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Review

Pain in neurodegenerative diseases with atypical parkinsonism: a systematic review on prevalence, clinical presentation, and findings from experimental studies

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Parkinson's disease-related pain has increasingly been investigated in research studies. Still, only a few studies have addressed the prevalence and clinical characteristics of pain in neurodegenerative disorders with atypical parkinsonism. The existing evidence, although scarce, suggests that, similarly as in Parkinson's disease, individuals with neurodegenerative diseases with atypical parkinsonism might be predisposed to the development of persistent pain. Today, as the global population is aging and we face an epidemic of neurodegenerative disorders, under-treated pain is taking a great toll on an ever-rising number of people. Here, we provide an up-to-date review of the current knowledge on the prevalence of pain, its clinical features, and findings from experimental studies that might signpost altered pain processing in the most prevalent neurodegenerative disorders with atypical parkinsonism: multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementia, and dementia with Lewy bodies. Finally, we point out the current gaps and unmet needs that future research studies should focus on. Large-scale, high-quality clinical trials, coupled with pre-clinical research, are urgently needed to reveal the exact pathophysiological mechanisms underpinning heightened pain and pave the path for mechanistically-driven analgesic interventions to be developed, ultimately leading to an improvement in the quality of life of individuals with neurodegenerative disorders.

Keywords

Pain; Atypical parkinsonism; Multiple system atrophy; Progressive supranuclear palsy; Cortico-basal syndrome; Frontotemporal dementia; Dementia with Lewy bodies

1. Introduction

While Parkinson's disease (PD) related pain has increasingly received attention and been researched, only a few studies have addressed the prevalence and clinical characteristics of pain in neurodegenerative disorders with atypical parkinsonism [1, 2]. Although scarce, the existing evidence suggests that in those disorders, similarly as in PD, pain may be highly prevalent and might have a substantial adverse effect on the quality of life [3–6].

In the following paragraphs, we provide an up-to-date, systematic review of the current knowledge on the experience of pain, a still largely under-researched realm, in the most prevalent neurodegenerative disorders with atypical parkinsonism: multiple system atrophy, progressive supranuclear palsy, cortico-basal syndrome, frontotemporal dementia and dementia with Lewy Bodies. Focusing on the prevalence of pain, its clinical characteristics, and objective findings that might signpost altered pain processing, we point out the current gaps and unmet needs that should be a center of attention for future research studies (Summarized in Fig. 1 and Table 1, Ref. [7–20]).

2. Materials and methods

In this systematic review, we attempt to gather all currently available evidence on the experience of pain in neurodegenerative disorders with atypical parkinsonism, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. The articles published in English-language until 1st June 2021 were selected from searches in PubMed, Web of Science, and Google Scholar, using the following search terms: ("*frontotemporal dementia*" OR "*dementia with Lewy bodies*" OR "*multiple system atrophy*" OR "*progressive supranuclear palsy*" OR "*cortico-basal syndrome*") AND ("*pain*" OR "*pain prevalence*" OR "*pain presentation*" OR "*pain treatment*" OR "*pain pathophysiology*" OR "*pain processing*"). Following the initial analysis of the titles and abstracts, full-text articles were obtained and comprehensively reviewed, including examining the references where appropriate. Interventional (randomized controlled

