Thieme

Pain and Neuropathic Pain in Rheumatic Diseases

Bedeutung des neuropathischen Schmerzes bei rheumatischen Erkrankungen

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ABSTRACT

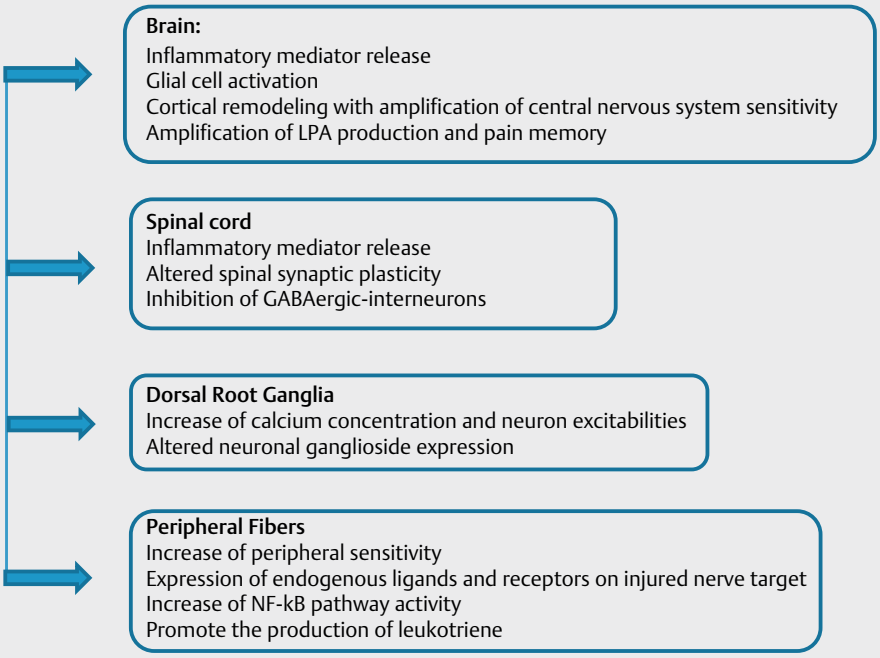
Pain is a challenge to rheumatologists. Not only patients with active arthritis but also patients with a good therapeutic response and even in remission complain of persistent joint pain. It has been proposed that a chronic pain stimulus may have a greater impact in a chronic inflammatory state, and the process towards a pain condition may be influenced by individual predisposition for development of chronic pain. In addition, features of peripheral pain processing may be exacerbated by inflammation, and disturbed pain processing may be a feature contributing to widespread pain. Furthermore, a neuropathic component may be part of the total pain experience of our patients. There are many different strategies of pain therapy in patients with rheumatic diseases, such as pharmacological and non- pharmacological modalities.

ZUSAMMENFASSUNG

Chronische Schmerzen sind eine Herausforderung im Alltag der rheumatologischen Praxis. Nicht nur die Patienten mit aktiver rheumatischen Erkrankungen, sondern auch die Patienten in Remission leiden an Schmerzen. Entzündliche Veränderungen können die individuelle Schmerzempfindlichkeit verstärken. Störungen der peripheren Schmerzregulation führen zur Verbreitung und Verstärkung der Schmerzempfindlichkeit und können als Folge die Persistenz der Schmerzen unterstützen. Bei vielen Patienten mit rheumatischen Erkrankungen und chronischen Schmerzen spielt ein neuropathischer Schmerz eine Rolle bei der Schmerzausprägung. Pharmakologische und nicht pharmakologische Methoden stehen als therapeutische Optionen zur Verfügung.

Introduction

In musculoskeletal diseases, pain is the symptom that weighs the most in disease [1]. In rheumatoid arthritis (RA), studies focusing on patients' reported outcomes highlight the fact that even when the disease seems to be controlled, more than 75 % of patients with RA still report moderate to severe pain. Moreover, more than 60 % of the patients report disappointment with their arthritis pain [2]. Notably, all rheumatic diseases have components of non-inflammatory pain and a higher prevalence of fibromyalgia (FM) compared to the overall population [3]. Hypothetically, a chronic pain stimulus may have stronger impact in a chronic inflammatory state, and the process towards a pain condition may be influenced by individual predisposition for development of chronic pain. In addition, the features of peripheral and central pain processing may be exacerbated by inflammation, and disturbed pain processing may be a feature contributing to widespread pain [4, 5]. There are many different strategies of pain therapy such as pharmacological and non- pharmacological in patients with rheumatic diseases [6, 7]. The approach to reduce pain in clinical trials and practice should be further developed.



▶ **Fig. 1** Pathophysiology of neuropathic pain [21–29]. lysophosphatidic acid (LPA), gamma-aminobutyric acid (GABAergic) interneurons, nuclear factor 'kappa-light-chain-enhancer' (NF-κB).

