

50 An Approach to Diagnosis and Management of Undifferentiated Arthritis

Abstract: There is an increased awareness of the existence of a group of well defined inflammatory arthropathy which cannot be classified by the existing ACR or EULAR criteria into a definitive type of arthritis.

They have been defined as undifferentiated or unclassified arthritis. About 25% of patients with UA at onset will evolve to defined connective tissue diseases during follow-up. Prevalence varies between

7-60% in various cohort studies all over the world. Clinical presentation are usually oligo or polyarticular. Compared to early RA, early UA presents more acutely. There is lower joint count and less hand involvement. Duration of morning stiffness is often shorter. With oligoarticular presentation ReA is excluded by no evidence of previous infection. Apart from clinical variables some investigations are also helpful to differentiate early RA or SpA. X-rays of hands and feet showing evidence of erosions in early RA is more common than in UA. MRI is however better in terms of bone edema. Ultrasound with power Doppler is very sensitive in picking up early synovitis even when there is no clinical evidence. One auto antibody which is very helpful in anti CCP which may be positive 7 to 10 years before clinical appearance of RA. Additional RA specific autoantibodies like AntiSA and anticitrullinated rat filaggrin are specific for early RA. Antibodies against AGE IgG are also specific for RA. Role of HLA typing for shared epitope is important in picking out early RA in the UA cohorts. CCP in the synovial biopsy and vascular patterns in the synovium is also an important marker. Prognostically about 50% may achieve spontaneous remission, 25% evolve into RA and 30-40% remains undifferentiated.

Factors suggesting disease progression to RA are duration of symptoms, erosions at presentation, polyarthritis with hand and foot involvement, presence of RF and anti CCP and shared epitope.

Treatment of UA is still not validated various studies have shown that one or two injections of methyl prednisolone depo preparation may abort the inflammatory process in the early stages.

Use of DMARDs are justified in those subjects who fulfill the criteria of rule of nine proposed by a dutch group of rheumatologist.

Key words: Undifferentiated Polyarthritis Syndrome, Undifferentiated arthritis, UCTD, Benign-arthritis.

Abbreviations used

ACR	– American College of Rheumatology,	DEXA	– Dual Energy X-Ray Absorptiometry
HLA	– Human Leucocyte Antigen,	CCP	– Citrullinated Cyclic Peptide
RA	– Rheumatoid Arthritis,	ReA	– Reactive Arthritis
UA	– Undifferentiated Arthritis,	SpA	– Spondylo Arthropathy
PsA	– Psoriatic Arthropathy,	DMARD	– Disease Modifying Antirheumatic Drug
NSAID	– Non-Steroidal Anti-Inflammatory Drug		
UPS	– Undifferentiated Polyarthritis Syndrome		
EULAR	– European League of Nations Against Rheumatism.		
AGE	– Advanced Glycation Endproduct.		

INTRODUCTION

It is common clinical experience of the existence of a group of well defined arthropathy which can not be categorized to any particular type by the existing ACR or EULAR criteria. There are however clinical and serological signs of some form of autoimmune inflammatory connective tissue disease. These patients have been variably defined as early UCTD; UCTD or undifferentiated polyarthritis syndrome. (UPS). With passage of time some develop into typical RA or SpA or undifferentiated SpA. Others remain as a more severe and persistent UA. From the existing literature it is evident that an average of 25% of patients with an undifferentiated disease at onset will evolve to well define arthritides during the follow-up.

Historical Perspective and Nomenclature

Population based studies of cohorts from 1950s to 1960s identified a group of patients with sero - ve polyarthritis who had complete or near complete remission after several years, these were termed "Benign Polyarthritis."¹ More recently "Early arthritis clinics" identified sizeable proportion of patients with early inflammatory arthritis which cannot be classified by ACR criteria. These heterogenous group were categorized " Undifferentiated Arthritis".²

Zeidler et al identified four subtypes of UA. These are (1) early stage of a defined arthritis. (2) Forms fruste or partial form of a classifiable CTD like latent lupus, UCTD or MCTD. (3) Overlap of more than one disease (4) Arthritis of unknown origin that may or may not become differentiated in future.³

Prevalence

Inception cohorts from Europe and North America have shown that UA is common and seen more frequently than RA. In various studies, it is estimated to range between 20 to 60% of early arthritis cohorts. This decreases with increasing disease duration as proportions of UA patients develop classifiable arthritis-like RA, SPA or reactive arthritis.⁴ Study of various patient populations for prevalence of UA and their follow up is being given in Table 1.

