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Early identification of Clinically Suspect Arthralgia (CSA) likely to progress to Rheumatoid Arthritis EULAR definition

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Rheumatoid arthritis is a chronic inflammatory joint disease affecting 0.5 to 1 % of the population.[1] There are ample evidences to suggest that early initiation of disease-modifying anti-rheumatic drug (DMARD) therapy in rheumatoid arthritis is more effective than with delayed initiation of such treatment particularly in modulating the erosive and persistent rheumatoid arthritis.[2] Preceding the onset of clinical arthritis, interventions in the initial phase of the clinical disease, may be more effective in reducing the risk of persistent disease and minimizing the damage.

In anticipation of the fact that clinical characteristic alone are insufficient for predicting RA, a combination of clinical as well as other factors e.g. auto-antibodies, imaging etc. become necessary for identification of patients with imminent RA. These could finally become part of criteria for imminent RA, but presently EULAR entrusted a task force aimed to define **arthralgia at risk for RA.** Differences in practice and experience of a clinician is a subjectivity drawback, otherwise use of concept of clinically suspect arthralgia (CSA) is appropriate in clinical practice. Hence, it is imperative to define CSA.

There is systemic inflammation, a characteristic for rheumatoid arthritis which as per evidence eventually lead to complications ranging from osteoarticular manifestations in rheumatoid arthritis to even increased risk of cardiovascular disease. These complications can be avoided if the disease is identified in the stage of arthralgia. EULAR has defined such **arthralgia suspicious for progression to rheumatoid arthritis.** It could be safely concluded that absence of inflammation or remission may be associated with reduced osteoarticular damage as well as a reduced risk of CVD in rheumatoid arthritis. Overall findings definitely lead to the hypothesis that achieving remission reduces the risk of damage to various systems in rheumatoid arthritis patient.

Rheumatoid arthritis evolves through a process which has multiple phases. Arthralgia, during its transition to rheumatoid arthritis, has clinically apparent synovitis before its transition to clinical arthritis. Many patients pass through a phase characterized by presence of symptoms without clinically apparent synovitis. A study group of EULAR differentiated various phases:

1) Presence of genetic and environmental risk factors for rheumatoid arthritis.
2) Systemic autoimmunity associated with rheumatoid arthritis.
3) Symptoms without clinical arthritis.
4) Unclassified arthritis.
5) Rheumatoid arthritis.[3]

The first opportunity to clinically recognized RA patient is the symptomatic phase preceding clinical arthritis. These are the **cases at risk for progression to rheumatoid arthritis.** This phase is less well studied in comparison to extensively studied other phases. A few studies reported on symptoms experienced by patients in this phase and on their impact on daily life.[4] No consensus based approach have yet been identified regarding the clinical characteristics specific for this phase.

Clinically suspect arthralgia (CSA) patients have articular symptoms without signs of arthritis. They are likely to be considered to be at increased **risk for progression to rheumatoid arthritis.**[5] Identification of the presence of CSA will always be based on expertise of the clinician. The available recent data reveals that patients with CSA constitute only a small percentage of all patients with arthralgia visiting any rheumatology OPD for the first time (~ 7%). ~ 20% of these CSA patients did indeed progress to rheumatoid arthritis during follow up.[6] It is noteworthy that rheumatoid arthritis could not be recognized by the rheumatologist in a minority of patients presenting with arthralgia. An accurate clinical experience is needed to distinguish patients with arthralgia at risk of developing rheumatoid arthritis from other patients with arthralgia.

EULAR study group consisting of 18 rheumatologists, 1 methodologist, 2 patients, 3 health professionals and 1 research fellow formed a **Task Force.** This task force had 3 phases in their study. Phase 1 considered a list of parameters characteristic for clinically suspect arthralgia. Phase 2 evaluated 50 existing patients on paper, classified them as CSA / no CSA and indicated their level of confidence. Finally, leading to derivation of provisional set of parameters, phase 3 studied this set of parameters for validation where all rheumatologists collected their patients with and without CSA from their outpatient clinics. This task

force summarized to identify a combination of clinical features which appropriately characterized patients with arthralgia, at risk of rheumatoid arthritis. CSA is not in itself a disease, but a combination of symptoms and signs. It is noteworthy that a similar approach was undertaken to define inflammatory back pain which got integrated in the Assessment of SpondyloArthritis international Society classification criteria.[7]

Various parameters were selected in history taking and physical examination. Frequencies of these parameters in the patients in phase 2 were categorized as CSA, no-CSA or were considered unclassifiable. **The history taking encompassed-**

a. Joint symptoms of recent onset of duration <1 year (4-10 joints with symptoms).
b. Symptoms in several small joint/joint regions-MCP (wrists, PIP, MTP).
c. Symmetric bilateral symptoms or signs in same joint region.
d. Duration of morning stiffness ≥60 minutes.
e. Most severe symptoms in the early morning.
f. Improvement of symptoms during day.
g. Increasing number of joints with symptoms over time.
h. Patient experience of swelling of small hand joints.
i. Presence of a first-degree relative with RA.

Apart from history taking, the parameters covered under physical examination included–

a. Difficulty with making a fist
b. Local tenderness in involved joints
c. Positive squeeze test of MCP and MTP joints

In phase 3, 78 patients with CSA and 61 patients with arthralgia without CSA were identified based on clinical information alone, without data relating to additional investigation. Finally, the combination of 7 parameters performed well to explain the clinical expertise, which performed equally well in identifying patients with arthralgia, who were considered to be at risk of RA by the experts. A sensitivity > 90% was obtained in the presence of ≥3 parameters and a specificity > 90% in the presence of ≥4 parameters.

This was unanimously agreed by the EULAR Task Force that arthralgia, suspected for progression to RA is defined by the seven parameters and these following parameters are to be used in patients with arthralgia without clinical arthritis and without other diagnosis or other explanation for arthralgia-

a. 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

a. Physical examination:
   - Difficulty with making a fist
   - Positive squeeze test of MCP joints

Arthralgia at risk of RA was finally established by describing a set of clinical characteristics. These seven parameters accurately reflected opinion of experts about CSA. Arthralgia at risk of RA can be defined by the presence of ≥3 parameters; presence of ≥4 parameters suggests high specificity. The predictive accuracy of these seven clinical parameters alone requires further studies.

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