Overlap connective tissue syndromes

R C ALLEN, C ST-CYR, P J MADDISON, AND B M ANSELL

Clinical Research Centre and Northwick Park Hospital, Harrow, Middlesex, and Royal National Hospital for Rheumatic Diseases, Bath

SUMMARY Twenty six children with overlapping features of more than one connective tissue disorder are reported. The median age of onset was 9.5 years and median duration of follow up 7.5 years. Common presenting symptoms included arthritis, tenosynovitis, Raynaud's phenomenon, myositis, and rashes. At follow up 14 patients had developed sclerodermatous skin changes, but significant systemic involvement was uncommon.

Only 16 of the 26 cases had antibodies to nuclear ribonucleoprotein; therefore, 10 did not satisfy criteria for mixed connective tissue disease. It was not possible to differentiate clinical patterns by the presence or absence of any particular antibody profile.

Mixed connective tissue disease (MCTD), described by Sharp *et al* in 1972, associated overlapping clinical features of systemic lupus erythematosus (SLE), scleroderma, and polymyositis with antibodies to nuclear ribonucleoprotein (anti-RNP).¹ Patients presented with Raynaud's phenomenon, tenosynovitis, arthritis, muscle weakness, and abnormal oesophageal motility, lacked renal involvement, and responded to corticosteroids. Follow up of the original patients found that the inflammatory features of arthritis, myositis, and fever became less frequent, although sclerodermatous manifestations persisted.² In adult patients severe systemic features are reported, pulmonary involvement being particularly prevalent;³ the prognosis, however, is generally reported as favourable.⁴ In contrast with adults, a number of reports of MCTD in children have noted thrombocytopenia and significant renal involvement, suggesting a potentially poorer outlook for children.^{5–7}

Anti-RNP antibodies have subsequently been shown to lack specificity for MCTD, even when in high titre, as they may also be found in patients with SLE.⁸ Ginsburg *et al* failed to differentiate clinical subgroups in a large series of adult patients presenting with overlap features of SLE, scleroderma, or polymyositis by either the presence or absence of anti-RNP.⁹ The purpose of this study, therefore, was to review a group of children who had presented with overlap features and to assess clinical patterns and prognosis in relation to anti-nuclear antibody profiles.

Patients and methods

A retrospective chart review of 26 children diagnosed as having 'overlap syndrome' was performed. All patients were referred from within the United Kingdom. All patients showed clinical features of more than one of the connective tissue diseases—SLE, scleroderma, juvenile chronic arthritis, and juvenile dermatomyositis. Clinical features included arthritis, tenosynovitis, muscle weakness, Raynaud's phenomenon, skin rashes consistent with dermatomyositis, and sclerodermatous skin involvement. All patients had been followed by one of us (BMA) throughout their illness for periods up to 24 years. Five patients have been described in a previous report.¹⁰

Patients' sera were stored at -70°C until tested. Anti-nuclear antibodies were detected by immunofluorescence on HEP2 cells or mouse kidney tissue substrate, or both, at a sera dilution of 1:40 and 1:160. Precipitating antibodies to extractable nuclear antigens—Sm, RNP, Scl-70, Ro/SS-A, and La/SS-B—were determined by counterimmunoelectrophoresis or Ouchterlony double diffusion, using calf thymus, rabbit thymus, and human spleen extracts as antigen source, or both.¹¹ Standard reference sera were used for defining the specific antibody system present. IgM rheumatoid factor was determined by a haemagglutination assay (RAHA, Fujirebio Inc) and anti-DNA antibodies by radioimmunoassay (Lupo-Tec, Wampole Laboratories).

Results

There were 24 girls and two boys; one girl was black, all other patients were white. The age of onset ranged from 6 to 15 years (median 9.5 years). Apart from one death three months after disease onset, follow up was from 18 months to 24 years (median 7.5 years).