Terminology of Pain

The present current definition of pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [8]. The note added to this definition adds that, "Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage". Therefore, historically, there have been definitions of potential mechanistic pain terminology. The first mechanistic definition for neuropathic pain was set in 1994 by The International Association for the Study of Pain (IASP) council as "Pain initiated or caused by a primary lesion or dysfunction in the nervous system" [5]. This definition was changed for a new one in 2005 when the nociceptive terminology appeared. Nociceptive pain was defined as "Pain due to stimulation of primary nociceptive nerve endings," and neuropathic pain was defined as "Pain due to lesion or dysfunction of the nervous system". Both definitions were periodically reviewed, and currently, nociceptive pain is a "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors," and neuropathic pain is a "Pain caused by a lesion or disease of the somatosensory nervous system" [2]. This dichotomy between pain mechanistic definitions created a gap for numerous patients without activation of neither nociceptors nor lesion or disease of the nervous system. In rheumatology setting, a large number of patients are concerned: nonspecific back pain, nonspecific peripheral joint pain, FM, and complex regional pain syndrome type 1. Given this situation with 2 descriptors and a large gray area in between, a third descriptor was proposed in 2016 [9]. The new descriptor chosen by the IASP council in 2017 is nociplastic pain. Nociplastic pain that arises from altered nociception despite no clear evidence of threatened tissue damage causing the activation of peripheral nociceptors or evidence of disease or lesion of somatosensory system causing the pain [10]. This choice was supported by abundant literature confirming changes in cerebral activation in once-called "dysfunctional diseases". Another frequently used terminology is the term "mixed pain". The proposed definition of mixed pain by the authors is "Mixed pain is a complex overlap of the different known pain types (nociceptive, neuropathic, and nociplastic) in any combination, acting simultaneously and/or concurrently to cause pain in the same body area. Either mechanism may be more clinically predominant at any point of time. Mixed pain can be acute or chronic. The current definition of mixed pain is a pain with "an overlap of nociceptive and neuropathic symptoms [11]. The patients experiencing mixed pain "showed a greater clinical complexity," had more comorbidities, had more adverse psycho-social factors, and had a lower health-related quality of life. These results were corroborated by a large cross-sectional Spanish study. In the latter, in primary care and orthopedics setting, pain had a mixed component in more than 59 % of the more than 5000 patients [2]. Moreover, patients with mixed pain responded less to treatments and had a higher utilization health care resource. To characterize of different kind of pain may also help defining a better tailored treatment by identifying those who are likely to respond better to centrally rather than to peripherally targeted therapies [2].

Diagnosis of Chronic Pain

Chronic pain interferes with daily functioning and often is accompanied by distress. Yet, pain is not represented systematically. The lack of appropriate codes renders accurate epidemiological investigations difficult and impedes health policy decisions regarding chronic pain such as adequate financing of access to multimodal pain management. In cooperation with the World Health Organi-

zation (WHO), an IASP Working Group has developed a classification system that is applicable in a wide range of contexts, including pain medicine, primary care, and low-resource environments [2]. Chronic pain is defined as pain that persists or recurs for more than 3 months. In chronic pain syndromes, pain can be the sole or a leading complaint and requires special treatment and care. In conditions such as FM or nonspecific low-back pain, chronic pain may be conceived as a disease in its own right (subgroup "chronic primary pain"). In 6 other subgroups, pain is secondary to an underlying disease: chronic cancer-related pain, chronic neuropathic pain, chronic secondary visceral pain, chronic posttraumatic and postsurgical pain, chronic secondary headache and orofacial pain, and chronic secondary musculoskeletal pain. These conditions are summarized as "chronic secondary pain" where pain may at least initially be conceived as a symptom [12]. The 11th version of the existing International Classification of Diseases (ICD-11) is based on so-called content models, which have 13 main parameters. One of them is functioning properties that, according to the WHO, consist of the activities and participation components of the International Classification of Functioning, Disability and Health (ICF). Recently, chronic pain codes were added to the 11th edition of the ICD, and hence, a specific set of functioning properties for chronic pain is required as a link to the ICF. In addition, pain is one of the 7 dimensions of the generic set of the ICF, which applies to any person. Thus, assessment and management of pain are also important for the implementation of the ICF in general. The combined use of ICD-11 and ICF is expected to improve research reports on chronic pain by a more precise and adequate coding, as well as patient management through better diagnostic classification [13].

The new ICD-11 classification introduces the concept of chronic primary and secondary musculoskeletal pain, and integrates the biomedical axis with the psychological and social axes that comprise the complex experience of chronic musculoskeletal pain. Chronic primary musculoskeletal pain is a condition in its own right, not better accounted for by a specific classified disease. Chronic primary pain (CPP) is chosen when pain has persisted for more than 3 months and is associated with significant emotional distress and/or functional disability, and the pain is not better accounted for by another condition. All subtypes of pain diagnosis are considered to be multifactorial in nature, with biological, psychological, and social factors contributing to each. Unlike the perspectives found in Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and ICD-10, the diagnosis of CPP is considered to be appropriate independently of identified biological or psychological contributors, unless another diagnosis would better account for the presenting symptoms. Such other diagnoses are called "chronic secondary pain" where pain may at least initially be conceived as a symptom secondary to an underlying disease [14]. Chronic secondary musculoskeletal pain is a symptom that arises from an underlying disease classified elsewhere. Such secondary musculoskeletal pain originates in persistent nociception in musculoskeletal structures from local or systemic etiologies, or it may be related to deep somatic lesions. It can be caused by inflammation, by structural changes, or by biomechanical consequences of diseases of the nervous system. It is intended that this new classification will facilitate access to patient-centered multimodal pain management and promote research through more accurate epidemiological analyses [15].

