Letters to the Editors

Prevalence of antibodies against mutated citrullinated vimentin and cyclic citrullinated peptide in children with juvenile idiopathic arthritis

Sirs,

Juvenile idiopathic arthritis (JIA) encompasses a heterogeneous group of different diseases. Signs of humoral autoimmunity are a common feature in JIA and testing for antinuclear antibodies (ANA) is frequently used in the diagnostic work-up of JIA (1). In rheumatoid arthritis (RA) the use of antibodies against cyclic citrullinated peptide (CCP) – a synthetic peptide mimicking the relevant epitopes of fillagrin – improved specificity and sensitivity (2). Antibodies against mutated citrullinated vimentin (anti-MCV antibodies) – a component of the intermediate filaments expressed in synovial tissues – have the same specificity and potentially even higher sensitivity as anti-CCP antibodies (3). Anti-CCP antibodies can be detected in the sera of patients with JIA (4-9). However, less is known about the presence of anti-MCV antibodies in sera of JIA patients yet. Therefore, we analysed the presence of these antibodies in JIA patients to correlate anti-MCV antibodies with anti-CCP antibodies and JIA subtypes.

Sera from 191 JIA patients (128 oligoarthritis (OA), 41 enthesitis-related arthritis (EAA), 6 rheumatoid factor (RF) positive polyarthritis (RF+PA) and 18 RF-PA) have been tested for the presence of anti-CCP (Human GmbH, Wiesbaden, Germany) and anti-MCV antibodies (Orgentec Diagnostika GmbH, Mainz, Germany) using commercially available ELISA kits. Adult RA patients (n=23) and healthy children (n=88) served as a control group.

Significantly increased frequencies of anti-CCP or anti-MCV positive patients could only be detected in the RF+PA subgroup (Table I). All of the anti-CCP antibody positive patients in this subgroup were also anti-MCV antibody positive, a phenomenon which could only be detected in the RF+PA JIA group as well as in the RA patients. Sensitivity of anti-MCV and anti-CCP antibodies for the diagnosis of RF+PA was 83.3% and 66.7%, respectively. The specificity (compared to healthy individuals) could be calculated as 91.1% and 98.9%, respectively. The specificity (compared to all other JIA subgroups) could be calculated as 93.5% and 99.5%, respectively.

Several groups have analysed the appearance of anti-CCP in JIA patents. As in our present study, the prevalence of anti-CCP antibodies seems to be very low in JIA patients (4-9). However, anti-CCP antibodies seem to be very specific for the RF+ PA subgroup of JIA. Sensitivity and specificity for diagnosing RF+ PA using anti-CCP as a serological test almost equalled those of RA (2). Anti-CCP antibodies in RA are not only highly specific, but also have prognostic value for an erosive disease course, which might also be true for RF+PA (5, 10). However, the number of anti-CCP positive JIA patients in this and other published cohorts are too small to transfer this hypothesis to anti-CCP positive JIA patients.

As already observed for anti-CCP antibodies, only few JIA patients indicated raised anti-MCV titres and the highest prevalence of anti-MCV positivity could be found in the RF+ PA subgroup of JIA. Even though the prevalence of anti-MCV antibodies in JIA subgroups other than RF+PA was higher than those of anti-CCP antibodies, most of these patients only showed slightly elevated antibody titres challenging the cut-off value of this ELISA system (data not shown).

In summary, we could show that anti-CCP and anti-MCV antibodies can be detected in very few patients with JIA, mainly the RF+PA subgroup. Therefore, ACPA testing cannot be recommended as screening tool for the diagnosis of JIA. Further studies would be necessary to analyse the appearance of ACPA and RF in the PA subgroup as a predictor of erosive joint course.

Table I. Prevalence of antibodies against mutated and citrullinated vimentin and cyclic citrullinated peptides in patients with juvenile idiopathic arthritis.

	no. of pts.	MCV		CCP					
		n	%	n	%				
JIA	191	17	8.9	5	2.6				
RA	23	19*	82.6	20*	87.0				
HI	88	6	6.8	1	1.1				
JIA subgroup		MCV		CCP		DMARD		Biological	
		n	%	n	%	n	%	n	%
OA	128	5	3.9	1	0.7	48	37.5	4	3.1
EAA	41	4	9.8	0	0.0	30	73.2	5	12.2
PA RF+	6	5*	83.3	4*	66.7	6	100	1	16.7
PA RF-	16	3	18.8	0	0.0	13	81.3	2	12.5

Prevalence of antibodies against mutated and citrullinated vimentin (MCV) or antibodies against citrullinated peptide (CCP) in patient with juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA) or healthy individuals (HI). The prevalence of these antibodes is shown for the JIA group in total as well as unravelled for the JIA subgroups oligoarthritis (OA), enthesitis asscoiated arthritis (EAA), rheumatoid factor positive polyarthritis (PA RF+) and rheumatoid factor negative polyarthritis (PA RF-). The prevalance of these antibodies in each group has been compared to those in healthy individuals (chi-square test).

*Statistically significant differences ($p<0.05$). The number of patients taking disease modifying anti-rheumatic drugs (DMARD, *e.g.* methotrexate or sulfasalazine) or biologicals (etanercept) is shown for the JIA subgroups.

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References

1. RAVELLI A, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767-78.
2. NISHIMURA K, SUGIYAMA D, KOGATA Y *et al.*: Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007; 146: 797-808.
3. BANG H, EGERER K, GAULIARD A *et al.*: Mutation and citrullination modifies vimentin to a novel autoantigen for rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 2503-11.
4. AVCIN T, CIMAZ R, FALCINI F *et al.*: Prevalence and clinical significance of anti-cyclic citrullinated peptide antibodies in juvenile idiopathic arthritis. *Ann Rheum Dis* 2002; 61: 608-11.
5. VAN ROSSUM M, VAN SOESBERGEN R, DE KORT S *et al.*: Anti-cyclic citrullinated peptide (anti-CCP) antibodies in children with juvenile idiopathic arthritis. *J Rheumatol* 2003: 30: 825-8.
6. LOW JM, CHAUHAN AK, KIETZ DA, DAUD U, PEPMUELLER PH, MOORE TL: Determination of anti-cyclic citrullinated peptide antibodies in the sera of patients with juvenile idiopathic arthritis. *J Rheumatol* 2004; 31: 1829-33.
7. KASAPCOPUR O, ALTUN S, ASLAN M *et al.*: Diagnostic accuracy of anti-cyclic citrullinated peptide antibodies in juvenile idiopathic arthritis. *Ann Rheum Dis* 2004; 63: 1687-9.
8. FERUCCI ED, MAJKA DS, PARRISH LA *et al.*: Antibodies against cyclic citrullinated peptide are associated with HLA-DR4 in simplex and multiplex polyarticular-onset juvenile rheumatoid arthritis. *Arthritis Rheum* 2005; 52: 239-46.
9. BRUNNER JK and SITZMANN FC: Anticyclic citrullinated peptide antibodies in juvenile idiopathic arthritis. *Mod Rheumatol* 2006; 16: 372-5.
10. GILLIAM BE, CHAUHAN AK, LOW JM, MOORE TL: Measurement of biomarkers in juvenile idiopathic arthritis patients and their significant association with disease severity: a comparative study. *Clin Exp Rheumatol* 2008; 26: 492-7.