Clinical manifestations. Arthritis occurred in 22 cases, of which 16 were polyarticular—that is, five joints or more—and six pauciarticular—that is, four joints or less. The arthritis was generally mild and, in one case, palindromic in nature. By contrast, tenosynovitis was often severe and particularly affected the flexor tendons. All patients with positive IgM rheumatoid factor had arthritis but did not necessarily show the typical features of seropositive juvenile chronic arthritis with extensive polyarticular joint distribution and early erosions. Radiology of affected sites showed osteopenia with variable joint space narrowing, but in only four cases were periarticular erosions seen, and two of these patients were seronegative.

Sclerodermatous skin changes have developed in 14 cases, 12 of whom had associated Raynaud's phenomenon. The hands and fingers were most affected, but some extended to involve the face and trunk. Skin involvement was unusual before two years of disease and could be as long as seven years after onset. By contrast, Raynaud's phenomenon occurred early in the course of the disease either at or within two years of onset. Other features related to scleroderma included widespread telangiectasia (seven cases), multiple small subcutaneous nodules (eight), and localised areas of subcutaneous calcification (four).

Eight patients had proximal and truncal muscle weakness, and a further four had pronounced myalgia. Raised muscle enzymes were found in 11 patients, all of whom had symptoms related to dermatomyositis. An abnormal electromyogram or biopsy specimen, or both, was found in four of the five cases examined. Ten children had rashes suggestive of dermatomyositis involving the face, elbows, and metacarpal/interphalangeal joints, two experienced severe vasculitic rashes, and four had non-specific erythematous rashes, particularly over the forearms.

Serious neurologic symptoms were uncommon. One child had a seizure presumed secondary to a cerebral vasculitis as she had an extensive coexistent cutaneous vasculitis. One patient died three months after onset of disease from an 'encephalitis', but the relation to the underlying overlap syndrome is unknown as no necropsy was permitted.

Specific investigations were performed dependent on clinical features. Oesophageal reflux, without evidence of abnormal peristalsis, was noted in one of seven barium studies. No manometric studies were performed. Chest x ray films yielded normal results in all but three cases associated with pericarditis and pleural reaction. Minor restrictive pattern abnormalities on testing of respiratory function were present in nine out of 10 patients measured. No evidence of renal abnormality was detected on routine urinalysis or measurement of serum creatinine/urea concentrations or 24 hour urinary protein excretion in any patient. The rate of glomerular filtration was normal in five patients in whom it was formally measured. No renal biopsies were performed. Only one patient developed thrombocytopenia, occurring nine years after onset of disease.

Anti-nuclear antibody specificities. All except one patient were positive for anti-nuclear antibodies on immunofluorescence. Fluorescent patterns varied, the most common being diffuse speckling with nucleolar sparing consistent with anti-RNP antibodies.¹² Anti-RNP was present in 16 out of the 26 cases, and four had precipitin lines to antigens of unknown specificity. In only four cases could no antibody to extractable nuclear antigens be shown. One patient had positive anti-DNA antibodies, and two had anti-Sm antibodies, as well as anti-RNP; none of these patients, however, satisfied criteria for a diagnosis of SLE. Anti-centromere antibodies were not detected.

Of most importance, no anti-nuclear antibody pattern or specificity correlated with any particular clinical picture. Specifically, anti-RNP did not differentiate patients by mode of onset, outcome, or other laboratory variables.

Follow up state. At time of last follow up, median 7.5 years from onset, nine patients are well, experiencing intermittent arthralgia and Raynaud's phenomenon only. Minor degrees of joint restriction due to persisting sclerodermatous change or residual arthritic involvement, or both, were noted in 10 patients; these, however, did not noticeably affect the patients' functional capacity. Only three patients experience appreciable functional impairment secondary to joint restriction. One patient has relapsing myositis three years after onset, and one patient developed a severe vasculitic disease after nine years of disease. One patient died from encephalitis three months after diagnosis.