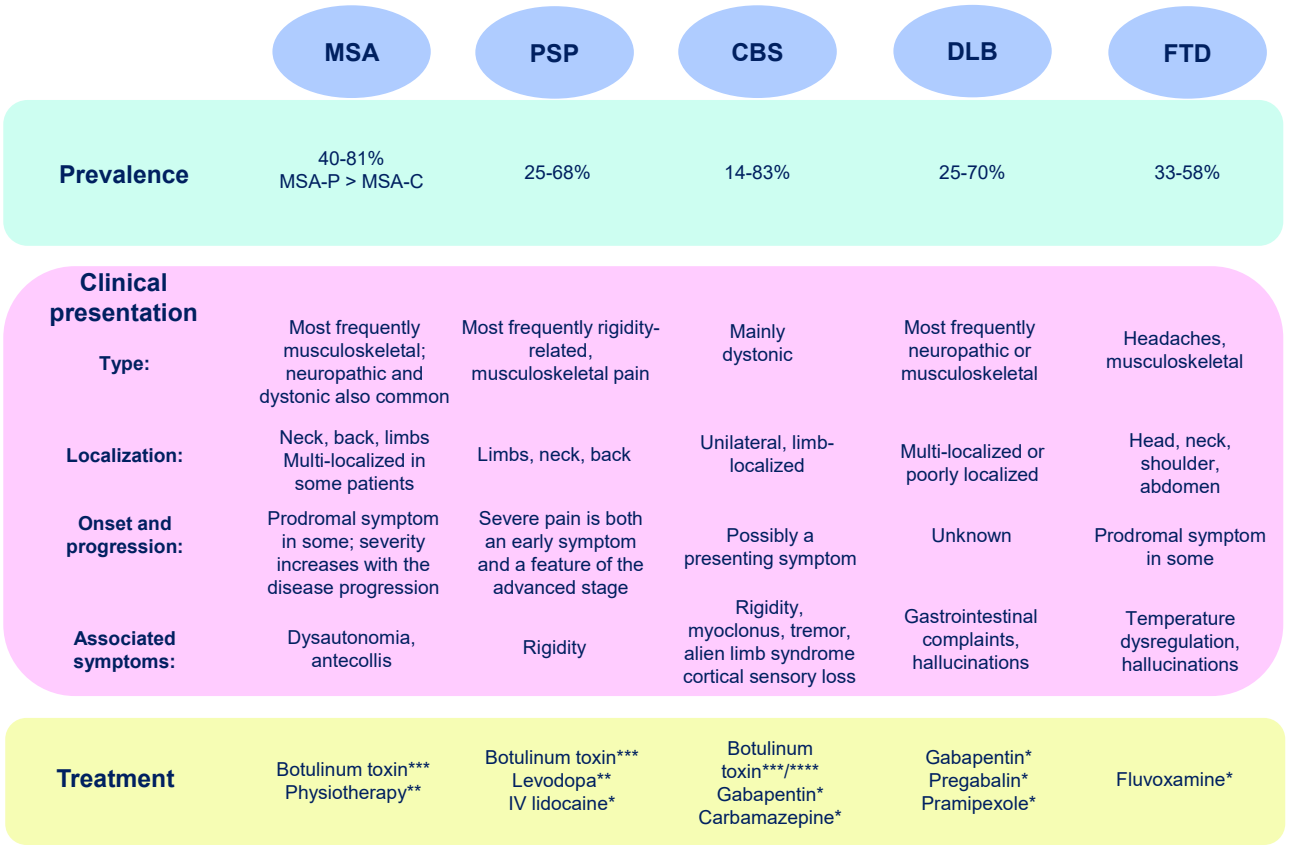

Fig. 1. Summary of evidence regarding prevalence, clinical presentation, and treatment (that have demonstrated efficacy) of pain in multiple system atrophy (MSA), progressive supranuclear palsy (PSP), cortico-basal syndrome (CBS), dementia with Lewy bodies (LBD), and frontotemporal dementia (FTD). * Case report. ** Cross-sectional study. *** Retrospective chart review. **** Prospective open-label study.

trials, open-label studies) and observational studies (longitudinal and cross-sectional studies, retrospective chart reviews, case series, and case reports) were included. We included studies where the pain was a primary, secondary, or exploratory endpoint. The final list of references was selected based on the relevance of the reported information for this review.

3. Results

3.1 Pain in multiple system atrophy

Multiple system atrophy (MSA) is a neurodegenerative disease neuropathologically characterized by α-synuclein–positive oligodendroglial cytoplasmic inclusions and neurodegenerative changes in striatonigral and olivopontocerebellar structures. Clinically, it may present with predominant parkinsonism (MSA-P) or predominant cerebellar features (MSA-C), in addition to varying autonomic and pyramidal symptoms [22].

Pain is among the most frequent non-motor symptoms (NMSs) in MSA, as identified through structured interviews in around 80% of 34 MSA patients enrolled in the PRIAMO (PaRkinson dIseAse non-MOtor symptoms) study, a cross-sectional longitudinal observational study addressing epidemiology of NMS in a large cohort of patients with PD and different forms of atypical parkinsonism [23]. The largest study (n = 286) on NMSs in MSA patients detected a pain prevalence of 78% using the EQ-5D tool (item 4, "*pain or discomfort*") [24, 25]. A meta-analysis of 10 datasets (n = 599) obtained a comparable pooled pain prevalence of 73% [6]. Compared to age-matched healthy controls, a MSA cohort (n = 65) reported pain 3x more frequently (46% vs 15%) on the Visual Analogue Scale (VAS) [26, 27]. Interestingly, a retrospective chart review found pain complaints in the clinical history significantly more common in female than in male MSA patients. The same study reported the mean onset of pain to be 2.9 years after the diagnosis. Notably, 30% of patients reported pain at or even before the disease onset (prodromal pain) [28]. Greater pain prevalence in MSA-P compared to MSA-C was found in a meta-analysis [6]. Two studies using the Non-Motor Symptoms Scale (NMSS) [29] and Short Form Health Survey tools (SF-36) [30], respectively, have also reported relatively greater pain intensity in MSA-P [31, 32]. Interestingly, the prevalence of pain is reportedly lower in Asian patients with MSA than in those of European or North American origin; the observed differences may, however, be attributable to the higher prevalence of MSA-C in Asian populations, while MSA-P predominates in Caucasians [33] (see Fig. 1).

