Diagnosing Late Onset Rheumatoid Arthritis, Polymyalgia Rheumatica, and Temporal Arteritis in Patients Presenting with Polymyalgic Symptoms. A Prospective Longterm Evaluation

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ABSTRACT. ***Objective***. To examine for demographic and clinical differences between late onset rheumatoid arthritis (LORA), polymyalgia rheumatica (PMR), and temporal arteritis (TA) patients presenting with polymyalgic symptoms (PMS) and to identify baseline clinical and laboratory features that would lead to a more accurate final diagnosis.

Methods. Three hundred forty-nine consecutive patients with new onset of symptoms suggestive of LORA, PMR, or TA presenting at or above age 60 years were enrolled in a prospective study.

Results. During followup, 9 patients diagnosed initially as PMR developed LORA (giving a final total of 145), 5 patients initially diagnosed as LORA changed diagnosis to PMR (final total 147), and 29 patients had PMS that predated TA symptoms (final total 57). The delay in diagnosis ranged from 1 to 30 months. DRB1*04 was associated with development of both LORA and TA.

Conclusion. In about 10% of patients the correct diagnosis of LORA, PMR, and TA in those presenting with PMS may be delayed due to similarities in initial clinical presentation. Longterm followup is essential to establish correct diagnosis. Laboratory tests tend to be unhelpful, although a positive rheumatoid factor or persistently raised plasma viscosity despite steroids might indicate RA, and the presence of HLA-DRB1*04 may indicate underlying RA or TA. (J Rheumatol 2005; 32:1043–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS POLYMYALGIA RHEUMATICA
TEMPORAL ARTERITIS PROSPECTIVE STUDY OUTCOME

The distinction between late onset rheumatoid arthritis (LORA), polymyalgia rheumatica (PMR), and temporal arteritis (TA) can be difficult at disease onset. Polymyalgic symptoms (PMS, i.e., shoulder/pelvic girdle early morning stiffness) are common in both elderly onset RA[1,2] and TA[3], while a transient symmetric pauci- or polyarthritis can occur in patients with PMR[4].

The purpose of this study was to identify patients in whom overlapping clinical features of PMR, LORA, and TA led to delay in correct diagnosis, and to identify clinical and laboratory features that would predict final diagnosis for these patients.

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MATERIALS AND METHODS

Patients. A standardized pro forma was used to prospectively collect demographic, clinical, and laboratory data at presentation and followup on all patients aged 60 years or older with features suggestive of recent onset LORA, PMR, or TA. We identified 145 patients with LORA, 147 patients with PMR, and 57 patients with TA.

Diagnostic criteria. LORA was defined as RA that fulfilled American College of Rheumatology (ACR) 1987 criteria for RA and had a disease onset at age > 60 years[5]. Patients with PMR fulfilled the Bird criteria[6] and patients with TA fulfilled ACR 1990 criteria for TA[7]. Patients who had TA prior to PMS symptoms or TA and PMS symptoms together were classified as TA, and those with PMS symptoms who went on to develop TA later were classified as PMR-TA.

Methods. Provisional diagnosis at the initial rheumatology consultation was based on clinical features, classification criteria, routine laboratory tests, and exclusion of other causes of myalgia, e.g., paraneoplastic syndrome. The final diagnosis was based on the clinical record and adherence to classification criteria. All patients had a minimum followup of 2 years. Demographic and disease characteristics were recorded by a combination of interview and clinical examination (Table 1). Laboratory methods have been described[2].

Differences between the 3 patient groups were evaluated using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables (provided the proportion of cells with an expected count of zero did not exceed 20%). The proportions of patients exhibiting different HLA-DRB1 types were compared (RA vs PMR; TA vs PMR) using Fisher's exact test. Comparisons were made only where the proportion of patients exhibiting the marker in question exceeded 10% in at least one

Table 1. Demographic and clinical features in patients with polymyalgic symptoms (PMS) at presentation who were finally diagnosed as late onset rheumatoid arthritis (LORA), polymyalgia rheumatica (PMR), or temporal arteritis (TA).

