Review

Geriatric syndromes in patients with rheumatoid arthritis: a literature overview

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease of unknown aetiology which principally affects the small joints of the hands and feet. The incidence of RA increases with age and peaks within the age range of 70 to 79 years. In the ageing population, therefore, it is expected that the number of patients with RA will grow proportionally and more patients will have comorbidities but also so-called geriatric syndromes (GS). GS are clinical and multifactorial conditions in older persons that are associated with poor health outcomes, do not fit into disease categories (comorbidities) and require a multidimensional treatment approach. Patients suffering from RA may be at increased risk for GS. Therefore, it is important that rheumatologists are knowledgeable about the constructs represented by GS, understand the main risk factors, and gain insight in how to recognise these syndromes. Limited awareness of the (risk for) GS in patients with RA among rheumatologists may lead to ineffective management of RA. Our objective was to provide a comprehensive overview about the prevalence, aetiologic factors and health consequences of the most important GS in patients with RA.

Introduction

By 2030, one quarter of the Western European residents will be aged 65 and over (1). Consequently, the number of elderly rheumatoid arthritis (RA) patients will also increase. Besides, the long-term survival of RA has improved dramatically following the introduction of highly effective anti-rheumatic treatment. As a result, more RA patients will develop comorbidities but also suffer from geriatric syndromes (GS) (2). The systemic inflammation inherent to RA may play an additional role in the risk of developing GS. Treating RA in geriatric patients will present a challenge to rheumatologists, since our current RA management strategies might not be directly translatable to geriatric RA patients. Therefore, for rheumatologists it is of interest to know whether and what GS might affect management of RA, including treatment strategies and monitoring for treatment side effects.

In 1909 the term "geriatric syndrome" was already defined. The original definition of a GS was: *"conditions experienced by older persons that occur intermittently, may be triggered by acute insults and often are linked to subsequent functional decline"* (3). The first GS, often called "the four geriatric giants", were immobility, instability, incontinence, and intellectual impairment (4). Other syndromes, such as sarcopenia, frailty (5) and problems concerning hearing and vision, nutrition, sleep, delirium and vertigo were added later (6, 7).

In the 21th century, GS became a key concept in geriatrics and the definition was modified towards: *"clinical conditions in older persons that do not fit into disease categories but are highly prevalent in old age, multifactorial, associated with multiple comorbidities and poor outcomes and are only treatable when a multidimensional approach is used"* (8).

To our knowledge, no comprehensive review has been written about GS in RA. Awareness, recognition and prevention of these syndromes is important, because GS substantially contribute to morbidity and mortality in RA via multisystem dysregulations leading to functional decline, decreased physiologic reserve and maladaptive responses to environmental and lifestyle stressors (9). Yet, a complicating factor

in research on GS in RA is the overlap between signs and symptoms of GS and RA. Several symptoms that are inherent to RA, such as immobility and sarcopenia, are also part of the constructs labeled as GS. The objective of this paper is to provide a comprehensive review of the literature in RA on the prevalence, possible aetiologic factors and health consequences of the six GS that are considered most relevant, namely immobility, instability, incontinence, intellectual impairment, sarcopenia and frailty. An electronic database search using EMBASE, Medline, PsycINFO, and PubMed was undertaken using the search terms GS, geriatric characteristics and RA. Moreover, in addition to combining the six individual geriatric syndromes with RA, MeSH terms and some related terms were used due to overlapping terms used in the current literature.

Summary of studies on immobility

Impaired mobility, a state in which the individual experiences or is at risk for experiencing limitation of physical movement, is one of the most common clinical presentations in elderly. It is almost invariably multifactorial, and the patient has often several other medical problems (10). RA is inherently associated with pain and joint swelling, resulting in immobility and disability. For example, the prevalence of foot impairment (*e.g.* pain and joint swelling or damage) and subsequent walking disability in recent-onset RA patients who have not been treated with disease-modifying anti-rheumatic drugs ranges from 35–70% (11). No comparative study is available on differences in immobility between elderly and younger RA patients. One of the challenges is to disentangle the relation between immobility due to ageing and immobility due to RA disease activity. In an accelerometry study by Hernández *et al*. (12), it was found that RA patients spend less time doing moderate and vigorous physical activity as compared to healthy controls (22 (15) minutes *vs*. 29 (21), p=0.05), and this was associated with higher disease activity measured by DAS28. On the same line, a cross-sectional review of 100 non-selected consecutive outpatients with RA in rheumatology clinics in 21 countries demonstrated that 71% of the RA patients performed no regular physical activity and only 14% reported participating in physical exercises at least 3 times per week (13).

