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The diagnosis and classification of mixed connective tissue disease

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ABSTRACT

The term "mixed connective tissue disease" (MCTD) concerns a systemic autoimmune disease typified by overlapping features between two or more systemic autoimmune diseases and the presence of antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1snRNP). Since the first description of this condition in 1972, the understanding of clinical manifestations and long-term outcome of MCTD have significantly advanced. Polyarthritis, Raynaud's phenomenon, puffy fingers, lung involvement and esophageal dysmotility are the most frequently reported symptoms among the different cohorts during the course of the disease. Moreover, in recent years a growing interest has been focused on severe organ involvement such as pulmonary arterial hypertension and interstitial lung disease which can accrue during the long-term follow-up and can still significantly influence disease prognosis. Over the last years, significant advances have been made also in disease pathogenesis understanding and a central pathogenetic role of anti-U1RNP autoantibodies has clearly emerged. Although controversies on disease definition and classification still persist, MCTD identifies a group of patients in whom increased surveillance for specific manifestations and prognostic stratification became mandatory to improve patient's outcomes.

1. Introduction

The term "mixed connective tissue disease" (MCTD) refers to a systemic autoimmune disease characterized by overlapping features between at least two systemic autoimmune diseases including Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (Ssc), polymyositis/dermatomyositis (PM/DM) and Rheumatoid Arthritis (RA). The presence of antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1snRNP) is considered as the serological hallmark of this condition.

Because of the similar clinical features and unique serologic pattern of the first patients described in 1972, Sharp et al. proposed that MCTD might represent a distinct rheumatic disease syndrome.

According to the first descriptions of the disease, MCTD patients appeared to have an excellent response to corticosteroid therapy and a favorable prognosis [1].

Since the first description, our understanding of the classification, clinical manifestations, long-term outcome and pathogenesis of MCTD have all advanced considerably. In this review, we will focus on the recent relevant literature published in the last decade and we will try to redefine the shape of the disease in the light of the new scientific advances.

2. The endless history of MCTD classification

The classification of rheumatic diseases is challenging because of the protean and frequently overlapping clinical and laboratory manifestations [2–5]. This problem is typified by the difficulty of classification and differential diagnosis of MCTD.

Indeed, since its first description in 1972 by Sharp et al., it is still a matter of debate whether this condition has to be considered a distinct clinical entity rather than an overlap syndrome between two or more CTDs.

Even if the anti-RNP reactivity is considered as the serologic hallmark with a well recognized diagnostic value, it is not restricted to MCTD patients being present also in SLE, SS, SSc patients as well as in Undifferentiated Connective Tissue Diseases (UCTD). However, while antibodies specifically directed against U1–70K are found in 75–90% of MCTD patients representing the most commonly detected U1-snRNP component, they are found in only 20–50% of SLE patients whose serum reacts with anti-RNP, thus suggesting a distinct serologic sub-profile [6].

To date at least three classification criteria for MCTD have been published [7–9].

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Comparative studies have reported similar results in term of sensitivity and specificity in capturing MCTD patients [10] while a recent study by Cappelli et al. found that Kasukawa's criteria were more sensitive (75%) in comparison to those of Alarcon-Segovia (73%) and Sharp (42%) in classifying MCTD patients over time [11].

The clinical need to define disease activity other than to classify them has clearly emerged over the years; in clinical practice, SLE-specific disease activity criteria have been also used in MCTD patients and experience-based activity criteria have been recently proposed by Carvalho JF et al. [12] but, similarly that for classification criteria, an international consensus on this matter is still lacking.

3. Epidemiology, clinical features and prognosis

The lack of internationally accepted classification or diagnostic criteria for MCTD led to a scarcity of epidemiological studies over the years and discordant data on the real prevalence and clinical course of this condition [13].

However, in recent years large studies have been published providing important advances on disease epidemiology, clinical and laboratory as well as long term prognosis.

In 2011, Gunnarsson R et al. performed a nationwide retrospective study to assess prevalence and incidence of MCTD in Norway founding 147 adult Caucasian with a definite diagnosis of MCTD and for a point prevalence of 3.8 per 100 000 adults and an incidence 2.1 per million per year during the period from 1996 to 2005 with a female predominance (76.9%) [14].

Prevalence of the clinical findings during the course of the disease as reported by the most recent literature (years 2003–2013) is summarized in Table 1.

Polyarthritis, Raynaud's phenomenon (RP), puffy fingers, interstitial lung disease and esophageal dysmotility are the most frequently reported symptoms among the different cohorts (Table 1) during the course of the disease.

The largest recent MCTD cohort has been described by Hajas A et al. in 2013; they found that at the time of diagnosis, polyarthritis, RP, puffy fingers and sclerodactily were the most prevalent symptoms reported in 65%, 53%, 50% and 35% respectively; however, during the 30 years of prospective follow-up patients tended to accrue over time new symptoms such as esophageal hypomotility, nervous system manifestations, pulmonary arterial hypertension (PAH), interstitial lung disease but no progression to other CTD was recorded. Interestingly, they also observed a significant progression

Table 1
Prevalence of the main clinical findings of MCTD as reported in the recent (2003–2013) literature.

Author, year, Country Type of study N of patients Classification criteria	Arthritis-RP	Lung involvement (case definition)	Oesophageal involvement (case definition)	PAH (case definition)
Fagundes MN, 2009, Brazil Prospective 50 Kasukawa's	–	ILD: 78% (on HRCT)	Oesophageal dilatation: 56% Gastroesophageal reflux: 50% Oesophageal motor impairment: 83%	–
Gunnarsson R, 2011, Norway Nationwide, retrospective survey 147 At least one (Sharp, Kasukawa or Alarcon-Segovia)	79%–99%	Self reported dispnea: 47%	Symptoms of oesophageal dysmotility: 50%	–
Hajas A, 2013, Hungary Prospective observational 280 Alarcon-Segovia	89.6%/59.5%	ILD: 47% (on HRCT and PFR)	Oesophageal dysmotility (on radiographic barium passage or radionuclide transit scintigraphy): 49.6%	17.8% (on DE ± right ventricle catheterization)
Szodoray P, 2012, Norway Prospective observational 201 Alarcon-Segovia	94.5%/78.6%	ILD: 52.7% (on HRCT and PFR)	Oesophageal dysmotility (on radiographic barium passage or radionuclide transit scintigraphy): 69.5%	23.8% (on DE ± right ventricle catheterization)
Gunnarsson R 2012, Norway Nationwide, cross-sectional 126 At least one (Sharp, Kasukawa or Alarcon-Segovia)	–	ILD: 52% (on HRCT)	–	–
Cappelli 2011, Italy Retrospective 161 Expert opinion	49.7%/85.1%	44.1% (on chest radiography or CT scan or PFR)	45.3% (on manometry or esophageal barium transit)	–
Maldonado ME, 2008, USA Cross-sectional 21 Alarcon-Segovia	–/86%	–	Gastroesophafeal reflux: 52%	–
Bodolay E, 2005, Hungary Cross-sectional 144 Alarcon-Segovia	–	66.6% (on HRCT)	–	–
Gunnarsson R 2012, Norway Nationwide, cross-sectional 147 At least one (Sharp, Kasukawa or Alarcon-Segovia)	–	–	–	3.4% (on Doppler echocardiography ± right ventricle catheterization)

ILD: interstitial lung disease; HRCT: high resolution tomography; PFR: pulmonary function tests; RP: Raynaud's phenomenon; PAH: pulmonary arterial hypertension; DE: Doppler echocardiography.