Polymyalgia rheumatica with normal erythrocyte sedimentation rate: Clinical aspects

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ABSTRACT

Polymyalgia rheumatica is a relatively common syndrome of the elderly characterized by severe pain and stiffness in the neck shoulder and pelvic girdles, along with increased acute phase reactants. The current diagnostic criteria include as a requirement an erythrocyte sedimentation rate (ESR) higher than 30 or 40 mm/1 hr.

Nevertheless, in several reports, a sizable proportion of patients with PMR, from 7% up to 22%, had an ESR that was either normal or slightly increased at the time of diagnosis, supporting the notion that an increased ESR should not be an absolute requirement for its diagnosis. This subset is characterized by a younger age, a less marked predominance of females, a longer diagnostic delay and a lower frequency of constitutional symptoms such as fever or weight loss. When determined, a majority of these patients had increased levels of C reactive protein.

The recognition of this subset of patients with PMR and a low ESR can be very useful to the clinician, avoiding unnecessary suffering of the patients and the risks of ineffective therapy with nonsteroidal antiinflammatory drugs. To avoid the over-diagnosis of PMR in patients with a low ESR, we propose a set of criteria that can be easily applied in daily practice to patients with a clinical picture consistent with PMR but with a normal or slightly increased ESR.

Polymyalgia rheumatica (PMR) is a relatively common syndrome of the elderly (1). The main clinical symptoms are severe pain and stiffness in the neck, shoulder, and pelvic girdle (2). Systemic manifestations, such as fever, fatigue, anorexia and weight loss are also frequent, and have been reported in around one-third of the patients (1, 2). Although isolated PMR is a benign and self-limited illness, it may be the first manifestation of giant cell arteritis (GCA), which sometimes produces severe neurologic and/or vascular complications (3, 4). Furthermore, a syndrome indistinguishable initially from PMR may be the first manifestation of other disorders, especially rheumatoid arthritis (RA) (1).

The cause of the characteristic proximal pain and stiffness symptoms in PMR is not fully understood. Evidence of mild to moderate proximal joint synovitis has been shown by different techniques, such as scintigraphy, arthroscopy, and synovial biopsy (1). More recently, Salvarani *et al*. (5) have shown by magnetic resonance imaging that 100% of PMR patients have bursitis of the subacromial and subdeltoid bursae. In addition, therapy with low-dose corticosteroids produce in parallel the clinical disappearance of symptoms and a complete resolution of the bursitis and proximal joint synovitis. Therefore, this study supports the hypothesis that the swelling of the proximal joints and adjacent bursae is the most likely cause of the severe discomfort in these patients.

Currently, the diagnosis of PMR is based upon its main clinical features, and all the sets of diagnostic criteria proposed include as a laboratory requirement a erythrocyte sedimentation rate (ESR) higher than 30 or 40 mm/1st hr (6, 7). Furthermore, ESR has been used as the main parameter for monitoring disease activity and as a prognostic marker (1). Even though the ESR is a very good indicator of disease activity in PMR and GCA, this parameter is not always elevated in patients with these diseases. In 1983, Ellis and Ralston were the first who called the attention to the existence of a subset of patients with PMR and a low ESR (8). In their series of patients with PMR and GCA, 22.5% had an ESR at diagnosis < 30 mm/1st hr. They concluded that ESR is not an entirely reliable guide in the diagnosis and monitoring of disease activity in patients with these syndromes, nor it can predict the development of complications.

In 1992, we started a cooperative multicenter retrospective study of patients with PMR and GCA. Three rheumatology divisions in northern Spain (Santander, San Sebastian and Lugo) included all of the patients diagnosed with PMR and GCA and treated during the last two decades (2, 3, 9). We have observed in our practice a significant number of patients meeting the clinical criteria for the diagnosis of PMR, but having as a distinct characteristic an ESR lower than 40. Based on this experience, we believed that those patients with a clinical picture consistent with PMR, even with low ESR, and resolution of their symptoms with low-dose prednisone (≤ 10 mg/day) should be diagnosed as having PMR.

