

REVIEW

Neurological Manifestations in Rheumatoid Arthritis: Scoping Review

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Introduction: Rheumatoid arthritis (RA) often presents with significant neurological complications, including peripheral neuropathy, central nervous system (CNS) vasculitis, cervical myelopathy, and cognitive impairments. These manifestations arise from systemic inflammation and autoimmune mechanisms that damage the nervous system, posing serious risks to patient prognosis. This scoping review aimed to synthesize existing literature on neurological manifestations in RA, focusing on their prevalence, underlying mechanisms, and therapeutic approaches.

Methods: Using a systematic methodology, relevant studies were identified from databases including PubMed, Scopus, and ProQuest. Articles published between 2020 and 2024 were selected based on specific inclusion and exclusion criteria.

Result: The findings reveal that neurological complications in RA range from peripheral neuropathy, affecting up to 50% of patients, to severe conditions like cerebral vasculitis and rheumatoid meningitis. Cognitive impairment, reported in approximately 31% of patients, highlights the long-term burden of the disease. Early diagnosis and tailored therapeutic interventions, such as immunomodulatory therapies, are critical to mitigating these impacts.

Conclusion: This review underscores the need for further research to bridge existing knowledge gaps, develop effective diagnostic tools, and improve management strategies for neurological complications in RA. Comprehensive understanding and multidisciplinary approaches are essential for enhancing patient outcomes and quality of life.

Keywords: Central Nervous System Vasculitis, Cervical Myelopathy, Neurological Manifestations, Peripheral Neuropathy, Rheumatoid Arthritis.

INTRODUCTION

The hallmark of rheumatoid arthritis (RA) is symmetrical, gradual joint deformity brought on by synovial proliferation and the ensuing erosion, laxity, and inflammation. Between 0.8%

and 1% of people globally have RA, and women are twice as likely as males to have it. The condition has a complex origin, and there is some indication that it is heritable. RA can be

diagnosed using criteria published by the American College of Rheumatology¹.

Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects the joints and causes inflammation and tissue damage². However, RA is also known to have various extra-articular manifestations³, including those affecting the nervous system. Neurological manifestations of RA may include peripheral neuropathy, cervical myelopathy, central nervous system vasculitis, and cranial nerve involvement⁴.

Recent studies have shown that neurological manifestations in RA are more common than previously thought. Peripheral neuropathy⁵ is the most common neurological complication, with a prevalence of approximately 10-50% among RA patients. These manifestations often arise as a result of vascular inflammation and direct damage to nerve fibres. In addition to peripheral neuropathy, central nervous system (CNS) vasculitis and spinal cord involvement, such as cervical myelopathy due to atlantoaxial instability, are also reported as complications that require immediate medical attention⁶.

Rheumatoid arthritis has a prevalence of about 0.8% to 1% globally and is more common in women than men⁷. Neurological complications in RA patients generally appear in the advanced stages of the disease and often involve the peripheral nervous system. However, there is also evidence that many RA patients may experience subclinical neuropathy⁸, which suggests that the true prevalence of neurological complications may be higher than documented. Neurological manifestations in RA are diverse and are often related to the severity of the disease as well as the underlying systemic inflammatory process⁹. Although peripheral neuropathy is the most common complication, spinal cord

involvement and vascular risks such as stroke also need to be recognised as they can have a significant impact on patient prognosis³. Early detection and aggressive intervention are essential to prevent more severe complications¹⁰.

Although these neurological complications can significantly affect patients' quality of life, information regarding the prevalence, types, and pathophysiological mechanisms underlying these conditions is still limited and scattered in separate studies. Therefore, a systematic study is needed to collect and synthesis information on the neurological manifestations of RA from various existing literatures.

This study aimed to conduct a scoping review to identify and map the available literature on neurological manifestations in patients with RA. The purpose of this scoping review is to gather information on the types, prevalence, and pathophysiological mechanisms of neurological manifestations of RA as well as interventions that have been reported in the literature. By conducting this mapping, this study is expected to identify knowledge gaps in research and clinical practice related to neurological complications of RA, as well as provide guidance for further research or development of clinical guidelines.

