Review

Undifferentiated connective tissue diseases (UCTD): A review of the literature and a proposal for preliminary classification criteria

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Clin Exp Rheumatol 1999; 17: 615-620.

Key words:
Undifferentiated connective tissue diseases, preliminary classification criteria.

ABSTRACT
The connective tissue diseases include a heterogeneous group of conditions characterized by a wide variety of signs and symptoms. There also exists, however, a group of systemic autoimmune disorders with signs and symptoms not sufficiently evolved to fulfill any of the accepted classification criteria for the defined connective tissue diseases. These conditions have been defined as undifferentiated connective tissue syndromes, latent lupus, incomplete lupus, and undifferentiated connective tissue diseases.
After an analysis of the existing literature, we discuss the possible significance of the undifferentiated diseases among the already defined connective tissue diseases and make a proposal for preliminary classification criteria for these conditions.

Introduction

The connective tissue diseases (CTDs) include a heterogeneous group of diseases characterized by a wide variety of signs and symptoms. Since most of the signs and symptoms of these diseases are not disease-specific and may overlap, the individual borders of the CTDs are often undefined. For this reason, in order to facilitate scientific communication, *ad hoc* committees (either independent or appointed by scientific societies) have laid down classification criteria for most of the connective tissue diseases (1-8).
The history of the undifferentiated connective tissue diseases dates back to 1980, when LeRoy and colleagues proposed the term "undifferentiated connective tissue syndromes" (UCTS) to refer to the early phases of connective tissue diseases that were at their onset indefinite, as opposed to the condition of mixed or overlapping syndromes (9). Although these terms have often been used interchangeably, undifferentiated connective tissue diseases are conditions in which the disease is not well defined, whereas in mixed or overlapping syndromes the disease appears to be defined, based on accepted criteria (10). Overlapping diseases share the features of two or more defined CTDs and fulfill the relevant classification criteria (10,11), while the mixed connective tissue diseases have their own classification criteria as proposed by Sharp in 1972 (2).
In the same paper, LeRoy pointed out that a certain proportion of patients with an undifferentiated profile do not develop a definite CTD, instead remaining undifferentiated indefinitely or experiencing a remission of all signs and symptoms (9).
Since the publication of LeRoy's paper, the concept of undifferentiated diseases has been used by many authors. However, studies focusing on these conditions began to appear only in 1989 (12, 13). Although these diseases have been denominated in a variety of ways (Table I), the different terms that have been used are broadly equivalent.
Analyzing the literature, it is possible to highlight important questions regarding the undifferentiated connective tissue diseases, such as their frequency, their rate of evolution to defined CTDs and the timing of this event, the factors predictive of this evolution, the clinical and serological profiles of undifferentiated patients and many others. In this paper we will review current knowledge regarding these issues.

How frequent are the undifferentiated diseases?

No epidemiological studies have been carried out on the UCTDs; therefore data

Table I. Terms and definitions used in the literature to indicate undefined connective tissue diseases.

Author	Term	Definition
LeRoy (1980, ref. 9)	Undifferentiated connective tissue syndromes	
Greer (1989, ref. 13)	Incomplete lupus erythematosus	Patients with fewer than four, but not less than two of the classification criteria for SLE.
Ganczarczyk (1989, ref. 12)	Latent lupus	Patients with features suggestive of SLE (one or two ARA criteria), but not fulfilling the classification criteria.
Alarcon (1991, ref. 14)	Early undifferentiated connective tissue diseases	Patients with RP*, isolated KCS*, UPA* or other manifestations suggestive of a CTD and a disease duration of less than 12 months.
Mosca (1998, ref. 19)	Undifferentiated connective tissue diseases	Patients with signs and symptoms suggestive of a CTD and at least one non-organ specific autoantibody, but not fulfilling the criteria for any defined CTD, and a disease duration of at least 12 months.
Danieli (1998, ref. 20)	Undifferentiated connective tissue diseases	Patients with signs and symptoms suggestive of CTD, lasting for at least 12 months.
Danieli (1999, ref. 21)	Undifferentiated connective tissue diseases	Patients with signs and symptoms of suspected autoimmune origin, not fulfilling the criteria for any defined CTD.
Dijkstra (1999, ref. 22)	Undifferentiated connective tissue diseases	Patients with ANA and features of CTD, but insufficient to fulfill the criteria for any established CTD.

