Chapter 8
Neurodegenerative Diseases and Pain

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Introduction

Many neurologic and neurodegenerative disorders are complicated by chronic and frequently debilitating pain. As our understanding of the physiology of pain evolves, the concept that the brain plays a pivotal role in the development and control of chronic aberrant pain signals has solidified. It is the current belief that pain may be a result of neurological disease and may often be considered a component of the disease. Multiple Sclerosis, Parkinson's disease, Syringomyelia and Stroke are a few of the neurologic disorders in which patients often experience some type of chronic pain which complicates their disease course and influences their quality of life. The degenerative diseases affecting the central nervous system are going to increase in parallel to the lengthening of survival. The management of Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and PD-related disorders, and motor neuron diseases (MND), is mainly targeted to motor and cognitive impairment, with special care for vital functions such as breathing and activities of daily living. Focused treatment of pain in these conditions may have a positive impact on the global burden of these devastating diseases.

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Parkinson's Disease

Parkinson's Disease is a chronic neurodegenerative disorder, with many disabling motor ramifications, resulting from depletion of dopamine in the substantia nigra. The disease is frequently associated with tremors, rigidity, and postural instability with functional deficits. Less known is the prevalence of chronic pain among Parkinson patients [1]. This non-motor effect is under recognized and often untreated. Up to 60% of Parkinson patients experience significant pain which affects their quality of life [2]. Many patients fail to mention pain to their physician which they are experiencing. Some physicians do not recognize their patient is in pain, or do not prioritize treatment for pain, while other physicians are uncomfortable or unfamiliar with treating chronic pain. Lastly, some physicians regard chronic pain in some patients as psychogenic. Analgesic use has been found to be lower for Parkinson pain patients than non-Parkinson patients despite evidence of more severe pain and impairment of quality of life [3].

There are multiple sources of pain in this population, such as dystonia, musculoskeletal pain, central pain, and nerve pain [2]. Management of Parkinson pain should be initiated as early as possible. It is imperative to distinguish Parkinson pain from non-Parkinson, and to separate the types of Parkinson pain, as treatment varies with the type of pain.

Dystonia may cause sustained muscle twisting with forceful or painful contractions. Dystonia can cause joint pathology, such as frozen shoulder, which elicits pain. Focal dystonia, such as in the foot, is quite painful and can be addressed with toxin injection. More diffuse dystonia may respond to anticholinergics, amantadine, baclofen or deep brain stimulation [4].

Parkinson rigidity may cause joint or muscle pain which limits function and usually presents with aching, cramping and muscle and joint pain. This can be treated with NSAID's, opiates, antidepressants, and analgesics. Range of motion and stretching of the muscles is effective and transcranial magnetic stimulation has shown some effect. Mobility is helpful in the context of rigidity and stiffness.

Neuropathic pain in Parkinson patients may be due to central basal ganglia dysfunction and some patients get relief of pain with levodopa. There is evidence of abnormal somatosensory processing in the basal ganglia [2]. An irritated nerve root may distribute radicular pain, can be diagnosed with electrodiagnostics, and treated with therapy or decompressive surgery if severe.

Muscle cramping and dystonia are the most frequent pain complaints in Parkinson patients [4]. Opioids and cannabinoids have shown to be effective for treatment of pain in Parkinson patients, but safinamide has proven to be most effective [3]. Safinamide is a selective, reversible monoamine oxidase B inhibitor which decreases dopaminergic degradation and reuptake. The drug also inhibits voltage gated sodium channels in the inactivated state; thus the pain reduction may be due to dopaminergic and non-dopaminergic actions. Opioids are analgesic and inhibit neurotransmission, while cannabinoids control pain by way of cannabinoid receptor agonism. A comprehensive multidisciplinary approach to pain in the Parkinson

patient has been shown to be effective, as have electrical therapy and Chinese therapies [3, 5].

Least effective in treating Parkinson pain are Dopa agonists, hydrotherapy, massage, mindfulness, and Pandoprunox, a partial Dopamine agonist used as an adjunct to Levodopa [3].

There is a known relationship between pain and depression, and such is true for Parkinson patients. They experience more severe depression, longer duration of depression, and lower mini-mental exam scores than other patients. The pain and depression decrease quality of life for Parkinson patients. Birgatta, et al. found that Parkinson patients felt a reduction in health-related quality of life, frequently related to pain [6].

There are no guidelines for the treatment of pain in Parkinson's Disease. There is a need for an algorithm or protocol to assist in treatment of this under recognized pathology which can affect function and quality of life.

Syringomyelia

Syringomyelia is a chronic spinal cord pathology in which a cavitation, or syrinx, develops within the spinal cord. It is rare (<1% of neurologic cases admitted) and most commonly associated with Chiari 1 malformation [5]. Pain is a common effect of the syrinx with 50–90% of syringomyelia patients experiencing chronic pain [7]. Frequently this presents with radicular pain, interscapular pain, or central spinal cord pain. 40% of patients' experience dysesthetic pain with burning, stinging, aching or pins and needles [7]. Symptoms are usually restricted to the upper limbs and thorax and can be aggravated by coughing or sneezing. There may be dermatomal pattern hypersensitivity. Skin symptoms may include hyperhidrosis, glossy skin, paleness, or coldness [7].

Animal studies have implemented substance P as a neurotransmitter having a role in pain modulation of spinal cord patients in which there is loss of spinal cord inhibition [7]. Some of the pain may be sympathetic-mediated, similar to causalgia peripherally. Studies have shown improvement with sympatholytic treatment such as stellate ganglion blocks and sympathectomy [7]. There appears to be a direct relationship between markers of spinal cord damage and central neuropathic pain [8].

Syringomyelia may alter neurotransmitter concentrations of gamma amino butyric acid, endorphins, enkephalins, cholesystokinins, neuropeptide Y, and others [7].

Cavitary lesions of the spinal cord can be defined with good resolution by MRI. Milhornt, et al. described dysesthetic pain in syringomyelia patients [9]. Fifty-one patients out of 131 reviewed experienced dysesthetic pain (37%). MRI revealed extension of the syrinx in the dorsolateral quadrant of the spinal cord ipsilateral to the pain in 43 of 51 patients (84%). Twenty-two of 37 (59%) improved with surgical treatment of the syringomyelia. Fifteen of 51 patients (41%) developed

post-operative dysesthetic pain refractory to medical treatment. Some improved with time but six patients continued to have pain 2–6 years post operatively. One patient achieved pain relief with stellate gangliotomy and one got transient relief with regional sympathetic blocks. The study concluded that dysesthetic pain may be caused by disturbance of pain modulating content in the dorsolateral quadrant of the spinal cord and may cause a causalgia-like syndrome [9].

Analgesics and neuropathic pain medications such as antiepileptics, antispasmodics, and anti-inflammatories have had minimal effect on syringomyelia pain [7]. There is a need for standardized treatment protocols for pain due to syringomyelia to improve the quality of life for these patients.

Stroke

Post stroke pain is a well-recognized condition to be a persistent neuropathic pain of central origin, and that cannot be attributed to peripheral (nociceptive or neurogenic) origins. Shoulder pain is more common affecting up to 72% of post stroke survivors [10]. It is largely refractory to medical and surgical and thereby constitutes an unmet medical need.

