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CONTENTS

Polyneuropathy in Rheumatoid Arthritis (literature review)

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Abstract. Rheumatoid arthritis is the most common rheumatological disease. In addition to joint pathology, it often causes damage of other organs and tissues. This article discusses the possibility of diffuse damage of the peripheral nervous system in rheumatoid arthritis - frequency, mechanisms of damage, peculiarities of the clinical symptoms. The relevance of this problem is due to the possibility of subclinical course of polyneuropathy in rheumatoid arthritis, and, consequently, the lack of diagnosis, while one of its variants - autonomic neuropathy, is a life-threatening pathology. In the presence of pain in the clinical picture of polyneuropathy, problems arise in its interpretation (neuropathic, nociceptive - joint pain), and, therefore, errors in dose adjustment of disease-modifying drugs are possible. For neurologists the problem of polyneuropathy in rheumatoid arthritis is interesting from the point of view of diagnosing the etiology of this disease, which is always a difficult task.

Keywords: rheumatoid arthritis, polyneuropathy, digital images.

1. Introduction

Rheumatoid arthritis (RA) is an immune-inflammatory (autoimmune) rheumatic disease characterized by progressive destruction of joints and damage of internal organs, the development of which is determined by a complex interaction of environmental factors and genetic predisposition, leading to global disturbances in the humoral and cellular immunity system [1]. The diversity of pathogenetic mechanisms of RA leads to the presence of various phenotypes and endotypes of the disease, which allows it to be considered not as "one disease", but as a clinical and immunological syndrome [2]. With the unconditional predominance of systemic autoimmune inflammation processes in the synovial membrane of the joints in RA there are also various extra-articular (systemic) manifestations: rheumatoid nodules, cutaneous vasculitis and vasculitis of other organs, neuropathy (mononeuritis, polyneuropathy - PNP), pleurisy and pericarditis, myocarditis, Sjogren's syndrome, eye damage, interstitial lung disease, generalized myopathy, damage to the blood system [3]. These seemingly minor manifestations often can play a leading or significant role in the clinical picture of the disease. This fully applies to polyneuropathy, although its presence in RA is not mandatory. The central place in the clinical picture of RA, of course, is occupied by pain, the source of which is joint inflammation and pathology of extra-articular soft tissues. However, rheumatologists often point out that the severity of pain does not correspond to the severity of inflammation. This circumstance can be explained by the chronic nature of the pain syndrome, which leads to the transformation of noci- and antinociceptive mechanisms with the formation of peripheral and central sensitization and gives pain an individual

character in each specific case [4, 5]. In addition, a number of researchers note that the characteristics of pain in RA do not always correspond to nociceptive pain and can acquire neuropathic features [6]. In this case, the question naturally arises about the possibility of developing PNP in RA (in addition to the well-known mononeuropathies and carpal tunnel syndrome) [7]. This issue is extremely important for the treatment of patients with RA, since an incorrect interpretation of pain can lead to both an unjustified escalation of cytostatic therapy and to the ineffectiveness of pain syndrome treatment. As for neurological diseases, the main problem of any PNP is to determine its cause, which is only possible in 50% of patients [8, 9]. If a patient suffers from RA, can this explain the PNP he has? To answer this question, we need to know the following: do PNP develop in patients with RA and what clinical features do they have?

2. Objective of the study

Objective of the study is to characterize the possibility of developing PNP in RA and describe its main clinical characteristics.

3. Research data and methodology

Four databases (PubMed, MEDLINE, Web of Science, and Scopus) were searched for systematic reviews, case reports, and clinical studies concerning the combination of PNP and RA.