Table 1. Summary of findings from pain-related electrophysiological, psychophysical, neuroimaging and neuropathological studies in multiple-system atrophy, progressive supranuclear palsy, cortico-basal syndrome, Lewy Body dementia and frontotemporal dementia.

	Multiple system atrophy (MSA)	Progressive supranuclear palsy (PSP)	Cortico-basal syndrome (CBS)	Dementia with Lewy bodies (LBD)	Frontotemporal dementia (FTD)
Electrophysiological and psychophysical studies: Objective pain thresholds	Reduced (NWR threshold) [7, 8]	Reduced (NWR threshold) [7]	-	-	-
Subjective pain thresholds	Reduced in the later-stages of the disease (thermal and electrical stimulation) [9, 10]	Reduced (electrical stimulation) or normal (thermal stimulation) [11]	-	-	Increased (tactile and electrical stimulation) [12]
Neuroimaging studies	-	-	Glucose hypometabolism in the S1 region and in the thalamus (PET) [13]	Lower grey matter volume in the right lateral temporal, right inferior frontal and right insular cortex, left posterior cingulate, left inferior parietal gyri [14, 15] Ventral, dorsal and pulvinar thalamus atrophy [17]	Reduced grey matter volumes within mid and posterior insula [16]
Neuropathological studies	-	-	-	Degeneration of locus coeruleus [18] Neuronal loss in dorsal and median raphe nuclei [19] Lewy Body presence in substantia nigra and periaqueductal grey [20]	

NWR, nociceptive withdrawal reflex; PET, Positron Emission Tomography.

3.1.1 Clinical characteristics of pain in MSA

Chronic musculoskeletal pain is the most frequently reported (in studies using chart review and clinical interview) pain sub-type in MSA patients, with a prevalence of up to 60% in pain-reporting patients. Musculoskeletal pain in MSA may be partly aggravated by the joint and skeletal deformities present in 68% of patients [34]. Neuropathic pain (both central and peripheral) is also prevalent (up to 36%; as declared using The Leeds Assessment of Neuropathic Symptoms and Signs pain scale, LANSS [35], Neuropathic Pain Symptom Inventory, NPSI [36], and clinical interview) [5, 10, 28, 37]. 4–13% of MSA patients have reported experiencing multiple pain types and localization in clinical interviews and the German Pain Questionnaire (DSF) [26, 37, 38].

In studies using chart reviews, DSF, and asking patients to locate their pain on a body map, MSA patients' most common localizations were limbs, neck, and back [5, 26, 28]. Notably, aching neck pain radiating to the occiput and the bilateral shoulders, or 'coat-hanger' pain, was reported by up to 53% of MSA patients via a custom questionnaire and has been linked to both dysautonomia and antecollis (forward flexion of neck) [28, 39, 40]. However, rarely, coat-hanger pain may also occur in PD patients with orthostatic hypotension, so, therefore, it may not be specific for MSA [5]. Similarly, low-back pain affects 25.4% of the general population aged >60 and is not MSA-specific [41].

The severity of pain appears to increase with the progression of the disease: while three cohorts of earlier-stage MSA patients (mean disease duration 2.35, 2.4, and 2.72 years) declared mild/moderate intensity of pain via the NMSS and VAS, severe pain (as measured by EQ-5D) predominated in two later-stage European and North American MSA cohorts (mean disease durations 5.9 and 6.3 years) [9, 24, 26, 32, 42]. Interestingly, Kass-Iliyya *et al.* [5] did not find pain intensity measured by the Short-Form McGill Pain Questionnaire (SF-MPQ) to correlate with disease duration or motor complications, but rather with the Hospital Anxiety and Depression Scale (HADS) scores [43].