Discussion

The clinical features in our patients, both at onset of

Table Clinical features and investigations of patients during course of overlap syndrome

Case no	Sex	Age at onset (yrs)	Follow up (yrs)	Presenting features	Clinical features during course								
					Arthritis	Teno-synovitis	Muscle	Rash	Sclero-dermatous skin	Raynaud's syndrome	Telan-giectasia	Calcinosis	Nodules
1	F	8	6	R/Ar/T	+	+			+	+	+		
2	F	11	10	Ar/T	+	+	M		+	+			
3	F	15	16	Arthralgia/R	+	+				+			
4	F	10	7	R/Ar	+	+	W	D	+	+			
5	M	14	6.5	Arthralgia/R	+	+	W			+			
6	F	8	10	Ar	+			+	+	+	+		+
7	F	6	11	Ar/rash	+	+		+		+	+		+
8	F	8	8.5	Ar	+	+		+	+	+	+	+	
9	F	9	10	Arthralgia/fever/M	+		M	D		+			+
10	F	7	8	Ar/T	+	+				+			
11	F	8	4	R/Ar/T	+	+				+		+	
12	F	11	3	Fever/M			W			+			
13	F	15	4	Arthralgia/fever/M	+	+	W	D	+	+			
14	F	15	0.25	R/Ar/M	+		M			+			
15	F	14	1.5	Rash/Ar/T	+	+	W	+		+			
16	F	7.5	6.5	Ar/T	+	+				+			
17	F	8.5	7	Fever/rash	+			D	+	+		+	
18	F	11	10	Arthralgia/scleroderma	+			D	+	+	+	+	+
19	F	13	24	Ar/pericarditis	+		M			+			
20	F	9.5	3.5	Rash/Ar/T/scleroderma	+	+		D	+				+
21	F	7	2.5	Fever/W/scleroderma			W		+		+		
22	F	7	9	Rash/W		+	W	D	+	+	+	+	+
23	F	10	2	Rash/W	+	+	W	D	+	+			+
24	M	11	3	Arthralgia/R/T	+	+			+	+			+
25	F	11	2.5	Rash/Ar/T	+	+		D					
26	F	11	1.5	R				D	+	+			

R=Raynaud's phenomenon; Ar=arthritis; T=tenosynovitis; M=myalgia; W=weakness; D=dermatomyositis related; JR=joint restriction; PS=persistent scleroderma.

RF=rheumatoid factor; CPK=creatinine phosphokinase activity; PFT=pulmonary function test; IgG=hypergammaglobulinaemia; A=abnormal; N=normal; + = present; - = absent; ? = not done; Und=undefined; ANA=anti-nuclear antibodies; ENA=extractable nuclear antigens; RNP=ribonucleoprotein.

disease and follow up, share many similarities to those reported by Sharp *et al* in the original description of MCTD. The presence of anti-RNP in only 16 out of the 26 cases, however, precludes a diagnosis of MCTD in all cases. Presenting features of arthritis, tenosynovitis, Raynaud's phenomenon, muscle involvement, and rashes were common, as were persistent sclerodermatous manifestations as the disease progressed. Such persistent sclerodermatous changes have been noted in other paediatric series with overlap features.^{5,6}

Although mild restrictive patterns on testing of pulmonary function were present in nine cases tested, no other internal organ features consistent with a primary diagnosis of scleroderma or SLE

were found. The patients with abnormal pulmonary function were asymptomatic, similar to the finding of Harmon *et al* that 69% of asymptomatic patients with MCTD may show abnormal pulmonary function.³ With a median follow up of 7.5 years it might well be concluded that evidence of pulmonary hypertension or fibrosis and oesophageal abnormalities or renal complications, or both, would be expected if scleroderma or SLE were the primary diagnosis. Severe renal involvement and thrombocytopenia have been reported in childhood MCTD,^{5,7} in contrast with adults.^{2,4,13} Only one patient in this series, however, showed thrombocytopenia associated with a severe cutaneous vasculitis.

