Laboratory investigations useful in the evaluation of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA)

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ABSTRACT

The most useful investigation in supporting the clinical diagnosis of PMR/GCA is elevation of the erythrocyte sedimentation rate (ESR) or viscosity. Acute phase proteins, particularly CRP, are also elevated but in most cases are not more helpful than the ESR in either diagnosis or follow-up. The definitive investigation is the demonstration of giant cell arteritis histologically, usually from temporal artery biopsy. Elevation of alkaline phosphatase of liver origin is seen in one-third to one-half of patients and may lead to delay in diagnosis. Measurements of α1-antichymotrypsin and IL-1β may be helpful in diagnosis and management but more studies are required.

A raised erythrocyte sedimentation rate (ESR) is widely considered to be important in the diagnosis and management of PMR/GCA. The American College of Rheumatology 1990 criteria for GCA include ESR > 50 mm/hr as one of three criteria (out of a possible five) required to make the diagnosis. A level of more than 30 mm/hr is usually regarded as significant, and the range is wide. Kyle *et al.* (1) found a range of 32-138 mm/hr on presentation in 74 patients; the mean value for PMR (70.21) was not significantly different from that in GCA (76.28).

However, up to 7% of patients have a low ESR at presentation and a normal ESR is occasionally found in patients with active biopsy-proven disease (2). Patients with a low ESR do not usually seem to have a different disease course with respect to corticosteroid dosage or duration, but the diagnosis may be delayed. However, Dolan and colleagues (3) suggest that pre-treatment ESR in PMR can give prognostic information about the length of treatment. They compared ESRs in PMR patients still on prednisolone after 24 months with ESRs in those off prednisolone at 24 months. They describe a higher pre-treatment ESR and higher ESRs at 12 and 24 months in the group who were still on prednisolone after 24 months. This group on treatment at 2 years represented a subgroup consisting of patients with more severe disease and reduced bone mineral density at the start of treatment and subsequently.

The acute phase proteins are also elevated in active PMR/GCA and a number of studies have compared them with the ESR. A study of 74 patients (1) found the ESR to correlate better than CRP with disease activity, both on presentation and during relapses. CRP fell more rapidly in the first 2 weeks after treatment. However, neither were elevated in around 50% of patients where clinical relapse had occurred. However, in practice the ESR is used by many general practitioners and hospital physicians to diagnose relapses. Chakravarty (4) found that two-thirds would increase prednisolone in response to a raised ESR in the absence of symptoms of PMR/GCA, while few considered increasing the corticosteroid dosage on the basis of symptoms alone.

α1-antichymotrypsin (α1-ACT) has been measured together with ESR, CRP and clinical disease activity in 44 patients (55). α1-ACT, like CRP, begins to rise 6-8 hrs after an inflammatory stimulus and reaches a peak at 2 to 3 days. α1-ACT has a longer half-life than CRP and its biosynthesis may also continue longer after the inflammatory stimulus. Hence, in chronic diseases a combination of CRP and α1-ACT may give complimentary information. We have shown that α1-ACT in PMR/GCA behaves in an entirely different way from CRP and the ESR, in that the circulating level of α1-ACT remains raised long after clinical suppression of the disease by corticosteroid treatment.

As has been mentioned, the diagnosis of relapse during treatment is often difficult, as the symptoms may be less florid

than at onset, and the ESR and CRP are usually not elevated. Pountain *et al.* (6) have measured plasma levels of IL-1β and IL-6 and serum level of soluble IL-2 receptor in an attempt to assess whether the measurement of cytokine levels is helpful in management. In the initial diagnosis of PMR/GCA, these three investigations had no advantage over the conventional investigation of ESR and CRP. In relapses IL-1β was more likely to be raised than ESR or CRP. In the future, more sensitive IL-1β assays may make this a useful investigation.

Antibodies to intermediate filaments have been found to be increased in active untreated PMR (7). The cytoplasm of eukaryotic cells contains a major filamentous system consisting of microfilaments (5-6 mm diameter, called 'actin filaments'), microtubules (20-25 mm diameter) and intermediate filaments (7-11 mm diameter). Antibodies to intermediate filaments are frequently found in the sera of patients with either viral or autoimmune diseases.

Intermediate filaments were found in 52% of the 88 sera samples examined but the levels decline and disappear, although more slowly than the acute phase response.

It is often diffficult to differentiate polymyalgia rheumatica from elderly-onset rheumatoid arthritis (RA). The possibility that PMR may sometimes include synovitis increases this diffficulty. Kassimos and colleagues (8) measured the serum levels of cytidine deaminase to assess whether they could distinguish between RA and PMR. Cytidine deaminase is a cytoplasmic enzyme involved in pyrimidine metabolism and converts cytidine into uridine. It is easily measured by a spectrophotometric method that is simple, reproducible, sensitive and inexpensive. Cytidine deaminase levels were high in active RA but not significantly raised in PMR, although there was some overlap between the values for the two conditions.

There have been several studies of circulating T cell subtypes in patients with PMR and GCA, with differing results. Dasgupta and colleagues (9) have reported reduced absolute numbers of CD8+ cells. However, Pountain *et al.* (10) could not confirm the findings of some groups that the percentage of circulating CD8+ cells was reduced in patients with PMR/GCA before treatment. They demonstrated that the percentage of CD8+ cells decreases during treatment with corticosteroids, and they illustrated design flaws that could distort data and lead to an erroneous conclusion that CD8+ cells are reduced in PMR/GCA. Published results may also be distorted in favour of an abnormality of CD8+ cells, in that negative studies are less likely to be published.

Liver function

Raised serum values for alkaline phosphatase are commonly found in polymyalgia. Sulphabromophthalein retention is also often abnormal and transaminases may be mildly elevated. Liver biopsies have shown portal and intralobular inflammation with focal liver cell necrosis and small epithelicoid cell granuloma. Abnormal liver scans may also occur. In patients presenting with nonspecific features, the findings of abnormal liver function tests and abnormal scans may be misleading and prompt investigations for malignancy.

Cardiolipin antibodies

A significant number of patients with PMR and/or GCA have elevated levels of anticardiolipin antibody (aCL) at presentation (11). These patients appear to be at increased risk of developing GCA or other major vascular complications. It is possible that aCL may be an independent prognostic marker for future vascular complications with PMR and/or GCA. Other studies have shown that aCL levels are higher in patients with active arteritis and fall rapidly after corticosteroid treatment.

Temporal artery biopsy

Clinicians vary in their use of temporal artery biopsy. Most feel that a biopsy is not necessary if clinical features are characteristic, but feel it can be reassuring in retrospect, as it confirms the diagnosis if patients develop side effects from therapy or are resistant to therapy. Others feel that a high false-negative rate diminishes the value of biopsy. In most instances, this high false-negative rate can be attributed to the focal nature of the inflammation. 'Skip' lesions as short as 350 μm are evident in about one-third of biopsies, some segments showing active disease. The rate of false-negative biopsies depends on many variables, including the size of the biopsy, the number of levels examined, whether biopsies are taken from one or both sides of the head, and the duration of corticosteroid therapy prior to the biopsy.

The guidelines for biopsy should be as follows:

1. Perform a biopsy if the diagnosis is in doubt, particularly if systemic symptoms predominate.
2. Biopsy is most useful within 24 hrs of starting treatment, but do not delay treatment for the sake of biopsy.
3. A negative biopsy does not exclude giant cell arteritis.
4. A positive result helps to prevent later doubts about the diagnosis, particularly if treatment causes complications.

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