The upcoming 11th revision of ICD of WHO offers a unique opportunity to improve the representation of painful disorders. The new classification lists the most common conditions of peripheral neuropathic pain: trigeminal neuralgia, peripheral nerve injury, painful polyneuropathy, postherpetic neuralgia, and painful radiculopathy. Conditions of central neuropathic pain include pain caused by spinal cord or brain injury, poststroke pain, and pain associated with multiple sclerosis. Diseases not explicitly mentioned in the classification are captured in residual categories of ICD-11. Conditions of chronic neuropathic pain are either insufficiently defined or missing in the current version of the ICD, despite their prevalence and clinical importance. Definitions and content models were established in collaboration with the Classification Committee of the IASP's Neuropathic Pain Special Interest Group (NeuPSIG). Up to 10 % of the general population experience neuropathic pain. The majority of these patients do not receive satisfactory relief with existing treatments. A precise classification of chronic neuropathic pain in ICD-11 is necessary to document this public health need and the therapeutic challenges related to chronic neuropathic pain [16]. Further development in classification of pain will facilitate access to patient-centered multimodal pain management and promote research through more accurate epidemiological analyses.

DEFINITION OF PAIN

Nociceptive: Pain due to stimulation of primary nociceptive nerve endings

Neuropathic: Pain caused by a lesion or disease of the somatosensory nervous system

Nociplastic: Pain that arises from altered nociception despite no clear evidence of threatened tissue damage causing the activation of peripheral nociceptors or evidence of disease or lesion of somatosensory system causing the pain

Mixed: Pain is a complex overlap of the different known pain types (nociceptive, neuropathic, and nociplastic) in any combination, acting simultaneously and/or concurrently to cause pain in the same body area. Either mechanism may be more clinically predominant at any point of time.

Neuropathic Pain

Neuropathic pain has been a productive clinical research field over the last 15 years. Studies concerned multiple aspects of these complex chronic pain syndromes including their definition, the elaboration of new diagnostic algorithms, epidemiology and development of specific tools for screening and measurement [17]. Neuropathic pain is characterized by abnormal hypersensitivity to stimuli (hyperalgesia) and nociceptive responses to non-noxious stimuli (allodynia) [18]. Studies in the United Kingdom and France that utilized screening tools to identify neuropathic pain have estimated that 6–8 % of patients with chronic pain experience neuropathic pain in the general population. A single Canadian study that used telephone-based questionnaires for determining neuropathic pain rates estimated a higher (18 %) rate in the general population [19]. In chronic inflammatory rheumatism, the existence of a neuropathic pain component was reported in some studies. In a cohort of 300 patients with RA, 9.3 % had likely/possible neuro-

pathic pain using the painDETECT questionnaire (PD-Q). In the DANBIO registry, more than 7000 patients (with RA, psoriatic arthritis, and other spondyloarthritis) completed PD-Q, and more than 20 % of the patients had likely a neuropathic pain component [2]. Furthermore neuropathic pain are observed in patients with primary Sjögren's syndrome (pSS). Pure sensory neuropathies and, more often, small fibre neuropathies are responsible for neuropathic pain in pSS. This is usually localised in the legs and arms with a characteristic glove or sock distribution [20].

Pathophysiology of Neuropathic Pain

Neuropathic pain arises due to injury of the somatosensory nervous system and is both common and disabling, rendering an urgent need for non-addictive, effective new therapies. Given the high evolutionary conservation of pain, investigative approaches from Drosophila mutagenesis to human Mendelian genetics have aided our understanding of the maladaptive plasticity underlying neuropathic pain. Successes include the identification of ion channel variants causing hyper-excitability and the importance of neuro-immune signaling. Recent developments encompass improved sensory phenotyping in animal models and patients, brain imaging, and electrophysiology-based pain biomarkers, the collection of large well-phenotyped population cohorts, neurons derived from patient stem cells [21].