* RP: Raynaud's phenomenon; KCS: keratoconjunctivitis sicca; UPA: unexplained polyarthritis.

on the prevalence of these conditions can only be obtained indirectly. In 1991 Alarcón *et al.* (14) reported that among 410 patients with connective tissue disorders of less than one year's duration being followed at the clinics participating in the Cooperative Systematic Studies of the Rheumatic Diseases Program, 213 (52%) had an undifferentiated profile (early undifferentiated connective tissue diseases, EUCTD). Among the patients with connective tissue diseases referred to our Unit between 1979 and 1998, about 20% were diagnosed as having undifferentiated connective tissue diseases (UCTD).

This difference in the ratio of UCTD to CTD patients can be attributed to differences in the patient selection procedures used. In Alarcón's study all patients with a disease course of less than 12 months were included, some of the clinical manifestations reported were of low disease specificity, and some of the patients had negative antinuclear antibody titers. Therefore, it is possible that her EUCTD patients included cases of transient disease or non-autoimmune conditions. For example, 10% of her patients with unexplained polyarthritis (UPA) experienced sustained remission during the first year of their disease; thus, they could be considered as having a transitory disease (15).

Despite these limitations to the small amount of data available, it seems clear that the undifferentiated diseases are far from rare and represent a sizeable proportion of patients with connective tissue diseases. It is obvious that rigorous epidemiological studies will be necessary to define the impact of these conditions within the context of the connective tissue diseases.

Do undifferentiated diseases evolve to definite diseases, and if so when?

As described above, the first to assess this question was LeRoy in 1980 (9); his aim, however, was to use the term undifferentiated connective tissue syndromes (UCTS) to define early undefined diseases which probably would evolve to definite diseases. While proposing this concept, he invited the reader to consider the possibility that some undifferentiated diseases might remain so.

Early data regarding this point are conflicting. In 1980 Lom Orta *et al.* (16) described a population of patients who did not fulfill the diagnostic criteria for SLE, and observed a high rate (21/31; 68%) of evolution to systemic lupus erythematosus (SLE) an average of 27.4 months after the disease onset. Based on these findings, the undifferentiated diseases were described by the authors as a subset of systemic lupus erythematosus (SLE) with a more benign evolution.

In 1989 Ganczarczyk *et al.* (12) followed 22 patients with latent lupus for a period of 5 or more years, and found that 7 cases evolved to SLE while 15 remained undefined. He concluded that the undifferentiated diseases may represent: (i) the mild end of the spectrum of SLE; (ii) an evolutionary phase of SLE; or (iii) a diathesis awaiting other provoking factors.

In the same year Greer *et al.* (13) studied a cohort of 38 patients whom he defined as cases of "incomplete lupus erythematosus" (ILE) since they did not fulfill all of the criteria for SLE. These patients were followed for a mean of 19 months and during this period only 2 developed a definite SLE, after 9 and 26 months of observation, respectively. The authors concluded that patients with ILE do not develop SLE, and remain undefined over time. Furthermore they proposed that ILE might be a frequent syndrome with a mild and stable profile that rarely evolves to an overt rheumatic disease. In particular, they stressed the hypothesis that ILE is not a subset of SLE, and suggested that such conditions be described as "undifferentiated tissue diseases".

In 1996 Calvo-Alén *et al* (17) published

Table II. Evolution of undifferentiated connective tissue diseases to definite diseases.

	No. of patients	Percentage evolving to definite CTD	Period of evolution (months)	Defined connective tissue diseases
Lom Orta (1980, ref. 16)	31	68%	27.4	SLE
Ganczarczyk (1989, ref. 12)	22	32%	n.r.*	SLE
Greer (1989, ref. 13)	38	5%	17.5	SLE
Calvo-Alén (1996, ref. 17)	143	29%	60	SLE, (13%) RA (10%), SSc (4%), PM/DM (2%)
Danieli (1998, ref. 20)	84	37%	48	SSc (15%), SLE (8%), RA (3%), MCTD (3%)
Mosca (1998, ref. 19)	91	13%	36	SLE
Danieli (1999, ref. 21)	165	6%	n.r.	SLE (3%), SS (2%), MCTD (0.5%), PM (0.5%)
Dijkstra (1999, ref. 22)	65	51%	24	RA (26%), SS (18%), SLE (6%)

* n.r.: not reported.

the results of a study on 143 patients with EUCTD who were followed 5 years; in 1999 the same cohort of patients was further analyzed by Williams *et al.* In the first study an evolution toward definite CTDs was observed in 29% of the patients. SLE was diagnosed in 13%, RA in 10%, SSc in 4%, and PM/DM in 2%. In 12/18 (67%) patients the evolution to SLE was observed within the first three years of follow-up and was "complete" by the fifth year. These data were confirmed in the second study, in which an evolution to a specific CTD in patients with an undifferentiated profile was seen in limited number of patients. These two studies reported another possible evolution of the EUCTDs, i.e. to a complete, sustained and sometimes spontaneous disease remission. Such remission was observed in 10% of the patients with unexplained polyarthritis, 10% of the patients with Raynaud's phenomenon, and 6% of the patients with UCTD.

