Clinically suspect arthralgia: unraveling the development of rheumatoid arthritis

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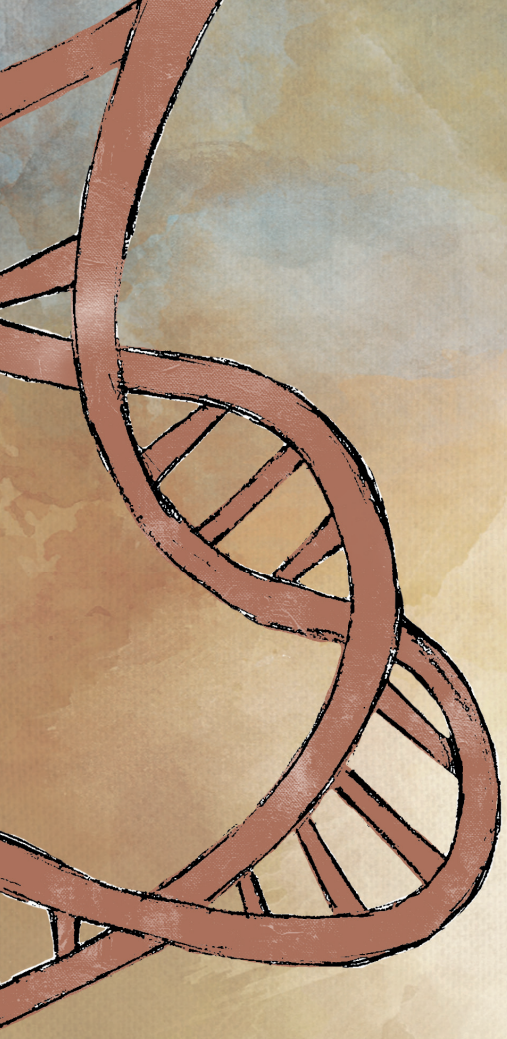

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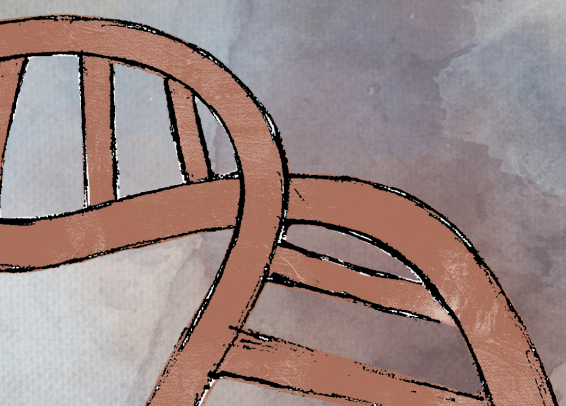
Introduction



Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterized by inflammation of synovial joints. The prevalence of RA in North America and Northern Europe is approximately 0.5-1.0%.[1] Data from Dutch general practitioners indicated a prevalence of 1.5% and over 12.000 new cases in the Netherlands in 2019.[2,3] Women are more often affected by the disease, approximately 75% of patients is female.[1] The etiology of RA is largely unknown, though several genetic and environmental risk factors have been established. The most important genetic risk factor is the human leukocyte antigen-shared epitope (HLA-SE),[4] the most well-known environmental risk factor is smoking.[1] Both factors associate predominantly with the development of autoantibody-positive RA.

Understanding the pathogenesis of RA is complicated by the heterogeneous origin of the disease. Largely, RA can be divided in autoantibody-positive and autoantibody-negative disease; in approximately 50% of early RA-patients autoantibodies are present.[1,5] The two autoantibodies that are generally acknowledged and most commonly used in clinical practice are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA).

Though underlying biological mechanisms may be different, the clinical presentation of RA at diagnosis is similar between autoantibody-positive and autoantibody-negative disease.[6,7] Patients often present with symmetrical complaints of pain, stiffness and swelling in small joints of hands and feet, though large joints can also be involved. The presence of arthritis often leads to functional limitations, and prolonged inflammation of the joints may result in damage of the surrounding cartilage and bone. The disease may also cause systemic comorbidities, e.g. cardiovascular disease or infection, and increase mortality risk.[1] Joint damage and severe long-term outcomes predominantly associate with ACPA-positive RA.[7] In both ACPA-positive and ACPA-negative RA the disease may lead to work disability, extending consequences to the societal level. The economic burden is further increased by the high costs of medication, especially since the introduction of biologicals.[8]

Emerging therapies and extensive research have led to major improvements in the treatment of RA. Although in the past it was not exceptional for the disease to lead to extensive joint damage, nowadays this is often prevented. One major contributor to this improvement is the early recognition and treatment of the disease. It is recommended to start treatment with disease modifying anti-rheumatic drugs (DMARDs) within 12 weeks after presentation with joint swelling, during the so-called 'window of opportunity', hereby preventing full maturation of the disease

pathogenesis and irreversible damage and impairment.[9] Yet, it is unclear whether even earlier treatment could prevent the onset of clinical arthritis altogether. To fully elucidate when and how to interfere with the disease processes, it is necessary to further explore the phases comprising RA-development.

