ARTICULAR SYNDROME IN THE ELDERLY: COMMON DIFFERENTIALS AND CHALLENGES

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Abstract
Articular syndrome includes a spectrum of inflammatory and non-inflammatory joint involvement ranging from arthralgia to arthritis. Its phenotype, differentials and management differ slightly in the elderly, considering the added effect of physiological changes with ageing, comorbidity and multimorbidity. This review aims to provide an overview of the common differentials of articular syndrome in the elderly, including the inflammatory and degenerative causes. The common inflammatory arthritis in the elderly includes late-onset rheumatoid arthritis, polymyalgia rheumatica, paraneoplastic arthritis, crystal arthropathies, and systemic vasculitis, including ANCA-associated vasculitis, to name a few. The non-inflammatory articular syndromes in this age group predominantly include osteoarthritis and osteoporosis. There are also evident alterations in the gut microbiome associated with inflammatory arthritis and with physiological ageing and osteoarthritis, which have possible mechanistic significance. The management aspect in the geriatric population comes with challenges of addressing multimorbidity, polypharmacy, drug interactions, and not just disease activity. An integrated approach with effective physical therapy, and vocational activities, tailored to each patient is essential for optimal management.

Keywords: Articular syndrome, geriatrics, multimorbidity, arthritis


Key Messages for Research and Practice

- The diseases under the purview of an articular syndrome in the elderly differ and may be the initial presenting feature of potentially organ or life-threatening conditions like systemic vasculitis or underlying malignancy.

- With the global burden of osteoarthritis increasing exponentially, a closer look into the spectrum, including metabolic syndrome and alterations in the gut microbiome will provide further evidence.

- An integrated approach to treatment, paying close attention to the associated multimorbidity and adopting effective rehabilitation strategies will ensure optimal outcomes.
Introduction

Though different definitions exist to chronologically define “older adults” or “elderly”, by convention, the term refers to a person aged 65 years or older [1]. As the population pyramid is changing, with the geriatric population expanding, the onus on providing quality equitable healthcare to our elderly is the absolute need. The normal process of ageing accompanies a multitude of physiological changes, one of which may be an increase in perceived pain in the bones and joints, which can contribute to a decline in the quality of life (QoL) in this population.

The term “articular syndrome” encompasses a wide spectrum of inflammatory and non-inflammatory diseases that present with arthralgia or arthritis. While arthritis is typically described to be associated with signs of inflammation over the joint, arthralgia is mostly pain described without clinical signs of active inflammation like redness, tenderness or warmth [2, 3]. The important inflammatory causes in the elderly include, but are not limited to, late-onset rheumatoid arthritis (LORA), polymyalgia rheumatica (PMR), paraneoplastic arthritis, systemic vasculitis, mostly ANCA-associated vasculitis (anti-neutrophil cytoplasmic antibody-associated vasculitis), while the non-inflammatory causes of articular syndrome predominantly involve the spectrum of degenerative bone diseases like osteoarthritis, diffuse idiopathic skeletal hyperostosis (DISH) or Forrester's disease; metabolic bone diseases like osteomalacia, osteoporosis; soft tissue rheumatism like fibromyalgia, myofascial pain syndrome, among others. Recognizing and differentiating these in the geriatric population is vital, as features like paraneoplastic arthritis can be the tip of the iceberg of an underlying catastrophe. The approach to articular syndrome and the differentials to be considered vary with age and presentation, and this review focuses on the nuances of joint pain in the elderly, common differentials, the approach to making the right diagnosis and the importance of a tailored comprehensive and integrated management.

Search strategy

A thorough search of PubMed/Medline, Scopus and Web of Science was conducted using the terms related to “arthralgia”, “arthritis”, “syndrome, articular”, “syndrome, arthritis” in the geriatric population in various combinations. Only articles available in English were selected for the review and also the articles that were cross-referenced from these were consulted. Finally, the authors selected articles that came under the purview of the review based on their experience and as recommended by the standards for writing a narrative review [4].

Differential diagnoses of Articular Syndrome in Elderly

Common Inflammatory causes:

While the conditions that are discussed below are more common, there is an exhaustive list of inflammatory articular syndromes that can occur in this age group ranging from crystal arthropathies like gout, calcium pyrophosphate deposition disease (CPPD) or other arthritides that may have an onset in the younger age and sometimes extend into old age without resolution, like spondyloarthritis (SpA), RA, psoriatic arthritis (PsA), or a different spectrum like relapsing polychondritis (RP).