In 1998 (19) we analyzed a group of 81 patients with undifferentiated diseases and a disease duration of at least 12 months; only 13% of these patients evolved to SLE during the first 3 years of their disease.

In 1998 Danieli *et al.* (20) published a study of 84 patients with undefined diseases who were followed for a period of 5 years. During the follow-up period (generally during the first 48 months of disease), 33 patients (37%) developed a well defined CTD, specifically SSc (15%), SS (8%), SLE (8%), RA (3%) or MCTD (3%). The authors suggested that those patients with undefined disease persisting for a period of 5 years could be considered to have a distinct condition which they termed UCTD. In this issue of *Clinical and Experimental Rheumatology* (21), the same authors report on 165 UCTD patients being followed as part of a multi-center study. In this study, the evolution to defined connective tissue diseases appears to be even lower (6%), thus supporting their findings reported in 1998.

A much higher rate of evolution to a defined CTD, i.e. 51%, was observed in 1999 by Dijkstra *et al* (22), who analyzed a population of 65 patients with undifferentiated diseases and a mean disease duration of 9 years. Like other authors, Dijkstra found that the evolution occurred within the first two years of follow-up in 75% of the cases and within the first 5 years in 90%. Most of these patients developed rheumatoid arthritis (26%), Sjögren's syndrome (18%) or SLE (6%). Nevertheless, the authors also found that in a certain number of patients the undifferentiated profile of the disease would remain so during the entire follow-up period (Table II).

Upon comparison, a number of discrepancies are immediately evident among these published data. In approximately half of the studies the undifferentiated disease evolved exclusively to SLE, while in the remaining studies a broader spectrum of CTDs was involved, ranging from Sjögren's syndrome to scleroderma, SLE, polymyositis/dermatomyositis and rheumatoid arthritis. Clearly this discrepancy arises from the fact that different studies used different patient selection methods, including patients with different disease durations or who underwent different diagnostic evaluations. Indeed, in its very early phases a UCTD may not be fully expressed, requiring several months for its various manifestations to appear. This could explain the higher rate of evolution to CTDs in those studies which recruited patients with very early disease, and would seem to be confirmed by the fact that most cases of such evolution were observed during the first year of disease. Furthermore, patients with very early disease who did not undergo a complete evaluation might have been erroneously diagnosed and included in the undifferentiated group.

Finally, as already observed, patients with very early disease may actually be suffering from transient symptoms not caused by an autoimmune disease and that may undergo spontaneous and persistent remission.

Are there features at disease onset predictive of a future evolution to definite diseases?

Since it has been observed that a certain percentage of patients with UCTDs will develop a defined CTD (23,24), much attention has been focused on the identification of the manifestations that may predict this evolution. In particular, since

Table III. Features at onset indicative of an eventual progression to SLE.

Authors	Predictive factors for the evolution to SLE
Lom Orta (1980, ref. 16)	Not evaluated
Smeenk (1985, ref. 25)	Anti-dsDNA
Ganczarczyk (1989, ref. 12)	Not found
Greer (1989, ref. 13)	Not evaluated
Calvo-Alén (1996, ref. 17)	Alopecia, serositis, Coomb's, anti-dsDNA, anti-Sm, ANA
Danieli (1998, ref. 20)	Anti-dsDNA, anti-cardiolipin
Mosca (1998, ref. 19)	Not found
Danieli (1999, ref. 21)	Not evaluated
Dijkstra (1999, ref. 22)	Not evaluated

evolution to SLE was the most common finding in different patient cohorts, many studies have analysed the correlation between UCTD and SLE (Table III).

Ganczarczyk *et al* (12) did not find any feature at disease onset that was indicative of an eventual progression to SLE. Our data support his observations. In fact, even upon multivariate analysis we did not find any factor that was predictive of an evolution to SLE (the presence of Raynaud's phenomenon, photosensitivity and sicca symptoms showed an inverse, but not statistically significant, correlation with the development of SLE) (19).