Although the distinct cause of neuropathic pain has been investigated in primary afferent neurons over the years, pain modulation by central sensitization remains controversial. Neuropathic pain is believed to be driven by cell type-specific spinal synaptic plasticity in the dorsal horn. Upon intense afferent stimulation, spinothalamic tract neurons are potentiated, whereas 'neurotransmitter' called gamma-aminobutyric acid (GABAergic) interneurons are inhibited leading to long-term depression. Growing evidences suggest that the inhibition of GABAergic neurons plays pivotal roles in the manifestation of neuropathic and inflammatory pain states. Downregulation of GABA transmission and impairment of GABAergic interneurons in the dorsal horn are critical consequences after spinal cord and peripheral nerve injuries. These impairments in GABAergic interneurons may be associated with dysfunctional autophagy, resulting in neuropathic pain [22]. The nerve injury of RA can promote the production of leukotriene B4 (LTB4), which act on their receptors, leading to the increased release of pro-inflammatory cytokines, to reduce neuron viability and pain threshold. Moreover, LTB4-BLT1 activation can also increase intracellular calcium concentration and neuron excitability as well as nuclear factor 'kappa-light-chain-enhancer' (NF-κB) pathway activation, which further promote the production of matrix metallopeptidase 9 and chemokine receptor 1. The mutual promotion between LTB4 and neutrophil accumulation accelerates the release of TNF-α and IL-β, which enhance both peripheral and central nerve system sensitisation. LTB4 also involve in the transient receptor potential cation channel subfamily V member 1 (TrpV1) channel activation and modulation of purinergic (P2X3) receptor activation. All above mechanisms contribute to the development of pain [23]. Furthermore in the dorsal root ganglia (DRG), neuro-immune cross talk following peripheral nerve injury is accomplished through the release of extracellular vesicles by neurons, which are engulfed by nearby macrophages. These vesicles deliver several determinants including microRNAs (miRs), with the potential to afford long-term alterations in macrophages that impact pain mechanisms. On one hand the delivery of neuron-derived miR-21 to macrophages for example, polarises these cells towards a pro-inflammatory/pronociceptive phenotype; on the other hand, silencing miR-21 expression in sensory neurons prevents both development of neuropathic allodynia and recruitment of macrophages in the DRG [24]. Moreover there is a growing appreciation of the role of cytotoxic immunity in response to nerve injury, focusing in particular on natural killer cells. There is some evidence for the expression of endogenous ligands and receptors on injured nerve targets and infiltrating immune cells that facilitate direct neuro-immune interactions, as well as modulation of the surrounding immune milieu. A number of chronic pain and peripheral neuropathies appear comorbid with a loss of function of cellular cytotoxicity suggesting such mechanisms may actually help to resolve neuropathic pain. Thus, while the immune response to peripheral nerve injury is a major driver of maladaptive pain, it is simultaneously capable of directing resolution of injury in part through the pathways of cellular cytotoxicity [25]. Gangliosides are one more possible pathophysiological factor of neuropathic pain. Different classes of gangliosides are expressed in nociceptive primary sensory neurons involved in the transmission of nerve impulses evoked by noxious mechanical, thermal, and chemical stimuli. Gangliosides, in particular GM1, have been shown to participate in the regulation of the function of ion channels, such as TRPV1, a molecular integrator of noxious stimuli of distinct nature. Gangliosides may influence nociceptive functions through their association with lipid rafts participating in the organization of functional assemblies of specific nociceptive ion channels with neurotrophins, membrane receptors, and intracellular signaling pathways. Genetic and experimentally induced alterations in the expression and/or metabolism of distinct ganglioside species are involved in pathologies associated with nerve injuries, neuropathic, and inflammatory pain in both human and animals. Genetic and/or pharmacological manipulation of neuronal ganglioside expression, metabolism, and action may offer a novel approach to understanding and management of pain [26]. Furthermore, for years, researchers have examined the role of the N-methyl-D-aspartic acid receptor 2B (NR2B) subunit of N-methyl-D-aspartate receptors (NMDAR) in chronic and neuropathic pain models. This NMDAR subtype can be found in the peripheral and central nervous system and it represents an effective therapy for RA pain management [27]. Moreover through the characterization of various types of peripheral and central neuropathic pain in mice, it was discovered that lysophosphatidic acid (LPA) plays roles in definitive mechanisms of the development and maintenance of neuropathic pain. It was found that LPA_1 receptor- and LPA_3 receptor-mediated amplification of LPA production could be a key mechanism underlying the initiation and maintenance of this pain. Throughout these studies, we found that LPA plays a key role in pain memory, and that LPA_1 receptor- and LPA_3 receptor-antagonists could reverse the established pain, and thereby cure the disease source of pain [28]. Chronicity of neuropathic pain is attributed to increased abundance of inflammatory mediators and ion channel dysfunction leading to afferent nerve sensitization; nerve damage and nerve-glia cross talk have also been implicated [29]. Further development in understanding of neuropathic pain mechanisms will help to identify new possibilities for pain treatment (▶ **Fig. 1**).

PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

- to be driven by cell type-specific spinal synaptic plasticity in the dorsal horn
- impairments in GABAergic interneurons may be associated with dysfunctional autophagy, resulting in neuropathic pain
- nerve injury (for example in patients with RA) can promote the production of leukotriene B4 (LTB4), which act on their receptors, leading to the increased release of pro-inflammatory cytokines, to reduce neuron viability and pain threshold