4. Results

There are few data on the possibility of PNP development in RA in the current literature. The available data on the frequency of PNP in RA vary considerably - it can be registered in 10.81% - 75.28% of patients [10]. That, apparently, depends on the method of diagnosis, duration of the disease [11] and variability of selection criteria; the assessment of prevalence is additionally complicated by a large proportion of asymptomatic patients. In particular, Agarwal V. et al., 2006 [12], examining 108 patients with RA, found clinical signs of PNP in the form of paresthesias in the limbs - in 23, decreased vibration sensitivity - in 9, decreased or absent tendon reflexes - in 28, electrophysiological - in 62, mainly in the form of signs of axonal lesions (only in 9 - demyelination). 23 biopsies of the calf nerve were performed and perineural thickening (n = 5, amyloid deposits n = 4), infiltrate of periva-vascular lymphomononuclear cells (n = 4), loss of myelinated fibers (n = 2) and necrotizing vasculitis (n = 1) were detected. No reliable conclusions about the pathogenesis of the detected disorders were made, as there was no association of neuropathy with RA duration, seropositivity, joint erosions and deformities, previous intake of disease-modifying drugs, and disease activity [12]. The authors suggested the vascular nature of PNP or the consequence of drug toxicity of anti-rheumatic drugs.

Bayrak A.O. et al., 2010 [13], having examined 60 patients with RA, revealed electrophysiological signs of PNP in 10 of them. Two patients had mild symmetrical sensory neuropathy and eight had mild symmetrical sensorimotor PNP, in all cases - axonal. The development of PNP was associated with a long course of the disease, high scores on the DAS28 (Disease Activity Scale for Rheumatoid Arthritis) [14], NSS (Neuropathy Symptom Scale) [15]. There was no connection with rheumatoid factor, therapy or joint deformation. There are data from a comprehensive Chinese survey [16] of 834 patients with RA, in which clinical signs of peripheral nervous system damage were detected in 51 (6%), including PNP in 28, ENMG examination was performed on 44 patients. All patients with PNP had sensory disturbances characteristic of peripheral nervous system damage (most often a feeling of numbness), including neuropathic pain. Motor disturbances (amyotrophy,

hyporeflexia) were less common. Comparison of various parameters of patients with PNP with similar parameters of patients without peripheral nervous system damage, as well as with patients with multiple peripheral nervous system damage, showed more pronounced parameters of inflammatory status (high levels of leukocytes, platelets, ESR, CRP and rheumatoid factor), but a lower level of albumin. According to the researchers, the most probable mechanism of the development of PNP in patients with RA was vasculitis vasa nervorum, which is part of generalized vasculitis in RA. The assumption about such a mechanism for the development of PNP in RA was made by Weller R.O. et al. back in 1970 [17]. These same authors noted the axonal nature of damage of the peripheral nervous system in RA.

Similar data about the relationship between PNP in RA and rheumatoid factor were obtained by Ding Y.Q. et al. (2021), who, comparing 46 patients with RA with PNP and 92 patients with RA without PNP, found that in the presence of PNP the rheumatoid factor ($p = 0.001$) was higher. They also supported the point of view to the mechanism of damage of the peripheral nervous system in RA mediated by generalized vasculitis, including vasa nervorum vasculitis, since in the group with PNP, the percentage of cutaneous vasculitis ($p = 0.042$) was higher [18]. The study with the selection of a specific contingent of patients is of interest - 51 people with diagnosed RA and foot deformity. Demographic and clinical characteristics of patients were recorded, and a detailed neurological examination was carried out. Surface sensation, pain, heat, vibration, and discrimination sensitivity were assessed in each foot, and their sum was used to determine the sensory deficit index (SDI) from 0 to 10. The presence of SDI was assessed by electrophysiological methods. Impaired sensitivity during examination was detected in 39 patients (74%); in 27 patients (52.9%) SDI was determined electrophysiologically. Patients with sensory deficit were found to have a statistically significant deterioration in the general health and functional capabilities of the foot, including mobility and walking, compared with patients with normal sensory function. Thus, PNP makes a significant contribution to the clinical picture of the disease in patients with RA [19]. In the study of Kaeley N. et al., 2019 [20] 89 patients with RA were examined, 75.28% ($n = 67$) of them had PNP revealed electrophysiologically (always axonal), while 20.89% (14 patients out of 67) had clinical disturbances of superficial sensitivity. There are studies in which PNP was detected in 39.19% of patients with RA [21] and in 33% [22].