3.1.2 Findings from experimental studies

The exact pathophysiological changes underlying the heightened experience of pain in MSA are yet to be fully clarified. At the cerebral level, MSA patients exert α-synuclein pathology and neurodegeneration in structures engaged in sensory-discriminative and affective-emotional facets of pain, including the anterior cingulate cortex (ACC) substantia nigra, putamen, insula, amygdala, dorsal raphe nuclei, locus coeruleus, and periaqueductal grey matter. It is tempting to speculate whether these changes might compromise the central processing of nociception [44–49].

Between 10–40% of patients with MSA show signs of peripheral neuropathy (mainly sensorimotor axonal neuropathy) upon nerve conduction studies and electromyography, possibly contributing to unpleasant neuropathic sensations which occur in a subset of MSA patients and might even be a presenting complaint in some [50–52].

Several studies have employed psychophysical techniques to investigate pain within MSA. Collectively, these studies indicate augmented responses to experimental pain, as summarized in Table 1. Lack of pain-processing abnormalities in early-stage patients may reflect a progressive alteration to central pain processing.

3.1.3 Treatment

Only 43–67% of MSA patients that declared pain (on EQ-5D, MDS-UPDRS, or VAS) received a pain-relieving treatment, indicating possible under-treatment of pain in this population [5, 26, 53, 54].

Optimizing dopaminergic therapy might alleviate pain intensity to a certain degree in some MSA patients, as shown in studies using DFS and SF-MPQ [5, 26]. Despite this, in two experimental studies, pain sensitivity measured as temporal summation threshold and subjective pain tolerance (time until heat stimulus became unbearable) in MSA patients post-L-DOPA treatment was unchanged or even worsened [8, 10].

In a chart review using a 5-point subjective Clinical Global Impression (CGI) score determined retrospectively based on the clinical notes, botulinum toxin produced pain relief in over 71.4% of 16 MSA patients treated for dystonia, sialorrhea or pain (mainly dystonic pain, off label indication) [55]. Of note, botulinum toxin injections are rarely effective for antecollis-related neck pain [40]. Regular focused physiotherapy improved pain intensity as measured by the DFS in 4 MSA patients [26]. Wiblin *et al.* [56] recommend pregabalin, gabapentin, and amitriptyline for neuropathic pain, but high-quality evidence is missing.

3.2 Pain in progressive supranuclear palsy (PSP)

Progressive supranuclear palsy (PSP) is a neurodegenerative syndrome with core clinical features of ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction, and characteristic neuropathological findings comprising neuronal loss and 4-repeat tau inclusions most pronounced in the basal ganglia, brainstem, and cerebellum and varyingly distributed in the frontal cortex [57, 58]. Clinical variants of PSP reflect regional heterogeneity of neuronal and tau pathology: the most common subtype is PSP-R (Richardson Syndrome), clinically diagnosed by vertical supranuclear gaze palsy, falls, bradykinesia, executive dysfunction, and speech abnormalities, among other symptoms, while in some patients initial clinical presentation might be dominated by parkinsonism (PSP-P), progressive gait freezing (PSP-PGF), frontal dysfunction (PSP-F), speech/language disorder (PSP-SL) or ocular motor dysfunction (PSP-OM) [57–59].

Pain is reported in 25–68% of PSP patients in questionnaire-based studies. The largest study (n = 188) reported a 56% pain prevalence using EQ-5D [24]. A meta-analysis of 8 questionnaire datasets (n = 242) found a 52% pooled prevalence of pain [6]. In recent studies comparing different atypical parkinsonism (using MDS-UPDRS and EQ-5D tools), the prevalence of pain in PSP was lower than in MSA and PD [5, 24].

Only one study to date compared the prevalence of pain in different PSP subtypes, finding no significant difference between PSP-R and PSP-P in pain prevalence or intensity as measured by NMSS [60].

3.2.1 Clinical presentation of pain in PSP

In PSP, the pain might be both — a presenting complaint and a feature dominating advanced, palliative stages of the disease, being one of the most common triggers for admissions to a palliative care unit (according to a retrospective chart review) [4, 61–63].