It is well-documented that strokes, particularly the structures along the spinothalamocortical tract (spinothalamic tract, lateral thalamus, thalamic–parietal projections), produce central pain syndromes (central post-stroke pain) [10, 11]. The mechanisms underlying the severe, spontaneous, burning pain that occurs with thalamic stroke remain unclear. Several studies clearly showed that damage to specific regions of the brain produces central pain.

A pseudo thalamic syndrome, producing pain asymbolia (absent or inadequate emotional responses to painful stimuli) [12], results from a stroke producing damage to the posterior insula region [13, 14]. This is consistent with evidence indicating a significant role of the posterior insula in processing of thalamic pain.

Several findings related to central pain shed light on pain processing: (1) damage to the classic pain sensory systems (spinothalamic tract) seems to be pivotal in producing central pain syndromes resulting from stroke. Loss of grey matter in chronic pain has been well described and the altered connectivity resulting from either direct damage or indirect changes may contribute to a central pain syndrome [15]; (2) in thalamic pain, there is increased excitability of thalamic regions. Although there may be diminished activation in the thalamus at rest, hyperactivity (including bursting activity) is found in central post-stroke pain, suggesting derangement of an oscillatory pattern inside a sensory thalamocortical loop [16]; and (3) other changes including alterations in neural connectivity (deafferentation) [17], decreases in opioid receptor concentrations damage to lateral nociceptive thalamoparietal fibers, and altered chemistry are present in central pain. Functional imaging studies of a patient with thalamic pain suggest that the release of activity in anterior cingulate and posterior parietal regions is a plausible mechanism for central pain [18]. Current consensus about the pathogenesis of post stroke pain with various theories have

been put forward, including hyperexcitability of thalamic neurons after interruption of ascending fibers in the spinothalamic pathway [19, 20], release of inhibition through a specific lesion to the lemniscal pathway or the spinothalamic tract [21], and release of inhibition through degeneration of corticothalamic neurons that project to the reticular nucleus and activate GABA-ergic inhibitory neurons which regulate neuronal excitability in the somatosensory relay nuclei of the thalamus [22, 23].

Treatment

It is not the intent of this section to provide details on pharmacological and nonpharmacological treatments of post stroke pain. Amitriptyline, a tricyclic antidepressant, is usually the drug of first choice [11, 20, 21]. However, its utility is limited by common adverse effects such as dry mouth, drowsiness, and constipation, as well as rarer instances of urinary retention, orthostatic hypotension and cardiac arrhythmia [20]. It is tempting to speculate that the apparent analgesic effect of amitriptyline may in fact stem from its mood-enhancing properties; however, it is not necessarily accompanied by a reduction in depressive symptoms [11].

Nonsteroidal anti-inflammatory drugs such as ibuprofen, acetylsalicylic acid and cyclo-oxygenase-2 inhibitors are not recommended. Antidepressants [12, 22, 23] such as amitriptyline and nortriptyline, as well as antiepileptics including lamotrigine, gabapentin, pregabalin and carbamazepine can be used as first-line treatments. For patients who are refractory to these treatments, opioids such as morphine [24] or levorphanol [25] may be prescribed, although no large studies have directly examined their efficacy for CPSP. Local anesthetics such as lidocaine [24], N-methyl-D-aspartate receptor antagonists including ketamine [26], cannabinoids, and botulinum toxin A are not recommended. In terms of combination therapy, gabapentin or pregabalin with amitriptyline is not effective. Gabapentin is relatively safe, with the most common side effects being dizziness and sedation. Lamotrigine is an anti-epileptic medication with non-NMDA anti-glutamatergic activity and is relatively well-tolerated, although there is documented potential for severe dermatologic adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Nonpharmacological interventions have also been used in the treatment of post stroke pain. For example, deep brain stimulation of the central grey matter was used years ago for intractable pain. Study showed that chronic epidural electrical stimulation of the motor cortex results in a reduction in pain [25–27]. Treatment of this condition can be frustrating and multi-modal approaches are frequently used. Physical and occupational therapy are the mainstay of treatment and function by decreasing the pain and improving function of the affected limb [23, 24]. Desensitization of the affected limb through sensory overload using various types of stimuli, contrast baths and massage are among the techniques and modalities that can help the patient overcome the pain [23]. At the same time, a concerted effort should be made to restore as much range of motion and motor strength as possible

to prevent limb dysfunction. Physical and occupational therapy are valuable adjuncts in the treatment and are generally safe. However, therapy does require effort and commitment on the part of the patient to participate but, sometimes, access or transportation to see a therapist can be a barrier to treatment.

The use of tissue plasminogen activator (tPA) for selected stroke patients significantly curtails the morbidity and mortality associated with acute ischemic stroke [28]. By salvaging the ischemic penumbra, tPA may also prevent damage to the spinothalamocortical tract, and thus reduce the subsequent risk of post stroke pain [29, 30].

It is important to note that patient with post stroke pain condition is likely to experience not only pain and sensory abnormalities, but also considerable emotional distress. Behavioral therapies, massage, physical therapy and acupuncture are therefore recommended for alleviation of the anxiety, depression and sleep disorders that often accompany chronic pain syndromes such as post stroke pain [30].

Spinocerebellar Ataxia

Spinocerebellar ataxias (SCAs) comprise an extensive and heterogeneous group of neurodegenerative diseases with autosomal dominant inheritance [31]. Despite their inherent heterogeneity, the SCAs present certain consistent characteristics, such as the obvious core features of an ataxic syndrome and its phenomenological correlates, and the pathological substrate of a degenerative process involving the cerebellum and/or its connections.

Machado–Joseph disease is the most common spinocerebellar ataxia, also known as spinocerebellar ataxia type 3 [32] and is a neurodegenerative disease that include ataxia with extracerebellar neurological manifestations, such as dementia, epilepsy, visual disturbances, peripheral neuropathy, supranuclear ophthalmoplegia, pyramidal tract signs, and movement disorders such as parkinsonism, myoclonus, chorea and dystonia [33–35]. Although classically described as affecting the cerebellum, it affects several other brain regions including brainstem, basal ganglia, thalamus, posterior columns, and cerebral cortex. In a small study, nearly 50% of patients reported chronic pain including muscle cramps. This prevalence was similar to that of amyotrophic lateral sclerosis and much higher than in cases of peripheral axonal neuropathy. The study focused into the underlying pathological changes demonstrating axonal excitability significantly greater in SCA3 patients than in normal subjects, probably reflecting axonal regeneration or collateral sprouting [36]. Muscle excitability abnormalities occur in >80% of these patients and peripheral nerve damage correlates with the extent of muscle fasciculations. In addition, widespread neurodegeneration is observed in somatosensory (although pain is not specifically delineated) as well as primary sensory systems with alterations in dopaminergic and cholinergic systems [32]. Sensory symptoms including pain are observed across subtypes of spinocerebellar ataxia, with 48% of subjects complaining of pain or discomfort.

One emerging concept is that the cerebellum may play a role in chronic pain, based on its complex role in cognitive and affective processing. Current data suggest that the cerebellum is an integrator of multiple effector systems including affective processing, pain modulation, as well as sensorimotor processing.