METHOD

This study used a scoping review design to map the literature and summarize findings on neurological manifestations in rheumatoid arthritis (RA) patients. The research procedure included collection and selection of studies based on inclusion criteria, extraction of data into structured tables, and analysis and synthesis of findings to obtain a comprehensive overview. The study population consisted of all studies on

RA and neurological manifestations published in scientific journals. The study sample included relevant articles found on databases such as PubMed, Scopus and ProQuest. The records were excluded based on specific criteria to ensure relevance and consistency with the research objectives. Only studies written in English were considered to maintain comprehensibility. The research specifically focuses on studies involving humans, excluding those centered on non-human subjects or purely theoretical work. The fields of interest are medicine and neuroscience, aligning with the primary scope of the study. Furthermore, only original articles and reviews were included to ensure the analysis is based on primary research findings. Lastly, the studies must be available as free full text, allowing unrestricted access to the complete content for thorough review and analysis. This approach ensures a targeted and comprehensive dataset for the research. The sampling technique used was purposive sampling, which selected relevant studies based on inclusion and exclusion criteria.

Data collection was conducted through three main steps. Firstly, a literature search was conducted using keywords such as 'Rheumatoid Arthritis' and 'Neurological Manifestations' to find relevant articles in the database. Second, study selection was performed using Mendeley to organize the articles found. Thirdly, data extraction was performed using a form that recorded important information from each article, such as author's name, year of

publication, research methods, and main findings.

The data obtained was analyzed thematically to identify the main themes that emerged from the literature reviewed. The results of the analysis were compiled in a narrative form that included comparisons between studies, in-depth explanations, and identification of research gaps. The results of this scoping review are expected to provide guidance for future research, including outputs in the form of a final report and additional contributions if needed.

RESULT

A total of 284 initial records were identified through searches in various databases, namely Scopus (88 records), PubMed (38 records), and ProQuest (158 records). Prior to the screening process, 151 records were automatically removed as they did not fulfil the inclusion criteria, such as publication period (2020-2024), article language (English), field coverage (medicine and neuroscience), article type (original article or review), and free full-text access. This left 133 records for the screening process.

After the screening process, 124 records were excluded due to irrelevant titles. Of the 9 reports considered for retrieval, 4 reports were excluded due to duplication. Next, 5 reports were evaluated for eligibility, and all met the criteria. Finally, a total of 5 studies were included in the review.