In contrast, Swaak reported in 1985 that positive anti-dsDNA antibodies, as detected by the Farr assay, were predictive of the evolution to SLE in a group of non-SLE patients, since 70% of the cases fulfilled the ARA criteria by the end of the first year of follow-up.

Calvo-Alén *et al* (17) found that alopecia, serositis and a positive Coomb's test correlated significantly ($p = 0.014$, $p = 0.064$ and $p = 0.032$ respectively) with the evolution to SLE. Furthermore, positivity for anti-dsDNA ($p = 0.002$), anti-Sm ($p = 0.006$), a positive test for syphilis ($p = 0.007$) and an ANA test with a homogenous pattern on immunofluorescence ($p = 0.014$) also were statistically significant for the evolution to SLE. On multivariate analysis the following were found to independently predict the outcome of interest: discoid lupus, serositis, ANA homogeneous pattern, and anti-Sm positivity.

In 1998, Danieli *et al* (20) evaluated the signs and symptoms predictive of the evolution of undifferentiated patients to SLE, SSc or SS. On univariate analysis sicca symptoms, Raynaud's phenomenon, sclerodactily, oesophageal dysfunction and ANA with a nucleolar pattern were found to be significantly predictive of the development of SSc. Raynaud's phenomenon, xerostomia and anti-SSA were predictive of Sjögren's syndrome, and fever, anti-cardiolipin antibodies and anti-dsDNA were predictive of SLE.

The studies by Greer (13), Williams (18), and Dijstra (22), and the second study by Danieli (21) do not discuss this point, due either to the small number of patients analyzed or to their having adopted a different approach to the problem.

The contrasting findings regarding the predictive role of anti-dsDNA could be explained by the different detection techniques used: the Farr assay in the Swaak, Calvo-Alén and Danieli studies, and IFI on Crithidia in our study.

Which are the clinical and serological manifestations of the undifferentiated diseases?

Since some patients appear to maintain an undifferentiated profile indefinitely, it is of interest to evaluate their clinical and serological profiles. Based on the data in the studies discussed above, the undifferentiated diseases seem to have a mild evolution and to require at most symptomatic therapy. Nearly all authors

Table IV. Clinical and serological manifestations of undifferentiated connective tissue diseases reported in various studies.

	Ganczarczyk (1989, ref. 12) 22 pts.	Greer (1989, ref. 13) 38 pts.	Alarçon (1991, ref. 14) 213 pts.	Mosca (1998, ref. 19) 91 pts.	Danieli (1998, ref. 20) 84 pts.	Dijkstra (1999, ref. 22) 22 pts.	Danieli (1999, ref. 21) 165 pts.	Weighted mean
Arthralgias	n.r.	n.r.	n.r.	80%	59%	77%	37%	55%
Raynaud's	33%	n.r.	46%	46%	56%	45%	56%	50%
Arthritis	40%	47%	70%	37%	23%	14%	22%	42%
Leukopenia	20%	n.r.	11%	41%	n.r.	n.r.	n.r.	20%
Anemia	n.r.	n.r.	23%	16%	n.r.	n.r.	n.r.	21%
Xerophthalmia	n.r.	n.r.	7%	41%	12%	18%	22%	18%
Xerostomia	n.r.	n.r.	7%	36%	12%	18%	22%	18%
Photosensitivity	13%	24%	10%	30%	n.r.	n.r.	n.r.	17%
Serositis	13%	16%	10%	5%	n.r.	n.r.	13%	11%
Malar rash	n.r.	13%	11%	6%	n.r.	n.r.	n.r.	10%
Oral aphtosis	27%	3%	12%	4%	n.r.	n.r.	n.r.	10%
Thrombocytopenia	33%	n.r.	2%	13%	n.r.	n.r.	n.r.	7%
ANA positivity	73%	82%	55%	100%	63%	100%	58%	67%

n.r. = not reported.

Table V. Autoantibody profiles in patients with undifferentiated connective tissue diseases.

	Clegg *et al*. (1991; ref. 27)	Mosca *et al*. (1998; ref. 19)	Danieli *et al*. (1998; ref. 20)
ANA	83%	100%	58%
Anti-dsDNA	4%	19%	5%
Anti-SSA	8%	30%	14%
Anti-SSB	1%	5%	n.r.
Anti-Sm	1%	1%	n.r.
Anti-RNP	12%	28%	n.r.

n.r. = not reported.

report that the most frequent manifestations of the UCTDs are arthralgias, arthritis, Raynaud's phenomenon, mucocutaneous manifestations, and sicca symptoms (12,13,15,19-22). In particular, major organ involvement, such as renal disease or SNC involvement, is very rare (Table IV).