	RA with PMS, n = 24	PMR, n = 147	TA with PMS, n = 42
Female:male ratio	3:1	2.2:1	4.3:1
Continuous variables, median (range)			
Age of onset of symptoms	73 (63–85)	70 (60–87)	71 (60–81)
Time to presentation, mo	4.5 (1.0–24.0)	3.0 (0.3–60.0)	3.0 (0.4–22.1)
[a] Morning stiffness, h	2.0 (1.0–12.0)	4.0 (0.3–12.0)	4.0 (0.0–12.0)
lnitial oral prednisolone dose, mg	15.0 (12.0–20.0)	15.0 (7.5–40.0)	30.0 (10.0–90.0)*
Categorical variables, frequency % (n)			
Systemic symptoms			
Fever	0	2.0	7.3
Weight loss	33	20	42*
[b] Symptom onset ≤ 2 days	33 (7)	39 (54)	44 (17)
Plasma viscosity > 1.73[†]	83	88	98
[c] Anemic at presentation	44 (10)	28 (36)	34 (12)
[d] Presence of RF	39 (9)	4 (4)	3 (1)
[e] Arthritis at onset	79 (19)	15 (22)	8 (3)*
Small joint (PIP, MCP, or wrist)	67	9	3
Large joint (hip, knee, or shoulder)	67	13	7*
[f] Arthritis at any time during followup	100 (24)	30 (38)	17 (5)*
Small joint	92	18	7*
Large joint	92	21	10*
[g] Clinical features of RS_3 PE syndrome	13	2	5
[h] Erosions at presentation	11 (2)	0	0
[i] Response to oral steroids ≤ 2 days	67 (4)	93 (125)	87 (32)
Systemic steroid use	79	99	100

* $p < 0.013$. [a] 202 patients were able to state duration of early morning stiffness; [b] 197 patients were able to recall pattern of onset clearly; [c] 187 patients had hemoglobin data recorded; [d] 170 patients had rheumatoid factor data recorded; [e] 205 patients had onset arthritis data recorded; [f] 181 patients had followup arthritis data recorded; [g] 49 patients had baseline hand plain radiographs; [h] 177 patients had steroid response data recorded; RS_3 PE: Remitting seronegative symmetric synovitis with edema. [†] Normal range 1.50–1.72 mPas.

group in each pair. Corrections for multiple comparisons were made within each family of statistical test, according to the Holm (1979) procedure. Critical P for testing at the $\alpha = 0.05$ level was therefore set at 0.013 for Kruskal-Wallis and chi-squared tests, and at 0.003 for Fisher's exact tests. Statistical analyses were performed using SPSS version 11.5 (SPSS, Chicago, IL, USA).

RESULTS

Demographic and clinical features and statistical results are shown in Table 1. In patients with PMR/TA the synovitis responded rapidly to steroids, was of short duration, and only occasionally recurred. Clinically, the pattern of joint involvement did not differ between those with PMR and TA.

One hundred sixty-seven patients were typed for HLA-DRB1. HLA-DRB1*04 was significantly increased in individuals with TA presenting with PMS when compared to the PMR population (OR 4.12, 95% CI 1.75–9.96, p = 0.001; Table 2). There was no increase in frequency of HLA-DRB1*04 in RA individuals presenting with PMS when compared with the PMR population. The distribution of different HLA-DRB1*04 subtypes was not significantly different in HLA-DRB1*04 positive individuals from each diagnostic group. HLA-DRB1* subtyping did not increase the strength of the above associations between PMR and RA or TA and PMR.