The most common type of pain is musculoskeletal (as reported by Stamelou *et al.* [11], who used a custom pain questionnaire (100%) and Yust-Katz *et al.* [37] (57.1%, based on structured interview). Musculoskeletal pain in PSP may be linked to postural changes, recurrent falls, and joint and skeletal deformities [34, 59]. Rigidity-related pain, with possible musculoskeletal involvement, was present in nearly half of all PSP patients admitted to a palliative care unit, according to a retrospective chart review [4]. In terms of localization, Kass-Iliyya *et al.* [5] noted 100% limb and 25% neck localization on body maps in 4 pain-reporting PSP patients. The lower limbs and neck were most commonly affected [55, 61, 64]. A retrospective chart review noted back pain being an early feature in patients with a PSP-PGF subtype [65].

3.2.2 Findings from experimental studies

In PSP patients, in addition to the striatonigral degeneration, the grey matter volume of the medial prefrontal and orbitofrontal cortices is reduced compared to controls [58, 66–68]. Furthermore, several brainstem structures involved in descending pain modulatory pathways (including periaqueductal grey (PAG), nucleus raphe magnus, and locus coeruleus) undergo neurodegeneration and pathological tau accumulation in PSP [69–71]. While spinal cord tau pathology is present in PSP patients, it is unlikely to interfere with pain processing given its localization to the anterior horn and intermediate grey matter [72].

The number of experimental studies investigating pain in patients with PSP is limited, and their results mixed. Importantly, the characteristic frontal dysfunction of PSP has been suggested to alter perception and self-estimation of pain [11]. For example, in one study, despite the thresholds of nociceptive flexion reflex, electrical pain, and heat pain comparable to PD patients (who more rarely have frontal dysfunction), significantly fewer PSP patients reported pain on VAS [11] (see Table 1).

3.2.3 Treatment

A high proportion (up to 88%) of PSP patients receive analgesics or non-pharmacological pain-relieving strategies (e.g., physiotherapy). However, it rarely leads to successful pain relief [4, 5, 53]. Interestingly, dopaminergic medication alleviated pain as measured on the SF-MPQ in only 25% of patients in a cross-sectional study [5]. In 29 pain-triggered palliative care unit admissions where anti-Parkinson drugs, antidepressants, opioids, NSAIDs, antispasmodics, benzodiazepines, and botulinum toxin injections were used to treat pain, successful pain relief was recorded in only 52% of the patients' medical records [4]. In another retrospective chart review, botulinum toxin injections improved predominantly dystonic pain in 66% of studied PSP patients (n = 6) [55]. A single case report found severe dystonic neck pain markedly improved on the VAS scale (from 10 to 2/10) with intravenous lidocaine; paracetamol, dipyrone, NSAIDs, tramadol, and oxycodone were ineffective [61].

3.3 Pain in cortico-basal syndrome (CBS)

Cortico-basal syndrome (CBS) is an asymmetrically-presenting neurodegenerative disorder comprising a wide range of motor features such as akinesia and rigidity, neurological and psychiatric symptoms (including limb apraxia, alien limb phenomenon, cognitive complaints and speech and language impairment) [73]. From the neuropathological point of view, clinical CBS can arise from a range of neuropathological syndromes, including (but not limited to) cortico-basal degeneration (CBD, 35%), Alzheimer disease (23%), PSP (13%), and frontotemporal lobar degeneration (13%), with cortical atrophy consistently observed in the primary motor cortex, and variably affecting the inferior parietal, left supplementary motor cortex, and basal ganglia [74, 75]. Historically, CBD and CBS were used as synonyms; however, they are now recognized as distinct but related pathological and clinical entities.

Epidemiological studies report varying prevalence of pain in CBS patients. For example, a meta-analysis of 3 datasets (n = 55) reported a pooled pain prevalence of 25% [6], while a *post-hoc* analysis of the PRIAMO study found a 36.4% pain prevalence in 11 CBS patients through a structured clinical interview [23]. Interestingly, the largest study (n = 147) found a pain prevalence of just 3% using a chart review method [76]. In another single-center chart review cohort (n = 66), pain accompanying dystonia was present in 24% of CBS patients [77].

3.3.1 Clinical characteristics of pain in CBS

According to several chart reviews and case reports, CBS patients frequently declare limb-localized pain that might be associated with dystonia or rigidity and, more rarely, with cortical sensory loss (impaired stereognosis, graphesthesia, and 2-point discrimination) [76–83]. Musculoskeletal pain has also been reported as the predominant subtype in 8 CBS patients (identified through the clinical interview) [37, 55]. Interestingly, neuropathic pain was an initial symptom in the clinical history of 29% of 14 pathologically confirmed CBD cases with CBS presentations [84]. 5 of 8 CBS patients in a cross-sectional study reported suffering "pain or paraesthesia" in a clinical interview, while a proportion of CBS patients in a chart review characterized their pain as 'burning', potentially reflecting a neuropathic manifestation [13, 78]. Another interesting case is of a CBS patient presenting initially

with complex regional pain syndrome - severe paroxysmal pain of the right upper limb, occurring spontaneously or induced by the extension of fingers [85].