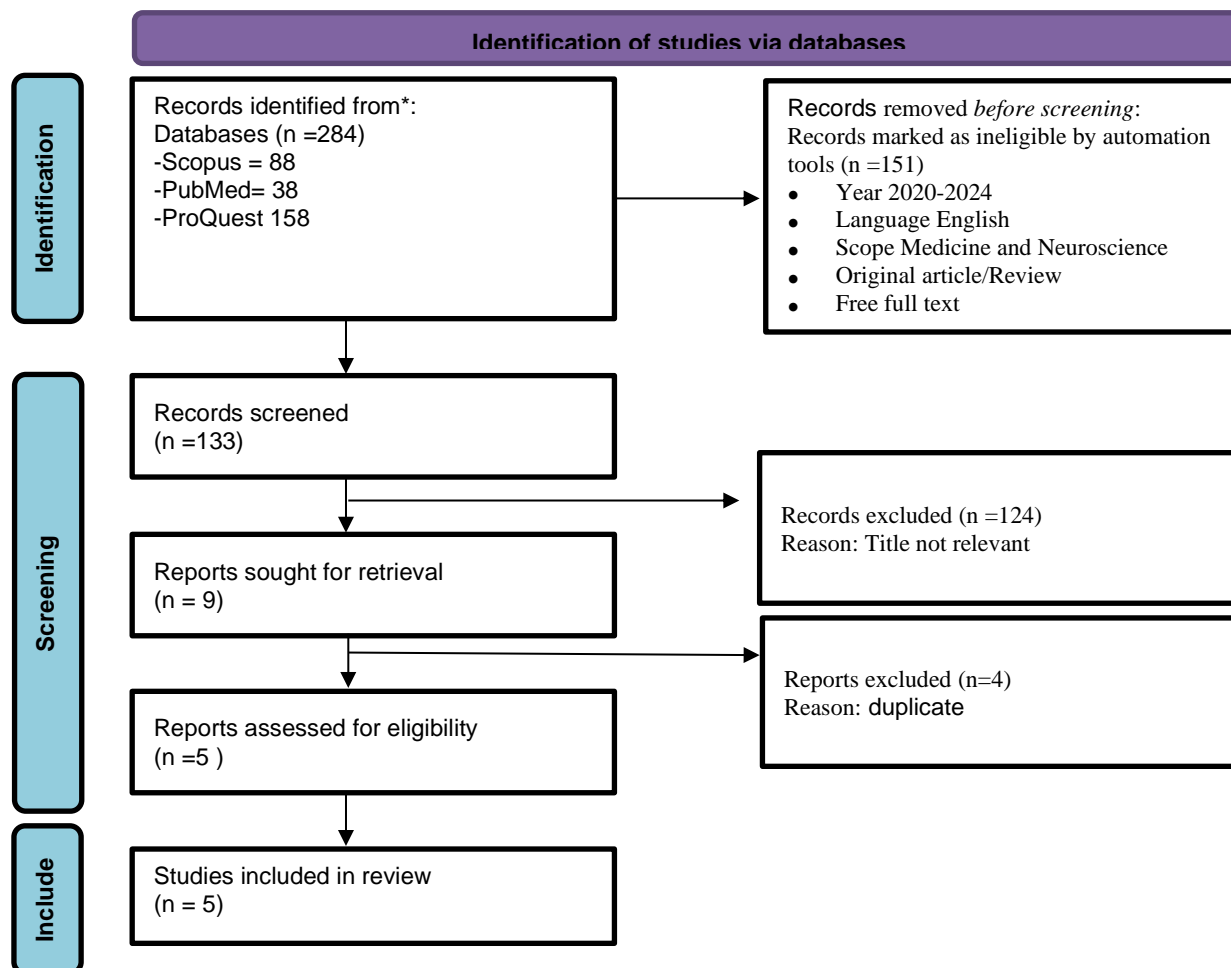


Figure 1. PRISMA Flowchart

Tabel 1. Extraction Data of Neurological Complications Associated with RA

Title	Aim	Design Study	Neurological Complication	Discussion
Neurological Complications of Rheumatic Disease ¹⁷	To describe specific neurological manifestations of autoimmune rheumatic disorders.	Literature Review	Central nervous system (CNS) inflammation, permeability of blood-brain barrier, adaptive immune response	Discusses immune mechanisms leading to CNS inflammation, including roles of CD4+, CD8+ T-lymphocytes, proinflammatory cytokines, and B-cell-mediated antibody production.

<p>Cerebral vasculitis as a major manifestation of rheumatoid arthritis ¹²</p>	<p>To highlight cerebral vasculitis (CV) as a rare but serious neurological complication of rheumatoid arthritis (RA).</p>	<p>Case Report (2 cases)</p>	<p>Cerebral vasculitis (CV) causing acute ischemia in the brain, presenting as facial weakness, upper extremity weakness, and speech difficulty.</p>	<p>CV due to RA is a rare but severe neurological complication that can be life-threatening. It is often associated with ischemic strokes and requires prompt identification and treatment. Two case studies showed successful response to therapies such as pulse methylprednisolone, azathioprine, and cyclophosphamide. Clinicians should maintain awareness of CV in patients with progressive strokes in RA to ensure timely and effective management.</p>
<p>Rheumatoid Meningitis: A Rare Extra-Articular Manifestation of Rheumatoid Arthritis: Report of 6 Cases and Literature Review ¹³</p>	<p>To describe the central neurological manifestations of rheumatoid arthritis (RA), specifically rheumatoid meningitis (RM), and their outcomes.</p>	<p>Case Series (6 cases)</p>	<p>Rheumatoid meningitis (RM) presenting with seizures, fever, headaches, frontal syndrome, leptomeninges's, and pachymeningitis.</p>	<p>RM is a rare but severe neurological complication of RA with high morbidity and mortality. Diagnosis requires exhaustive assessment, including imaging, lumbar puncture, and histological examination. Treatments such as intravenous steroids, immunoglobulins, or biologic DMARDs showed varied outcomes, ranging from complete recovery to death. Physicians should maintain vigilance for central neurological manifestations in RA patients, even in cases of quiescent or longstanding RA, as prompt recognition and management are essential.</p>