As compared with other neurodegenerative disorders such as Parkinson's disease, quantitative and validated assessment tools are less developed [37]. The patients generally experience problems with mobility, usual activities, pain/discomfort, depression/anxiety, and self-care. Different population surveys have shown that 19% to 64% of patients report pain as a problem in selected SCA conditions [38]. In the same study, multivariate analysis revealed three independent predictors of subjective health status: ataxia severity, extent of noncerebellar involvement, and the presence of depressive syndrome. Although pain is not a primary invalidating factor in such patients, it may influence the quality of life as part of depression-related symptoms cohort and noncerebellar features.

In a recent systematic review reporting data from 1062 publications and 12,141 patients with different neuromuscular disorders, pain was found to be reported in 1 among 30 SCA sufferers [39]. However, pain may often be underestimated though it can be severe when related to dystonia. In SCA conditions, pain can be misdiagnosed and mistreated but successfully ameliorated by, for example, botulinum toxin therapy [40].

There are currently no cures for SCA and treatments (pharmacological therapy and physical therapy) target the symptoms such as pain, spasticity, tremor, stiffness, postural balance, gait disabilities, sleep problems, and depression. However, there are some very preliminary and nonvalidated data suggesting the use of umbilical cord mesenchymal stem cells in SCA [41].

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by degeneration of upper and lower motor neurons in the cerebral cortex, brainstem, and spinal cord. This results in a characteristic phenotype of muscle weakness, dysphagia, dysarthria, respiratory failure, and eventual death usually within 2–4 years from symptom onset. ALS has traditionally been viewed as a purely motor disease. Because of this misconception, pain has been a largely neglected symptom in ALS patients until recently. Studies have shown that up to 85% of patients with ALS experience pain at some point during the course of their disease. If left untreated, pain has been correlated with a significant decline in quality of life [42].

The three most common sources of pain in ALS patients include musculoskeletal pain, muscle cramps, and spasticity [42]. Although electrodiagnostic studies and skin biopsies show evidence of somatosensory dysfunction, patients with ALS do not commonly endorse neuropathic pain features.

Musculoskeletal pain (or nociceptive pain) originates from injury to non-neural structures, such as bones, ligaments, tendons, or muscle tissue. Muscle atrophy, muscle weakness, and reduced mobility may result in injury to musculoskeletal structures. Peripheral nociceptors in these structures transmit pain signals to the central nervous system, leading to the development of nociceptive pain [43]. Patients may present with articular pain, pain from pressure injuries, and neck or low back pain [44]. In the late stages of ALS, pain may become chronic and patients may complain of diffuse pain that is hard to localize. In these stages, central sensitization is hypothesized to play a role in the maintenance of pain, although this has never been directly studied [44]. Patients with ALS who have been started on mechanical ventilation may develop novel sources of pain, such as pain from suctioning and pain from skin lesions caused by facial pressure from non-invasive ventilation masks [44].

Muscle cramps are another source of pain for ALS patients. Cramps likely originate from neuronal hyperexcitability of unstable motor units. They occur universally in ALS patients, affecting approximately 95% of patients at some point during the disease course and are a major source of pain in a quarter of these patients [45]. Cramps are frequently present during the early stages of the illness and there is a trend towards fewer cramps as the disease progresses [46]. Patients display a wide variability in the frequency and severity cramps from 1 month to the next. If patients do not experience cramps at the time of diagnosis, they tend to never develop frequent cramps as the disease progresses. Those older than 60 years of age and those with limb-onset disease experience more cramps than younger patients and those with bulbar-onset disease [46]. Cramps most commonly occur in the thighs and calves, followed by the hands and feet [46]. They may be worsened by cold temperatures and decreased circulation caused by maintaining muscles in static positions for prolonged periods of time [47].

Lastly, ALS patients may endorse pain from spasticity. Although spasticity itself does not cause pain, it can result in muscle fatigue and painful cramps [48]. If severe, spasticity may immobilize joints and lead to muscle contractures resulting in pressure injuries. Furthermore, spasticity can result in distorted biomechanics causing abnormal postures and gait, thus leading to new pain generators [48].

Treatment

After identifying the cause of pain, the appropriate non-pharmacological and pharmacological interventions should be implemented to appropriately manage pain. There are currently no treatment guidelines available to aid clinicians in managing pain in patients with ALS. Therefore, pain in these patients is managed based on expert opinion largely backed by case series and a small number of randomized controlled trials rather than published guidelines. Two sources of

published recommendations are provided by the European Guidelines on the Clinical Management of ALS [46] and the Practice Parameters of the American Academy of Neurology [48].

For patients with musculoskeletal pain, non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are used as first-line treatment options, while opioids are used as second-line options when pain was difficult to control, particularly in advanced disease stages [44]. In these patients, opioids are also used to manage symptoms of respiratory insufficiency, such as poor sleep and dyspnea. Cannabinoids may be an effective option to improve pain in some patients. If used, side effects may include confusion, tachycardia, and amotivational syndrome. For patients with reduced mobility, it is important to initiate a daily exercise regimen consisting of stretching, assistive range of motion (ROM) exercises. Modalities such as ultrasound and laser therapy can be used as adjunct treatment options.

For ALS patients with muscle cramps, levetiracetam has been shown to reduce the severity and frequency of cramps in this population. Common side effects include fatigue, somnolence, and headache. Second-line treatment options include quinine sulfate and mexiletine. Quinine sulfate is commonly used in the off-label treatment and prevention of nocturnal leg cramps of any cause. It carries a black box warning cautioning against serious hematologic reactions and clinicians should monitor complete blood counts when prescribing. Mexiletine carries an off-label indication to manage painful muscle spasms in ALS patients. It is safe and well tolerated at doses of 300 mg per day with dose-dependent adverse effects including cardiac arrhythmias occurring at 900 mg per day. Once prescribed, medications should be weaned once cramps are adequately controlled since the frequency of cramps decreases as the disease progresses. Non-pharmacologic options that may be of benefit include stretching, massage, physical therapy, and hydrotherapy.

The mainstay of treating spasticity in ALS patients is physical therapy consisting of daily stretching, assistive ROM exercises, and moderate physical activity. Neutral-position splints can provide static stretching to the distal extremities. Although not formally studied in this population, baclofen, tizanidine, dantrolene, and benzodiazepines have been used with success as has botulinum toxin A. In ALS patients with intractable spasticity despite oral medications, intrathecal baclofen remains an option.

Clinicians should vigilantly assess ALS patients for pain as this symptom may develop early or late in the disease course and can contribute a significant decline in the patients' quality of life.

Patients with ALS may experience pain from a variety of causes. However, the three most common sources of pain include musculoskeletal pain, muscle cramps, and spasticity. When addressing these sources of pain, it is important to utilize both pharmacologic and non-pharmacologic treatment options. In addition to assessing for pain, clinicians should address factors that could aggravate pain, such as sleep disturbances and depression.