Summarizing these data with the results of the other studies we can note the main features of PNP in RA: it can occur both clinically obvious and subclinically [23, 24], some patients may not have it. Neuropathy mainly occurs in seropositive patients [25] at late stages of the disease [26], accompanying other extra-articular manifestations such as rheumatoid nodules and purpura. Motor PNP in RA is rare [27, 28], the number of observations is small and does not provide reliable information about its nature, however, it is known that it can be acute or subacute, and the possibility of its occurrence indicates a variety of mechanisms of the development of PNP in RA [29]. By the nature of the clinical symptoms, PNP in RA is most often sensory [29], with mainly superficial sensitivity affected, its decrease is often accompanied by neuropathic pain. By the nature of the damage, the PNP in RA is most often axonal [30]. Thus, PNP in RA could be classified as a neuropathy of small fibers in the presence of damage of the autonomous peripheral formations. And there are such studies proving the presence of autonomic neuropathy (AN) in patients with RA. However, the data from such studies are poorly comparable with each other and do not meet modern methodological requirements for a comprehensive assessment of the autonomic nervous system using 5 standard tests (changes in heart rate during slow deep breathing, Valsalva test, orthostatic test, 30:15 test, isometric load test) [31], or by studying heart rate variability [32], pharmacological tests, as well as specific methods that reveal autonomic dysfunction in the gastrointestinal, urogenital, and respiratory systems [33]. Most studies used only one of the indicators, as a result,

the data on the state of the AN in patients with RA are not very representative. There is a systematic review by Adlan A.M., 2014 [34], which, based on the analysis of 40 studies, concludes that 60% of patients with RA have autonomic dysfunction with a decrease of parasympathetic activity and an increase of sympathetic activity of the autonomic nervous system, the same review notes the insufficient data to determine the cause-and-effect relationships between inflammation and dysfunction of the autonomic nervous system in RA. A meta-analysis of 35 studies of heart rate variability in patients with RA and spondyloarthritis [35] showed the presence of cardiac AN with a decrease of parasympathetic influences in this category of patients, and the indicators of autonomic dysfunction were associated with markers of inflammation. Most of these studies examined ESR and/or CRP, with one article [36] reporting an inverse association between serum IL-6 and autonomic dysfunction. Most studies, with the exception of one [37], found no association between RA duration and AN values. These results suggest that inflammation in RA plays a greater role in the development of AN than disease duration [35]. In summary, RA is one of the most common causes of small fiber PNP, yet in most patients with RA, AN is not assessed and, therefore, the diagnosis of small fiber PNP is not established [38,40]. The use of skin biopsy to measure intraepidermal nerve fiber density is probably the most widely used and studied method for diagnosing small fiber PNP and should be kept in mind in clinical practice [40].

The pathogenesis of immune axonal neuropathies, including those in RA, is complex [41, 42]. The vital activity of peripheral nerves is provided both by neuronal bodies due to axonal transport and by blood vessels, the latter being especially important for nerves with long axons [43]. The complex structural and functional organization of the vasa nervorum in combination with the low pliability of the perineurium, which prevents an increase of endoneurial volume, may explain the vulnerability of peripheral nerves to a slight increase in capillary permeability: endoneurial edema sharply increases hydrostatic pressure and leads to vascular compression and subsequent decrease in blood flow and ischemia [44]. Systemic vasculitis, including those in RA, can involve the vasa nervorum (Figure 1) [45].

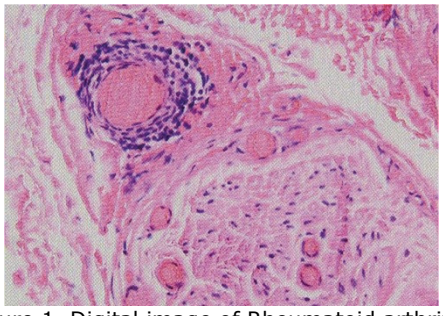

Figure 1. Digital image of Rheumatoid arthritis.