Cognitive Impairment in Persons With Rheumatoid Arthritis ¹⁴	To explore the prevalence and predictors of cognitive impairment in persons with RA.	Longitudinal cohort study (115 subjects)	Cognitive impairment: 31% of subjects classified as impaired, based on standardized neuropsychological assessments.	The study highlights a significant burden of cognitive impairment in RA patients. Independent predictors include low education, low income, glucocorticoid use, and increased cardiovascular risk factors. These findings underline the need for future research to identify specific etiologic contributors and develop interventions to mitigate cognitive impairment among RA patients.
Endothelial Dysfunction and Extra-Articular Neurological Manifestations in Rheumatoid Arthritis ³²	To assess the mechanisms of endothelial dysfunction and its role in extra-articular manifestations of rheumatoid arthritis (RA) and explore lifestyle/nutritional interventions as therapeutic options.	Review article.	Peripheral nerve disorders (prevalence ~20%) due to vasculitis of nerve vessels, vascular ischemia, axonal degeneration, and neuronal demyelination.	Endothelial dysfunction and BNB (brain-nerve barrier) alterations contribute to neurological complications in RA. Lifestyle and dietary interventions, such as polyphenols and the Mediterranean diet, could maintain endothelial integrity and potentially mitigate complications.

The table 1 describes several neurological complications associated with rheumatoid arthritis (RA), including study objectives, study design, neurological complications found, as well as discussion related to each condition. Firstly, the literature study on Neurological Complications of Rheumatic Disease highlights the role of the central nervous system (CNS) in autoimmune diseases with mechanisms such as inflammation, blood-brain barrier permeability, and abnormal immune responses ¹¹. This research emphasizes the importance of early detection to prevent severe complications.

Secondly, Cerebral Vasculitis as a Major Manifestation of Rheumatoid Arthritis through two case reports showed that cerebral vasculitis can cause cerebral ischemia with symptoms of facial weakness and speech impairment ¹². This condition requires rapid treatment with therapies such as steroids and immunosuppressants to reduce the risk of death. Thirdly, Rheumatoid Meningitis case studies report complications of rheumatic meningitis (RM), characterized by symptoms such as seizures, fever and frontal syndrome ¹³. Its diagnosis requires intensive

examination, while treatment involves steroids, immunoglobulins or biological DMARDs.

Finally, the longitudinal study Cognitive Impairment in Persons with Rheumatoid Arthritis showed that approximately 31% of RA patients had cognitive impairment, especially those with low education and glucocorticoid users¹⁴. This study highlights the need for further research to understand the causes of cognitive impairment and develop effective interventions. Overall, neurological complications in RA have a wide spectrum, ranging from CNS inflammation to cognitive impairment, which requires a comprehensive diagnostic and therapeutic approach.

DISCUSSION

Neurological complications in rheumatoid arthritis (RA) demonstrate the complexity in the relationship between autoimmune diseases and the nervous system¹⁵. From the studies summarized in the table, there are some important findings.

Broad-spectrum Neurological Manifestations of RA^{4,11,16-19}

Rheumatic diseases, including RA, can affect both the central and peripheral nervous system (CNS). This occurs through inflammatory mechanisms, blood-brain barrier disruption, and pathological immune responses. The literature reviewed suggests that immune factors, such as CD4+ activation and proinflammatory cytokines, play an important role in these complications. Early detection of these mechanisms is crucial as delayed diagnosis can lead to irreversible damage to the CNS.