Huntington Disease

Huntington disease (HD) is a fatal neurodegenerative disorder inherited as an autosomal dominant manner and characterized by motor, cognitive, and behavioral changes. It results from a mutation in the huntingtin gene causing abnormal repetition of the CAG DNA sequence eventually resulting in a misfolded gene product. This protein causes degeneration of medium spiny neurons, which are mainly concentrated in the striatum [49]. The striatum primarily regulates the affective and cognitive dimensions of pain and thus plays a role in processing feelings related to pain unpleasantness and the emotional response to pain. The striatum also plays a role in analgesia and contains a high concentration of endogenous opiates and receptors. It is believed that patients with HD experience disturbed pain processing due to the degeneration of medium spiny neurons in the striatum. Additionally, patients with HD often do not report pain even after experiencing significant trauma. This is believed to be related to "unawareness" caused by impaired frontal-striatal networks [50]. A recent systematic review and meta-analysis reported the prevalence of pain to be approximately 41% in this population [51].

Studies evaluating pain in patients with HD are scarce and therefore, there are currently no treatment guidelines available to aid clinicians in managing pain in this population. Common causes of pain in HD include dystonia, chorea, contractures, musculoskeletal injuries including occult fractures, pressure injuries, constipation, and urinary retention [52]. Treatment mainly focuses on managing the underlying disorder. Due to cognitive dysfunction, patients with HD may not endorse pain when questioned or may have significant communication deficiencies that prevent the accurate assessment of pain. Clinicians should monitor for atypical manifestation of pain in this population such as increased confusion, agitation, and depression [53].

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder and a common form of dementia characterized by cognitive and behavioral impairments. AD is often comorbid with chronic pain with an estimated prevalence of 45.8% [54]; however, this may be underestimated given that some patients with Alzheimer's disease are unable to effectively communicate their pain compared to cognitively intact individuals [55]. Other studies have showed that pain is observed with a higher prevalence in patients with severe dementia [54, 56], and that pain intensity is positively correlated with dementia severity, neuropsychiatric symptoms, depression, agitation, and quality of life [57].

The neuropathophysiology involved in AD affects both pain processing and pain perception. To understand this, a distinction must be made between the medial and lateral pain systems. The medial pain system primarily involves the spinothalamic

tract which projects directly to the intralaminar thalamic nuclei, the spinoreticular tract which projects to the reticular formation, and the spinomesencephalic tract which projects to the mesencephalon. The medial pain system is involved in the motivational-affective and cognitive-evaluative features of pain, which involves the memory for pain and the autonomic-neuroendocrine responses evoked by pain. The lateral pain system involves the spinothalamic tract neurons that project to the somatic sensory cortical areas, and it is involved in the sensory-discriminative features of pain, or the intensity, location, quality, and duration of pain [58].

The pathophysiological changes that occur with AD selectively affect most of the medial pain system while leaving the lateral pain system relatively well preserved. This clinically manifests as the perception of unaltered acute pain while there is an overall decrease in chronic pain in AD patients. Pickering et al. found that analgesic consumption in acute pain was not significantly different for AD patients and cognitively intact patients, whereas chronic pain analgesic consumption was significantly lower for AD patients. This is further evidence for the dissociation between the sensory-discriminative of the lateral pain system, and the motivational-affective of the medial pain system aspects of pain in AD patients [59]. Other studies have found that AD patients have fewer of the affective components of pain than non-demented elderly people. Several studies have shown that the pain threshold in response to an electrical stimulus is not changed in AD patients compared to cognitively intact patients, suggesting that the sensory-discriminative component of the lateral pain system is preserved in AD [58].

AD has been associated with neuronal loss in the locus ceruleus of the medial pain system [60]. Conversely, Song et al. proposed a mechanism of how chronic pain can accelerate AD pathogenesis. Chronic pain induces dysfunction in the locus ceruleus noradrenergic system, leading to neuroinflammation and enhanced norepinephrine transmission. This results in increased excitability in specific areas of the brain like the prefrontal cortex and hippocampus, which is suggested to induce microglial proinflammatory activation that promotes further AD pathogenesis [61].

Cognitive impairments in AD include memory deficits and impaired reasoning, which can affect the patient's ability to describe their pain. Furthermore, pain is often ignored, underestimated, or underreported in the elderly with dementia, and thus improperly treated. Pain in this cohort can manifest in various ways, including sleep disorders, decreased mobility, falls, malnutrition, depression, agitation, aggression, delirium, and reduced social participation. This can have serious consequences on health, the ability to perform activities of daily living, and overall quality of life. Prior to treatment, an assessment of pain should be made. While self-assessment scales are considered the gold standard, the presence of cognitive decreases their reliability and utility. The American Geriatrics Society published guidelines in 2002 for assessing behavioral indicators of pain, which includes evaluating for any persistent pain that impacts physical function, psychosocial function, or other aspects of quality of life. This may be supplemented by a physical exam, routine lab work, and evaluating patients' social support systems.

The goal in treating pain may not be to completely eliminate the pain entirely, but to decrease and reduce its intensity, duration, and frequency of the episodes in order

to maximize independence in activities of daily living while minimizing adverse effects of the treatments. Treatment of chronic pain includes pharmacologic and non-pharmacologic approaches. Nonpharmacologic approaches include a wide variety of options including therapy, modalities, osteopathic manipulative medicine, acupuncture, and psychological therapy. Multimodal cognitive behavioral therapy has shown to significantly decrease pain. Gagliese et al. proposed that pain in older patients with dementia is the result of an intricate network of interactions between biopsychosocial phenomena, and that treatment of depression in older people with osteoarthritis can have a significant impact on function and pain [62].

When utilizing the pharmacologic approach, polypharmacy in the elderly must be taken into account, as well as age-related differences in pharmacokinetics and pharmacodynamic properties of drugs. Furthermore, a study by Benedetti found that the placebo mechanism was reduced in AD patients, who may require higher dosages of pain medications to obtain the analgesic effect that is normally reached in cognitively healthy individuals [63].

Non-opioid analgesics are recommended first, with gradual increases in dosages in order to monitor for adverse effects and build tolerance to the medication. Acetaminophen is an effective first-line approach for pain in patients with dementia. Other medications include nonsteroidal anti-inflammatory drugs (NSAIDs) , such as ibuprofen or naproxen. NSAIDs have shown to exhibit a “ceiling effect” where further increases in the dose does not correspond with more pain relief; however, these higher doses are associated with an increased risk for adverse effects such as gastrointestinal or cardiovascular disorders which can be life-threatening. The use of opioids in the long-term treatment of pain in the elderly with cognitive deficits lacks evidence. Drugs for neuropathic pain including gabapentinoids should be used cautiously and be monitored for side effects. Tricyclic antidepressants are not recommended because of the anticholinergic side effects as well as other side effects including urinary incontinence, hypotension, sedation, glaucoma, and cardiac arrhythmia. Serotonin and norepinephrine reuptake inhibitors are a good alternative to NSAIDs and opioids due to their ability to raise the pain threshold with a lower side effect profile; for example, duloxetine can be effective and is generally well tolerated. There is insufficient data on the use of antiepileptics for the treatment of pain in patients with dementia [55].

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by the degeneration of alpha motor neurons in the spinal cord, leading to progressive muscle weakness and paralysis. It is caused by a deletion or mutation in the SMN1 gene. SMN1 is responsible for producing a protein called survival motor neuron protein (SMN) in all somatic cells. Although the exact pathogenesis is not known, it is thought to disrupt cellular functions that are unique to motor neurons leading to the selective degeneration of alpha motor neurons in the spinal cord, which results in progressive muscle weakness and paralysis.

