Polymyalgia rheumatica vs late-onset rheumatoid arthritis

Polymyalgia rheumatica (PMR) is a well-defined acute musculoskeletal inflammation of ageing people and characterized by clinical symptoms that may create some difficulties in the differential diagnosis with late (elderly) onset RA (LO-RA or EO-RA, respectively) as well as with LO-RA with PMR-like onset (LO-RA/PMR) [1].

PMR as an inflammatory condition of multifactorial aetiology is generally characterized at least at the beginning by aching and stiffness in the shoulder and in the pelvic girdles. It occurs in people over the age of 50–60 yrs, and it usually responds rapidly to low doses of glucocorticoids and has a favourable prognosis. Genetic causes and polymorphisms of additional genes involved in the initiation and regulation of inflammatory reaction have been considered to be possible susceptibility factors for PMR [2]. In particular, TNF-α, and IL-1 receptor antagonist (IL-1Ra) gene polymorphisms are predisposing factors and may be implicated in the pathogenesis of PMR [3]. On the other hand, increased production of IL-6 is a characteristic finding in patients with PMR, and glucocorticoids rapidly reduce serum levels of IL-6 [4]. The suppression of the hypothalamic-pituitary-adrenal (HPA) axis as consequence of chronic stress and/or the endocrinosenesence could contribute to the pathogenesis of PMR [5].

The occurrence of peripheral arthritis, particularly in both hands, may create some difficulties in the differential diagnosis between PMR and LO-RA. Symmetrical peripheral involvement, RF seropositivity, development of joint erosions and extraarticular manifestations differentiate adult RA from PMR. Anti-citrullinated peptide (CCP) antibodies may also be useful in the differential diagnosis between PMR and LO-RA.

However, several patients with seronegative LO-RA show a relatively mild symmetric synovitis, characterized by a rapid and complete response to glucocorticoid and a non-erosive course. Symptoms and signs of both PMR and LO-RA might alternate during the follow-up of the patients [7]. These patients show a clinical condition different from classic RA, which more closely resembles PMR, moreover at the beginning of the disease. On the other hand, a prospective study on clinical features of PMR and LO-RA with PMR-like onset showed that 20% of PMR patients developed overt RA during the follow-up period [8].

Genetic and clinical differences

PMR and its sister disease, giant cell arteritis, are probably polygenic diseases in which multiple environmental and genetic factors influence susceptibility and severity. As for RA, HLA-DRB1*04 and DRB1*01 alleles are associated with PMR occurrence and severity. A genetic basis for PMR is also suggested by its higher incidence in the Anglo-Saxon population in comparison with the Mediterranean one.

In this issue of the journal, Pease et al. [9] tried to describe the pattern of arthropathy and HLA-DRB1 alleles associated with PMR in order to develop a diagnostic algorithm that could help distinguish PMR and RF–ve LO-RA at presentation [10].

To obtain these data the authors realized a prospective study of all patients presenting with PMR or LO-RA over a 10-yr period to one physician. Demographic, clinical and laboratory data were collected at presentation and during a minimum of 5 yrs follow-up.

Interestingly, peripheral synovitis was observed in 23% of the PMR patients. In comparison with RF–ve LO-RA, PMR patients were younger (P < 0.001), had more frequent myalgia 100% vs 16% (P < 0.001) and arthritis of PIP, MCP and wrist was less frequent (P < 0.001). The combination of wrist + MCP/PIP or wrist + PIP + MCP was highly suggestive of RF–ve LO-RA (P < 0.001). HLA-DRB1*0101/0102 and *0401 were significantly increased in PMR patients compared with healthy controls. However, overall, there were no consistent differences in the HLA-DRB1 allele distributions between PMR and RF–ve LO-RA.

Plasma viscosity (PV) and arthritis in the wrist, in combination with at least one MCP or PIP joint at disease onset, were predictive of whether a non-erosive RF–ve patient would ultimately be diagnosed as having RF–ve LO-RA or PMR (±/arthritis). The major conclusion was the confirmation that RF–ve LO-RA is a separate disease entity to PMR despite some phenotypic and immunogenetic similarities at disease onset [10].

Different markers of inflammation

A recent study on the laboratory markers of inflammation in both PMR (and LO-RA with PMR-like onset) patients suggested a stronger inflammatory involvement when compared with LO-RA patients, as shown by their significantly higher values of ESR, CRP, as well as IL-6 [11].

Differently, IL-1Ra was significantly more frequent in LO-RA than in LO-RA/PMR patients, suggesting a possibly more efficient anti-inflammatory endogenous milieu in LO-RA patients, exerted by IL-Ra. Interestingly, since IL-1Ra wields a protective effect on bone damage, the higher IL-1Ra serum levels observed in LO-RA patients might support the low erosive activity typical of the elderly subset of RA [12].

Concerning the LO-RA/PMR patients vs the PMR patients, both IL-6 and IL-1Ra as well as the ESR values, showed a similar behaviour at the time of the basal analysis when compared with LO-RA patients. However, at that time all the analysed cytokines were significantly more frequent in the three groups of patients than in the control group [11].

During the follow-up of the glucocorticoid treatment, the decrease of the inflammatory markers was more evident in PMR patients than in LO-RA patients. In particular, the decrease of TNF-α, IL-6, ESR and CRP was significantly higher in LO-RA/PMR patients, whereas IL-1Ra increased significantly only in both PMR (and LO-RA/PMR) patients, and no statistically significant variation was observed in LO-RA patients.

