



Mixed Connective Tissue Disease

Clinical and paraclinical Manifestations

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Introduction

- Historically, Sharp explained it as
 - Overlapping features of SSc, SLE and PM/DM
 - High levels of anti-U1snRNP
 - Low steroid requirements with good prognosis

Sharp et al. Am J Med 1972

Introduction

- But, this description was challenged in next decades.
 - Some patients lacked high levels of anti-U1RNP
 - Lung and renal disease occurred
 - The steroid requirement could be high

Nimelstein et al. Medicine 1980

Black et al. Rheumatology 1992

Swanton et al, Rheum Dis Clin N Am 2005

Introduction

?

Originally definition is true

Separate disease entity

Introduction

- Sparse studies could be found about MCTD
 - Not enthusiasm of some researchers
 - Rarity of the disease
 - No clear disease definitions
 - Lack of internationally accepted consensus criteria

Gunnarsson et al. Best Practice & Research Clinical Rheumatology 2016

Clinical Manifestations

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- 2 Cohort studies addressed MCTD

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 - Norwegian Cohort
 - Hungarian Cohort

Clinical Manifestations

- 2 Cohort studies addressed MCTD
 - Norwegian Cohort (147 patients)
 - ≥ 18
 - Diagnosed with MCTD by a rheumatologist
 - Sharp's criteria / of Alarcon-Segovia and /or Kasukawa criteria
 - Exclusion of other CTD

Clinical Manifestations

- 2 Cohort studies addressed MCTD
 - Hungarian Cohort
 - 280 patients
 - F/U for 32 y

Clinical Manifestations

Raynaud's Phenomenon

- 99% of patients

Gunnarsson et al. Ann Rheum Dis 2011

Sullivan et al. Medicine (Baltimore) 1984

Lundberg et al, J Rheumatol 1991

Clinical Manifestations

Raynaud's Phenomenon

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Lundberg et al, J Rheumatol 1991

- Capillaroscopy findings?
 - 38% had a scleroderma capillaroscopy pattern

Hajas et al. J Rheumatology 2013

Clinical Manifestations

Puffy hands (Swollen)





Aringer et al. Best Pract Res Clin Rheumatol 2007

Clinical Manifestations

Puffy Hands (Swollen)

- Tenosynovitis and/or endothelial cell dysfunction

Aringer et al. Best Pract Res Clin Rheumatol 2007

- 60- 94% of patients

Kitridou et al. Semin Arthritis Rheum 1986

Lundberg et al, J Rheumatol 1991

Burdt et al. Arthritis Rheum 1999

Clinical Manifestations

Myositis



Clinical Manifestations

Myositis

- Rarely present at disease onset

Burdt et al. Arthritis Rheum 1999

Clinical Manifestations

Myositis

- Rarely present at disease onset

Burdt et al. Arthritis Rheum 1999

- 35-79% will develop signs of myositis during the course of the disease

Sharp et al. Am J Med 1972

Lundberg et al, J Rheumatol 1991

Kitridou et al. Semin Arthritis Rheum 1986

Clinical Manifestations

Myositis

- Clinically, similar to PM/DM
- Less Damage

Lundberg et al. Semin Arthritis Rheum 1992
Ciang et al. Rheumatology 2017



Clinical Manifestations

Arthritis/ Arthralgia



Clinical Manifestations

Arthritis/ Arthralgia

- Common in most studies
- Polyarthritis
- Erosive or non-erosive
- RF + 30- 100%
- Anti-U1RNP More Aggressive

Lundberg et al. Semin Arthritis Rheum 1992
Hajas et al. J Rheumatology 2013
Ciang et al. Rheumatology 2017



Clinical Manifestations

Cardiovascular





Clinical Manifestations

Cardiovascular



- Prevalence 13-65%
- Pericarditis Most common
- 2.1% of patients Cause of Death

Burdt et al. Arthritis Rheum 1999
Ungprasert et al. Int J Cardiol 2014
Ciang et al. Rheumatology 2017



Clinical Manifestations

Lung Involvement

- Interstitial Lung Diseases
- Pulmonary Hypertension

Clinical Manifestations

Interstitial Lung Diseases

- One of the most severe disease complications

Wiener-Kronish et al. Am Rev Respir Dis 1981

Sullivan et al. Medicine (Baltimore) 1984

Prakash et al. J Thorac Imaging 1992

Burdt et al. Arthritis Rheum 1999

Saito et al. J Comput Assist Tomogr 2002

Gunnarsson et al. Ann Rheum Dis 2011

Clinical Manifestations

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Burdt et al. Arthritis Rheum 1999

Saito et al. J Comput Assist Tomogr 2002

Gunnarsson et al. Ann Rheum Dis 2011

- In Norwegian study

— 52% had abnormal HRCT (Fibrosis in 35%)

Gunnarsson et al. Ann Rheum Dis 2011



Clinical Manifestations Pulmonary Hypertension



Clinical Manifestations

Pulmonary Hypertension

- Data on PH in MCTD are limited.