As shown on Figure 1, biopsy of the calf nerve reveals perivascular inflammation of epineural vessels and scattered perineural and endoneural dilated capillaries with thickened walls. Paraffin section stained with hematoxylin and eosin [45].

Inflammatory damage of the vessel walls, their thrombosis, limit blood flow, causing nerve ischemia [45]. A pathogenetic model with the following sequences has been proposed: autoreactive T-cells are recruited to the peripheral nervous system, recognize antigens presented by macrophages, endothelial cells and Schwann cells, undergo activation by cell adhesion molecules and chemotactic cytokines and ultimately mature or recruit cytotoxic T-cells, which mediate the destruction of vessel walls [46]. Although humoral immune mechanisms are of lesser importance, they also contribute to vasculitis of the vasa nervorum, as evidenced by deposits of

immunoglobulin and complement in the walls of epineurium vessels, implying either in situ formation of immune complexes or deposition of immune complexes with subsequent activation of the complement system and recruitment of phagocytes [47]. Nerve biopsy is indicated whenever there is a high suspicion of vasculitis but there is no confirmatory evidence from other paraclinical tests [48]. The classic histopathological findings of vasculitic neuropathy are: inflammatory infiltration of the vasa nervorum with wall destruction, fibrinoid necrosis of the sheath with fragmentation of the internal elastic lamina, and centrofascicular axonal degeneration. In older lesions, fibrinoid necrosis is replaced by extensive fibrosis, but inflammatory cells are still present at the periphery [49].

In addition to vasa nervorum vasculitis, which leads to ischemic damage of the axon in patients with immune axonal neuropathy, direct damaging mechanisms are also involved - immune, inflammatory and metabolic [50,51,52,53], that is, there is direct damage of nerve axons by cytokines [54], antibodies [55] or cytotoxic cells [56].

As for drug-induced PNP in RA, judging by the literature, it is unlikely. It is known that toxic PNP that occur under the influence of chemotherapy in [57]. Those drugs that are used to treat RA do not damage the peripheral nervous system. The most common disease-modifying drug used in RA is methotrexate. PNP is not in the list of side effects of this drug. The study by Muanda FT et al. [58], based on the analysis of treatment of 6909 elderly people with RA, showed that the structure of adverse events does not include damage of the peripheral nervous system. Other cytostatics used to treat RA (leflunomide, sulfasalazine) also do not cause PNP [2]. Monoclonal antibodies for the treatment of RA also do not have PNP in the list of adverse events [59]. The exception is anti-TNFα drugs, which very rarely, but can contribute to demyelination, but not of the peripheral, but of the central nervous system [60]. And only in the work of Delcoigne B. et al [61] there is an indication of the possibility of demyelination of the peripheral nervous system during the treatment of RA with anti-TNFα drugs (they observed a total of 179 neuroinflammatory events over 267,314 person-years, including PNP in the form of Guillain-Barré syndrome, chronic inflammatory demyelinating PNP and multifocal motor neuropathy).

5. Conclusions

In summary, current evidence suggests that PNP, overt or subclinical, is common in RA patients, particularly in seropositive, and in the late stages of the disease. It is often axonal and sensory in its clinical manifestations, often - small fiber PNP. Dysfunction of the ANS is a feature of PNP in RA, although it does not occur in all patients. The profile of autonomic nervous system dysfunction found in RA patients (reduced parasympathetic and increased sympathetic activity) is associated with an increased risk of cardiovascular disease and mortality. Further studies are needed to determine the true prevalence of AN in RA, to characterize RA patients with impaired autonomic nervous system function, and to determine the prognostic role of autonomic nervous system assessment in predicting cardiovascular and mortality risk in RA patients. The mechanisms of PNP damage in RA are vasculitis and direct inflammatory autoimmune reactions. Thus, knowledge of the possibility of developing of PNP in RA and understanding its pathogenesis will allow us to adequately assess the clinical picture of the disease and make adjustments to therapy.

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