Summary of studies on instability

Instability is the inability to control and maintain proper balance and orientation. In the literature, falls are the major marker of instability. Approximately one out of four elderly people fall each year (14). Although literature suggests that RA patients, regardless of age, are at high risk of falls (15), a higher prevalence of falls in elderly RA patients (≥65 years) compared to younger RA patients (<65 years) has been demonstrated (2, 16). Comparative literature on the prevalence of falls in RA patients *versus* controls remains contradictive (9).

Fall incidences within 1 year range between 27–54% in RA patients with a mean age of 59 years (SD 14.2) (17). Additionally, about 68% of patients have an increased risk of falling (17), and almost 20% of RA patients experience multiple falls over a one year follow-up period (18). Among RA patients a 95% excess risk of death due to falls has been observed compared to the general Italian population using age- and gender-specific mortality rates (19).

Summary of studies on incontinence

Incontinence is an involuntary and inappropriate voiding or leakage of urine or feces. Incontinence should not be regarded as a normal part of ageing. More specifically, it is associated with sphincteric damage, loss of neurological control mechanisms, especially in dementia or stroke, and with severe disability, chronic illness and frailty. In 18% of RA patients with a median age of 59 years (IQR 49–69 years) urinary incontinence, measured with a self-report question, was present. Additionally, 38% of patients reported difficulties in controlling their urine (20). Arthritis in general has been shown to be strongly associated with lower urinary tract symptoms including incomplete emptying and storage symptoms such as hesitancy, nocturnal and day-time frequency, and urgency (21, 22). RA usually does not directly affect the bladder or bowel function. Chen *et al*. (2) did not find a difference regarding the prevalence of incontinence amongst elderly compared to younger RA patients. In a study by Lee *et al*. (23), lower urinary tract symptoms (including voiding dysfunction) were equally reported between RA patients and controls. In theory, lower urinary tract symptoms or incontinence in RA patients may occur as a medication adverse effect (24), and the loss of mobility and joint stiffness can hamper the patient from being able to reach the toilet or remove their clothing on time (22).

Summary of studies on intellectual impairment

Intellectual impairment is characterised by intellectual difficulties as well as difficulties in conceptual, social, and practical areas of living. Several deficits occur in cognitive functions, such as attention and concentration, mental flexibility, visuospatial and planning functions, problem solving, and reasoning. Moreover, adaptive functioning can be affected which significantly impedes conforming to developmental and sociocultural standards and meeting social responsibility. In a cross-sectional study including 40 RA patients and 40 healthy controls, 30% of RA patients were classified with general cognitive impairment compared to 7.5% of controls (25). Domain-specific impairments in visuospatial and planning functions have been reported in 71% patients and impaired attention and mental flexibility in 38% of patients, in a study including 30 RA patients with a mean age of 55.6±11.1 years (range 32–71 years) (26). Moreover, a meta-analysis of 3 cohort studies and 2 cross-sectional studies demonstrated an excess risk of 61% for dementia among RA patients (27). The pathogenic mechanisms of cognitive decline in RA remain unknown, however risk factors can be multivariable (Table II).

Summary of studies on sarcopenia

Sarcopenia is a syndrome characterised by lower skeletal muscle quantity,

Table I. Geriatric syndromes compared between elderly and younger RA patients and RA patients compared to controls.

	Elderly *vs*. younger RA patients	RA patients *vs*. controls
Immobility	No studies available.	Minutes of moderate activity (22 (15) *vs*. 29 (21) minutes, p=0.05) lower in RA patients (n=50) *vs*. healthy controls (n=50) in accelerometry study. (12)
Instability	Falls 29% ≥65 years (n=65) and 4% <65 years (n=25); p=0.01. (2)	No difference in falls incidence rate RA (n=208) *vs*. age- and gender-matched controls (n=205). (9)
Incontinence	Urinary incontinence 23% ≥65 years (n=65) and 16% <65 years (n=25); p=0.5. (2)	Severity of LUTS, including voiding dysfunction did not differ between RA (n=198) and controls (n=679). (23)
Intellectual impairment	Cognitive impairment 17% ≥65 years (n=65) and 0% <65 years (n=25); p=0.03. (2)	Cognitive impairment 30% in RA (n=40) and 7.5% in controls (n=40); p<0.05. Worse verbal fluency, logic memory and short memory in RA; all p<0.05. (25)
Sarcopenia	No studies available.	Lower skeletal muscle mass (81.8±10.1 g *vs*. 94.9±11.6 g) in RA (n=20) *vs*. controls (n=20). (29)
Frailty	No studies available.	No studies available.