Diagnosis of Neuropathic Pain

Compared to nociceptive or inflammatory pain, individuals with neuropathic pain suffer from more severe disease, greater costs, and relatively reduced health related quality of life. Direct and indirect costs of neuropathic pain represent a substantial economic burden on the Canadian healthcare system with per patient costs estimated at $2567 (± $2711) per three month care period. While rates of neuropathic pain -associated conditions (e. g., diabetic neuropathy etc) are well documented, rates of neuropathic pain not are difficult to quantify and under-diagnosed. Limitations and lack of standardization of diagnostic methods increase the potential for undetected or poorly classified cases. There is no recognized objective gold standard for assessing neuropathic pain. However, the NeuPSIG of the IASP has set out a grading system that has been used to guide clinical assessment and diagnosis. This approach involves multiple steps including obtaining a clinical history of pain, assessing the neuroanatomical plausibility of pain, using sensory assessments to confirm nervous system involvement, and running diagnostic tests to confirm nervous system lesions or disease. Other less resource intensive methods of diagnosis have been documented and may be especially useful in primary care. These strategies include, but are not limited to neuropathic pain screening tools. These tools are comprised of an interview component and, in some cases, the addition of a brief bedside clinical assessment. Many of these tools have been translated for application in other languages and populations. Improved diagnostic procedures may facilitate improvements in treatment approaches [19].

The Douleur Neuropathique 4 (DN4), IDentification Pain questionnaire (ID Pain), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), PainDETECT (PD-Q), and Neuropathic Pain Questionnaire (NPQ) have been recommended as screening questionnaires for neuropathic pain [30–34]. The DN4 is one of the questionnaires that can be useful in diagnosing neuropathic pain. It has components of how the pain feels to the patient but also requires the examining health professional to assess whether there is reduced sensation (hypaesthesia) to touch or pinprick and whether light brushing increases or causes pain (allodynia). The scale has been widely used since 2005 because of its simplicity. It evaluates neuropathic pain following central and peripheral neurological lesions [30]. ID-Pain is a 6-item questionnaire, with the ability in discriminating neuropathic from nociceptive pain in non-headache chronic pain patients. ID Pain appeared to accurately indicate the presence of a neuropathic component of pain, as a brief, self-administered screening tool [31]. LANSS is based on the analysis of sensory description and bedside examination of sensory dysfunction, and provides immediate information in clinical settings. It was developed in two populations of chronic pain patients with nociceptive and neuropathic pain [32]. PD-Q, a simple and reliable screening questionnaire of neuropathic pain, was developed in 2004 in cooperation with the German Research Network on Neuropathic Pain. The initial aim was to implement quality management and to improve the situation of neuropathic pain patients in Germany with low back pain [33]. NPQ is a 12 item questionnaire to differentiate between neuropathic and non-neuropathic pain groups. These items were able to differentiate neuropathic pain patients from non-neuropathic pain patients in a holdout sample with 66.6 % sensitivity and 74.4 % specificity. Consequently, it can be used for monitoring of neuropathic pain treatments and as an outcome measure [34]. Multivariate analysis of thirty-seven studies of recruited participants from pain clinics was showed that the original version of the DN4 (French) and NPQ (English) had the most number of satisfactory measurement properties. The ID Pain (English) demonstrated satisfactory hypothesis testing and reliability, but all other properties tested were unsatisfactory. The LANSS (English) was unsatisfactory for all properties, except specificity. The PD-Q (English) demonstrated satisfactory hypothesis testing and criterion validity. In general, the cross-cultural adaptations had less evidence than the original versions. Overall, the DN4 and NPQ were the most suitable for clinical use [35]. Furthermore, more than 300 000 patients were assessed by PD-Q, providing the basis for one of the world's largest datasets for chronic pain. Among others, the extensive pool of PD-Q data triggered the idea of subgrouping patients on the basis of their individual sensory profiles which might in future lead to a stratified treatment approach and ultimately to personalized therapy [36] (▶ **Table 1**).

Identifying of neuropathic pain by utilizing screening questionnaires should not replace a thorough clinical and neurophysiological assessment in neuropathic pain conditions [35]. Electrophysiological techniques demonstrate abnormalities in somatosensory transmission, hence providing objective evidence of 'somatosensory lesion or disease' which is crucial to the diagnosis of neuropathic pain. Since most instances of neuropathic pain result from damage to thermo-nociceptive pathways (thin fibres and spino-thalamo-cortical systems), specific activation of these is critical to ensure

▶ **Table 1** Sensitivity and Specificity of Questionnaires [30–34].

Questionnaire	Sensitivity %	Specificity %
The Douleur Neuropathique 4 (DN4)	80	92
IDentification Pain questionnaire (ID Pain)	91.9	97
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)	88.7	76.6
PainDETECT (PD-Q)	85	80
Neuropathic Pain Questionnaire (NPQ)	66.6	74.4