SMA is divided into four types based on age of onset and motor function. SMA type 1 (Werdnig-Hoffman disease) is the most severe and most common type, accounting for about 60% of patients with SMA. It manifests during the first 6 months of age with onset of clinical signs including ataxia, hypotonia, symmetrical flaccid paralysis greater in the lower than upper extremities, and the inability to sit unsupported. Most infants with SMA type 1 die before age two due to bulbar dysfunctions and pulmonary complications. SMA type 2 is usually diagnosed between 6 months of age and 2 years. There is often a delay or failure in meeting motor milestones and are unable to walk independently, but patients achieve the ability to sit unsupported. SMA type 3 (Kugelberg-Welander disease) is typically diagnosed after 18 months of age and before 3 years, although it can be diagnosed much later in teenage years. Patients with SMA type 3 usually meet all major motor milestones, including walking independently; however, some may develop proximal muscle weakness and require wheelchair assistance later in life. They may also have scoliosis and joint contractures, and their disease course is usually slowly progressive. SMA type 4 is very rare, and usually is diagnosed in adulthood. It is characterized by mild motor impairments [64].

SMA patients have muscle weakness that can lead to multifactorial causes of pain, including contracture formation, spinal deformity, limited functional mobility, fractures, osteoporosis, and increased risk of pain. The exact pathogenesis of chronic pain in SMA patients has not been widely explored. Qu et al. studied SMA mice models, and found that there was a pronounced increase in response to both noxious and innocuous stimuli correlated with the hyperexcitability of nociceptive neurons in the dorsal root ganglion. They also found significantly elevated levels of norepinephrine which suggested that there may additionally be a peripheral process that induces pain hypersensitivity. Further exploring the pathophysiological mechanisms can guide future therapeutic approaches to treat chronic pain [65].

A study by Lager et al. showed that pain is a frequent problem in adolescents with SMA, affecting up to 71% adolescents with SMA. Pain was most frequently reported in the neck, back, and legs. This was attributed to a number of causes, including history of spinal surgery with continued pain, vertebral compression fractures due to immobility-induced osteoporosis and corticosteroid treatment. Furthermore, profound muscle weakness may contribute to pain as it can increase the total load on the musculoskeletal system; pain was commonly reported to be worse with sitting and relieved with change in position [66]. Another study by Abresch et al. showed that SMA adult patients did not experience pain to the same degree as other slowly progressive neuromuscular disorders despite significant muscle atrophy and deconditioning, and also that there was no increase in pain sensitivity compared to the general population [53].

Supportive care can help reduce disease impact and burden in SMA patients. Since pain can be exacerbated by muscle overuse and weakness, conservative treatment can include finding ways to conserve energy and achieving a balance between activity and rest. Patients may also benefit from electrical wheelchairs that can recline and tilt. Furthermore, therapy to prevent progression of contractures including stretching and orthotics can be beneficial. Orthoses can also help achieve assisted ambulation. Spinal bracing can be helpful for early prevention of scoliosis, while spinal surgery may be required for others [67].

Multiple Sclerosis

Multiple sclerosis [MS] is the most common immune-mediated inflammatory disease of the central nervous system. It affects women more than men (at a rate of more than 2:1) and this gap is increasing for unknown reasons. For the majority of these patients, the average age at onset is between 28–31 years old and is usually a few years earlier in women than men although it varies based on subtype (earlier in relapsing-remitting [25–28, 68] and later in primary progressive [38–40]) [69].

While no single presenting sign or symptom is pathognomonic for MS some are highly characteristic. These signs and symptoms include optic neuritis, headaches, sensory loss, paresthesias, motor dysfunction, ataxia, Lhermitte's sign, bowel and bladder dysfunction, weakness and *pain*. Pain in MS is not very well understood but certain pain syndromes appear more frequently in MS than the general population and warrant further investigation.

The prevalence of pain over the lifetime of a PwMS has been shown to be above 50% and the comorbidity of pain with depression is around 30% suggesting that chronic pain can leave one feeling helpless and depressed. A study of 157 patients showed that more than two-thirds felt they had insufficient pain care by their physicians suggesting that it is also a frequently undertreated condition in PwMS [69].

When treating pain experienced in MS it is important to distinguish a number of factors such as whether the pain is neuropathic or non-neuropathic, sensory or motor and whether the pain is primary or secondary [70]. Keep in mind that it is often not just one or the other, rather a combination of the two especially as the disease progresses over time.

There are 8 main types of pain experienced by PwMS. They are optic neuritis, central neuropathic pain, dysesthetic extremity pain, trigeminal neuralgia, Lhermitte's sign, painful tonic spasms, back and musculoskeletal pain and headaches. Current treatment of pain associated with MS is largely guided by a few RCTs conducted in patients with other central neuropathic pain conditions (post-stroke, SCI). General first line agents are medications such as gabapentin, pregabalin, lamotrigine and TCAs. As a second line, there is evidence for tramadol, opioid analgesics and SNRIs in the treatment of peripheral neuropathic pain [71, 72].

Starting with optic neuritis; MS is the most common cause of inflammation of the optic nerve and occurs in about 50% of individuals at some point during the course of their illness [72]. Most cases of ON occur in women, typically between 20-40 yrs. old, it is usually monocular and develops over hours to days. Treatment for ON is effective and well established with IV methylprednisolone, typically for 3 days followed by PO prednisone taper over 10 days [73].

Central neuropathic pain defined by Osterberg et al. as "if the distribution of pain was consistent with a CNS lesion and a thorough evaluation for nociceptive and peripheral neuropathic pain was negative, including a detailed history and physical exam, focused blood tests, and electrophysiology" [74]. Their study looked at a sample of 364 MS patients, 27.5% had what was considered definite central neuropathic pain, including 18 with trigeminal neuralgia. Of these, 91% had pain at the

time of evaluation, most had constant daily pain and it disproportionately affected the lower extremities. Nearly all patients had abnormal sensory exams, with the most common abnormality being decreased cold sensation, which the authors interpreted as support for the hypothesis that central neuropathic pain in MS patients often results from lesions in spinothalamocortical pathways [74].

Dysesthetic extremity pain (sometimes referred to as central neuropathic extremity pain), is usually a chronic form of pain described as a "burning", typically bilateral, affecting the legs and feet, usually worse at night and can be exacerbated by physical activity [75, 76]. It is thought to be caused by lesions in spinal cord nociceptive pathways affecting the inhibitory function of GABA interneurons, the differentiating factor from central neuropathic pain.

For treating neuropathic pains, the focus is on three targets; reducing CNS activity, enhancing reuptake of serotonin and noradrenaline, and influencing adrenoreceptors. This can be achieved through the action of anticonvulsants, benzodiazepines, baclofen, SSRI's, SNRI's, TCAs and clonidine. Overall evidence is lacking but what does exist, suggests starting with TCAs, then gabapentin/pregabalin and lastly lamotrigine. Should all of those fail to provide relief, the last line is generally opioids.