RA: rheumatoid arthritis; LUTS: lower urinary tract symptoms.

higher fat accumulation in the muscle, lower muscle strength and lower physical performance. A systematic literature review on body composition in RA compared to controls revealed a significant lower fat free mass or lean body mass (indicators of sarcopenia) in RA patients in 17 out of 23 available studies (28). As an example, in an observational study including 20 RA patients and 20 controls by Walsmith *et al*. (29), it was found that RA patients (mean age 47±14 years) had significantly lower skeletal muscle mass as measured by whole body counting of potassium-40 as compared to controls (mean age 47±14 years) (81.8±10.1 g *vs*. 94.9±11.6 g). In a recent study (30) sarcopenia was observed in almost 40% of 123 RA patients with a mean age of 52.3 years (SD 13.2). Many risk factors and mechanisms take part in the development of sarcopenia in RA patients (Table II).

Due to the lack of simple clinical, biochemical, or imaging measures, it is difficult to establish a widely accepted definition of sarcopenia that is suitable for use in research and clinical practice. Several screening tools for sarcopenia are available (31), with the DEXA scan being one of the most commonly used and low cost technology for measuring body composition and muscle mass. However, no study compared body composition between younger and elderly RA patients or elderly RA patients and controls regarding skeletal muscle mass measures, which are associated with physical disability (32).

Summary of studies on frailty

Frailty is considered the opposite of vitality and reflects unsuccessful ageing (5). Frailty manifests as (1) weakness, (2) unintentional weight loss, (3) exhaustion, (4) low physical activity, and (5) slower walking speed. Although there are different opinions about how to assess frailty, the Fried criteria are often used. The Fried frailty phenotype classifies a person as frail when simultaneously three or more of these five phenotypes are present. Patients with one or two features are considered as pre-frail (5). Frailty has been associated with heightened vulnerability to adverse

Table II. Possible risk factors for the individual geriatric syndromes.

Geriatric syndrome	Risk factors
Immobility	Pain and joint swelling, contractures, comorbidities (*e.g*. neuropathy, severe dementia), visual impairment, history of hip fracture (40, 43)
Instability	Loss of muscle strength, impaired postural reflexes and balance, visual impairment, history of prior fall(s), fatigue, psychotropic medications, polypharmacy, pain and joint swelling, increased HAQ-DI, gait problems, using assistive device for ambulation, low physical activity levels (15, 17, 18, 44)
Incontinence	Sphincteric damage, loss of neurological control mechanisms (10, 20)
Intellectual impairment	Clinical features (*e.g*. fatigue and pain), psychological comorbidities (*e.g*., anxiety, and depression and cardiovascular disease), environmental factors (*e.g*. adverse life events), inflammatory markers (*e.g*. C-reactive protein level or interleukin-6), lifestyle factors (*e.g*. smoking), cultural factors (*e.g*. socioeconomic status), or social factors (*e.g*. isolation and interpersonal contacts), commonly prescribed medication for RA (*e.g*. immunosuppressive agents or glucocorticoid therapy) (41)
Sarcopenia	Low physical activity levels, malnourishment, low lower limb strength, high levels of tumour necrosis factor α, interleukin 1 β and C-reactive protein, pain and joint swelling, increased energy expenditure during rest (42)
Frailty	Inflammation, anaemia, endocrine system alteration, age, under-or overweight, low physical activity levels, low socioeconomic status, comorbidities (*e.g*. cardiovascular disease, hypertension, obesity, cognitive impairment, depression) (38, 39)

clinical events and outcomes such as disability, dependence, and mortality (5). A higher prevalence of frailty (13% (33) and 4–11% (34, 35) respectively), as well as pre-frailty (69% (33) and 40–55% (34, 35) respectively), has been shown in RA patients compared to older people. A Mexican study in 500 RA patients with a mean age of 51.3 years, of whom 23.4% met frailty criteria, demonstrated that frail RA patients use multiple prescription medications and are more likely to be diagnosed with comorbidities, including systemic hypertension (25.2%) and obesity (18.2%) as the most frequent ones (36).