The stages of rheumatoid arthritis development

In the development of RA several phases can be discerned, as shown in Figure 1.[10,11] First of all, we can distinguish an asymptomatic (A-C) and a symptomatic phase (D-F). In the asymptomatic phase signs and symptoms of imminent joint disease are absent, though genetic and environmental risk factors may be present. Subsequent development of autoantibodies associated with RA, such as RF and ACPA, can occur in the asymptomatic phase.[12,13]

The symptomatic phase is characterized by the presence of joint symptoms and comprises of three clinical presentations. The first symptomatic phase (D) is characterized by complaints of the joints suggestive of rheumatic disease, but in absence of clinically apparent inflammatory arthritis (i.e. clinical joint swelling confirmed by physical examination of the rheumatologist). In the second symptomatic phase (E) clinical arthritis is apparent, though the disease cannot (yet) be classified as RA, and is therefore termed undifferentiated arthritis (UA). The third phase is RA (F), which can be classified according to the 1987 and/or 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria.[14,15] Importantly, not all patients progress through all phases during development of RA.

Figure 1. The phases of RA-development

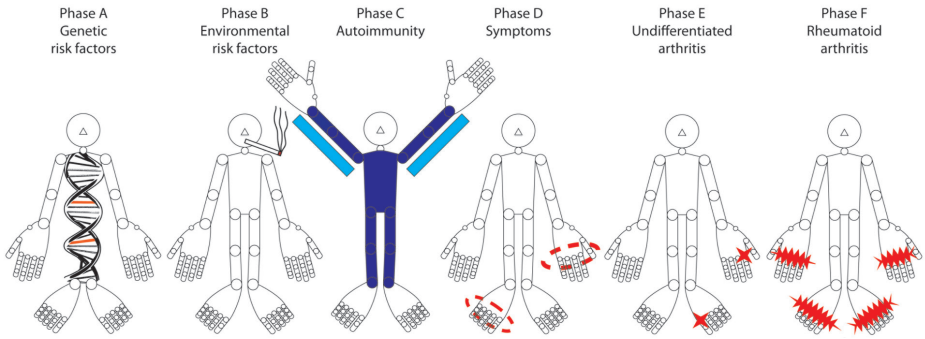


Image obtained from van Steenbergen et al.[10]

Over the years, a lot of research has been performed in UA and RA to establish the characteristics of patients developing the disease. This has improved the recognition and early treatment of these patients tremendously. Improvements have also been made in recognition of the disease even before presentation with arthritis. At-

risk populations have been defined by presence of certain risk factors, e.g. genetic predisposition or having a family member with RA, presence of autoantibodies, imaging findings or a distinct clinical presentation. Several trials are exploring, or have explored, treatment effects in at-risk populations.[16-22] Nevertheless, before preventive treatment can be implemented, risk stratification needs to be optimized. Presently a significant part of at-risk patients, despite presence of risk factors, will not develop RA. To avert preventive treatment in patients who would not develop RA after all (overtreatment), it is crucial to define an at-risk population with a high probability of developing RA. We therefore explore the beginning of the symptomatic phase; the moment when first contact between patient and physician is generally made.

Clinically suspect arthralgia

In line with Dutch guidelines for general practitioners, quick referral of patients with unexplained arthralgia, suspected arthritis or imminent rheumatic disease to the rheumatology outpatient clinic is encouraged.[23] Based on the clinical presentation and expertise of the rheumatologist, patients with arthralgia can further be classified as having clinically suspect arthralgia (CSA); this distinction has been shown to increase the chance of developing RA with an odds ratio (OR) of 55.[24] Patients with CSA often have arthralgia in small joints of the hands and feet for less than a year, which can be accompanied by morning stiffness and functional limitations. To standardize the definition of CSA, the EULAR definition of arthralgia suspicious for progression to RA was developed, see Table 1.[25] When applied in CSA-patients (as defined by the expertise and 'gut feeling' of the rheumatologist), presence of ≥3 out of 7 characteristics was shown to further double the risk for development of inflammatory arthritis.[26]

Table 1. EULAR characteristics describing arthralgia suspicious for progression to RA