A common cause of inflammatory arthritis in the geriatric population is late-onset rheumatoid arthritis (LORA), which is defined as the onset of RA in an individual over 65 years of age [5]. This differs from the garden variety or early onset RA in that it has a more balanced sex predilection, higher functional limitation and greater anatomical damage [6]. However, additional factors like the process of ageing and degeneration, and inflamm-aging may be confounding [7]. Though the genetic predisposition of LORA is not as well-established as early onset RA (≤40 years), there was some HLA association observed that was similar to PMR, especially in the seronegative cases [8]. While early-onset RA is associated with HLA-DRB1*04 [9], LORA was shown to be associated with HLA-DRB1*01 and this association was more in patients who were seropositive for rheumatoid factor. The seronegative cases of LORA displayed an increased association with HLA-DRB1*13/*14; an interesting finding here was that this was also observed in PMR without giant cell arteritis (GCA) [8]. This finding is of value as LORA and PMR may often be indistinguishable clinically as up to 25% of PMR can present with peripheral synovitis [10]. Additionally both these arthritis are amenable to low-dose steroids. There is contrasting evidence on the association of rheumatoid factor and antibody to cyclic citrullinated peptide (anti-CCP) in LORA. However, seropositivity is a predictor of a more chronic and severe erosive course of the disease and aids in prognostication [6].

While LORA may be more common in certain geographies, PMR is a close differential while approaching articular syndrome in the elderly. It is vital for the treating physician to be
Polyarthritis, which is of relatively acute onset and associated with other organ manifestations like renal, ocular, ENT, and respiratory would mostly point towards anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, with supportive serological evidence of anti-myeloperoxidase (anti-MPO) or anti-proteinase-3 (anti-PR3) antibodies [19]. A strong index of suspicion and an emergent initiation of definitive treatment with high-dose steroids and immunosuppression (cyclophosphamide or rituximab), based on the severity of organ involvement is vital to prevent long-term organ-threatening complications [20].

**Common Non-Inflammatory Causes**

The most common cause of non-inflammatory articular syndrome in the geriatric population is osteoarthritis (OA). We have been witnessing a steep rise in lifestyle diseases, with a 102% increase in the incidence rate in OA between 1990 and 2017, majorly driven by the ageing global population [3]. The risks for primary OA are multifactorial, the most important being advancing age and obesity [21]. Other factors associated with the risk of OA are female gender, injury, occupational hazards, joint loading, and a sedentary lifestyle [3]. Being non-inflammatory, mechanical and degenerative, it mostly involves the weight-bearing large joints, though it is reported to occur in small joints (like the first carpometacarpal joint of hands, nodal OA of hands) and the pain is typically a non-inflammatory type of pain. The pain worsens with activity and improves with rest, though patients may experience the phenomenon of “gelling” after prolonged periods of rest in a particular posture. The presence of crepitus without warmth or erythema is characteristic of osteoarthritis [22].

Pain generation in OA is complex and multifactorial. It may be nociceptive, which is due to a local tissue injury from an osteophyte, or neuropathic [23, 24].

Another interesting clinical pearl in OA is that often the clinical presentation does not correlate with the extent of radiological damage and the pain characteristics vary significantly between individual patients, which can be attributed to the complex pathophysiology of OA [25]. Factors such as central and peripheral pain sensitization, older age groups, female sex, associated psychosocial factors, sleep disturbances, and degree of mobility have been implicated in pain-associated phenotypes OA [26, 27].

Another important cause of inflammatory arthritis in the elderly autoimmune arthritides spectrum is paraneoplastic. These patients tend to present with acute or subacute onset polyarthritis akin to RA, which has a poor response to low-dose steroids. This form of arthritis can be associated with any internal organ malignancy. Evidence from the literature suggests an association more commonly with lung and haematological malignancies, though this may be due to their overall higher incidence [15]. The phenotype can mimic spondyloarthritis (SpA) or RA, though the latter is more common. The onset is commonly subacute and dramatic. Lung cancers are more often described to have a symmetrical RA-like polyarthritis [16], though an axial SpA-like phenotype is not uncommon [17]. Beyond lung and haematological malignancies, urinary tract, gastrointestinal, breast, ovarian, endometrial, and thyroid cancers are also among the malignancies that have been reported to be associated with paraneoplastic arthritis, with arthritis sometimes being the presenting symptom [15]. Unlike RA, they don’t favour the female sex, and have poor responses to low dose steroids or other disease modifying anti-rheumatic drugs (DMARDs) or even non-steroidal anti-inflammatory drugs (NSAIDs). The mainstay of treatment in this subset of patients is the treatment of the underlying malignancy with targeted chemotherapy, which almost always results in the near-complete resolution of clinical synovitis [18].

