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Personal attributes as determinants of timely care in rheumatoid arthritis

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Recently, early intensive treatment has become important in the treatment of rheumatoid arthritis (RA). Evidence from clinical trials and from patient cohorts in daily practice has shown that early disease modifying antirheumatic drug treatment is mandatory to avoid damage and loss of function.¹ Therefore, patients with suspicion of RA should be referred to a rheumatologist as soon as possible.

This has led to the development of “early arthritis clinics”.² However, a diagnosis of early RA is difficult for general practitioners (GPs),³ sometimes leading to inappropriate referrals. A solution may be joint consultations of GPs and rheumatologists⁴ or specific training of GPs.

A few years ago, the Patient Partner Program (PPP) was established in Belgium. The PPP is an educational programme in which trained patients with RA teach medical students and general practitioners how to diagnose and evaluate RA.⁵ A direct objective is to improve musculoskeletal examination skills of physicians, leading to appropriate early referrals.

Other hurdles for timely care appear to be patient related. Women are often referred later than men⁶; however, it is not clear if this is due to sex alone, gender behaviour or other interfering factors.

Patient partners are selected by their treating rheumatologist based on communication skills, motivation, and positive attitude towards their disease and learning capacities. Such characteristics might also influence their behaviour of seeking health care.

As part of an evaluation of the PPP in Belgium, we assessed the association of being a patient partner with disease characteristics (medical records), disability (Health Assessment Questionnaire (HAQ)), perceived health status (Dutch AIMS⁷), and coping (UCL⁸). Twenty one patient partners were compared with 28 randomly selected patients with RA who were not patient partners. All were receiving regular ambulatory care.

The patient partner group had a significantly longer disease duration, but age and sex distribution were similar (table 1). We found that patient partners had more social activities ($p = 0.013$), had a better ability to work ($p = 0.043$), had a lower stress level ($p = 0.002$), and had a more positive mood ($p = 0.016$). Patient partners also demonstrated more active coping strategies ($p = 0.026$), more reassuring thoughts ($p = 0.040$), and less depressive reactions ($p = 0.001$). Interestingly enough, we observed that the time between onset of symptoms and the diagnosis of RA was significantly shorter in the patient partner group than in the control group.

Although the differences in health status and coping are logically explained by the selection criteria for becoming a patient partner, the personal attributes of these patients apparently resulted in an earlier diagnosis of RA, even when they were not yet trained as patient partners. We feel that these findings add to the understanding of determinants of timely care in patients with RA, such as coping and personality styles. Investigations of the influence of gender

Table 1 Patient characteristics

Characteristics	Patient partners (n = 21)	Control group (n = 28)	p Value
Sex (% female)	95	98	
Mean age (years)	45.3	47.9	0.424†
Mean disease duration (years)	15.7	9.3	<0.01‡
Mean time between complaints and diagnosis (years)	0.8	2.7	0.001†
Surgical intervention for RA (%)	71	57	0.305*
Disability score (mean HAQ)	1.4	1.2	0.321†

* χ^2 Test; †Mann-Whitney U test; ‡t test.

on timely referral should also include variables as discussed above. This is also suggested in gender studies in other health domains⁶. Multivariate analyses in large prospective studies will allow firm conclusions to be reached.

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Characterisation of Th1/Th2 type, glucose-6-phosphate isomerase reactive T cells in the generation of rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterised by an unknown inflammatory process in multiple joints. The K/BxN T cell receptor transgenic mouse model is a striking model of inflammatory arthritis characterised by arthritic manifestations similar to those of RA.¹ Matsumoto *et al* reported that arthritis could be provoked by linked T and B cell recognition of a ubiquitously expressed self antigen glucose-6-phosphate isomerase (GPI).² Recently, immunisation with recombinant human GPI was reported to induce T cell dependent arthritis in DBA/1 mice,³ supporting the notion that GPI reactive T cells have a crucial role in the induction of arthritis.

In our previous study we reported the presence of high titres of anti-GPI antibodies (Abs) in some patients with RA, although a few control subjects were also positive.⁴ To examine the role of GPI-specific T cells in patients with RA, we investigated the spontaneous Th1/Th2 response to GPI in patients with RA, systemic lupus erythematosus (SLE), and in healthy subjects with anti-GPI Abs.

To select anti-GPI Ab positive patients, an enzyme linked immunosorbent assay (ELISA) was performed using two different sources of GPI: a recombinant human GPI (huGPI), and a rabbit muscle GPI (raGPI; Sigma Chemical Co, St Louis, MO, USA), which have been described in detail previously.⁴ Fifteen anti-GPI Ab positive patients with RA (from 185 with RA), four patients with SLE (from 135 with SLE), and four healthy subjects (from 145 controls) were studied (table 1). To analyse the possible relationship between HLA-DRB1 and anti-GPI Ab positivity, HLA-DRB1 alleles were screened. As shown in Table 1, 10 (67%) patients with RA and anti-GPI Abs shared the HLA-DRB1*0405 allele,

which is one of the genes for susceptibility to RA in Japanese people, and five (33%) patients were DRB1*0901. In a recent report, the DRB1*0405 and *0901 alleles showed the most significant associations with RA in Korean people.⁵ However, none of the four patients with SLE or four control subjects positive for anti-GPI Abs retained these alleles, suggesting a strong linkage between anti-GPI positive patients with RA with anti-GPI Abs and HLA DRB1*0405 and *0901 alleles (table 1).

To investigate the pathogenic relevance of GPI reactive T cells in subjects with anti-GPI Abs, a magnetic activated cell sorting cytokine secretion assay was performed using peripheral blood mononuclear cells plus GPI (in the presence of 10 µg purified human GPI protein digested by thrombin or 13.5 ng thrombin as a control). As a positive control, we used staphylococcal enterotoxin B (1 µg/ml). Cells (2 × 10⁶) were harvested Ab-Ab directed against CD45 and either interferon (IFN) γ or interleukin (IL) 4 conjugates, and stained with phycoerythrin (PE)-conjugated anti-IFNγ or anti-IL4. Cells were magnetically labelled by anti-PE Ab microbeads, and were analysed on a FACSCalibur flow cytometer (Becton Dickinson). IFNγ secreting T cells were detected in seven (47%) patients with RA (RA3, 6, 7, 9, 10, 11, 15). IFNγ may be produced by GPI reactive T cells (table 1). IL4 secreting T cells were detected in four (27%) patients (RA1, 3, 7, 10), although they were less frequent than IFNγ+ T cells. Three patients (RA3, 7, 10) had both IFNγ and IL4 secreting T cells. In contrast, only one healthy subject (control 2) showed weak response to GPI (IFNγ and IL4). Interestingly, all seven patients with RA bearing GPI reactive IFNγ+ T cells shared either DRB1*0405 or *0901 (table 1). Our results demonstrated that GPI-specific Th1 and Th2-type cells (especially