Trigeminal neuralgia [TN] occurs at roughly 20x the prevalence of the general population and is the presenting symptom of MS in around 14% of cases. Of those with MS who have TN, up to one third are bilateral, they tend to be younger, are less likely to have an ophthalmic nerve distribution and more commonly experience autonomic symptoms including lacrimation, conjunctival injection and rhinorrhea. Treatment of TN is well studied in the general population and carbamazepine or oxcarbazepine are the first line treatment. If initial therapy does not provide adequate relief, alternative medications such as gabapentin, lamotrigine and baclofen have been shown to provide some relief. Surgical interventions following failed medical therapy are available although there is some evidence that surgery may be less effective in PwMS than those without MS [77, 78].

Lhermitte's sign, or more accurately Lhermitte's symptom, is defined as "a transient short-lasting sensation related to neck movement felt in the back of the neck, lower back or other parts of the body". It is associated with MRI lesions in the posterior columns of the cervical spinal cord and is thought to be caused by hypersensitivity of demyelinated cervical sensory axons to stretching [79]. Lhermitte's symptom is generally self-limiting over weeks to months but if it is medically managed, it can be treated in a similar fashion to TN with anticonvulsants as first line agents [80].

Painful tonic spasms [PTS] are referring to a specific type of painful spasm often found in PwMS. Studies have shown that in patients with PTS, they usually occur several times per day, last a couple of minutes, can be triggered by touch, movement, hyperventilation or emotions and can even be preceded by what is described as a "somesthetic aura". MRI lesions associated with PTS have been demonstrated throughout the brainstem and spinal cord, and symptoms are thought to be the result of ephaptic spread of spontaneous discharges generated by demyelinated axons [81].

PTS are treated the same as any other condition involving spasticity, usually starting with physical modalities including stretching, ROM exercises, splinting and casting. From here, there are multiple ways to approach medical management of

spasticity. Oral agents include baclofen (GABA B agonist), dantrolene (hydantoin derivative), tizanidine (alpha 2 receptor agonist), gabapentin (voltage gated calcium channel inhibitor), benzodiazepines (GABA A agonist). For more focal spasticity (individual muscle group or joint) chemodenervation may be more effective using Botox or phenol. More generalized spasticity may require intrathecal agents such as baclofen (much more effective for lower extremity spasticity than upper extremity spasticity), clonidine or gabapentin.

Headaches are consistently shown in studies to be more common in PwMS. In one cohort of MS patients, 41% of headaches were migraines (accounting for 22% of the MS patients in the cohort) and the remainder were classified as "muscle contraction headaches". Watkins and Espir found migraine in 27% of MS patients, compared to just 12% of other age and sex matched patients [82]. Keys for migraine management include being mindful of triggers, practicing good sleep habits, losing excess weight, regular aerobic exercise and trying to treat the migraine early (NSAIDs, acetaminophen, triptans, antiemetics). If these fail to achieve an adequate response, it may warrant preventative treatment with beta-blockers, TCAs, anticonvulsants or Botox.

Back and other musculoskeletal pains are under-diagnosed in PwMS. Often in this patient population, back pain is musculoskeletal in nature and a result of prolonged standing or sitting. Musculoskeletal pain is treated similar to how you would manage a patient without MS (PT/OT, physical modalities, exercise, analgesics, lifestyle changes etc.) with a few important caveats. Demyelination makes nerves more vulnerable to heat-related changes so thermoregulation in PwMS becomes more difficult and can lead to Uhthoff's phenomenon (transient worsening of neurologic signs and symptoms in MS, can be physical and cognitive). For this reason, patients should avoid modalities such as hot packs, saunas, hot tubs etc.

This often leads to the question, is it okay for patients with MS to exercise? Yes. Exercise is helpful for PwMS with no evidence for deleterious effects as long as the intensity, duration and frequency are matched with the patient's symptoms, heat tolerance, strength and endurance.

Evidence for MS specific pain management is lacking and much of how we treat it is based on patients with similar pain without MS. What we do know, is that PwMS experience specific pain syndromes at higher rates than the general population. Work with them to find out what they're experiencing, what treatments are providing relief and what are not. Pain can be a huge barrier to quality of life and effective management can breathe new life into an often discouraging disease.

Neurofibromatosis

Neurofibromatosis [NF] is an autosomal dominant disease of the nervous system. There are three distinct types of neurofibromatosis that present differently both clinically and genetically: NF1, NF2 and schwannomatosis. Of the three, NF1 is the most common and is often recognized by its two hallmark features,

café-au-lait spots and neurofibromas. This section will be discussing pain specific to NF1.

Pain location and acuity plays a large role in surveillance of current tumors, new tumors and malignant transformation of known tumors. Because of this, guidelines incorporate changes in pain to their recommendations for new imaging when assessing tumors [83].

Current focus on managing pain in NF1 is on management of symptomatic tumors and is primarily treated with surgery. In a study by Buono et al., all of the 255 patients who participated reported having had at least 1 surgery to remove an NF1 tumor. This is often problematic given the tumors are of nerves themselves, in close proximity to vascular structures, and tumor regrowth is common. Nearly half of the 255 patients experienced complications following surgery including permanent weakness affecting their activities of daily living [84].

The large prevalence of this population utilizing surgery for management of tumor related pain illustrates that it is as or more heavily relied on for relief than medications alone. Neuropathic pain is inevitable and the frequently utilized agents include gabapentin, pregabalin and TCA's. From here the addition of SNRI's and certain anticonvulsants can be trialed. Opioids can be appropriate when disease has progressed beyond the confines of the nervous system, treatment is limited by comorbidities or other options have been exhausted.

While it has been shown by Meldrum that chronic pain symptoms, specifically tumor-related, do not respond well to opioids, medical management with opioids is common in this patient population [85]. One study demonstrated that 17% of patients actively take opioids to manage their pain [86]. When this subgroup was looked at more closely, they reported higher levels of pain and interference with daily life suggesting that opioid induced hyperalgesia may be contributing to the experienced pain.

Some alternative therapies have shown promise when combined with surgical and medical management. Particularly yoga, massage therapy and physical therapy have shown efficacy with improving pain thresholds [87]. Multiple studies looking at populations with similar pain prevalence and symptoms have shown that complementary therapies can be effective in reducing both chronic and acute pain [88]. Psychology plays an often understated role in the experience of pain and should always be incorporated into the treatment plan. Helping manage expectations, anxiety and future potentials is vital to helping guide patients through their disease.

References

1. Antonini A, Tinazzi M, Abbruzzese G, Berardelli A, Chaudhuri KR, Defazio G, et al. Pain in Parkinson's disease: facts and uncertainties. Eur J Neurol. 2018;25(7):917–e69.
2. Rana AQ, Kabir A, Jesudasan M, Siddiqui I, Khondker S. Pain in Parkinson's disease: analysis and literature review. Clin Neurol Neurosurg. 2013;115(11):2313–7.
3. Qureshi AR, Rana AQ, Malik SH, Rizvi SFH, Akhter S, Vannabouathong C, et al. Comprehensive examination of therapies for pain in Parkinson's disease: a systematic review and meta-analysis. Neuroepidemiology. 2018;51(3–4):190–206.