diagnostic accuracy. This is currently achieved using laser pulses or contact heat stimuli, and in a near future probably also with contact cold and intra-epidermal low-intensity currents. Standard electrical stimuli, although of lesser diagnostic yield, are useful when large and small fibres are affected together. Nociceptive evoked potentials to laser (LEPs) and contact heat have shown adequate sensitivity and specificity to be of clinical use in the differential diagnosis of NP, in conditions involving Aδ of C-fibres and spino-thalamo-cortical pathways. LEPs have also a role in the detection of patients at risk of developing central post-stroke pain after brainstem, thalamic or cortical injury. Cognitive cortical responses and autonomic reactions (sympathetic skin responses) reflect pain-related arousal and can document objectively positive symptoms such as allodynia and hyperalgesia. They are of help in the differential diagnosis of somatisation disorders, by discriminating conscious simulation (malingering) from conversive sensory loss. The electrophysiological approach to patients suspected, or at risk, of neuropathic pain is a cost-effective procedure that should never be absent in the diagnostic armamentarium of pain clinics [37]. Microneurography is a neurophysiological technique which enables recording from single peripheral nerve fibres in persons who are awake. Microneurography has contributed to the understanding of pain under physiological conditions and in chronic pain conditions, in particular peripheral neuropathic pain. For example, signs of hyperexcitability have been found in peripheral nerve fibres in connection with neuropathies and peripheral neuropathic pain conditions, and the proportion of hyperexcitable nerve fibres has been shown to be greater in neuropathy patients with chronic pain than in neuropathy patients without pain. Findings indicate that so-called mechano-insensitive C-units nociceptors play an important role in chronic neuropathic pain [38]. The diagnostic evaluation of neuropathic pain includes also histopathologic analysis of nerve tissue, serum studies, and sometimes autonomic testing and cerebrospinal fluid analysis [39].

EPIDEMIOLOGY OF NEUROPATHIC PAIN

6–8 % of patients with chronic pain in the general population
About 20 % patients with chronic inflammatory rheumatism

Neuropathic pain

Screening questionnaires

The Douleur Neuropathique 4 (DN4)
IDentification Pain questionnaire (ID Pain)
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
PainDETECT (PD-Q)
Neuropathic Pain Questionnaire (NPQ)

Neurophysiological assessment

Electroneurography: to verify abnormalities in somatosensory transmission
Nociceptive evoked potentials to laser and contact heat: to determine type of neuropathies
Autonomic reactions (sympathetic skin responses): to document objectively allodynia and hyperalgesia
Histopathologic analysis of nerve tissue: to verify type of neuropathy

Treatment of Neuropathic Pain

Most of the available treatments for neuropathic pain have moderate efficacy and present side effects that limit their use; therefore, other therapeutic approaches are needed for patients [18].

Pharmacological Approach

Recommendations for the pharmacologic management of pain in inflammatory arthritis have been published by the "3e (evidence, expertise, and exchange) initiative," involving 17 nations. The authors based their recommendations on Cochrane Database and other systematic reviews. 3e initiative recommends gabapentin and pregabalin as potential adjuvant treatments that were shown to reduce the release of neurotransmitters in peripheral pain syndromes [40].

The gabapentinoid drugs **(**gabapentin and pregabalin) were originally developed as antiseizure drugs but now are prescribed mainly for treatment of pain. Pregabalin is approved for the treatment of FM in the United States, Japan, and 37 other countries. For gabapentin, the only pain-related indication approved by the US Food and Drug Administration is post herpetic neuralgia. Despite these limited indications, gabapentin and pregabalin are widely prescribed off-label for various other pain syndromes. Such use is growing, possibly because clinicians are searching increasingly for alternatives to opioids. Clinicians who prescribe gabapentinoids off-label for pain should be aware of the limited evidence and should acknowledge to patients that potential benefits are uncertain for most off-label uses [41]. In a meta-analysis of eleven randomized, double-blind, placebo-controlled clinical studies the safety and tolerability profile of pregabalin was addressed. Dizziness and somnolence were the most common adverse events reported. Furthermore, pregabalin in combination with other pharmacotherapies (7 studies) is also efficacious. Post-hoc analyses have demonstrated the onset of pregabalin efficacy as early as 1–2 days after starting treatment, examined the effect of pregabalin on other aspects of sleep beyond quality, and shown it is effective irrespective of the presence of a wide variety of patient demographic and clinical characteristics [42].

Neuropathic pain is a common complication of spinal cord injury. Recent advances have provided evidence of efficacy for 2 promising drugs. Baclofen was able to provide good, long-lasting pain relief. Ziconotide, a voltage-gated calcium channel blocker, was studied in a small trial and was able to provide good analgesia in most participants. However, several participants had to be withdrawn because of worrisome creatine phosphokinase elevations, and further studies are required to define its safety profile [29].

The analysis of efficacy and safety of opioid and nonopioid agents for the neuropathic pain demonstrate that while there are several nonopioid pharmacologic options that are clinically effective, opioids maintain a role in the treatment of certain chronic pain conditions and should continue to have an important place in the armamentarium of clinicians [43].

Milnacipran is a serotonin-norepinephrine reuptake inhibitor that is sometimes used to treat chronic neuropathic pain. To assess the analgesic efficacy and associated adverse events of milnacipran for chronic neuropathic pain in adults a meta-analysis found no difference in pain scores between milnacipran 100–200 mg daily or

placebo after 6 weeks (very low quality evidence). There was no evidence to support the use of milnacipran to treat neuropathic pain conditions [44].

