSA, CBD, PSP and LBD

The random-effects analysis revealed that the pooled pain prevalence was 25% for CBD ($p = 0.022$), 38% for LBD ($p = 0.022$), 73% for MSA ($p < 0.0001$) and 52% for PSP ($p > 0.05$), (Fig. 1). The heterogeneity analysis revealed that heterogeneity was moderate for CBD ($I^2 = 44.56\%$, $p = 0.165$), unimportant for LBD ($I^2 = 0.00\%$, $p = 0.490$), substantial for MSA ($I^2 = 65.57\%$, $p = 0.002$) and moderate for PSP ($I^2 = 47.94\%$, $p = 0.062$), (Fig. 2). Removing the pain prevalence data of an Asian sample from [15] resulted in nearly all heterogeneity being removed from MSA ($I^2 = 6.85\%$, $p = 0.378$). The pain prevalence of MSA excluding the [15] study was 75% ($p < 0.0001$). A fairly symmetric funnel plot resulted from the data (Fig. 3), with the Egger's test being insignificant ($p = 0.170$).

Pain prevalence in MSA-C and MSA-P

The overall prevalence of pain in MSA-P was 63% (120/190) compared to 41% (67/164) in MSA-C. The

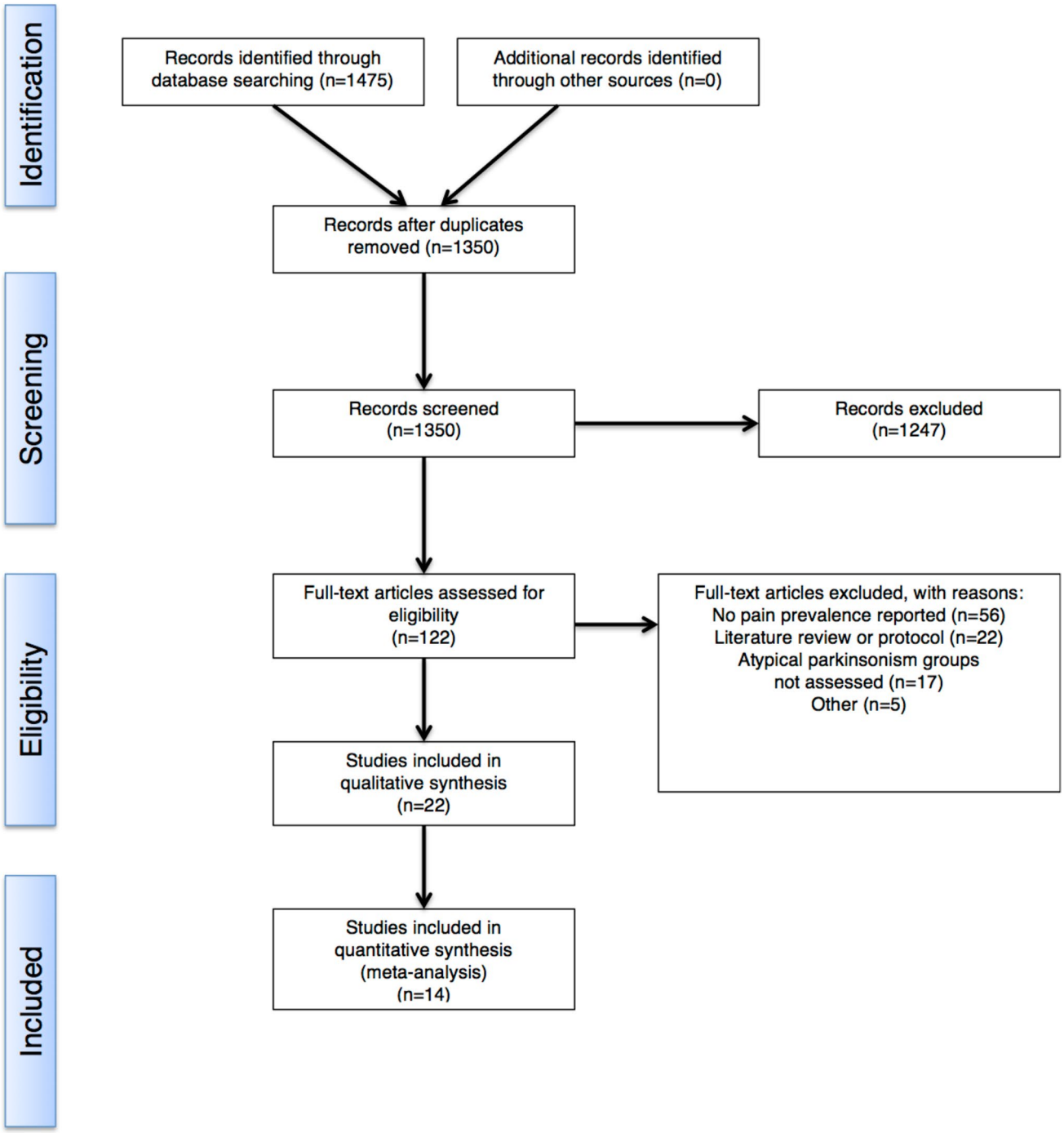

Fig. 1 Preferred reporting items for system reviews and meta-analyses (PRISMA) flow chart