4. Ford B. Pain in Parkinson's disease. Clin Neurosci (New York, NY). 1998;5(2):63–72.
5. Rukavina K, Leta V, Sportelli C, Buhidma Y, Duty S, Malcangio M, Chaudhuri KR. Pain in Parkinson's disease: new concepts in pathogenesis and treatment. Curr Opin Neurol. 2019;32(4):579–88.
6. Quittenbaum BH, Grahn B. Quality of life and pain in Parkinson's disease: a controlled cross-sectional study. Parkinsonism Relat Disord. 2004;10(3):129–36.
7. Todor DR, Mu HT, Milhorat TH. Pain and syringomyelia: a review. Neurosurg Focus. 2000;8(3):1–6.
8. Hatem SM, Attal N, Ducreux D, Gautron M, Parker F, Plaghki L, Bouhassira D. Clinical, functional and structural determinants of central pain in syringomyelia. Brain. 2010;133(11):3409–22.
9. Milhorat TH, Kotzen RM, Mu HT, Capocelli AL Jr, Milhorat RH. Dysesthetic pain in patients with syringomyelia. Neurosurgery. 1996;38(5):940–7.
10. Zorowitz RD, Smout RJ, Gassaway JA, Horn SD. Usage of pain medications during stroke rehabilitation: the post-stroke rehabilitation outcomes project (PSROP). Top Stroke Rehabil Fall. 2005;12(4):37–49.
11. Bowsher D, Leijon G, Thuomas KA. Central poststroke pain: correlation of MRI with clinical pain characteristics and sensory abnormalities. Neurology. 1998;51:1352–8.
12. Garcia-Larrea L, Perchet C, Creac'h C, Convers P, Peyron R, Laurent B, et al. Operculo-insular pain (parasylvian pain): a distinct central pain syndrome. Brain. 2010;133:2528–39.
13. Berthier M, Starkstein S, Leiguarda R. Asymbolia for pain: a sensory-limbic disconnection syndrome. Ann Neurol. 1988;24:41.
14. Hong JH, Bai DS, Jeong JY, Choi BY, Chang CH, Kim SH, et al. Injury of the spino-thalamocortical pathway is necessary for central post-stroke pain. Eur Neurol. 2010;64:163–8.
15. Lumer ED, Edelman GM, Tononi G. Neural dynamics in a model of the thalamocortical system. I. Layers, loops and the emergence of fast synchronous rhythms. Cereb Cortex. 1997;7:207–27.
16. Borsook D, Becerra L, Hargreaves R. Biomarkers for chronic pain and analgesia part 1: the need, reality, challenges, and solutions. Discovery Med. 2011a;11:197–207.
17. Seghier ML, Lazeyras F, Vuilleumier P, Schnider A, Carota A. Functional magnetic resonance imaging and diffusion tensor imaging in a case of central poststroke pain. J Pain. 2005;6:208–12.
18. Henry J, Lalloo C, Yashpal K. Central poststroke pain: an abstruse outcome. Pain Res Manag. 2008;13(1):41–9.
19. Yang S, Grabois M, Brian B. Postroke-pain. Pract Pain Manag. 2011;9:5.
20. Koyama S, Katayama Y, Maejima S, Hirayama T, Fujii M, Tsubokawa T. Thalamic neuronal hyperactivity following transection of the spinothalamic tract in the cat: involvement of N-methyl-D-aspartate receptor. Brain Res. 1993;612:345–50.
21. Hansson P. Post-stroke pain case study: clinical characteristics, therapeutic options and long-term follow-up. Eur J Neurol. 2004;11(Suppl 1):22–30.
22. Leijon G, Boivie J. Central post-stroke pain – a controlled trial of amitriptyline and carbamazepine. Pain. 1989;36:27–36.
23. Lampl C, Yazdi K, Röper C. Amitriptyline in the prophylaxis of central poststroke pain. Preliminary results of 39 patients in a placebo-controlled, long-term study. Stroke. 2002;33:3030–2.
24. McQuay HJ, Tramèr M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain. 1996;68:217–27.
25. Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D. Effects of IV morphine in central pain: a randomized placebo-controlled study. Neurology. 2000;58:554–63.
26. Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med. 2003;348:1223–32.
27. Vick PG, Lamer TJ. Treatment of central post-stroke pain with oral ketamine. Pain. 2001;92:311–3.

28. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7.
29. Gordon A. Best practice guidelines for treatment of central pain after stroke. In: Henry JL, Panju A, Yashpal K, editors. Central neuropathic pain: focus on poststroke pain. Seattle: IASP Press; 2007.
30. Backonja MM, Serra J. Pharmacologic management part 2: lesser-studied neuropathic pain diseases. Pain Med. 2004;5(Suppl 1):S49–59.
31. Klockgether T, Lüdtke R, Kramer B, Abele M, Bürk K, Schöls L, et al. The natural history of degenerative ataxia: a retrospective study in 466 patients. Brain. 1998;121:589–00.
32. Rub U, Brunt ER, Deller T. New insights into the pathoanatomy of spinocerebellar ataxia type 3 (Machado-Joseph disease). Curr Opin Neurol. 2008;21:111–6.
33. Teive HAG. Spinocerebellar degenerations in Japan. New insights from an epidemiological study. Neuroepidemiology. 2009;32:184–5.
34. Harding AE. The hereditary ataxias and related disorders. Edinburgh: Churchill Livingstone; 1984. p. 129–65.
35. Durr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. Lancet Neurol. 2010;9:885–94.
36. França MC Jr, D'AbreuA NA, Lopes-Cendes I. Mucle excitability abnormalities in Machado-Joseph disease. Arch Neurol. 2008;65(4):525–9.
37. Johansson J, Forsgren L, Sandgren O, Brice A, Holmgren G, Holmberg M. Expanded CAG repeats in Swedish spinocerebellar ataxia type 7 (SCA7) patients: effect of CAG repeat length on the clinical manifestation. Hum Mol Genet. 1998;7(2):171–6. https://doi.org/10.1093/hmg/7.2.171.
38. Szende A, Williams A, editors. Measuring self-reported population health: an international perspective based on EQ-5D. Budapest: SpringMed Publishing: Euro-Qol Group; 2004.
39. Rossi M, Perez-Lloret S, Doldan L, et al. Autosomal dominant cerebellar ataxias: a systematic review of clinical features. Eur J Neurol. 2014;21(4):607–15. https://doi.org/10.1111/ene.12350.
40. Whaley N, Uitti R. Clumsy gait and leg pain. In: Reich S, editor. Movement disorders: 100 instructive cases. Boca Raton: Taylor & Francis Group; 2008. p. 239–44.
41. Miao X, Wu X, Shi W. Umbilical cord mesenchymal stem cells in neurological disorders: a clinical study. Indian J Biochem Biophys. 2015;52(2):140–6.
42. Chiò A, et al. Pain in amyotrophic lateral sclerosis. The Lancet. Neurology. 2017;16(2):144–57. https://doi.org/10.1016/S1474-4422(16)30358-1.
43. de Tommaso M, Arendt-Nielsen L, Defrin R, Kunz M, Pickering G, Valeriani M. Pain in neurodegenerative disease: current knowledge and future perspectives. Behav Neurol. 2016;2016:7576292.
44. Chiò A, Canosa A, Gallo S, Moglia C, Ilardi A, Cammarosano S, Papurello D, Calvo A. Pain in amyotrophic lateral sclerosis: a population-based controlled study. Eur J Neurol. 2012;19(4):551–5.
45. Caress JB, Ciarlone SL, Sullivan EA, Griffin LP, Cartwright MS. Natural history of muscle cramps in amyotrophic lateral sclerosis. Muscle Nerve. 2016;53(4):513–7.
46. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360–75. https://doi.org/10.1111/j.1468-1331.2011.03501.x.
47. Handy CR, et al. Pain in amyotrophic lateral sclerosis: a neglected aspect of disease. Neurol Res Int. 2011;2011:403808. https://doi.org/10.1155/2011/403808.
48. Miller RG, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2009;73(15):1227–33. https://doi.org/10.1212/WNL.0b013e3181bc01a4.