Incidence

Estimates are variable in various population studies. Wiles N, et al made a very pertinent remark -"Estimating the incidence of UA is like trying to hit a moving target". They found that RA incidence increases and UA incidence decreases with increasing disease duration.⁵ In one study from Sweden, which has a very good social security and registration system, it was observed that an annual incidence rate for all inflammatory arthritis with mean symptom duration of 2 months (range 0-17) months) was 115 per 100,000 population. Out of which UA 54, RA 31, ReA 28 and other arthropathies, less than 10 per 100,000 population.⁶ In the Norfolk arthritis registry cohort (NOAR) study, out of 532 cases with inflammatory arthritis, 354 could be followed up. 254 (72%) were RA and 100 (28%) were UA.⁷

Clinical presentation of UA

Asymmetrical Polyarticular

Compared to RA they usually present more acutely.⁸ However total joint count (especially swollen joints) is usually lower with less hand joint involvement and less symmetric joint involvement compared to classical RA. Usually there is absence of temporomandibular, sternoclavicular or acromioclavicular involvement.

Duration of early morning stiffness is often shorter. HAQ score (functional disability index) or grip strength is significantly less.⁹ Oligoarthritis, particularly of large joints is common (in about 50% of cases) at presentation.

Acute phase reactants like CRP and ESR are elevated in both but serum amyloid A level is higher in RA than UA.¹⁰

Asymmetrical Oligoarticular

They may represent some of the cases of reactive arthritis without history of preceding infection.

Some investigators have found evidence of preceding bacterial infection through culture, serology or DNA testing in 30-50% cases of early UA.¹¹

Reactive arthritis should be excluded by negative evidence of previous infection by history, clinical examination, culture and serology particularly for infections like Chlamydia.

UA should be classified after exclusion of the above.

Diagnostic Work-up

This consists of the following :

- Imaging
- Auto antibodies
- HLA testing
- Dexa scan
- Synovial biopsy

Imaging

X-ray-conventional or digital: They pick up joint space narrowing and erosions which are late findings. They are more common in early RA than UA, but can be seen in 35% of polyarticular UA at presentation.¹²

MRI: Plain or contrast is more sensitive in detecting bone erosion and is able to detect bone marrow edema and synovitis which precedes erosions.

Ultrasound with Power Doppler

Able to detect synovitis better than clinical examination. Power Doppler can assess synovial vascularity which is increased in synovitis.

Ultrasound has an edge over MRI due to flexibility of examining multiple joints at a time and can be used in clinic and being much cheaper.¹³

Role of Auto Antibodies

IGM RF is positive in 6-20% , IgA RA is positive in 6% and anti CCP is positive in 3-20% of UA Patients.¹⁴ IgA RF if positive is associated with more severe diseases.

Although the clinical usefulness of anti CCP is more in RF negative patients, but with other clinical parameters it can predict disease persistence, progression and development of erosions better than RF.^{15,16}

In the Leiden Cohort of 936 patients, 127 of 318 UA patients progressed to RA. In those UA patients, anti CCP and ACR criteria (especially polyarthritis), symmetric arthritis and erosions, predicted the development of RA.¹⁵ These studies indicate that in early UA, anti CCP, in combination with clinical variables, identifies patients requiring closer follow up and potentially more aggressive therapy.

Newer RA Specific Auto Antibodies

Anti SA, which targets citrullinated vimentin identify patients with greater potential for erosive disease.¹⁶ Autoantibodies recognizing citrullinated rat filaggrin in an ELISA using citrullinated

and non-citrullinated recombinant proteins as antigens are highly diagnostic for rheumatoid arthritis.¹⁷

As in diabetes mellitus, inflammation and oxidative stress leads to non enzymatic glycosylation with formation of advanced glycosylation end products (AGE). Antibodies to AGE damaged IgG – both IgG and IgM are elevated in RA.