Hormonal differences

No statistically significant differences were observed concerning cortisol (CO) levels between the three groups of patients and the control group [11]. The results confirm recent research showing a reduced production of adrenal hormones (CO, DHEAS) at baseline in patients with active and untreated PMR [12]. The defect seems mainly related to altered adrenal responsiveness to the ACTH stimulation, at least in untreated patients. One-month
glucocorticoid treatment reduced the production of inflammatory mediators (i.e. IL-6) in a stable manner, which persisted following glucocorticoid tapering [12]. Therefore, PMR might be considered an HPA axis-driven disease [13]. Interestingly, the decrease of serum CO levels induced after 1 month of glucocorticoid therapy was more evident, in both PMR and LO-RA/PMR patients, suggesting their higher HPA axis responsiveness when compared with LO-RA patients.

The frequent observation of reduced CO and adrenal androgen secretion during testing in RA patients not treated with glucocorticoids, should clearly be regarded as a ‘relative adrenal insufficiency’ in the setting of a sustained inflammatory process, as shown by high serum IL-6 levels [11].

Similarly, DHEAS levels were significantly less frequent in LO-RA/PMR patients when compared with controls, whereas in the present study, no statistically significant difference was detectable in PMR patients. The reduction of DHEAS is a general feature of chronic inflammatory diseases. In the biosynthesis of steroids, the 17,20-lyase (P450c17) enzyme is suppressed both during ageing and in response to inflammatory stimuli, such as TNF-α, IL-1 and TGF-β1 [14]. Therefore, during ageing and under conditions of systemic inflammation (such as PMR), the suppression may be due to an inhibition of the adrenal 17,20-lyase, since CO under the same circumstances is increased in relation to DHEAS.

A significant increase of PRG levels in both basal condition and after ACTH stimulation was described in patients with recent-onset untreated PMR compared with age-matched controls and it is now confirmed in the present study, even in other groups of patients (LO-RA and LO-RA/PMR) [11].

The reasons for a functional 21α-hydroxylase impairment (involved in PRG metabolism) in PMR may include genetic defects or an age-related increase of serum TNF-α in healthy women or elevated serum IL-6 and TNF-α levels during chronic systemic inflammatory stimuli (i.e. PMR) [14]. Indeed, TNF-α was shown to inhibit the 21α-hydroxylase.

Therefore, the hormonal changes observed in PMR (and LO-RA/PMR) patients might reflect a more severe interference of the inflammatory cytokines on the steroid hormone metabolism when compared with LO-RA patients. In addition, the effects of the glucocorticoid treatment, acting as a replacement for the reduced endogenous cortisol production, seems again to be more efficient in both PMR (and LO-RA/PMR patients) (i.e. significant decrease of serum IL-6 and PRG), than in LO-RA patients, at least in a short time (1 month).

In conclusion, PMR (and LO-RA/PMR) patients seem to be characterized by a more intensive inflammatory reaction and they seem to be more responsive to the glucocorticoid treatment than LO-RA patients.

**Treatments**

As a consequence of the low cortisol, especially in PMR patients, the mandatory therapy is oral steroids with prednisone at dosages of 10–20 mg that usually suppress inflammation dramatically [15]. The preferred initial daily dose is probably 15 mg prednisone, because doses <10 mg were frequently associated with relapses and doses >20 mg were associated with a too high incidence of side-effects [16]. On the contrary, in RA patients the prednisone dosage might be much lower from the beginning and its early effects are not so dramatic as in PMR.

Concerning the use of MTX, its administration in RA patients represents almost a mandatory requirement, particularly in combination therapy, although other DMARDs might be employed (i.e. LEF).

Among the different possible steroid-sparing agents in PMR, MTX is by far the most widely studied compound, with conflicting results [17]. In a recent study, 87.5% of MTX-treated patients and 53.3% of patients treated with prednisone alone were no longer on steroids at 76 weeks, a difference that persisted after adjustment for CRP concentration and duration of symptoms in a multivariate model [18]. Significantly fewer patients on MTX had at least one flare up by the end of follow-up.

Regarding the TNF blockers, their use in RA is well established and effective.

In PMR, a randomized, double-blind, placebo-controlled, multicentre trial to evaluate the efficacy and safety of prednisone plus infliximab as initial treatment in 51 patients with newly diagnosed PMR was recently published [19]. However, no differences were observed among groups: the proportion of patients who were free of relapses/recurrences at 22 and 52 weeks was similar after adjustment for duration of symptoms, HAQ and CRP level in a multivariate model. The proportion of patients no longer taking steroids at Weeks 22 and 52 were similar in the two treatment groups (55 and 50% in the infliximab group vs 64 and 54% in the placebo group) as was the median and total prednisone dose (0.91 and 1.71 g in the infliximab group vs 0.91 and 1.22 g in the placebo group). The rate and severity of adverse events were similar.

**Conclusions**

The careful analysis of clinical, laboratory (acute-phase reactants and cytokines) and hormonal differences in aged patients with an acute inflammatory and symmetrical musculoskeletal condition might help for the differential diagnosis between PMR and LO-RA.

In particular, it will aid the early diagnosis of PMR vs LO-RA in the age group of over 60 yrs, permitting the earlier initiation of more appropriate treatments.

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**References**


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