Amitriptyline is a tricyclic antidepressant that is widely used to treat chronic neuropathic and is recommended in many guidelines. To assess the analgesic efficacy of amitriptyline for chronic neuropathic pain a review could include 21 studies (1 437 participants). Doses of amitriptyline were generally between 25 and 125 mg, and dose escalation was common. There was no top-tier evidence for amitriptyline in treating neuropathic pain. The analysis showed that even using this potentially biased data, only about 38 % of participants benefited with amitriptyline and 16 % with placebo; most participants did not get adequate pain relief. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many patients with neuropathic pain or fibromyalgia. There is no good evidence of a lack of effect; rather our concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain, but only a minority of patients will achieve satisfactory pain relief [45].

Experimental Approach

So-called specialized pro-resolving lipid mediators (SPMs) are biosynthesized from the omega-3 fatty acids arachidonic acid, eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid. Despite effective for a fraction of patients with rheumatic diseases and neuropathic pain, current analgesic therapies such as biological agents, opioids, corticoids, and gabapentinoids cause unwanted side effects, such as immunosuppression, addiction, or induce analgesic tolerance. A growing body of evidence demonstrates that isolated SPMs show efficacy at very low doses and have been successively used as therapeutic drugs to treat pain and infection in experimental models showing no side effects. Moreover, SPMs work as immunoresolvents and some of them present long-lasting analgesic and anti-inflammatory effects (i. e. block pain without immunosuppressive effects [46].

Cell based therapies are gaining increasing ground as novel treatment modalities for a variety of pain pathologies that include, but are not limited to, neuropathic pain. A recent review identified studies that use stem cells as a novel therapeutic strategy for neuropathic pain with promising results. However, additional clinical studies will be needed to validate the benefit of the technology for clinical use [47].

Zucapsaicin is a synthetic cis isomer of natural capsaicin that has shown therapeutic efficacy in pain accompanying osteoarthritis of the knee. It is also currently under investigation for the relief of severe pain in adults suffering from neuropathic pain. The mechanism of action and clinical indications of zucapsaicin are similar to that of its naturally occurring isomer, capsaicin. However, in contrast to capsaicin, zucapsaicin is better tolerated. In the future, zucapsaicin could become a valuable drug for treating pain relief. Indeed, it is possible, in addition to providing neuropathic pain relief, that it may have a use in treating osteoarthritic pain [48].

Non Pharmacological Treatment

Non-pharmacological therapeutic options for drug refractory neuropathic pain include the following approaches [49–52]:

- peripheral and central neurostimulation
- physical therapies (e. g., massage, ultrasound, transcutaneous electrical nerve stimulation (TENS), laser, and mirror therapy exercise training)
- psychological therapies (cognitive behavioural therapy (CBT), psychotherapy, and internet-delivered psychological therapies).

The strength of recommendations of such therapies in the treatment of neuropathic pain is inconclusive, and the quality of evidence is low [49]. In particular, there is no data about efficacy such approaches in patients with rheumatic diseases.

A systematic review revealed that exercise therapy combined with psychological therapy (such as mindfulness meditation, and mindfulness-based stress reduction), aerobic exercise (e. g., walking), and Thai Chi (as a strength-stability exercise) showed a moderate effect on the physical activity and quality of life in patients with neuropathic pain [50]. In chronic neuropathic pain conditions, well-designed clinical studies of psychological treatments are lacking. Two small clinical trials on cognitive behavioural therapy and psychotherapy demonstrated insufficient evidence concerning its efficacy and safety in chronic neuropathic pain [51]. Further non-medical interventions include brain sensitization and biofeedback techniques. These methods revealed recently encouraging results. Case reports of non-conventional techniques, such as hypnosis, were also reported [29]. In addition, it has been suggested that the importance of pain rehabilitation techniques will increase over time and that these measurements will play a larger role in the management of neuropathic pain. However, it is now too early to comment on these methods due to the lack of adequate studies [52].

Natural products

A growing interest for the treatment of patients suffering from chronic pain is directed towards pleiotropic natural products. Many substances, such as omega-3 polyunsaturated fatty acids (n-3 PUFA), curcumin, resveratrol, theanine, theafavin derivatives, and α-lipoic acid, can be incorporated into pharmacotherapies to improve therapy outcomes. These compounds, when combined with pharmaceutical drugs, showed improved efficacy and safety in preclinical and clinical studies of neuropathic pain. Treatment with curcumin seems to lessen mechanical allodynia and thermal hyperalgesia through downregulation of TNF-α and TNF-α receptor 1 expression. On the rat model of neuropathic pain, curcumin can markedly alleviate nerve injury-induced neuropathic pain. This analgesic effect may be attributed to the inhibition of astrocyte hypertrophy in the spinal dorsal horn and phosphorylation of the extracellular-signal-regulated kinase signalling pathway [53].

A multimodal management plan in neuropathic pain as well as patient education is essential. Complementary therapies such as physical therapy modalities, rehabilitation techniques etc. are important options and must be considered when pharmacotherapy alone is not sufficient [52].