sensitized to the presentations of PMR and initiate early treatment as up to 15-20% of these cases are associated with GCA and this may portend imminent visual loss if not treated emergently [11]. PMR is usually differentiated from LORA with its classical presentation of involvement of the shoulder and the hip girdle with the peripheral arthritis being less significant [12]. Evidence from tissue biopsies has aided in establishing an adequate granulomatous inflammatory pathology in GCA, however, the exact pathology in PMR is still incompletely understood. The strong HLA association that is seen with RA and also with GCA is lacking in PMR. Though histological evidence from PMR reveals adventitial infiltration of activated dendritic cells, T cells are mostly inconspicuous in the media [13]. PMR is probably a milder form of GCA given the overlapping pathogenesis, where overt vascular inflammation has not yet ensued. Prompt initiation of treatment with prednisolone of up to 20mg is warranted (in the absence of GCA) and a dramatic response to glucocorticoids confirms the diagnosis. However, the effect of long-term glucocorticoids in the elderly is not without its array of metabolic adverse effects. Recently, the FDA approved sarilumab, an interleukin-6 receptor antagonist for treating relapsing PMR during a steroid taper [14].

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In recent times, the effect of gut microbiota on nutrition, absorption, inflammation, and disease processes has been widely studied. Specific changes to the gut microbiome have been identified with normal ageing, which includes reduced biodiversity, an increase in pathobionts, and reduced inter-individual variability. [28]. These changes have also been linked to various musculoskeletal disorders including muscle loss and frailty.

Changes in the gut microbiota have been commonly studied in the setting of inflammatory arthritis, predominantly RA, inflammatory bowel disease (IBD), SpA, including reactive arthritis (ReA) [29–31]. While a specific inflammatory milieu in the form of a low Firmicutes to Bacteriodetes ratio is demonstrable in IBD and ReA [30, 31], OA also displayed alterations in the microbiome in the elderly, where they found increased bacteria from the phylum Proteobacteriaceae which are associated with inflammatory cytokines in circulation adding to the physiology of ageing and the concept inflammaging which plays a role in the pathogenesis of OA [32–34].

The gut microbiome is a fairly under-researched topic in the geriatric population. The correlation found between OA and gut microbial shifts should be reproducible in large-scale multicenter studies to establish a causal link. The inciting event and the route of transport of microbial products into joint spaces is an area of potential research for the development of prevention and therapeutic protocols in the future.

Osteoporosis is another common disorder in the elderly, which may be primary (mostly postmenopausal) or secondary [35]. Osteopenia usually goes undiagnosed until the patient progresses to osteoporosis and/or sustains a fragility fracture, in which case they present with acute pain. Most commonly the patient presents with a vertebral compression fracture or an appendicular fracture involving the femur or the distal end of radius. Vertebral compression fractures are associated with a sudden onset back pain which is aggravated on standing or sitting and is relieved in a recumbent position. It is associated with limitations in spine mobility, paravertebral muscle spasms, and pain-free intervals between fracture events [36]. The proximal femur or distal radial fractures after minor trauma or daily activities can also be the presenting complaints in patients with osteoporosis.

Additionally, in the setting of an autoimmune inflammatory rheumatic disease (AIRD), which warrants treatment with glucocorticoids, with a potential risk of developing glucocorticoid-induced osteoporosis (GIOP), the onus is on the rheumatologist to aim for not just disease remission, but also tailor a comprehensive treatment plan for the individual patient, that includes osteoprotection with adequate calcium and vitamin D supplementation, cardioprotection if indicated and also increased emphasis on physical activity and lifestyle modifications. The American College of Rheumatology (ACR) in 2022 published guidelines on the management of GIOP, where they lay out guidelines for the assessment of fracture risk and treatment of adults who have been on ≥2.5mg prednisolone for >3 months [37].