Nine patients with a working diagnosis of PMR were eventually reclassified as LORA (Figure 1). The delay in reaching final diagnosis was 13 months (range 1–30). All 9 patients presented with significant shoulder girdle stiffness consistent with PMR. Four of these 9 also had initial mono/pauciarticular joint involvement. In the other 5 patients, joint involvement was delayed for up to 18 months. All 9 patients were dependent on a higher dose of steroids than normally expected at that stage of their disease. In retrospect, some joint symptoms, which had been accepted as coexisting osteoarthritis (OA), were due to RA or RA-OA combination. In all patients initial synovitis was suppressed by steroids only to return and become persistent once the steroid dose was lowered. Initial plasma viscosity in these patients was higher than is typical for early RA (mean 2.00 vs 1.86 in the classical RA group who presented with myalgia). Over several years all 9 patients developed erosive joint disease. Four out of 8 patients were rheumatoid factor (RF) positive at the initial visit, which is significantly different from those eventually diagnosed with PMR. During

Table 2. Frequency of HLA-DRB1 alleles in patients with polymyalgic symptoms (PMS) finally diagnosed as polymyalgia rheumatica (PMR), rheumatoid arthritis (RA), or temporal arteritis (TA) compared with healthy controls. Values are percentages.

	RA with PMS, n = 18[a]	PMR, n = 114[a]	TA with PMS, n = 35[a]
HLA-DRB1			
*01	33.3	29.8	20.6
*15/*16 (*02)	22.2	25.4	11.4
*03	16.7	30.7	25.7
*04	61.1	44.7	77.1[b]
*0401	38.9	28.1	42.9
*0402	0	0.01	0
*0403	0	0.01	0.03
*0404	16.7	13.2	17.1
*0405	5.6	0.01	0
*0407	0	0.03	0
*05	0	0	2.9
*06	5.6	7.0	5.7
*07	27.8	12.3	20.0
*08	0	0.9	2.9
*09	0	1.8	0
*10	5.6	0.9	0
*11	0	8.8	11.4
*12	5.6	0.9	2.9
*13	5.6	13.2	8.8
*14	0	2.6	0

[a] HLA-DRB1 data were available on 167 patients. Frequency of individuals with a single or double copy of each allele. [b] $p < 0.003$.

followup one patient became RF positive and one patient not tested initially was later found to be RF positive. HLA-DRB1*04 was present in 5 of 8 patients who had haplotyping performed.

Five patients with a working diagnosis as LORA were finally diagnosed as PMR. All 5 presented with joint symptoms (acute oligo/polyarticular arthritis) with PMS. The median time delay until diagnosed as PMR was 3 months (range 0.5–6.0). In all patients arthritis resolved with steroid treatment and did not recur following steroid reduction, although there was a flare of PMS on dose reduction. These patients have since stopped steroids without recurrence of symptoms. The plasma viscosity at first presentation was consistent with levels found in RA. One patient had borderline positive RF (negative on retesting), HLA-DRB1*04 was absent. All 5 patients remained nonerosive.

Forty-two patients had PMS symptoms and TA, of whom 29 patients had PMS that predated TA symptoms (time from onset of PMS to diagnosis of TA: median 17 mo, range 1–135). These 29 patients did not differ from the other PMR patients in their symptoms or plasma viscosity at initial presentation. HLA-DRB1*04 was more frequently found in this group (69%) compared to PMR patients who never developed TA (45%), although this was not statistically significant. Seven of 42 patients with TA had PMS symptoms at presentation and 6/42 patients had TA symptoms prior to PMS (median 14 mo, range 3–29).