According to three chart reviews, dystonic and neuropathic pain are typically localized in the more affected hand and arm [77, 78, 84]. Yet, some patients might have bilateral limb pain, or, in rare cases, pain can also localize to the knees, neck, chest, and orofacial areas [86–88].

Existing chart reviews and case reports suggest that rigidity, tremor, hand myoclonus and alien limb phenomenon can all co-occur with pain in the affected arm and hand, and patients might suffer concomitant anxiety [77, 81, 89–91].

The intensity of pain in CBS is largely described by patients as severe and adversely affects activities of daily living, as revealed in chart reviews and case reports [78, 85, 86].

Pain is a presenting symptom in 11–29% of CBS cases in chart reviews [78, 84, 86]. Of note, according to a chart review, in patients with prominent early sensory symptoms and pain, the pain remained severe at follow-up (mean 5.2 years after initial symptoms). Still, new onset of pain was not noted in any of the participants [78].

3.3.2 Findings from experimental studies

While the heightened experience of pain in CBS might arise from motor symptoms in the affected limb, it is likely aggravated by central mechanisms [78, 85, 86]. For example, abnormalities in evoked potentials and glucose hypometabolism (measured by PET) have been observed in the S1 and thalamus in pain-reporting CBS patients [13, 90]. However, both studies severely lack statistical power to generalize these findings, and even these limited samples demonstrated heterogeneity.

To date, no experimental electrophysiological studies have investigated pain processing in CBS patients.

3.3.3 Treatment

Although controlled trials are lacking, prospective studies and retrospective chart reviews (using clinical interview, VAS scores, or CGI) support the analgesic efficacy of botulinum toxin injections for dystonic and musculoskeletal limb pain in CBS, without notable side effects [55, 77, 92, 93]. An exception was a case report of a CBS patient initially presenting with a complex regional pain syndrome, where botulinum toxin injections significantly worsened pain. At the same time, gabapentin produced moderate pain relief [85].

Medical record reviews note the failure of non-steroidal anti-inflammatory drugs, benzodiazepines, muscle relaxants, and high-dose opioids in producing pain relief in CBS patients [77, 86, 90]. Carbamazepine successfully alleviated neuropathic pain in one case report [78]. Physical rehabilitation has both alleviated and worsened pain in recent case reports [94, 95].

3.4 Pain in dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is neuropathologically characterized by abundant cortical Lewy bodies containing α-synuclein, while its core clinical features comprise fluctuating cognition, recurrent visual hallucinations, REM (rapid eye movement) sleep behavior disorder and parkinsonism [96]. Although there is an overlap between DLB and Parkinson's disease dementia (PDD), with some clinicians placing them on the same disease continuum, current consensus diagnostic criteria categorize them as two specific disorders based on the temporal onset of dementia relative to parkinsonism: dementia occurring within the first year following the onset of parkinsonism is diagnosed as DLB [96, 97]. Here, we focus primarily on DLB, as pain in Parkinson's has been reviewed elsewhere [1, 2, 98, 99].

A handful of studies have investigated the prevalence of painful syndromes in DLB patients, with findings ranging from 25–70% [3, 23, 37, 100]. Notably, the majority of studies utilized non-standardized clinical interviews to assess pain prevalence, and no study has yet assessed pain in DLB patients using dementia-validated tools such as the Pain Assessment in Advanced Dementia (PAINAD) Scale or the electronic Pain Assessment Tool (ePAT) [101, 102]. Two studies used the EQ-5D (which rates five dimensions of quality of life, including "pain or discomfort" at 3 possible levels) and Brief Pain Inventory, respectively: the former is reliable in mild dementia but has validity concerns in moderate-to-severe dementia, while the latter has not yet been validated in dementia [3, 100, 103]. Thus, it is currently difficult to draw any conclusions on pain prevalence in DLB.