Beyond OA and osteoporosis in the elderly, in the setting of long-standing diabetes or diabetic neuropathy, a common complication could be a neuropathic joint or a Charcot’s joint. It is uncommon as opposed to degenerative joint disorders which often leads to a delay in diagnosis. The global prevalence of diabetic Neuropathic arthropathy is 0.08-13% although the exact number is not known [38]. Charcot arthropathy presents as unilateral joint swelling with minimal pain associated with oedema and sometimes erythema and no history of incidental trauma. The diagnosis is often missed until later in the disease course when the patient presents with characteristic foot deformities like mid-foot collapse leading to rocker bottom feet, or pressure sores and non-healing ulcers which sometimes may require amputations [39, 40].

Articular syndrome & multimorbidity

The alarming rate at which chronic disorders are progressing led to the concept of multimorbidity which is defined as the co-existence of at least two chronic medical conditions in an individual [41]. The estimated prevalence of multimorbidity was 64.9% amongst those aged 65-84 years and 81.5% over 85 years or older [42]. Ageing and inflammation is one of the three broad areas under which multimorbidity is usually explained. The hallmarks of ageing are well-defined and this complex interlink plays a major role in multimorbidity [43].

OA may be a part of discordant multimorbidity where the diseases existing don’t have a unifying pathogenesis, for example, coronary arterial disease (CAD), bronchial asthma and OA. In the presence of multimorbidity, there arises an issue with polypharmacy and drug interactions, where the NSAID that the patient may take for OA may pose a cardiovascular risk, especially in the presence of an underlying CAD. Additionally, fibromyalgia, and depression may accompany...
multimorbidity and these may also present clinically as a spectrum of articular syndromes and pose a diagnostic dilemma. They contribute to a poor quality of life, increased work disability, and increased healthcare costs [44]. Risk factors such as age and female gender are the most important non-modifiable risk factors for articular syndrome as well as multimorbidity [45] and the modifiable risk factors include obesity, smoking, physical inactivity, and social deprivation [46, 47].

Some arthritides create an inflammatory milieu in the body, that causes accelerated atherosclerosis and this is demonstrated well in RA with cardiometabolic multimorbidity. This was also associated with bDMARD failure these patients [48]. OA and back pain are commonly seen in patients with hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, or cancer and have a strong association with frailty in geriatric patients [49]. It has been suggested that a simple comorbidity count would help understand the disability risk and need for rehabilitation in geriatric patients than the spectrum of multimorbidity [50]. Multimorbidity is also associated with reduced social interactions, and cardiometabolic and musculoskeletal disorders associated with multimorbidity particularly limit ambulation in older patients [51].

Challenges in the elderly

Challenges can be in the context of diagnosis or management of the articular syndrome in the elderly. At the diagnostic level, the diseases tend to deviate from the classical phenotype, which may pose a dilemma. To tackle this, a systematic approach with thorough history taking, followed by a systematic clinical examination, with close attention to subtle signs like temporal artery pulsations, shoulder girdle weakness, and visual blurring may help clinch the diagnosis. Another barrier is that the elderly, sometimes may not be able to express all their concerns optimally, owing to poor memory or coherence. So the onus is on the treating physician to clinch the subtle clinical signs to arrive at the right diagnosis to provide the optimal treatment.

Once the right diagnosis is made, next comes the greater challenge of tailoring treatment. Polypharmacy is a great cause for concern in the geriatric population. The most common definition of polypharmacy is the usage of five or more medications per day [52]. This sometimes leads to the patient discontinuing the essential drug once they experience marginal improvement, as they feel they are taking one “too many” medicines for the condition. Another major issue with polypharmacy is the drug interactions, which is more unpredictable in the elderly. Unless the health care system, primary or hospice is well trained to double-check the interactions before dispensing, there is a risk of “inappropriate polypharmacy” that can lead to adverse events.

While drugs are one part of the treatment, rehabilitation plays a major role too. Effective physiotherapy and occupational therapy that is accessible and affordable is to be integrated into the treatment plan for all elderly with articular syndromes for optimal response and outcomes.

Conclusion

The importance of understanding the nuances in the differentials of articular syndrome in the elderly is vital, to prevent delay in initiation of treatment or referral. Beyond autoimmunity or degenerative joint, the syndrome in the elderly is often complicated by comorbidity and multimorbidity that needs an integrated approach. It may often lead to frailty, sarcopenia, and polypharmacy which further results in the decline in QoL and loss of independent lifestyle in geriatric patients [53]. The association of these syndromes can probably be mitigated in such patients with the help of individual care and attention to early rehabilitation and social support.

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REFERENCES