Cerebral Vasculitis as a Major Complication of RA^{12,20,21}

Cerebral vasculitis, although rare, is a life-threatening neurological complication of RA. Case studies show that patients with cerebral vasculitis often have cerebral ischemia that can trigger facial weakness, speech impairment and other neurological symptoms. Timely treatment with immunosuppressive therapy such as methylprednisolone or azathioprine can prevent worsening of the condition. Therefore, it is important for doctors to be alert to neurological signs in RA patients with vasculitis.

Rheumatic Meningitis: Diagnostic and Treatment Challenges

Rheumatoid meningitis (RM) is a severe neurological complication of rheumatoid arthritis (RA). Villa et.al found this disease recurrence occurred in 31.2% of cases, with 14% resulting in fatal outcomes²². Rheumatic meningitis (RM) is a rare but serious complication with a high morbidity rate^{23,24}. Symptoms, such as seizures, fever and frontal syndrome, often overlap with other infections, requiring careful diagnostic evaluation, including lumbar puncture and histological analysis. Treatment using steroids²⁵, immunoglobulins and biological DMARDs has shown promising results, but RM still requires intensive medical attention due to the potential for fatal complications.

Cognitive Impairment as a Long-term Impact of RA^{26,27}

In addition to acute complications, the neurological impact of RA is also seen in chronic cognitive impairment. Longitudinal studies

show that approximately 31% of RA patients experience cognitive impairment ²⁶, which is often associated with low education, glucocorticoid use, and cardiovascular risk factors. These impairments not only affect patients' quality of life, but also add to their psychosocial burden. Therefore, a multidisciplinary approach is needed to identify modifiable risk factors, such as vascular risk management and optimization of RA therapy.

Importance of Further Research

These studies highlight gaps in the understanding of the pathophysiology of neurological complications of RA ²⁸. Further research is needed to identify specific immune mechanisms, relevant biomarkers, and the development of more effective therapies to prevent and treat these complications. In addition, patient education programs that focus on early recognition of neurological symptoms may also help prevent more serious complications.

Clinical Recommendations

Clinicians need to increase awareness of the possibility of neurological complications in RA patients, especially in patients with unexplained neurological symptoms. A comprehensive neurological evaluation should be performed, including the use of CNS imaging and laboratory examinations to support a prompt diagnosis. Because common rheumatic diseases can have incapacitating but frequently curable neurologic aftereffects. Early diagnosis and treatment are crucial. For better results, it is essential to be aware of the typical presentations and the most recent methods of diagnosis and therapy ¹⁷. The therapeutic approach should be tailored to the patient's condition, given that the

neurological complications of RA have multifactorial causes ^{29,30}. Patients with RA should be educated about the risk of neurological complications ³¹, including the importance of reporting symptoms such as seizures, cognitive impairment, or fatigue.

CONCLUSION

In conclusion, neurological complications in rheumatoid arthritis (RA) patients include various serious conditions, such as central nervous system (CNS) inflammation, cerebral vasculitis, rheumatic meningitis, and cognitive impairment. These complications are often potentially life-threatening and require early diagnosis and appropriate treatment, including the use of immunomodulatory therapies such as steroids, immunoglobulins, or biological DMARDs. Risk factors such as low education, glucocorticoid use and cardiovascular risk also contribute to cognitive impairment. These studies highlight the importance of early recognition, in-depth evaluation, and development of interventions to reduce morbidity, mortality, and neurological impact in RA patients. Further research is needed to understand the underlying pathophysiology and improve the management of these complications.

ACKNOWLEDGEMENTS

We would like to express our sincere gratitude to the Institute for Research and Community Service (LPPM) at Universitas Ahmad Dahlan (UAD) for their support and funding under contract number PD-007/SP3/LPPM-UAD/XI/2024. We also extend our appreciation to the researchers and authors whose articles

have provided valuable insights and references for this study.

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