TREATMENT OF NEUROPATHIC PAIN

- gabapentin and pregabalin as potential adjuvant treatments
- amitriptyline should continue to be used as part of the treatment of neuropathic pain
- no sufficient data about neuropathic pain reduction under DMARDs
- best choice to treat with a combination of multiple therapeutic approaches, which starts with patient education, and the treatments include complementary, medical treatment modalities.

Influence of Antirheumatic Therapy on Pain

Traditional DMARDs

Traditional DMARDs, such as methotrexate, sulphasalazine, and leflunomide, reduce joint pain while suppressing inflammation over several weeks, maintaining these effects over months, and their rapid introduction is recommended by current guidelines, preferably in combination. Many common DMARDs may have some of their adverse effects potentiated by specific analgesic medications; however, a Cochrane systematic review concluded that NSAIDs in combination with methotrexate are generally safe, though recommending appropriate monitoring and avoidance of ASA [54]. In the presence of active disease and pain that is inadequately controlled by methotrexate, addition of a biologic agent may be useful. Biologic agents reduce joint pain in RA by reducing inflammation, decreasing peripheral and central sensitization, and preventing long-term joint damage [53]. There is no data concerning neuropathic pain under DMARDS.

Biologicals (JAK Kinasen)

Chronic pain is nowadays considered not only the mainstay symptom of rheumatic diseases but also "a disease itself" [53]. Cytokines and their receptors are constitutively expressed by and act on neurons in the central nervous system, in both its normal and its pathological state. The binding of cytokines to these receptors induces homo- or hetero-dimerization of receptors and triggers activation of intracellular signalling cascades then alter cell functions. This may include the upregulation and/or downregulation of several genes and their transcription factors, resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition [55]. In the last years, the the Janus Kinase-Signal Transducer, Activator of Transcription (JAK-STAT) pathway has been recognized as a pivotal component both in the inflammatory process and in pain amplification in the central nervous system [53]. They signal through a gp130 receptor complex that activates JAK-STAT and Mitogen-Activated Protein Kinase (MAPK) Signal Transduction pathways. Cytokines and other products of the immune cells can modulate the action, growth, differentiation, and survival of neuronal cells, while the neurotransmitter and neuropeptide release play a pivotal role in influencing the immune response. Accumulating evidence indicates that the latent transcription factors, STAT, play an essential role in cytokine signaling pathways. Astrocytes and microglia are the major source of IL-6 and IL-6 members in nervous system, a process which requires stimulatory effect by different factors such as cytokines, PGE2 and neurotransmitters. Neurons can also bind these cytokines and initiate signaling [55]. Many of the key cytokines use the JAK-STAT pathway to exert their effects rendering them amenable to therapeutic blockade with JAK inhibitors. Given the apparent pathogenic role of a variety of cytokines like IL-6, IL-12, IL-23, interferons, and GM-CSF in RA and other autoimmune diseases, the ability of JAK inhibitors to block such cytokines is likely a major aspect of their mechanism of action. Next to the already existing tofacitinib, baricitinib and upadacitinib, a number of other JAK inhibitors are currently in development for the management of RA, with differing in vitro specificities towards the various members of the JAK family [56]. Tofacitinib is so far the most extensively studied JAK inhibitor, and its effect on the clinical and laboratory measures of RA (ACR20, ACR50, ACR70, DAS28, etc.) is well documented in reviews and meta-analyses [57]. The results show a significant reduction in RA patients' assessment of pain with tofacitinib compared to placebo. Some patients report pain relief within the first 24 h of JAK inhibitor administration, well before a demonstrable effect on inflammation. Data on the patients' assessment of pain and/or patient's global assessment (PtGA) of the disease are available from further seven clinical studies. Tofacitinib, administered 5 mg bid, was associated with a 45–54 % improvement in the patients' assessment of pain and a 44–60 % improvement in PtGA, while placebo resulted in less improvement (29 % for pain and 39 % for PtGA). Overall, it can be concluded that patients' assessment of pain and disease demonstrate that tofacitinib is more effective than placebo [58]. Adalimumab was associated with 30–32 % improvements in patient's assessment of pain and global assessment of disease, which are lower than those seen with tofacitinib 5 mg bid [59]. In addition, for baricitinib) as well as for upadacitinib pain was chosen as an important outcome parameter. Clinical studies for better compounds demonstrated the incremental number needed to treat with JAK-Inhibitores to report clinically meaningful improvement from baseline ranged from 4 to 8 patients [58, 60]. Further studies are needed to verify mechanisms of peripheral and central pain reduction under various DMARDs.

Conclusions

Pain is still a great challenge today. Not only definition of pain but also the pathophysiologic understanding of different types of pain are in development. It was proposed that a chronic pain stimulus may have stronger impact in a chronic inflammatory state, and the process towards a pain condition may be influenced by the individual predisposition for development of chronic pain. In addition, features of peripheral pain processing may be exacerbated by inflammation, and disturbed pain processing may be a feature contributing to widespread pain. In daily practice it is useful and not complicate to determine the presence of neuropathic pain in patients with rheumatic disease with the help of a suitable questionnaire. The strategy of pain therapy should take into account the pain phenotype to achieve the best possible result for our patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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