In contrast, data are very scanty regarding the autoantibody profile of these patients (Table V). Most papers report little data apart from ANA positivity. Ganczarkzyk *et al* (12) found ANA positivity in 73% of his patients, and anti-dsDNA antibody positivity in 13%. Greer *et al* (13) observed positive ANA in 81% of his patients and no positivity for anti-dsSNA or anti-Sm antibodies. Finally, Dijstra *et al* (22) reported ANA positivity in 100% of his patients.

In our study (19), we monitored autoantibody specificities and their changes over the disease course in order to detect any eventual serological patterns for the undifferentiated diseases. Using this approach we found that a high percentage of UCTD patients (82%) have a very simple autoantibody profile characterized by the presence of a single specificity (30% anti-Ro/SSA antibodies alone, 28% anti-RNP alone). Furthermore, regular monitoring of autoantibody specificities during the study follow-up showed that patients with undifferentiated diseases have a stable profile and do not develop new specificities. An analysis of the clinico-serological correlations was carried out and showed that the presence of anti-RNP antibodies alone was significantly correlated with Raynaud's phenomenon and arthritis, while the presence of anti-Ro/SSA alone was correlated with xerostomia and xerophtalmia.

Table V summarises the autoantibody profiles reported in the three studies which included more complete serological analyses. The (small) differences between the findings by Clegg *et al*. (27), Danieli *et al*. (21), and ourselves may be explained by the fact that different tecniques were used for the detection of the autoantibodies (Farr assay versus Crithidis for anti-dsDNA), different sample sizes, and different patient selection criteria.

From the table it clearly emerges that all the authors have focused their attention on ANA positivity as a serological hallmark of the undifferentiated connective tissue diseases. This is not surprising given the well-established role of ANA in the diagnosis and management of most of the defined connective tissue diseases (28). It would appear advisable in future studies to include a more precise analysis of the autoantibody profiles of these patients, in order to improve the quality of the existing data.

Data on the characterization of the ANA specificities of the undifferentiated diseases are also scant, but agree in showing the low incidence of disease-specific autoantibodies (anti-Sm, anti-dsDNA, anti-centromere and others) and the presence of a simple profile that remains stable over time (19).

Conclusions

On the basis of the data reviewed above, there is little doubt that the undifferentiated diseases represent in most instances well-defined conditions characterized by a mild clinical picture that changes little over time and by a limited and stable autoantibody repertoire with a low incidence of disease-specific autoantibodies. Such cases make up a sizeable proportion of those patients with connective tissue diseases who are seen at major referral centers and thus could constitute a particularly interesting problem for study by rheumatologists.

While growing awareness of these conditions has attracted the attention of researchers, a critical review of the available data shows the need for carefully designed, ad hoc epidemiological and prospective studies on large cohorts of patients, in order to find the answers to many of the questions that remain regarding these conditions.

A preliminary condition for comparing the results among different centers is to define precisely what we mean by the term "undifferentiated connective tissue diseases". To define the classification criteria for systemic rheumatic diseases, usually the international community relies on *ad hoc* multi-center studies and clearly standardised methods (29). Given the absence of validated and internationally accepted criteria for what is increasingly recognised as an important set of syndromes, we would like to tentatively propose a definition of the UCTDs based on a critical survey of the existing literature. A similar approach has already been adopted in the past for other rheumatic syndromes, such as the primary antiphospholipid syndrome (30).

We would suggest defining as cases of UCTD those patients with signs and symptoms suggestive of a connective

Table VI. Suggested preliminary classification criteria for UCTD.

1. Signs and symptoms suggestive of a connective tissue disease, but not fulfilling the criteria for any of the defined CTDs* for at least 3 years.
2. Presence of antinuclear antibodies determined on two different occasions.

If the disease duration is less than 3 years, patients may be defined as having an early undifferentiated connective tissue disease (EUCTD).

*Using established classification criteria as described in the following references: for SLE ref. 1, MCTD ref. 2, SSc ref. 3, PM/DM refs. 4 and 5, RA ref. 6, and SS ref. 7.

disease but who do not fullfill the criteria for any one of the defined CTDs. They must also have antinuclear antibodies (positive in two different determinations) and a disease duration of three years. Cases with these clinical and serological features, but a shorter disease duration could be described as early undifferentiated connective tissue syndromes (EUCTD) (see Table VI).

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