We studied 201 patients who, apart from their ESR at the time of diagnosis, fulfilled the diagnostic criteria proposed in 1982 by Chuang *et al*. (6). Forty-one patients (20.4%) from the whole PMR population had an ESR < 40 mm/1st hr. Patients with a low ESR were characterized by a male predominance, younger age, and a lower frequency of fever (9). The mean ESR at the time of diagnosis in the group with low ESR was 25 mm/1st hr compared to the value of 77 in the group with classic PMR. Patients with low ESR had also a lower frequency of anemia and abnormal protein electrophoresis results. Otherwise, the clinical syndrome, response to therapy, and frequency of relapses were similar in both groups. The mean delay to diagnosis was slightly longer in patients with a low ESR but it did not reach statistical significance. Therefore, the lower ESR in this subset of patients cannot be attributed to a shorter duration of their illness prior to diagnosis.

A majority of the patients in both groups (73-80%) have been previously treated with non-steroidal-anti-inflammatory drugs (NSAIDs) without improvement. After a long-term follow-up of more than 18 months, there were no significant differences regarding the duration of treatment or the development of RA. In the whole population of PMR patients, when the ESR was analyzed as a continuous variable, there was a positive correlation of ESR with several clinical features such as the number of areas clinically involved, the presence of fever and weight loss, and the presence of anemia and abnormal protein electrophoresis results.

In 1994 we presented our preliminary observations on this subgroup of PMR patients at the ACR meeting (10). As shown in Table I, our preliminary results regarding the existence of PMR patients with normal or slightly raised ESR were later supported by an increasing number of authors from different countries (11-19). Although the incidence of PMR with a low ESR differs in these reports, ranging from 7% up to 22%, all of them support the notion that an increased ESR should not be an absolute requirement for the diagnosis of this entity.

If we consider together the main studies reported during the last 3 years (9, 11-16), it is feasible to characterize the main distinctive features of the subset of patients with PMR and normal or slightly raised ESR (Table I).

1) They are somewhat younger, without the clear predominance in women classically observed in PMR.

2) They usually have a longer duration of symptoms prior to diagnosis, which may reflect the hesitancy of many clinicians to diagnose PMR in the absence of an elevated ESR.

3) Except for a lower frequency of systemic features (fever and weight loss), patients with PMR and low ESR have the same clinical syndrome, which does not respond to NSAIDs.

4) Other laboratory abnormalities that reflect the acute phase response such as anemia or abnormal protein electrophoresis show normal or slightly abnormal results.

5) Finally, the disease duration, therapeutic requirements, and number of relapses or development of RA on long-term follow-up are similar in patients with low and high ESR. It is worth noting that none of our patients with a low ESR developed GCA.

The reason for the low ESR in this subgroup of patients is unknown. It is unlikely that the normal ESR in some patients could be explained by a clinical misdiagnosis. Arthritis in our whole series of PMR was infrequent and those patients with arthritis in the small joints were excluded from the study (9). Furthermore, after a long term follow-up only one of the patients in the PMR subgroup with low ESR developed RA. A careful clinical evaluation, appropriate laboratory studies, and follow-up ruled out other possible diagnoses such as other connective tissue disorders, fibromyalgia, Parkinson's disease, or metabolic diseases (1). Although it has been

Table I. Main characteristics of polymyalgia rheumatica patients with normal or low erythrocyte sedimentation rate.

