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Undifferentiated connective tissue diseases (UCTD): a new frontier for rheumatology

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Patients with signs and symptoms suggestive of a systemic autoimmune disease but not fulfilling the classification criteria for defined diseases are common in clinical practice. Such conditions have been defined as undifferentiated connective tissue diseases (UCTDs). Since the 1980s, many studies have analyzed different aspects of the UCTDs – their frequency and epidemiological characteristics, the rate of evolution to defined CTD, and their clinical and serological characteristics. It is agreed that UCTDs represent around 60% of diseases with an undifferentiated onset, that they are systemic autoimmune diseases characterized by simplified clinical and serological profiles, and that they have a good prognosis. Although many aspects of these conditions have been studied and clarified, there is still no agreement on how best to identify UCTD patients after the onset of their disease. However, such identification is of paramount importance, and further analysis is necessary to improve the sensitivity and specificity of the proposed classification criteria.

Key words: classification criteria; connective tissue diseases; systemic lupus erythematosus; undifferentiated connective tissue diseases.

INTRODUCTION

Connective tissue diseases (CTDs) are heterogeneous disorders characterized by a wide variety of signs and symptoms. As few clinical manifestations are disease

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specific, there is a certain degree of overlap between the different conditions and the individual borders of CTD often appear undefined.[1–4] For this reason, and to facilitate more effective scientific communication, classification criteria have been developed for most of the CTDs.[5–17]

It is not uncommon for patients with signs and symptoms that suggest a systemic autoimmune disease not to fulfill the classification criteria for a defined disease. The history of undifferentiated diseases dates back to 1980, when LeRoy et al proposed the concept of 'undifferentiated connective tissue syndromes' (UCTS) to define the early phases of CTDs, which tended to be characterized by the presence of Raynaud's phenomenon and puffy hands as opposed to mixed or overlapping syndromes.[2] LeRoy et al suggested that whereas patients with an undifferentiated onset might evolve to definite conditions, they might also remain indefinitely undifferentiated or experience a remission of all pathologic features.

Over the last 25 years, undifferentiated diseases have been variably defined (Table 1) and many studies have analyzed aspects such as their frequency and epidemiological characteristics, the rate of evolution to defined CTD, and their clinical and serological characteristics.[18–34] This chapter examines the literature on undifferentiated diseases and discusses the issue of their diagnosis/classification.

EPIDEMIOLOGICAL DATA

No classical epidemiological data are available on undifferentiated diseases and the existing data can be compared only with difficulty, mainly due to the absence of an accepted definition. For example, studies enrolling patients with a short duration of disease (less than 1 year) might include transient diseases or diseases that are evolving into a definite condition, such as systemic lupus erythematosus (SLE) and polymyositis/dermatomyositis (PM/DM). Equally, studies including patients without autoantibodies might include manifestations that are not attributable to an autoimmune disease (e.g. post-infective arthritis) or undifferentiated/early inflammatory arthritis.

Based on disease duration, two different types of epidemiological data can be obtained: (1) the number of patients diagnosed as having an undifferentiated connective tissue disease (UCTD) shortly after disease onset (less than 1 year); or (2) the prevalence of patients with long-standing (more than 1 year) UCTD at specific referral centers.

Alarcón et al[21] reported that among 410 patients with CTDs of less than 1 year duration observed at the participating clinics of the Cooperative Systematic Studies of the Rheumatic Diseases Program, 213 (52%) had an undifferentiated profile (early undifferentiated connective tissue diseases; EUCTD) versus 57 (14%) with rheumatoid arthritis (RA), 57 (14%) with SLE, 46 (11%) with scleroderma, and 37 (9%) with polymyositis (PM).

In our own unit, of 304 patients newly referred for CTD (excluding RA) over a 1-year period, 55 (18%) presented with undifferentiated disease. Stable, undifferentiated disease represents about the 13% of the CTD patients comprehensively followed at our unit.

Agreement exists on the fact that the majority of patients (80–99%) are female, with a mean age at disease onset ranging from 32 to 44 years.[19–21,23–25,28,30–34] Clearly, epidemiological studies are necessary if the impact of these conditions, in the context of CTD, is to be better defined.