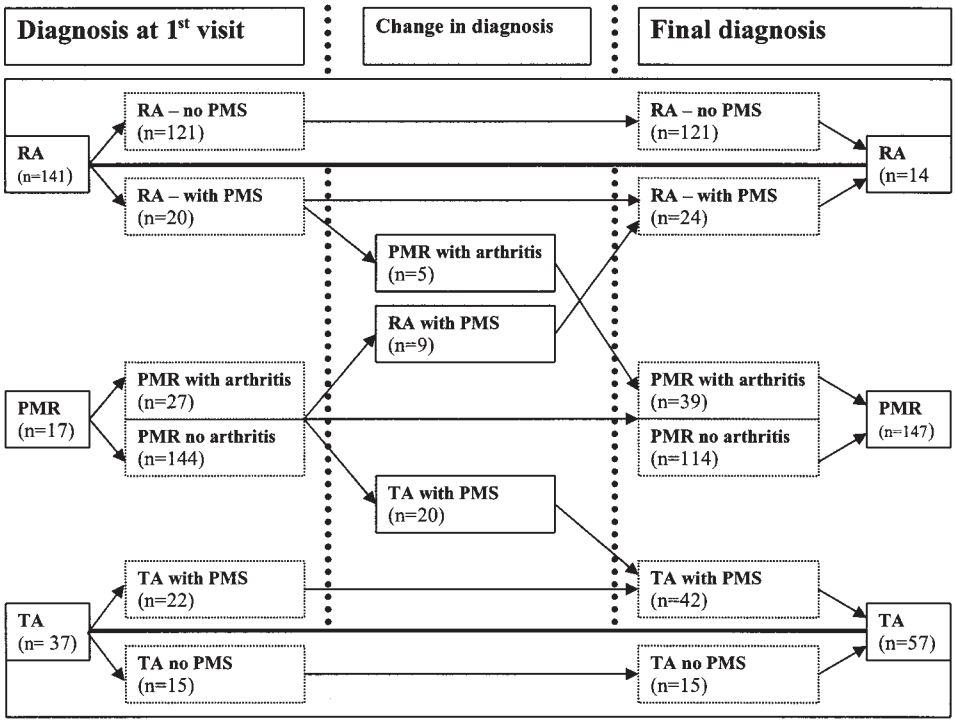

Figure 1. Changes in diagnostic classification of older patients presenting with RA, PMR, and TA.

DISCUSSION

No single clinical or laboratory feature was on its own able to differentiate between LORA with PMS and PMR. The diagnosis of LORA was delayed from between 1 to 30 months in 6% of cases. A delay in diagnosing RA occurs in 3–11% of individuals[4,8]. In our study, RF positivity was not an exclusion factor in considering the diagnosis of PMR. It is reported that in the general population RF positivity increases with age, so that 12% of "healthy" people over age 60 will be RF positive[9]. However, our results do suggest that RF positivity is a strong indicator of LORA in someone presenting with PMS.

Clinically, the arthritis of LORA and that presenting in PMR can be similar. However, detailed imaging of some of our cases with magnetic resonance imaging has shown significant differences in the arthropathy of PMR compared to RA[10,11].

PMS symptoms were common in our TA cohort. Sixty-nine percent of patients with TA had PMS symptoms that started before onset of classical TA symptoms. The time to onset of TA symptoms varied considerably (up to 11 yrs). HLA-DRB1*04 was more common in those developing TA who had PMS than those with PMR alone. Similar results for PMR-TA or indeed TA without PMR have been reported[12-14]. In other parts of Europe no association with HLA-DRB1*04 has been found[15]. The HLA-DRB1 typing for patients with PMR was not different from those patients with RA presenting with PMS.

We felt that those cases finally diagnosed as LORA had subclinical RA at presentation, rather than the disease evolving into RA. The presence of high titer RF at first presentation may be an indicator of underlying RA in those presenting with PMS, even in the absence of typical arthritis. The RF-negative RA patients had persistent joint disease despite steroids, and all became erosive over time.

In this group of conditions with overlapping clinical features and where diagnostic features may be delayed, the change of the initial diagnosis should be flexible, with a final diagnosis dependent on the evolving clinical picture and response to treatment. HLA-DRB1 typing and RF status may in some patients help to clarify the diagnosis and predict future TA in those with PMS.

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