Frailty can be identified using standardised questionnaires, a single assessment (*e.g.* the measurement of grip strength, slow gait speed, pulmonary function, medication review or cognitive impairment), or a comprehensive geriatric assessment to determine a person's functional, medical, and psychological capability (37). Yet, its practical limitation is the time and expertise that the process requires.

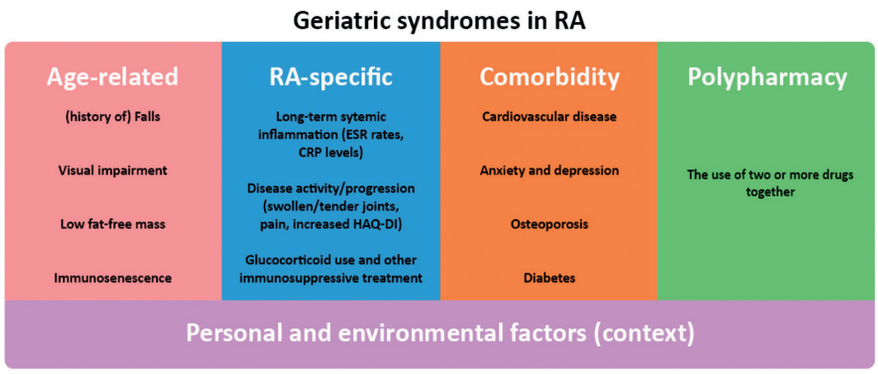

Fig. 1. Risk factors or mechanisms by which RA patients might be at increased risk of geriatric syndromes. Risk factors for geriatric syndromes include age-related factors, RA-specific factors, comorbidities, polypharmacy, but also personal factors (*e.g.* coping, isolation and few interpersonal contacts) and environmental factors (*e.g.* physical inactivity).
ESR: erythrocyte sedimentation rate; CRP: C- reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; RA: rheumatoid arthritis.

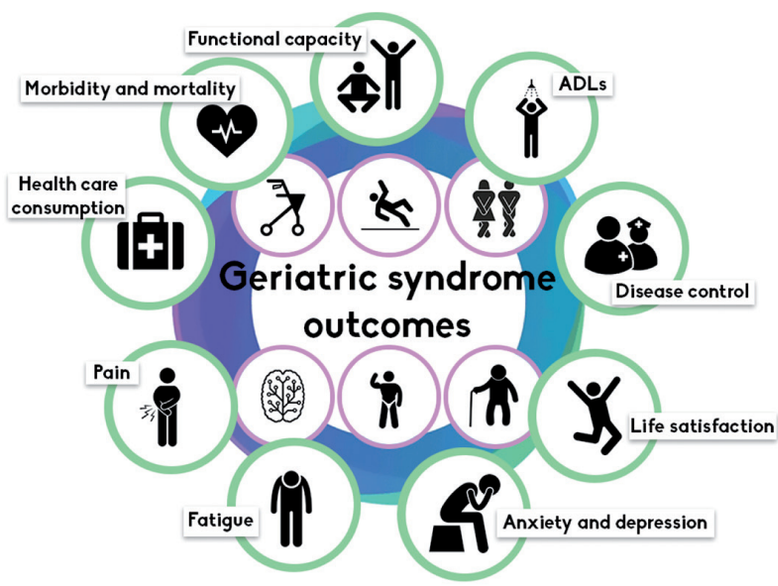

Fig. 2. Geriatric syndromes (in purple circles: immobility, instability, incontinence, intellectual impairment, sarcopenia and frailty) can have an impact on health-related outcomes (in green circles). ADLs: activities of daily living.

Possible risk factors for geriatric syndromes and the burden of all syndromes

Several GS overlap in causes and consequences. For example, sarcopenia may lead to instability, and instability can lead to immobility. Table II summarises several possible mechanism and risk factors for GS (10, 15, 17, 18, 20, 38-44). As depicted in Figure 1, risk factors can be RA-specific, age-related, or related to comorbidities, polypharmacy, personal or environmental factors. Moreover, risk factors may work together to influence an outcome as mediating, moderating, independent, overlapping, or proxy risk factor (45).

Relevance to clinical practice

Awareness and recognition

Since the burden of all GS (Fig. 2) is sufficiently large, it is important to take action to increase awareness, prevention, detection, and treatment of GS in RA. However, research in rheumatology seems to discard GS, likely resulting in limited awareness of this increasingly important burden of disease among rheumatologists. In addition, elderly people also relate certain health problems to unavoidable aspects of ageing. For example, the occurrence of urinary incontinence events are forgotten (46), falling incidents are not reported (47), or the significance of symptoms are not being recognised by the patient. Educational programs may support healthy ageing. For example, RA patients who are at risk for falls should be informed about falls and their consequences and encouraged to take preventive measures (15).