3.4.1 Clinical characteristics of pain in DLB

DLB patients might experience a range of painful syndromes. For example, musculoskeletal pain (reported in 2 of 8 DLB patients through clinical interviews) might be further aggravated by motor symptoms and recurrent falls that sometimes result in fractures [37, 104]. Reports of neuropathic pain include 2 cases with suspected central neuropathic pain (affecting the lower abdomen, lower back, vulva, and lower limbs) associated with sensations of coldness and numbness, respectively, and a description of continuous pain in both lower limbs of likely peripheral neuropathic origin associated with restless leg syndrome (RLS) and co-occurring with tactile hallucinations [105, 106].

Interestingly, hallucinations, a core feature of DLB, can be closely linked to the experience of pain, modifying and individualizing the painful sensations, such as in a case report of a DLB patient reporting a fishhook stabbing their finger and causing terrible pain [107].

A poorly localized pain (affecting thorax, abdomen, genitals, joints, and/or head) with gastrointestinal disturbances was reported by 17.9% of 162 DLB patients in a prospective, cross-sectional cohort study (using clinical interviews and performing a chart review). It may be present as a prodromal symptom [108]. This particular subtype of pain seems to be more prevalent in DLB than in other neurodegenerative diseases (AD, PSP, MSA, FTD), possibly being a red flag for DLB. However, there are some similarities with the pheno-

type of an unexplained lower limb pain (persistent pain affecting proximal anterior thigh region with extension occasionally to the pelvic area, ranging from unilateral to bilateral, and, in some cases, associated with whole-body pain) as described by Wallace and Chaudhuri in PD patients [108, 109].

In terms of intensity, DLB patients have described their pain as 'severe' or 'intolerable' in case reports, while a case-control study recorded "severe" pain in 41% of DLB patients on the EQ-5D tool, adversely affecting the quality of life and activities such as sleeping [100, 106, 107, 110].

3.4.2 Findings from experimental studies

Presently, few conclusions can be drawn regarding the pathophysiology of pain in DLB, given the lack of pain-related experimental studies employing psychophysics or neuroimaging methods.

In DLB, widespread neuropathological changes at the cerebral level may affect numerous structures involved in diverse aspects of pain processing pathways, as summarized in Table 1. In addition, Lewy body pathology is present in both the spinal cord dorsal horn and unmyelinated fibers of the cutaneous peripheral nerve of DLB patients, possibly interfering with pain processing on spinal and peripheral levels [111–114].

3.4.3 Treatment

In several case reports, calcium channel modulating anticonvulsants gabapentin and pregabalin successfully relieved neuropathic pain in DLB patients and were well tolerated, but high-quality data are lacking [105, 106]. Of note, caution and specialist monitoring is required, as higher doses of pregabalin might exacerbate parkinsonism [115]. In another case report, pramipexole ameliorated central neuropathic pain in a DLB patient [106].

The analgesic efficacy of L-DOPA in DLB is not known, and there is also currently no evidence on treatments for musculoskeletal pain in DLB.

3.5 Pain in frontotemporal dementia (FTD)

Frontotemporal dementia (FTD) represents a spectrum of clinically, pathologically, and genetically specific neurodegenerative syndromes characterized by frontal and temporal lobe atrophy [116]. Core clinical subtypes include the behavioral variant (bvFTD) and the language-dominant subtypes: non-fluent/agrammatic variant, primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA). TDP and tau are observed major protein depositions; *C9ORF72*, *GRN*, and *MAPT* mutations account for almost all familial cases [117]. FTD was included in this review as parkinsonism may precede, coincide, or follow the onset of its behavioral or language-predominant features [118].

Overall, the presentation of pain in FTD is highly variable [16, 119, 120]. The largest epidemiological study across all FTD subtypes thus far (n = 97) found a 39% prevalence of pain through chart review method [120]. Regarding the FTD subtypes, svPPA patients appear to have the greatest pain burden; 55% of caregivers reported exaggerated pain responses in a semi-structured interview [16, 121, 122]. In comparison, 35–40% of bvFTD patients report pain in clinical interview [3, 119, 122, 123]. However, specific variants within bvFTD might be more prone to pain: the disinhibited form more than the apathetic form (a chart review), and *C9ORF72* carriers more than non-carriers (based on caregiver-completed questionnaires) [16, 124, 125].

In a chart review, pain in FTD patients was not associated with gender, age at onset, disease duration, or prevalence of depressive symptoms [120]. Notably, pain complaints were present only during the first half of the disease course; progressive decline in expressive language and ability to interpret symptoms might explain the lower prevalence of pain at later stages of FTD [12, 120]. Interestingly, another chart review found 24% of bvFTD patients self-report pain as an initial disease symptom, compared to 0% in svPPA and 13% in nfvPPA [126].