History taking
Joint symptoms of recent onset (duration <1 year)
Symptoms located in MCP joints
Duration of morning stiffness ≥60 min.
Most severe symptoms present in the early morning
Presence of a first-degree relative with RA
Physical examination
Difficulty with making a fist
Positive squeeze test of MCP joints

Imaging

In addition to clinical aspects, imaging can be applied to further define patients at risk for progression to RA. Musculoskeletal ultrasound (US) and magnetic resonance imaging (MRI) can be used to detect subclinical inflammation, even before clinical arthritis becomes apparent.[27-29] Several inflammatory features can be distinguished; synovitis, tenosynovitis and bone marrow edema (BME), the latter only detectable with MRI. Presence of these inflammatory features is predictive for the development of clinically apparent inflammatory arthritis,[30,31] with tenosynovitis as the strongest predictor for progression.[31]

In addition to inflammatory features, imaging modalities can depict bone erosions. Bone erosions are a hallmark of RA, and are even in early arthritis frequently detectable on radiographs.[32] MRI is more sensitive than radiographs,[33] depicting small erosions even in symptom-free subjects.[34] Previous studies in early arthritis have identified several MRI-detected erosion characteristics specific for RA.[35] Even though the value of inflammatory features in CSA-patients has been extensively studied, there is no information on the predictive value of erosions for progression to RA.

While imaging modalities become more available and techniques continuously improve, the risk for overinterpretation of subclinical inflammation or erosions increases. MRI-detected erosions and inflammatory features are also present in symptom-free subjects from the general population.[34] This indicates that presence of a feature is not always indicative of (imminent) disease. Even presence of inflammatory features that are uncommon in symptom-free individuals cannot predict development of inflammatory arthritis with certainty; in some arthralgia patients these features may even spontaneously resolve.[36] Prescription of medication based solely on presence of subclinical inflammation may therefore lead to substantial overtreatment. This stresses the importance of further research improving the predictive value of imaging.

Furthermore, despite its advantages imaging is also costly, time consuming and requires training to consistently interpret the images. It is therefore valuable to investigate whether presence of subclinical inflammation can be estimated with clinical assessments.

Genetics and biomarkers

At-risk patients can also be distinguished by presence of genetic risk factors and serological and immunological markers. The most well-known genetic risk factor is found within genes encoding for HLA class II molecules; molecules involved in the presentation of antigens to T-cells. Several HLA-DRβ1 alleles that predispose for

RA have a similar amino acid sequence, the shared epitope, in the peptide binding groove of the HLA-DRβ1 molecule.[4] Presence of the HLA-SE is associated with ACPA-positive RA in particular.[37] In UA-patients the HLA-SE has been shown to independently associate with development of ACPA, and not with RA-development as such.[38] Predictive value of HLA-SE in autoantibody-positive arthralgia-patients were contrasting,[39,40] therefore the effect and value of HLA-SE in the phase of CSA is still unclear.

However, the value of ACPA and RF in the phase of CSA is extensively studied and clearer. Predominantly ACPA is highly predictive for development of RA,[31,39,41,42] RF was also associated with disease progression, though not independently from ACPA.[42] Nevertheless, of CSA-patients with both ACPA and RF, more than 30% does not develop clinical arthritis during two years of follow-up,[42] indicating that presence of these autoantibodies is also not fully indicative of (imminent) RA.

Over the years, other auto-antibodies associated with RA have been discovered. Similar to ACPA and RF, anti-carbamylated antibodies (anti-CarP) are also detectable years before disease onset and have been shown to associate with future RA,[43,44] though the added predictive value to ACPA and RF in arthralgia-patients remains questionable.[45,46] Anti-acetylated antibodies (AAPA) were highly specific (86%) for RA-patients, when compared to patients with persistent non-RA or resolving arthritis.[47] The presence and predictive value of AAPA have not yet been studied in the phase of CSA.

Still, the mere presence of autoantibodies does not yield 100% specificity; meaning autoantibodies can be present is subjects that do not develop RA. It is suggested that autoantibody-response maturation might be involved in progression from autoantibody-positivity to autoantibody-positive disease. Studies on RA-development have shown an increase in autoantibody levels, even before presentation of arthritis,[12,13,43] an increase in number of autoantibody isotypes,[48] expansion of the antigen recognition profile (epitope spreading),[49] and increased glycosylation within the variable domain of ACPA IgG during RA-development.[50] The exact timing of these events, whether they occur during the phase of CSA and their role in progression to clinical arthritis and RA remains to be elucidated.

Environmental factors

Closely linked to genetic factors and autoantibodies is environmental risk factor smoking. Similar to HLA-SE, smoking poses a high risk for autoantibody-positive RA in particular,[51] its effect influenced by the presence of HLA-SE.[52,53] Even though the risk of smoking has often been demonstrated in case-control studies, smoking was

not predictive for progression to RA in autoantibody-positive arthralgia and CSA-patients.[31,39,40] This might indicate that the risk imposed by smoking exerts its effect in another phase of RA-development.