Clinical Manifestations

Pulmonary Hypertension

- National PAH registry in the UK (60 million)
 - 36 MCTD patients with PH
 - Prevalence 0.6 / 1000000

Condliffe et al. Am J Respir Crit Care Med 2009



Clinical Manifestations

Pulmonary Hypertension

- Norwegian cohort 3.4%
- Hungarian cohort 18%

Duration of F/U

Population-based vs. CTD center

Gunnarsson et al. Ann Rheum Dis 2011

Hajas et al. J Rheumatology 2013

Clinical Manifestations Pulmonary Hypertension

- Ciang et al in their recent review

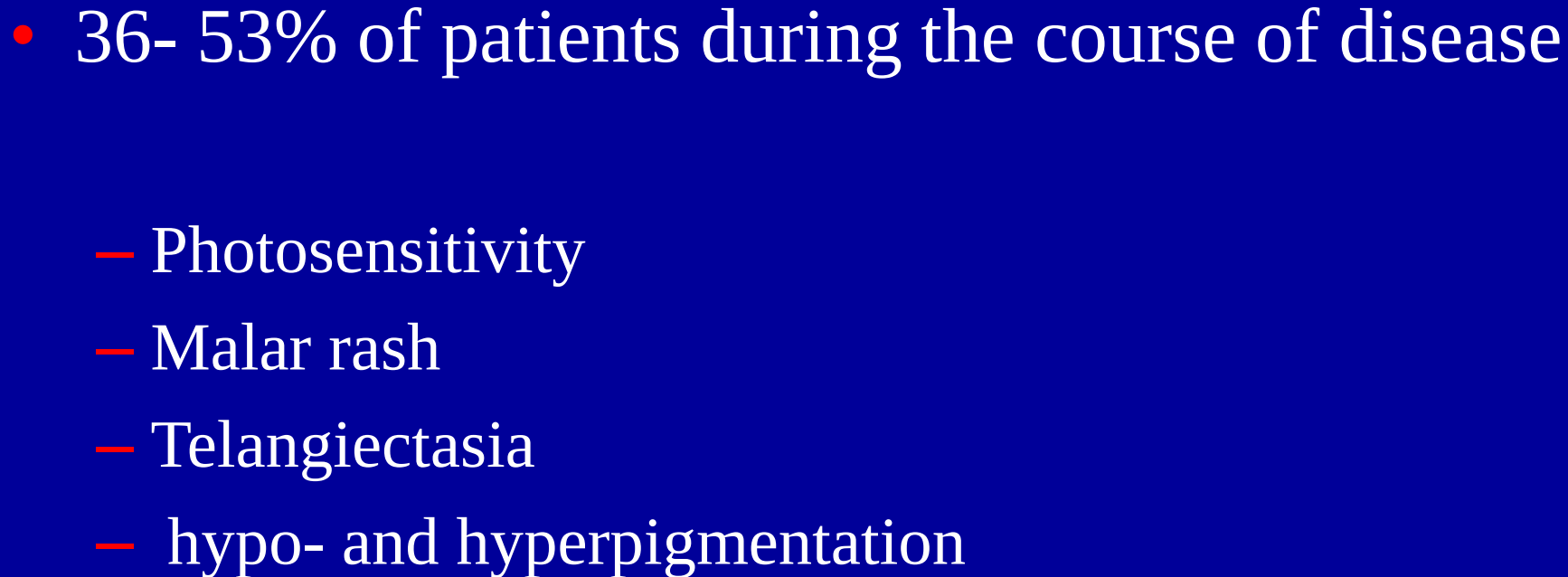
10-50%

Ciang et al. Rheumatology 2017



Clinical Manifestations Skin





Burdt et al. Arthritis Rheum 1999
Hajas et al. J Rheumatology 2013



Clinical Manifestations

Gastrointestinal Involvement

Clinical Manifestations

Gastrointestinal Involvement

- Esophageal dysmotility and hypomotility
- Severe oesophageal dysfunction 64%
- Abnormal acid reflux 50%