Eberhardt *et al* have suggested that clinical

Other	Follow up state	Investigations					Antinuclear antibody specificity					
		IgM	RF	CPK	PFT	IgG	Other	ANA	ENA	RNP	Other	DNA
Splenomegaly	PS	+		N	*	+		+	+	+	Sm	-
parotitis												
Alopecia;	Arthralgia/	+		A	A	+	IgA deficiency	+	+	+		-
dysphagia	mild scleroderma											
	Well	-		*	*	+	Erosions	+	+	+		-
Migraine;	R/PS	-		A	A			+	+	+		-
dysphagia												
Pericarditis	JR	+		A	A		Erosions	+	+	+		-
							effusion					
Vasculitis	Vasculitis/JR	+		*	A	+	Thrombocytopenia	+	+	+		-
Xerostomia	Well	+		*	*	+	Sialectasis	+	+	+		*
Keratoconjunctivitis	JR	-		N	*	+		+	+	+		-
sicca												
Alopecia	Well/R	+		N	*	+		+	+	+		*
Pericarditis	Well/R	+		*	*		Effusion	+	+	+		-
	Well	*		*	*			+	+	+		-
Vasculitis	Avascular hip	*		A	*		EMG positive	+	+	+		-
seizure;	necrosis											
alopecia												
Pleuritis	Mild scleroderma	-		A	A	+	Erosions	+	+	+		-
Encephalitis;	Died	-		A	A		EMG/muscle	+	+	+	Sm	*
hepatomegaly							biopsy positive					
	Well	+		N	*	+		+	+	+		-
	Well	+		*	*		Erosions	+	+	+		-
	PS	-		N	*	+		+	+	+	Und	-
	Severe scleroderma	-		N	A	+		+	+	+	Und	-
	JR											
Keratoconjunctivitis	Well/R	+		*	*	+		+	+	-	Ro/La	-
sicca												
Migraine	Well	-		A	N		Barium	+	-	-		-
							swallow - A					
Migraine	Relapsing myositis	*		A	A		EMG/muscle	+	-	-		+
							biopsy positive					
	PS	-		A	*			+	+	-	Und	-
	JR/PS	*		A	*		Muscle biopsy	+	-	-		-
							positive					
Splenomegaly	JR	*		*	*			+	-	-		-
	JR	+		N	*	+		-	+	-	Und	-
	PS	*		A	A	+		+	+	-	Scl-70	-

patterns in children may fall into two groups—benign and malignant.⁶ If that were the case, most of our patients fall into the more benign course. This may reflect the referral nature of the patients as half were being treated as having 'juvenile chronic arthritis' before attending our clinic. The presence of Raynaud's phenomenon in 22 of the patients was an important guide to the diagnosis being other than juvenile chronic arthritis. IgM rheumatoid factor positivity, in the presence of a generally mild arthritis without progression to erosive change radiologically, is a further indicator that these patients are atypical for juvenile chronic arthritis¹⁴ and warrant consideration of an alternative diagnosis. Ragsdale *et al* have reported the progression

of juvenile rheumatoid arthritis into SLE.¹⁵ All their patients developed anti-DNA antibodies, however, as they progressed to clinical SLE; only one of our patients had positive anti-DNA antibodies, that being a girl with a predominant scleroderma-dermatomyositis picture, and none have satisfied criteria for a diagnosis of SLE.¹⁶

The lack of specificity of anti-RNP for MCTD, even when in high titre, has lessened the diagnostic importance of this particular antibody.⁸ Although anti-RNP was shown in 16 of the 26 cases, no clinical features differentiated those with from those without the antibody, a finding consistent with other studies.^{9 17} Grant *et al* have reported that the anti-RNP titre may alter with time.¹⁸ Others,

however, have found such fluctuation only in SLE and not MCTD.¹⁹

In summary, we report 26 children with overlap features. Although most followed a clinical pattern similar to that described for MCTD, serologically less than two thirds were found to have anti-RNP antibodies; for this reason we prefer to use the term overlap syndrome. The prognosis is usually good, but some patients progress to a sclerodermatous picture. Awareness of possible involvement of internal organs requires regular review.

