Anti-α-fodrin autoantibodies are not useful diagnostic markers of primary Sjögren's syndrome

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Fodrin, an actin binding protein found in the cytoskeleton of most eukaryotic cells, would seem to be an important organ-specific autoantigen in Sjögren's syndrome (SS). Fodrin is, moreover, detected in the salivary glands of patients with primary SS (pSS) but not in controls. It was thus recently claimed that antibodies against α-fodrin are a sensitive and specific serological marker for pSS.[1]

In this study we investigated the prevalence of autoantibodies against α-fodrin in patients with pSS, as compared with healthy subjects and patients with other autoimmune diseases.

METHODS AND RESULTS

The study group included 107 patients with well defined pSS (mean age 57.5 years), 32 patients with systemic lupus erythematosus (SLE; mean age 40.1 years), 43 patients with rheumatoid arthritis (RA; mean age 59.0 years) with no signs of secondary SS, and 48 healthy blood donors (mean age 84.3 years). A diagnosis of SLE, RA, or pSS was established using the revised American College of Rheumatology criteria and the American-European Consensus Group criteria,[2] respectively. The presence of anti-α-fodrin (IgG and IgA) antibodies in the serum was investigated using a commercial

Table 1 Anti-α-fodrin antibodies in Sjögren's syndrome and other autoimmune diseases: analysis of published reports

		sSS					
Anti-α-fodrin method	**pSS**	**SLE**	**RA**	**SLE**	**RA**	**MS**	**Controls**
Witte *et al*[8]							
Number	85	15	7	50	12		160
ELISA						ND	
IgA	64	47	86	2	17		<1
IgG	55	40	43	2	42		2
Witte *et al*[1]							
Number	136						207
ELISA		ND	ND	ND	ND	ND	
IgA	78.7						2.9
IgG	66.2						3.4
De Seze *et al*[9, 10]							
ELISA (n)	84	ND	ND	38	ND	60	160
IgA or Ig G	64.5*/73.6†			15.8		13.3	6.3
Zandbelt *et al*[4]							
ELISA (n)	21	4	ND	6	12	ND	28
IgA	43	75		0	8.3		0
IgG	48	75		0	50		0
Ruffati *et al*[5]							
ELISA (n)	80	ND	ND	50	30	ND	60
IgA	32.5			32	46.7		1.7
IgG	21.3			26	13.3		8.3
Haneji *et al*[6]							
Number	43	8	ND	21	14	ND	15
Immnublotting	95.4	87.5		0	0		0
Watanabe *et al*78]							
Number	9	15	ND	44	ND	ND	ND
Immunoblotting	78	60		7			
Nordmark *et al*[3]							
Number	56	14	ND	ND	53	ND	ND
Immunoprecipitation	29	21			47		
Current report							
ELISA (normal <15 U/l) (n)	107	ND	ND	32	43	ND	48
IgA	17.7			25	23.3		12.5
IgG	5.6			21.8	2.32		0
Home made (normal (0.280) (n)	52			ND	ND		29
IgA, IgG, IgM (%)	7.6						0

Results are expressed as percentage.
pSS, primary Sjögren's syndrome; sSS, secondary Sjögren's syndrome; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MS, multiple sclerosis.
*pSS with neurological manifestations; †pSS without neurological manifestations,

enzyme linked immunosorbent assay (ELISA) technique (Aesku Lab Diagnostika, Wendelsheim, Germany), which employs recombinant 93 kDa α-fodrin as the antigen, and a home produced ELISA using as the antigen a synthetic α-fodrin peptide corresponding to the 20 amino terminal residues of human α-fodrin (RQKLEDSYRFQFFORDAEEL).

Only two (1.9%) patients with pSS had both IgA and IgG anti-α-fodrin antibodies. The home produced ELISA (anti-human IgA, IgM, and IgG horseradish peroxidase conjugate) confirmed these results with only four positive patient in the pSS group (n = 52). Among the 19 patients with IgA anti-α-fodrin antibodies, 15 patients also had anti-Ro60 antibodies and eight anti-La antibodies, while all six of the IgG positive sera contained anti-Ro60 and three of them anti-La antibodies.

DISCUSSION

The autoantibody response against α-fodrin as detected by the ELISA test does not appear to be a relevant serological marker of pSS. However, some discrepancies with immunoblotting or immunoprecipitation data need to be discussed.

Our findings confirm previous reports of the low sensitivity (<60% in the present study) of anti-α-fodrin antibodies for the diagnosis of pSS using ELISA or immunoprecipitation techniques[3–5] (table 1). Conversely, the present data are discordant with the results of some other studies,[1 6–10] which found a higher prevalence of these antibodies (up to 95% in one study) in patients with pSS using immunoblotting[6 7] or the same ELISA test as in our study.[1 6 9 10]

The low sensitivity of the ELISA methods could be related to the absence of dominant epitopes in either the synthetic oligopeptide or the recombinant α-fodrin used in the commercial assay. Alternatively, a potential degradation of the recombinant protein cannot be ruled out. Thus the possibility of a lack of stability of the recombinant antigen led us to repeat the ELISA assay in all samples using a second kit from the same manufacturer, but with no improvement in the test sensitivity (data not shown). The reported discrepancies between different ELISA systems, which we also observed in the present study, would make such confirmation procedures mandatory.

The potential diagnostic value of anti-α-fodrin antibodies for patients with pSS without anti-Ro60/La antibodies appears to be very limited, given the large overlap between the presence of anti-α-fodrin and of anti-Ro60/La antibodies. Only four (3.7%) patients with pSS were positive for IgA or IgG anti-α-fodrin antibodies and negative for anti-Ro60/La.

The presence of anti-α-fodrin antibodies seems to be of little help in discriminating between pSS and other autoimmune diseases such as SLE or RA. The prevalence of IgA antibodies against recombinant α-fodrin was in fact lower in pSS (17.7%) than in SLE (25%) or RA (23.3%). This apparent lack of specificity of anti-α-fodrin antibodies, which has already been reported, requires confirmation using larger cohorts including various autoimmune diseases. Moreover, the presence of asymptomatic secondary SS in patients with RA or SLE cannot be ruled out. Thus all previous studies detected antibodies against α-fodrin in subjects with primary or secondary SS (RA, SLE) (table 1).

In conclusion, the anti-α-fodrin antibodies detected by ELISA appear to be neither a sensitive nor a specific serological marker of pSS and the presence of such antibodies would seem to be of limited discriminatory value and of little interest in daily rheumatological practice.

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Successful treatment of acute visual loss in Muckle-Wells syndrome with interleukin 1 receptor antagonist

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Muckle-Wells syndrome (MWS) is a dominantly inherited autoinflammatory disease characterised by urticarial skin rash, intermittent fever, arthralgia, and the frequent development of systemic AA amyloidosis. It is caused by mutations in the gene known as *NALP3* or *CIAS*, which encodes a member of the purine superfamily of death domain fold proteins that are implicated in the regulation of inflammation through activation of nuclear factor κB (NF-κB) and regulation of interleukin 1 (IL1) processing.[1 2] Over recent years, therapeutic trials with the human recombinant