Utility of C-reactive protein in the diagnosis of giant cell arteritis: better than the erythrocyte sedimentation rate?

"No laboratory test alone can substitute for a careful history and physical examination to initially characterize giant cell arteritis, nor does it provide sufficient information to direct optimum management. C-reactive protein, therefore, should be used in conjunction with other clinical and laboratory data to make decisions about care."

KEYWORDS: C-reactive protein ■ diagnosis ■ giant cell arteritis ■ sedimentation rate

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"When one admits that nothing is certain one must, I think, also admit that some things are much more nearly certain than others"
–Bertrand Russell.

Since its discovery more than 80 years ago by Tillett and Francis at Rockefeller University (NY, USA), C-reactive protein (CRP) has been recognized as the prototype acute-phase reactant [1]. Originally identified by a precipitin reaction with pneumococcal C-polysaccharide, it is now commonly measured with ease and good reproducibility by latex-based immunoturbidimetric assays or nephelometry.

The unique binding characteristics of CRP allow it to play a key function within the innate immune system, acting like an opsonin and promoting phagocytosis [2]. It also binds to Clq, activating the classical pathway of the complement system [3]. Thus, in addition to serving as a diagnostic aid for inflammation and necrosis, it also has an important protective role particularly in the early stages following inflammatory stimuli.

Circulating CRP is one of the principal downstream mediators of the acute-phase response and is primarily derived via IL-6-dependent hepatic biosynthesis. It is the most sensitive of the acute-phase proteins, with levels rising as much as 1000-fold with acute inflammatory processes [4]. Levels begin to rise within 4–6 h of the onset of signs of tissue injury and peak 24–48 h later. Levels also fall rapidly as the inflammatory process resolves. Unlike the erythrocyte sedimentation rate (ESR), its levels are relatively insensitive to age, sex, plasma viscosity and other hematological parameters. Despite these advantages and being a direct measure of the acute-phase response, it has not been accepted and utilized as much as some traditional tests, such as the (Westergren) ESR that is an indirect measure of fibrinogen elevation in response to inflammatory stimuli.

Giant cell arteritis (GCA) is the most common idiopathic systemic vasculitis affecting large- and medium-sized arteries in adults over the age of 50 years. It classically presents as headache, scalp tenderness, amaurosis fugax, diplopia, jaw and/or tongue claudication or a combination of these, accompanied by an intense acute-phase response. Polymyalgia rheumatica symptoms develop in 40–60% of patients. GCA can be an ophthalmologic emergency, with complete vision loss due to anterior ischemic optic neuropathy. Visual loss may occur in up to 13–50% [5–10] of patients and is often irreversible. The second eye also has a high probability of becoming affected within 1–2 weeks, if left untreated. Early and accurate diagnosis of GCA is therefore critical so that high-dose corticosteroids can be started to prevent ischemic complications.

The diagnosis of GCA can pose serious challenges. Not all patients present with the classic combination of symptoms listed above, in particular, those with vision loss. Up to 15% of patients can have fever of unknown origin as their initial presentation. Other atypical presentations include isolated aortic arch syndrome with arm claudication, large vessel vasculitis with lower extremity claudication, stroke, vertebrobasilar insufficiency, aortic dissection or thoracic aortic aneurysms [11,12].

The 1990 American College of Rheumatology criteria were designed to classify patients with GCA and distinguish them from other vasculitides with a good sensitivity (93.5%) and

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specificity (91.2%) [13]. These were not meant to help diagnose GCA in individual patients but are often used for this purpose by default in the absence of a specific laboratory test or biomarker for GCA. Most patients have elevated markers of inflammation, including both ESR and CRP. These tests aid clinicians in selecting patients for temporal artery biopsy (TAB), which remains the gold standard for diagnosis, and prompt treatment for this rapidly progressive and potentially sight-threatening disease.

Traditionally, an extremely elevated ESR (~ >100 mm/h) has been considered a hallmark of this disease and ESR >50 mm/h constitutes one of the five American College of Rheumatology classification criteria for GCA [13]. However, in up to 22.5% of cases in some series [14], the ESR is normal while the TAB is positive. The frequency of normal ESR varies depending on the method and formula used [15] to determine ESR values and the cutoff utilized for classifying it as normal. A population-based study from Olmsted county [16] showed that, at disease presentation, 3.6% patients, 5.4% patients and 10.8% patients with TAB-confirmed GCA had ESR values of <30, <40 and <50 mm/h, respectively. Thus, depending on ESR alone to guide diagnostic decision-making can result in missed diagnoses and higher chances of presentations with ischemic sequela of vision loss, myocardial infarction or stroke.