References

- ¹ Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease—an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med* 1972;**52**:148–59.
- ² Nimelstein SH, Brody S, McShane D, Holman HR. Mixed connective tissue disease: a subsequent evaluation of the original 25 patients. *Medicine (Baltimore)* 1980;**59**:239–48.
- ³ Harmon C, Wolfe F, Lillard S, Held C, Cordon R, Sharp GC. Pulmonary involvement in mixed connective tissue disease (MCTD). *Arthritis Rheum* 1976;**19**:809.
- ⁴ Bennett RM, O'Connell DJ. Mixed connective tissue disease: a clinicopathologic study of 20 cases. *Semin Arthritis Rheum* 1980;**10**:25–51.
- ⁵ Singen BH, Bernstein BH, Kornreich HK, Koster-King K, Hanson V, Tan EM. Mixed connective tissue disease in childhood. *J Pediatr* 1977;**90**:893–900.
- ⁶ Eberhardt K, Svantesson H, Svensson B. Follow-up of 6 children presenting with a MCTD-like syndrome. *Scand J Rheumatol* 1981;**10**:62–4.
- ⁷ Baldassare A, Weiss T, Auclair R, Zuckner J. Mixed connective tissue disease (MCTD) in children. *Arthritis Rheum* 1976;**19**:788.
- ⁸ Lemmer JP, Curry NH, Mallory JH, Waller MV. Clinical characteristics and course in patients with high titre anti-RNP antibodies. *J Rheumatol* 1982;**9**:536–42.
- ⁹ Ginsburg WW, Conn DL, Bunch TW, McDuffie FC. Comparison of clinical and serologic markers in systemic lupus erythematosus and overlap syndrome: a review of 247 patients. *J Rheumatol* 1983;**10**:235–41.
- ¹⁰ Peskett SA, Ansell BM, Fizzman P, Howard A. Mixed connective tissue disease in children. *Rheumatol Rehabil* 1978;**17**:245–8.
- ¹¹ Reichlin M, Mattioli M. Correlation of a precipitin reaction to an RNA protein antigen and a low prevalence of nephritis in patients with systemic lupus erythematosus. *N Engl J Med* 1972;**286**:908–11.
- ¹² Tan EM. Autoantibodies to nuclear antigens (ANA): their immunobiology and medicine. *Adv Immunol* 1982;**33**:167–240.
- ¹³ Fortin M, Lavy MR, Hughes GRV. Severe thrombocytopenia in an adult with mixed connective tissue disease. *J Rheumatol* 1982;**9**:597–8.
- ¹⁴ Williams RA, Ansell BM. Radiological findings in seropositive juvenile chronic arthritis (juvenile rheumatoid arthritis) with particular reference to progression. *Ann Rheum Dis* 1985;**44**:685–93.
- ¹⁵ Ragsdale CG, Petty RE, Cassidy JT, Sullivan DB. The clinical progression of apparent juvenile rheumatoid arthritis to systemic lupus erythematosus. *J Rheumatol* 1980;**7**:50–5.
- ¹⁶ Tan EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1985;**25**:1271–8.
- ¹⁷ Itzkowitch D, Alexander M, Famaey JP, Appelboom T. Overlapping connective tissue diseases in children. *Clin Rheumatol* 1983;**2**:375–80.
- ¹⁸ Grant KD, Adams LE, Hess EV. Mixed connective tissue disease—a subset with sequential clinical and laboratory features. *J Rheumatol* 1981;**8**:587–98.
- ¹⁹ Nishikai M, Okano Y, Mukohda Y, Sato A, Ito M. Serial estimation of anti-RNP antibody titers in systemic lupus erythematosus, mixed connective tissue disease and rheumatoid arthritis. *J Clin Lab Immunol* 1984;**13**:15–9.

Correspondence to Dr Roger Allen, Division of Rheumatology, Clinical Research Centre, Watford Road, Harrow, Middlesex.

Received 18 November 1985