pooled OR was 2.11 ($p = 0.038$; 95% CI 1.04–4.28) with moderate heterogeneity ($I^2 = 45.12\%$, $p = 0.141$). Egger's test for publication bias was insignificant ($p = 0.683$).

Discussion

This meta-analysis investigated the prevalence of pain in atypical parkinsonism. Overall, we found a moderate heterogeneity between studies with the exception of LBD.

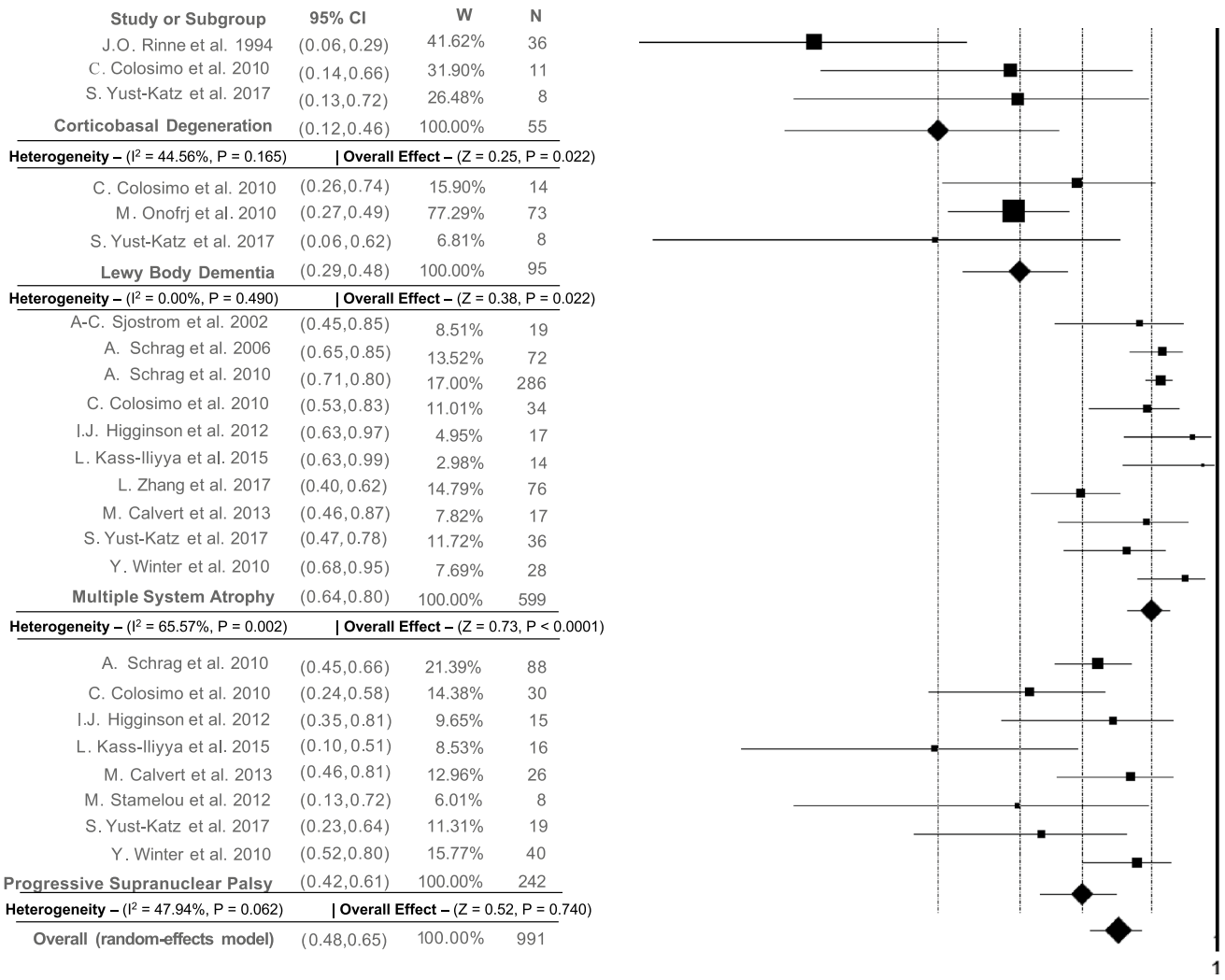

Fig. 2 Forest plot for the pooled pain prevalence (event rate) in atypical parkinsonism