3.5.1 Clinical presentation of pain in FTD

In terms of localization, pain in FTD mostly affects the head, neck, abdomen, and, less commonly, chest and legs [120, 121, 125]. Headaches are common across all FTD subtypes and are reported by 18–26% of patients in studies using chart review and the Autonomic Symptoms Questionnaire [120, 121]. Musculoskeletal pain (14%) and gastrointestinal/genitourinary pain (12%) were also reported [120]. Neck and shoulder pain is more common in svPPA and potentially linked to autonomic dysfunction [121]. Altered temperature responses frequently co-occur with pain [16, 122]. According to the chart reviews, pain in FTD might be coupled with psychotic (such as hallucinations) and affective symptoms that may alter the way patients experience pain [122, 125] (Fig. 1).

12–20% of bvFTD patients additionally develop motor neuron disease and parkinsonism; subsequently, these patients may suffer pain characteristic to these diseases [116, 127, 128]. In rare cases, FTD occurs in the context of inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD), a rare familial disorder associated with aching bone and joint pain affecting hips, lower back, and pelvis [129, 130].

3.5.2 Findings from experimental studies

In a large MRI study (31 FTD patients and 50 healthy controls) investigating the neuroanatomical correlates of altered pain and temperature responses as characterized by a semi-structured caregiver questionnaire, symptoms suggesting abnormalities of pain and/or temperature processing (reported by 53% of FTD patients and 71% of those with bvFTD) were associated with reduced grey matter volumes within mid and posterior insula in all FTD patients, as well as bilateral posterior thalamus in those carrying *C9orf72* mutations [16] (Table 1).

As seen using voxel-based morphometry, atrophy has been described in the right cingulo-insulo-amygdalar net-

work previously implicated in deficiencies of interoception (ability to perceive internal bodily sensations) [131]. Interoception is especially impaired in svPPA, which may hold some explanatory value for the higher prevalence of pain symptoms in these patients than in other FTD variants [122, 131].

Interestingly, in a longitudinal study involving clinical and neuropathological characterization, no robust relationships were found between somatic complaints or abnormal pain responses (noted in medical records of 40.2% of the 97 FTD patients) and brain protein pathology, regional pathology, or asymmetric hemispherical atrophy [120].

To date, psychophysical evidence remains scarce, with only one study having employed the robust quantitative sensory testing battery in FTD patients [12]. Both self-reported pain thresholds and tolerance were increased relatively to controls with no divergent responses across FTD variants (Table 1). However, despite being the gold standard for assessing pain thresholds, quantitative sensory testing relies on self-report, which may also be influenced by the loss of pain awareness (more prevalent in bvFTD than svPPA and nfvPPA) or diminished ability to communicate pain in FTD patients [16, 122, 132].

3.5.3 Treatment

There have been no controlled trials on analgesia specifically for FTD [133]. Pain may be undertreated in FTD outpatients, with a Dutch cross-sectional study reporting analgesic use in just half of the 14 patients who declared pain in clinical interviews [3]. Fluvoxamine, an SSRI used to treat behavioral symptoms in FTD, conferred marked self-reported analgesia for lumbar and abdominal pain in a case report of two FTD patients [134].

4. Conclusions

Individuals with neurodegenerative diseases with atypical parkinsonism may be predisposed to the development of persistent pain. In general, when selecting the most appropriate treatment for pain relief, choosing a mechanism-based strategy is key. However, the current evidence on exact pathophysiological mechanisms underpinning heightened pain in specific neurodegenerative disorders is poor. In addition, in some patients, pain reporting might be compromised by cognitive complaints or speech and language alterations, possibly hindering an accurate capturing of pain and producing unreliable findings in clinical studies using clinical assessment tools and/or quantitative sensory testing. Today, as the global population is aging and we face an epidemic of neurodegenerative disorders, under-treated pain is taking a great toll on an ever-rising number of people. A global consensus on strategies to overcome those challenges is urgently needed and will allow for large-scale, high-quality clinical trials in the future to be conducted. Ultimately, this will pave the path for mechanistically-driven analgesic interventions to be developed and lead to an improvement in the quality of life of numerous individuals living with neurodegenerative disorders.

Abbreviations

CBS, cortico-basal syndrome; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MSA, multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

Author contributions

KR and KRC conceived the idea and designed the manuscript. JYC and KR drafted the manuscript. TL and KRC provided revisions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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