Detection and prevention

As noted by World Health Organisation in 2001, the International Classification of Functioning, Disability, and Health (48) emphasises that the evaluation of health status should focus on "components of health" instead of on diseases. By doing this, ambiguous signs, symptoms and manifestations can be traced which may be an indication for GS. Indeed, in community-dwelling persons aged 75 years and older at least one major health problem often remained unknown or suboptimally treated (49). This highlights the importance for early recognition, detection and focusing on risk factors (Fig. 1) in routine clinical care. For example, a history of falls may identify those at high risk and in need of intervention (44). Regu-

lar monitoring and home safety assessments therefore can reduce disability through early detection.

Additionally, preventing older people from disability and dependence is seen as one of the most important strategies to achieve healthy ageing. A comprehensive geriatric assessment (CGA) takes into consideration the multiple interacting medical and social needs of the patient, and the impact of the disease on functioning and healthcare outcomes. However, there is no CGA that takes into account RA specific risk factors for GS (20). It is possible that physiological characteristics of ageing are being amplified by RA itself or by drugs typically prescribed in RA (for example corticosteroids), which might explain an RA-specific vulnerability for GS (Fig. 1). Screening and preventive strategies focusing on the clinically most relevant risk factors, such as comorbidities, polypharmacy, and socioeconomic status may prevent the onset and consequences of GS (50). However, since biological ageing is a gradual process, the question should be raised when to start screening. On this line several papers in our review reported on GS in RA populations without selection based on age, and already found high prevalence rates (2, 9, 11, 14, 16-18, 20, 23, 25, 26, 30, 33, 51). Future studies therefore should include elderly patients with RA to enhance our understanding of the relationship between GS and RA in the (very) old RA population.

Treatment

After geriatric health problems are recognised and detected, care facilities will need to be tailored to the needs and preferences of the patient in order to prevent unwanted results (Figure 2). The patient will need to be actively involved in decision-making. Even in the absence of a clear aetiology or diagnosis, treatments based on clinical manifestations of GS can be useful. For example, management of symptoms of intellectual impairments (*e.g.* memory training, exercise and the use of external memory aids) can help patients to maintain mental functionality (52). Moreover, the implementation of individual tailored physical therapy or inpatient rehabilitation programs should be recommended since they can have direct beneficial effects on GS such as immobility (improving physical ability) and instability (reduce the risk of falls), but also might improve independency, pain intensity, well-being, hospital admissions and mortality (53). Also, the management of drug therapy should be optimised in case of multimorbidity and GS, as polypharmacy is often a co-existing problem. The implementation of care for GS therefore requires accepting new paradigms in the personalisation of pharmacological and non-pharmacological interventions.

Future research

The first area of future research to pursue is that of a better recognition of GS in RA patients and its underlying concepts. Indeed, a limitation of the current research is the lack of common or shared definitions of GS and inconsistency in terminology and outcomes. Moreover, several GS overlap in causes and consequences. For example, sarcopenia may lead to instability/falls and instability/falls can lead to immobility. Additionally, the current literature not always specifies the source and type of RA patient (*e.g.* late onset or longstanding chronic RA patients). Longitudinal study designs in larger cohorts will be necessary to identify shared common pathophysiologic mechanisms and to determine the extent to which specific clinical characteristics combinations (using physical and neuropsychological measures and cofactors) affect GS in RA. Second, further work at a population level is needed on exploring interventions to prevent the development and/or progression of single or multiple GS. These interventions should be communicated through RA-specific recommendations and clinical guidelines. Interventions targeting multiple GS or a factor common to multiple syndromes (*e.g.* polypharmacy) may be the most feasible and effective approach.

Conclusions

In summary, GS appear to be a relevant concept in RA. It is possible that RA patients have risk factors similar to the physiological characteristics of ageing which predispose them to GS. Although comparisons in prevalence rates of GS between RA patients and healthy controls remain scarce, these syndromes have a significant impact on the quality of life and life satisfaction of RA patients. However, rheumatologists are insufficiently prepared to care for elderly RA patients and to address GS in assessment, management and treatment. Future research is needed to generate more evidence whether and how management recommendations for RA patients should be adjusted for the presence of GS.

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