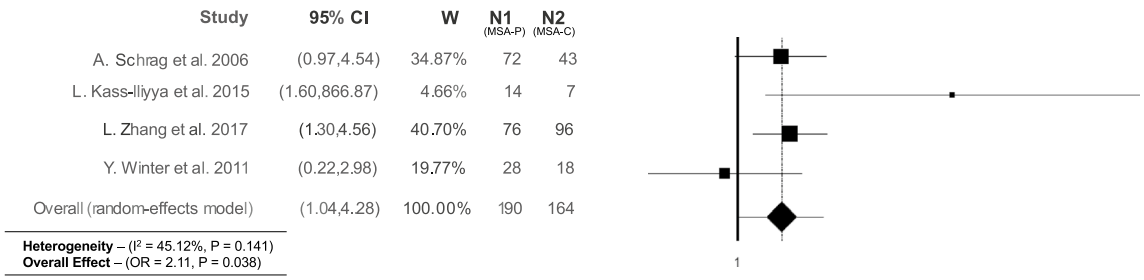

Fig. 3 Forest plot for the analysis of pooled pain prevalence (OR) in atypical parkinsonism

The random-effects analysis revealed that the pooled pain prevalence was greatest for MSA and least for CBD which correlates to a moderate heterogeneity for CBD, unimportant for LBD, substantial for MSA and moderate for PSP (Fig. 2). Removing the pain prevalence data of an Asian sample, resulted in nearly all heterogeneity being removed from the MSA category [15]. Another key finding was that the overall prevalence of pain was quite greater in MSA-P patients compared to MSA-C patients. The pooled OR was of moderate heterogeneity compared to the four subgroup heterogeneities for each of the types of atypical parkinsonism. Though there was large variety between the 14 studies

in the meta-analysis, the subgroup analyses did lead to a reduction of heterogeneity as the calculated prevalence in individual subgroups was primarily in the moderate range. We did not find subgroup factors that could clearly explain the large variety in results between the studies. Examples of differences in study methods that may lead to clinical heterogeneity include differences in participant demographics, risk or severity of disease, the settings in which the research was conducted, the frequency and intensity of the intervention, and how outcomes were measured across studies. Other important factors to consider are age and disease duration. Several individual studies have shown that chronic pain in atypical parkinsonism increases with age and longer disease duration [2, 10, 13, 16, 25–27]. These factors used throughout the studies are influential towards the variety in our results for all the types of atypical parkinsonism.

Classification of pain in atypical parkinsonism

Pain is classified by the separation of tissue pain receptors from the nerves that transmit pain signals. Pain can be nociceptive which relates to tissue damage implicating the pain receptors in the skin, bones or surrounding tissues; as neuropathic, indicating pain arising in nerves; or as a mixed pain syndrome involving neuropathic pain. This includes persistent tremor, muscle rigidity, dystonia, musculoskeletal injury and inflammation. In comparison to our results, we also noticed various studies mentioning numerous patients experiencing some form of chronic pain at a specific location, as pain is typically well localized to the affected body part and it may fluctuate with medication dosing [11, 13, 16]. Pain caused by dystonia can be diagnosed when there is cramping or posturing of the painful body part [11]. In practical terms, it often proves helpful to conceptualize the experience of pain in parkinsonism as relating to one or more of the following five categories: pain from the muscles or skeleton, pain from nerves or spinal roots, pain related to sustained twisting or writhing, discomfort from akathisia and pain caused directly by changes in chemicals in the brain due to PD [16].