	Helfagott (11) (n = 117)	Gonzales-Gay (9) (n = 201)	Kanik (14) (n = 20)	Cantini (15) (n = 177)	Sivri (16) (n = 34)	Proven (13) (n = 232)
Proportion with low ESR (%)	22.2	20.4	?	8.5	14.7	7.3
ESR cut-off value (mm/1st hr)	30	40	35	40	30	40
Predominande of males	No *	Yes	No *	Yes	No *	No
Younger age	No	Yes	Yes	ND	No	No
Longer delay to diagnosis	Yes	No	Yes	ND	Yes	No
Less systemic features	No	Yes	Yes	Yes	Yes	Yes
Less lab abnormalities	Yes	Yes	Yes	Yes	Yes	Yes
Refractory to NSAIDs	Yes	Yes	ND	ND	Yes	ND

* No statistically significant predominance in male, but with decrease in the typical female/male ratio seen in classic series of PMR patients. ND: no data.

reported that approximately 20% of PMR patients may respond to NSAIDs (6), it is likely that the majority of these responders are never seen in hospitals. Nevertheless, an alternative explanation for the low ESR in some PMR patients, might be that they were previously treated with NSAIDs, and although these drugs were not clinically effective, they may have partially controlled the acute phase reactants. However, our data do not support this hypothesis because a similar proportion of patients with low and high ESR received previous NSAID therapy.

It appears that for some unknown reasons, this subset of patients lacks the brisk inflammatory response classically associated with PMR. The finding of a lower frequency of fever together with the absence of anemia in patients with a low ESR corroborates the finding of a blunted acute phase response in this subgroup of PMR patients (9). It seems that ESR is not as clinically significant for diagnosing PMR as had been thought. Considering the results of a recent prospective study from Italy (15) and the preliminary data of an on-going prospective study from Spain (unpublished observations), the majority of patients with low ESR have increased C-reactive protein (CRP) levels. Therefore, CRP should be considered as an alternative diagnostic criteria for PMR patients.

As there is no specific diagnostic test for PMR and a highly increased ESR is the most distinctive and objective parameter supporting the clinical diagnosis of PMR, some rheumatologists expressed concern about the possibility of overdiagnosing PMR with a low ESR (20). We share this concern, and to minimize the risk we believe that we should apply more strict diagnostic criteria for the diagnosis of PMR with normal or slightly raised ESR. To this end we have recently proposed that this diagnosis should be made only if the patients meet the 4 criteria shown in Table II (21). Obviously, the 2 classical criteria based on the age at onset of symptoms and the typical clinical features of PMR should be present. To avoid misdiagnosis we have substituted the presence of high ESR by the absence of arthritis in the small joints and, even more importantly, a complete resolution of symptoms in less than one week with 5 mg of prednisone twice daily.

In summary, from this review we can conclude that PMR with low ESR does exist and its recognition could be very useful to the clinician. Furthermore, it could avoid unnecessary suffering to the patients and the high risk of toxicity with ineffective NSAIDs therapy in this age group (1, 12). The determination of ESR in the assessment of a patient with suspected PMR remains as a very useful tool in the majority of patients (1), but the presence of a normal ESR should not exclude the diagnosis of PMR. The work-up of patients with suspected PMR should include along with the ESR the determination of CRP levels. In a patient with good clinical evidence for PMR based on the history and clinical findings, a normal ESR should be ignored and the patient should undergo an empirical trial with low-dose corticosteroids (never more than 10 mg/day of prednisone). The absence of arthritis in the small joints along with a rapid and complete resolution of the clinical syndrome with low dose prednisone should be essential for the diagnosis of PMR in patients with normal pretreatment ESR values.

Table II. Proposal of diagnostic criteria for polymyalgia rheumatica with normal or low erythrocyte sedimentation rate. The patient should meet the following 4 criteria (21).

1. Age at disease onset ≥ 50 years.
2. Bilateral moderate or severe pain and stiffness lasting ≥ 1 month involving at least 2 of the following areas: neck, shoulder and pelvic girdle.
3. Absence of arthritis in the small joints.
4. Complete resolution of the syndrome in less than 7 days, with low-dose prednisone (5 mg. of prednisone/ 12 hr. or equivalent).

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