Gunnarsson et al. Ann Rheum Dis 2011

Hajas et al. J Rheumatology 2013

Ling et al. J Clin J Clin Gastroenterol 2001

Ciang et al. Rheumatology 2017

Clinical Manifestations

Hematological Involvement



Lundberg et al. J Rheumatol 1991
Burdett et al. Arthritis Rheum 1999
Gunnarsson et al. Ann Rheum Dis 2011
Hajas et al. J Rheumatology 2013

Clinical Manifestations

Neurological Involvement

Clinical Manifestations

Neurological Involvement

- Trigeminal neuropathy

Hajas et al. J Rheumatol 2009

Gunnarsson et al. Best Pract Res Clin Rheumatol. 2016

- Sensory-neural hearing loss

Hajas et al. J Rheumatol 2009



Clinical Manifestations

Renal Involvement

Clinical Manifestations

Renal Involvement

- Kidney Involvement 20%
- Membranous glomerulonephritis common
- Subclinical
- Good Prognosis

Clinical Manifestations Based on Antibody Profile

Group	Clinical Picture	Serologic Feature
I	• PAH • Raynaud's phenomenon • Livedo Reticularis • Vascular Thrombosis	• AECA • aPL
II	• ILD • Esophageal Dysmotility • Myositis	• No anti-Jo-1 Ab • Deposition of C3 • Deposition of IgM
III	• Erosive Arthritis	• Anti-CCP

Juvenile vs. Adult

Clinical Features	Adult onset %	Juvenile onset%
Raynaud phenomenon	99	93-100
Puffy hands	93	61-91
Anti-RNP positive	100	93-100
SLE-like manifestations		
Arthritis	79	78-97
Facial erythema	41	9-69
Leukopenia	31	30-50
Thrombocytopenia	12	6-21
Pleuritis	14	10-21
Pericarditis	12	16-28
Lymphadenopathy	N/A	21-43
SSc-like manifestations		
Sclerodactyly	34	26-86
Pulmonary fibrosis on CT	35	25-30
Hypomotility or dilatation of esophagus	50	7-21



Clinical Features

Adult onset%

Juvenile onset%

PM-like manifestations		
Muscle weakness	33	29-70
Elevated CK	33	35-68
Myogenic pattern in EMG	N/A	25-38
Other manifestations		
Pulmonary arterial hypertension	4	9
Nephritis	3	6-21
Anemia	27	64

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Gunnarssonal. et al. Best Practice & Research Clinical Rheumatology 2016

Serologic Features

Serologic Features

- Anti-U1 RNP

Mandatory

— Not Specific for MCTD

- SLE 20-40%
- SSc 2-14%
- Myositis 6-9%
- RA -

Ciang et al. Rheumatology 2016

Outcome

- In their initial report, MCTD described as
 - A mild disease
 - With favorable outcomes
 - An excellent response to oral prednisolone

Sharp et al. Am J Med 1972

Outcome

- Is it true for all Patients?

Outcome

- 1/3 Favorable outcome
- 1/3 Good outcome
 - Require continuous therapy
- 1/3 More aggressive disease

Mosca M. 2014

Outcome

- 5 studies
- Mean of 10 years (11-17 years)
- 406 patients

- 50 deaths

Nimelstein et al. Medicine 1980
Sullivan et al. Medicine 1984
Burdtt et al. Arthritis Rheum 1999
Hajas et al. J Rheumatol 2013
Piirainen et al. Br J Rheumatol 1990

- Crude mortality rate of 12%

Predictors of Mortality

Depends to involved Organ

Predictors of Mortality

- Anti-U1RNP antibodies Good

Sobanskiet al. Arthritis Rheumatol 2016

Predictors of Mortality

- Cardiovascular events
- Esophageal Hypomotility
- Serositis
- Secondary APS
- aCL
- anti- β 2-GPI
- AECA

Hajas al. J Rheumatol 2013

Causes of Death

- Pulmonary Hypertension
- ILD
- Infections
- Malignancies

Nimelstein et al. Medicine 1980
Sullivan et al. Medicine 1984
Burdett et al. Arthritis Rheum 1999
Hajas et al. J Rheumatol 2013
Piirainen et al. Br J Rheumatol 1990

When We suspect?

When We suspect?

- A key feature is unexplained Raynaud phenomenon
 - If SSc can be ruled out
 - Speckled-pattern , High titer ANA

Further immunological testing

How to Deal with a Patient with MCTD



How to Deal with a Patient with MCTD

- Screening for lung involvement in recent-onset MCTD
- PAH Screening
 - NTproBNP?

Gunnarsson. Rheumatology 2013

Gunnarsson. et al. Best Practice & Research Clinical Rheumatology 2016

11th Annual Congress of Iranian Rheumatology Association