Pain differences in MSA-P versus MSA-C

Our main finding from our meta-analysis results was that pain in MSA was significantly more intense and prevalent compared to PSP (Fig. 2). Moreover, pain was more burdensome in MSA-P than MSA-C [14]. The greater involvement of the basal ganglia in MSA-P compared to MSA-C could account for the observed difference in pain prevalence. Additionally, patients with MSA-P could have head drop which could cause musculoskeletal neck pain. MSA patients exhibited reduced heat pain sensitivity and there was no significant difference in electrical pain sensitivity. Spinal nociception was detected between MSA-C and MSA-P patients. Patients also did not differ clinically regarding the prevalence and severity of chronic pain syndrome. In contrast to a recent study showing increased spinal nociception and increased spinal temporal summation but unaltered psychophysiological pain ratings in MSA-P patients, the present data did not show any difference compared to controls concerning spinal nociception at an early stage of the disease [16]. Interestingly, we found a more pronounced impairment of the dimension 'mobility' in patients with predominant cerebellar dysfunction MSA-C than in patients with parkinsonism of MSA-P type [19]. It has been previously suggested that the 'off-drug' state may increase pain sensitivity and different types of pain in atypical parkinsonism. However, pain symptoms in MSA patients may result from other mechanisms. It is conceivable that pain sensitivity, as well as the frequency of pain complaints, may increase over the years with disease progression in MSA [16]. In contrast, patients with progressive supranuclear palsy (PSP), exhibited a more pronounced spinal nociception and electrical pain sensitivity but a reduced heat sensitivity [6]. Thus, MSA and PSP patients may have some difficulties to determine heat pain threshold themselves, that increase or decrease stimulus intensity. MSA patients showed increased spinal nociception rather than a reduced sensitivity [6]. A similar process is able to occur later in MSA, since MSA-P patients also showed increased spinal nociception at advanced stages [16]. Therefore, in MSA there is a difference only in the timing of the development of symptoms, but not in the final "pain pattern".

Disease duration and target group

Disease duration and age were also different between the groups reflecting the age groups at which these conditions were present. However, these studies did not explicate the cause of this difference, so pain was more evident in patients with rigidity and/or akinesia [16]. There was no difference in the presence of clinical signs between the patients with or without pain; therefore, there was no relation between motor and sensory symptoms, despite the fact that patients with pain claimed to have greater difficulty in walking or getting dressed [14]. The most frequent manifestation reported was muscle-skeletal pain, with a daily frequency that could be improved with the use of medication; this manifestation was characterized as having a rheumatologic origin as pain was not related to the period of effect of the antiparkinsonian medication [14]. Majority of the studies reviewed did not vary in results with reference to sex or geographic distribution. However, pain, fatigue, and psychiatric complaints were more commonly reported in women. Pain associated with dystonia seen in CBD patients may be related to

involuntary muscular contraction and may be best managed with botulinum toxin whereas neuropathic pain may be related to a central dopaminergic deficit. Response to dopamine replacement therapy (e.g., levodopa or dopamine agonists) in MSA and PSP has been shown to be limited [14]. Therefore, knowing characteristics of the pain is important when considering therapy initiation.

Limitations in the study

A limitation to consider is that the design of the included studies were predominantly cross-sectional, retrospective and case-control, with few being prospective. Also, there was no controlling for pre-existing musculoskeletal issues causing unrelated pain. The lack of data for all ethnicities was missing as studies had predominantly patients of Caucasian or Asian descent. The location of the study varied throughout and the Caucasian effect on the pain prevalence was predominant in all studied types of atypical parkinsonism. There was also a lack of correlation with dose of levodopa. Furthermore, motor disability was not evenly matched between the four groups; as atypical parkinsonian syndromes are more aggressive conferring higher motor scores. However, pain intensity in PSP and MSA was either less or matching pain intensity despite higher motor disability. Therefore, the discrepancy in motor scores is unlikely to have contributed to the difference in reported pain. Also, this study only looked at the neurodegenerative variants of atypical parkinsonism and did not address vascular or traumatic types.

Conclusion

Pain is an under-recognized and under-treated symptom in atypical parkinsonism patients. The main results of this study are summarized as follows: MSA had the highest pain prevalence amongst the four types of atypical parkinsonism, characterization of pain was mainly musculoskeletal throughout all types of atypical parkinsonism, while for CBD, patients experienced dystonic pain along with central pain and for LBD, multi-localized pain was seen. Moreover, pain was more prevalent in women compared to men. For patients experiencing pain, the disease onset was more common after 60 years of age and an average disease duration of 2–3 years from onset correlated with the previously published data on idiopathic PD [6, 13, 22, 24, 28].

The manifestation of pain occurs at a certain frequency in atypical parkinsonian patients who can show a significant improvement with the use of appropriate treatment. It is evident that pain in atypical parkinsonism is severe and affects the older age group. The treatment of chronic pain helps patients improve their performance of daily-life activities, as well as their quality of life. The pain threshold is lower in the later phases of the disease, when patients do not have a good response to levodopa and pain is more common and intense in MSA than in PSP and CBD and LBD. The current treatment of the atypical parkinsonian syndromes is symptomatic and supportive. Despite decades of research, the exact cause and pathophysiology of pain in atypical parkinsonian disorders are still unknown and further research in this field is needed.

Author contributions AQR: Research project conception and organization. ARQ: Research project conception; statistical analysis design, execution, review and critique; manuscript-writing of the first draft. OS: Manuscript writing of the first draft; statistical analysis execution. ZS: Research project organization and execution. RR: Research project organization and execution.

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Compliance with ethical standards

Conflict of interest The study authors received no funding and report no conflicts of interest.

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