49. Jimenez-Sanchez M, et al. Huntington's disease: mechanisms of pathogenesis and therapeutic strategies. Cold Spring Harbor perspectives in medicine. 2017;7(7):a024240.
50. Wheelock V. The motor disorder. In: Nance M, Paulsen JS, Rosenblatt A, Wheelock V, editors. A Physician's Guide to the Management of Huntington's Disease. 3rd ed. Huntington's Disease Society of America; 2011. p. 39.
51. Sprenger GP, et al. The prevalence and the burden of pain in patients with Huntington disease: a systematic review and meta-analysis. Pain. 2019;160(4):773–83.
52. Suchowersky O. Huntington disease: management. In: Post TW, Hurtig HI, Eichler AF, editors. UptoDate; 2021.
53. Abresch RT, Carter GT. Assessment of pain and health-related quality of life in slowly progressive neuromuscular disease. Am J Hospice Palliative Care. 2002;19(1):39–48.
54. van Kooten J, Smalbrugge M. Prevalence of pain in nursing home residents: the role of dementia stage and dementia subtypes. J Am Med Dir Assoc. 2017;18(6):522–7.
55. Cravello L, Di Santo S. Chronic pain in the elderly with cognitive decline: a narrative review. Pain Ther. 2019;8(1):53–65.
56. van Kooten J, Binnekade TT. A review of pain prevalence in Alzheimer's, vascular, frontotemporal and lewy body dementias. Dement Geriatr Cogn Disord. 2016;41:220–32.
57. Rajkumar AP, Ballard C. Epidemiology of pain in people with dementia living in care homes: longitudinal course, prevalence, and treatment implications. J Am Med Dir Assoc. 2017;18(5):453.e1–6.
58. Scherder EJA, Sergeant JA. Pain processing in dementia and its relation to neuropathology. The Lancet Neurology. 2003;2(11):677–86.
59. Pickering G, Jourdan D. Acute versus chronic pain treatment in Alzheimer's disease. Eur J Pain. 2006;10:379–84.
60. Zarow C, Lyness SA. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch Neurol. 2003;60:337–41.
61. Song Cao DW. The link between chronic pain and Alzheimer's disease. J Neuroinflammation. 2019;16(204):1–11.
62. Gagliese L, Gauthier LR. Pain, aging, and dementia: towards a biopsychosocial model. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;87:207–15.
63. Benedetti F, Arduino C. Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. Pain. 2006;121(1–2):133–44.
64. D'Amico A, M. E. Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6(71):1–10.
65. Qu R, Yao F. SMN deficiency causes pain hypersensitivity in a mild SMA mouse model through enhancing excitability of nociceptive dorsal root ganglion neurons. Nat Sci Rep. 2019;9(6493):1–15.
66. Lager C, Kroksmark AK. Pain in adolescents with spinal muscular atrophy and Duchenne and Becker muscular dystrophy. Eur J Paediatr Neurol. 2015;19:537–46.
67. Dubowitz V. Muscle disorders in childhood. Philadelphia, PA: W.B Saunders; 1978.
68. Gladstone D, Black S. Overview of current and emerging therapies for acute stroke. In: Henry JL, Panju A, Yashpal K, editors. Central neuropathic pain: focus on Poststroke pain. Seattle: IASP Press; 2007. p. 13–25.
69. Pöllmann W, Feneberg W, Erasmus L-P. Pain in multiple sclerosis--a still underestimated problem. The 1 year prevalence of pain syndromes, significance and quality of care of multiple sclerosis inpatients. The Neurologist. 2004;75:135–40.
70. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. Pain. 2008;137(1):96–111.
71. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Archiv Neurol. 2003;60:1524–34.
72. Finnerup NB, Otto M, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain. 2005;118:289–305.

73. Beck RW, Cleary PA, Anderson MM Jr, Keltner JL, Shults WT, Kaufman DI, Buckley EG, Corbett JJ, Kupersmith MJ, Miller NR, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. New England J Med. 1992;326(9):581–8.
74. Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis: prevalence and clinical characteristics. Eur J Pain. 2005;9:531–42.
75. Solaro C, Brichetto G, Amato MP, Cocco E, Colombo B, D'Aleo A, et al. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. Neurology. 2004;63:919–21.
76. Indaco A, Iachetta C, Nappi C, Socci L, Carrieri PB. Chronic and acute pain syndromes in patients with multiple sclerosis. Acta Sci Neurol (Napoli). 1994;16:97–102.
77. Broggi G, Ferroli P, Franzini A, Pluderi M, La Mantia L, Milanese C. Role of microvascular decompression in trigeminal neuralgia and multiple sclerosis. Lancet. 1999;354:1878–9.
78. Sandell T, Eide PK. The effect of microvascular decompression in patients with multiple sclerosis and trigeminal neuralgia. Neurosurgery. 2010;67:749–53.
79. Kanchandani R, Howe JG. Lhermitte's sign in multiple sclerosis: a clinical survey and review of the literature. J Neurol Neurosurg Psychiat. 1982;45:308–12.
80. Al-Araji AH, Oger J. Reappraisal of Lhermitte's sign in multiple sclerosis. Multiple Sclerosis J. 2005;11:398–402.
81. Spissu A, Cannas A, Ferrigno P, Pelaghi AE, Spissu M. Anatomic correlates of painful tonic spasms in multiple sclerosis. Movement Disord. 1999;14:331–5.
82. Watkins SM, Espir MLE. Migraine and multiple sclerosis. J Neurol Neurosurg Psychiatry. 1969;32:35–7.
83. Stewart DR, Korf BR, Nathanson KL, Stevenson DA, Yohay K, American College of Medical Genetics. Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20:671–82.
84. Buono FD, Grau LE, Sprong ME, Morford KL, Johnson KJ, Gutmann DH. Pain symptomology, functional impact, and treatment of people with Neurofibromatosis type 1. J Pain Res. 2019;12:2555.
85. Meldrum ML, American Medical Association. A capsule history of pain management. J Am Med Assoc. 2003;290:2470–5.
86. Daubresse M, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000–2010. Medical Care. 2013;51(10):870–88.
87. Thomas D-A, Maslin B, Legler A, Springer E, Asgerally A, Vadivelu N. Role of Alternative Therapies for Chronic Pain Syndromes. Curr Pain Headache Rep. May 2016;20(5):1–7.
88. Krebs EE, Bair MJ, Damush TM, Tu W, Wu J, Kroenke K. Comparative responsiveness of pain outcome measures among primary care patients with musculoskeletal pain. Medical Care. 2010;48(11):1007.