In the NIH early arthritis cohort study, AGE IgG was present in 20% of patients regardless of diagnosis. But in RA they are persistently elevated in high titres compared to transient elevation in UA.¹⁸

Role of HLA Testing

The shared epitope doubles the risk of developing RA especially in anti CCP positive patients.¹⁹ Studies in UA cohorts have shown variable associations between HLA DRBI shared epitope and disease persistence or severity of erosions.¹⁹ It has been proposed that HLA DRBI shared epitope and HLA DQBI molecules DQ3 and DQ5 increase susceptibility to RA, whereas in patients with a specific peptide sequence DERAA gives protection against severe RA.²⁰

UA patients having HLA DRBI and DQBI are more likely to progress to RA, where as UA patients having HLA DRBI with protective DQ5 molecule and peptide sequence DERAA are less likely to progress to RA.²⁰

UA patients presenting with oligoarthritis and who are HLAB27 positive along with metatarsal pain and genitourinary symptoms are more likely to develop reactive arthritis.²¹

DEXA SCAN

Periarticular bone loss in an early feature of RA which can be picked up by DEXA of hands. It can be helpful in UA patients who are likely to progress to RA.²²

SYNOVIAL BIOPSY

Synovial tissue can be obtained by closed needle biopsy or by arthroscopy. Vascular patterns are important. In RA vessels are relatively straight and remain so regardless to treatment. Whereas in SpA they are tortuous. Early UA patients with tortuous or mixed pattern of vessels are less likely to progress to RA. But by far the most important diagnostic and prognostic aspect of synovial biopsy in the presence of CCP locally in the synovium which is very specific for RA.²³

PROGNOSTIC STRATIFICATION

It is important to stratify to UA patients to predict future outcomes:

- Whether the patient's synovitis will remit.
- Whether the synovitis will persist.
- Whether it will result in erosive joint damage.
- Whether criteria for RA or another defined arthritis will be met.

PROGNOSTIC OUTCOME

13–60% experience remission. 7–65% evolve into RA or other definable arthritis. 10–40% remain undifferentiated with persistent disease.²⁴ These figures are from various studies in specifically reporting outcomes for UA.

A review of monoarthritis on the other hand has shown that remission 60% cases, progress to chronic oligoarthritis or polyarthritis in 10 to 40% cases, while remaining remain UA.²⁵

Predictors of Progression to RA

Subacute Symptoms at Presentation

- Polyarthritis with hand and foot involvement.
- Presence of RF, anti-CCP and shared epitope.
- Resistance to initial corticosteroids.
- Incomplete response to DMARDS.

Predictors of Progression to Re A

- Oligoarticular presentation.
- More acute onset with dactylitis.
- Enthesopathy
- Metatarsal (foot) pain
- Genitourinary symptoms along with increased acute phase reactants (esp CRP)
- HLA B27 positivity. These above have a sensitivity of 69% and a specificity of 94%.²¹

Table 1 shows the prognostic outcome of some selected cohorts around the world of early inflammatory arthritis, including RA and UA. They have identified various clinical features and laboratory investigations associated with disease persistence, development or erosions, functional status, or a final diagnosis of RA or other arthropathy.

In the Leeds early arthritis cohort, disease duration of more than 12 weeks was the strongest predictor of persistent disease at 6 months for both RA and UA.²⁶

In another study of early undifferentiated polyarthritis of the hands, the presence of synovitis at 12 weeks predicted the need for DMARDS (required by 30%) over the course of 1 year.²⁷

In the Schumacher's Pennsylvania cohort of 121 early arthritis patients with mean disease duration of 3 months. There were 21% monoarthritis, 34% oligoarthritis and 45% polyarthritis. They were followed up for at least 1 year (medium 5 years). It was observed that 50% of UA patients had persistent disease and 50% remitted compared to active disease in 90% of RA and 85% of spondyloarthropathy.²⁸

There is still dilemma regarding use of aggressive treatment in early UA as 40-50% of these patients achieve remission spontaneously without any investigation, but about 1/3 rd of them will ultimately progress to RA. Treatment with NSAIDs alone will miss the window of opportunity for those destined to evolve into RA. Conversely generalized use of DMARDS may subject patients to unnecessary potential toxicity. Recently a group of rheumatologists from Leiden University Medical Center, Netherlands has developed a prediction model based on simple scoring system, 9 key predictive variables.³⁰

There are 9 clinical variables which gives a score from 0-14. With 0 representing the lowest risk and 14 the highest risk of developing RA.