Pathogenesis

Although many predictive factors have been discovered, thus far not a single factor, or combination of factors, can replace the rheumatologists judgement in establishing the diagnosis of RA. It is therefore important, in addition to the search for new (combinations of) predictive factors, to improve knowledge on disease pathogenesis and timing of risk factors during disease development. Knowing when certain factors are present, and when they exert their effect, may improve early diagnosis and optimize treatment targets in the different phases of RA-development.

Clinically suspect arthralgia cohort

The CSA-cohort, a longitudinal inception cohort started in 2012 at the rheumatology outpatient clinic of the Leiden University Medical Centre (LUMC), the Netherlands, was studied to answer the research questions of this thesis. Included patients had recent-onset (<1 year) arthralgia of small joints and were, based on the clinical expertise and pattern recognition of the rheumatologist, at risk for development of RA. Patients were excluded if clinical arthritis was already present, or if a different explanation for the joint pain was more likely, e.g. osteoarthritis or fibromyalgia. Since general practitioners in the area of Leiden are discouraged from performing autoantibody tests, autoantibody status was largely unknown at the time of inclusion; the CSA-cohort therefore comprises of both autoantibody-negative and autoantibody-positive patients.

Baseline visits consisted of physical examination, blood sampling, questionnaires and a contrast-enhanced 1.5T MRI of the hand (metacarpophalangeal (MCP) joints 2-5 and wrist) and foot (metatarsophalangeal (MTP) joints 1-5). MRIs were scored for presence of subclinical inflammation (synovitis, tenosynovitis and BME) and erosions in line with the RA MRI scoring system (RAMRIS) and Haavardsholm et al.,[54,55] and evaluated with symptom-free controls as reference.[34]

Patients were followed for two years, with scheduled visits at 4, 12 and 24 months. In case of an increase in symptoms, or suspected arthritis, additional visits were performed. During follow-up treatment with DMARDs (including corticosteroids) was not allowed. Follow-up ended after two years, or when the main outcome was reached; clinically apparent inflammatory arthritis (IA) as determined by physical examination of the rheumatologist.

Aims and outline of this thesis

This thesis has two main aims:

1. to improve prediction and early detection of rheumatoid arthritis
2. to improve understanding of pathogenesis underlying rheumatoid arthritis development

In **Part I** the predictive value of several clinical and imaging factors is evaluated in patients with CSA.

In **Chapter 2** the value of an easy clinical test, the ability of a patient to make a fist, is studied. Difficulties making a fist in CSA is considered a risk factor for the progression to IA, however, its predictive value has never been studied separately. In addition, the underlying cause of difficulties making a fist is evaluated by studying the presence of MRI-detected subclinical inflammation in patients presenting with and without fist problems.

Chapter 3 focusses on a second clinical test often used to quickly assess the presence of synovitis in hands and feet; the squeeze test. It was investigated whether the squeeze test in CSA, in absence of clinical arthritis, is able to detect presence of subclinical synovitis as measured with MRI. The predictive value of the squeeze test is evaluated as well.

Several factors have led to a growing number of patients already being treated before the onset of clinical arthritis. Among which the emergence of imaging in clinical practice, as well as research indicating the predictive value of subclinical inflammation in the development of RA. In **Chapter 4** the presence of subclinical synovitis as starting point for treatment with DMARDs is evaluated, as well as its potential for overtreatment.

The predictive value of subclinical inflammation is widely investigated. In addition to inflammation, MRI-detected erosions are also frequently observed in the phase of CSA. The predictive value of MRI-detected erosions is investigated in **Chapter 5**.

In **Part II** the underlying pathogenesis of RA is further explored.

Development of autoantibodies often occurs prior to diagnosis of RA. In **Chapter 6** autoantibody presence and autoantibody-response maturation in the symptomatic phase of CSA is investigated. The potential role of autoantibody-response maturation in progression to IA is evaluated by analyses of three autoantibodies (ACPA, anti-CarP

and AAPA) in three different isotypes (IgM, IgG and IgA) at two timepoints.

In **Chapter 7**, the genetic risk factor HLA-SE and the environmental risk factor smoking are investigated. In this chapter the timing of these factors and their relation with autoantibodies in the development of RA is evaluated by analyses of previously reported literature on asymptomatic individuals, and data from three cohorts with symptomatic at-risk individuals.

Finally, in **Chapter 8** the summary and general conclusions from this thesis are provided. In **Chapter 9** the summary and conclusions are provided in Dutch.

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