The clinical variables are:

- Patient's gender
- Patient's age
- Location of affected joints(hand and feet joints : symmetric localization)
- Degree of morning stiffness.
- Number of tender joints
- Number of swollen joints
- C-reactive protein level.
- Rheumatoid factor positivity.
- Anti-CCP antibody.

Based on their findings the researchers recommend a cut off scores of 6 and 8 to guide treatment decisions. In their study, 91% of the UA patients with a score of 6 or less did not develop RA and 84% of patients with a score of 8 or greater did develop RA.²⁷

Leiden Rule of Nine

- Patients with a score of 8 or higher should be treated aggressively with DMARDs.
- Patients with a score of 6 or less should be monitored and put on NSAIDs.
- But there is still a dilemma regarding patients between a score of 6 and 8.
- There are various management protocols of UA.
- The important ones are given below.

Leeds Early UA Cohort Study

All patients with clinical synovitis were treated with IM or intra-articular , methyl prednisolone 80 to 120 mg.

Reevaluated after 2 weeks, DMARDs were considered if patients progressed to polyarthritis after 12 weeks or if additional corticosteroids treatments (IA) were required to the same joints.²⁶

In the NOAR cohort, earlier treatment, within 6 months of symptom onset by DMARDs especially SS2 or corticosteroids resulted in less radiographic damage than delayed treatment even in patients without erosions at baseline.²⁴

The SAVE study (Stop arthritis very early) is another placebo-controlled study which recommends a single injection of methyl prednisolone IM in UA patients of less than 16 weeks duration.²⁹

We at our institution did a small study in a cohort of 105UA patients with the following aims.

1. Evaluated the course of patients of persistent UA
2. Compared the clinical features of recent onset UA (<1 yr) with a cohort of persistent UA (>3 yrs)
3. Compared the clinical features of persistent oligo and polyarticular UA of 3 yrs duration.
4. Compare late UA with RA of same duration.

The results are given in Tables 2, 3 and 4.

CONCLUSION

As we continue to see patients earlier in the course of their disease, the proportion of UA cases are likely to increase. Instead of assigning a diagnosis, the need is to identify patients at risk of developing persistent synovitis, erosive disease and functional disability.

Rule of 9 is an important prediction model along with serological markers like anti-CCP, shared epitope and ultrasound with power doppler.

Regarding therapy there is no validated protocol but it is important to control the inflammatory process promptly with corticosteroid which may attenuate or abort pathological immune processes.

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MULTIPLE CHOICE QUESTIONS

1. **On an average 25% of patients with undifferentiated arthritis at onset evolve to well-defined arthritis:**
True/False
2. **NOAR cohort study follow-up showed that 72% patients of UA evolve into RA:**
True/False
3. **Symmetrical UA usually presents more acutely than RA:**
True/False
4. **All are true except:**
 - A. UA has less early morning stiffness
 - B. Absence of involvement of sternoclavicular/temporomandibular joint involvement
 - C. Serum amyloid A level is higher in RA than UA
 - D. Is always rheumatoid factor positive
5. **MRI is very sensitive in detecting bone marrow edema early:**
True / False
6. **US power Doppler can detect early synovitis by assessing synovial vascularity.**
True/False.
7. **All are newer RA specific antibodies except:**
 - A. Anti CCP
 - B. Anti SA
 - C. Anti AGE-IgG
 - D. Anti Sm
8. **Patients with HLADRB1 and HLADQB1 are susceptible to develop RA?**
True/False
9. **Which of the peptide sequence in HLA gives protection against RA:**
 - A. MRSA
 - B. TORRA
 - C. DERRAA
 - D. PMTSE
10. **CCP in the synovium is the most diagnostic feature of a mono/oligo articular RA:**
True/False
11. **Synovial vessels are tortuous in sporiatic arthritis:**
True/False
12. **All are predictors of progress to RA except:**
 - A. Polyarthritis with hand and feet involvement
 - B. Presence of RF, Anti-CCP and shared epitope
 - C. Sub-acute symptoms are presentation
 - D. Resistance to initial corticosteroids
 - E. Presence of enthesopathy
13. **Single dose of IM - Methylene Prednisolone is useful in UA Management:**
True/False

1. True 2. True 3. True 4. D 5. True 6. True 7. D 8. True 9. C 10. True 11. True 12. E
13. True