Performance characteristics of the ESR and CRP tests were recently evaluated in a large study of 1106 patients who underwent TAB at our center [17] and had an ESR and CRP tested in the 6 weeks prior to biopsy. Elevated CRP (normal ≤8 mg/l) was found to have a slightly higher sensitivity (86.9 vs 84.22%) than elevated ESR (normal ≤22 in men and ≤29 mm/h in women) for a positive TAB, while the specificity of both individually was low (30.5 vs 29.5%). Combining the ESR and CRP modestly increased the specificity to 41%. Of note, the negative predictive values were high for both tests, with the CRP again performing somewhat better than the ESR (88.6 vs 86.1%). The odds of having a positive TAB increased (odds ratio: 3.06; 95% CI: 2.03–4.63) among patients with both elevated ESR and CRP, while they were reduced (odds ratio: 0.49; 95% CI: 0.29–0.83) if both CRP and ESR were normal. The optimal cutoff for CRP was >26.9 mg/l to yield a sensitivity of 75% and specificity of 51% for predicting a positive TAB.

These findings are similar to the CRP cutoff values reported by Hayreh *et al.*, who reported a cutoff value of CRP >2.45 mg/dl (i.e., >24.5 mg/l) for predicting a positive biopsy [18]. Using this cutoff value, Walvick *et al.* in a large population-based study of >3000 patients showed that the odds of a positive TAB were increased more than fivefold [19]. Finally, Ramstead *et al.* also found CRP to have a higher sensitivity than ESR (96 vs 83%) for detecting GCA in a North American population of Aboriginal descent [20].

Unlike systemic lupus, thus far, none of the four (of 84 currently known) studied polymorphisms in the CRP gene have been shown to confer susceptibility to GCA, nor its clinical presentation (polymyalgia rheumatica, ischemic complications) [21]. Hence, while the measured CRP value is helpful in disease activity assessment and in predicting the results of a TAB, polymorphisms specific to GCA have not been identified.

What are the implications of an elevated CRP in a patient with GCA? IL-6 induces angiogenesis both in *ex vivo* and *in vivo* models [22] and its levels both in terms of circulating IL-6 and expression of IL-6 mRNA and protein in tissue from temporal artery samples are significantly lower in GCA patients with ischemic events than in those without ischemic complications [22]. Hence, a higher CRP level at presentation in GCA may not only aid in the diagnosis but indicate a lower risk of visual loss, possibly because compensating mechanisms in the form of inflammation-induced angiogenesis have been activated.

Can GCA present with a normal CRP and does that mean these patients will definitely develop ischemic sequela? Like the ESR, there are few reports of normal CRP at presentation in GCA [15]. Estimates range between 2 and 14% depending on the study. In most reports however, either one measure, the ESR or CRP, were usually elevated. Parikh *et al.* reported only one of 119 (0.8%) patients with a positive TAB had a normal ESR and CRP at presentation [15].

Kermani *et al.* found as many as 18 out of 177 (10.2%) patients with a positive TAB had a normal ESR and CRP at presentation [17]. Most (11 out of 18) of these patients were on corticosteroids, which may have affected the level of acute-phase reactants. However, seven (4%) had a normal ESR and CRP even in the absence of glucocorticoid use. These patients were on average younger, had a longer duration of symptoms prior to diagnosis, higher prevalence of polymyalgia rheumatica symptoms and fewer constitutional symptoms than their counterparts with elevated ESR and/or CRP, although these differences did not reach statistical significance. They also had a lower prevalence

of anemia or thrombocytosis suggesting an overall blunted acute-phase response. Three of those seven (42.8%) patients with normal acute-phase reactants developed partial (two out of seven) or complete vision loss (one out of seven), suggesting a worrisomely higher than expected risk of ischemic complications.

What about using CRP for guiding treatment and predicting relapse? Most clinicians tend to base their judgment on clinical improvement along with supportive evidence from normalization of inflammatory markers. Unfortunately, clinical symptoms and laboratory measures of acute phase response are often discordant. The CRP generally normalizes early after initiation of systemic corticosteroids, while normalization of ESR usually takes at least 3–4 weeks. We suggest initiating the corticosteroid taper at 4 weeks as long as the patient is clinically improving, and then gradually reduce the dose every 2 weeks by 10% of the total daily dose [23] while closely following the clinical symptoms and CRP.

A high percentage of patients relapse during the glucocorticoid taper especially when the prednisone dose is below 7.5 mg daily. There is no supporting data to determine whether CRP is better than ESR in predicting relapse or recurrence in GCA, but a number of studies [24] have shown that both tend to rise from baseline values prior to the onset of recurrent clinical symptoms. This is true of other inflammatory biomarkers like ICAM-1, TNF-α and IL-12p40 that also increase prior to relapses [25]. There is also evidence to suggest that circulating IL-6 levels may be more accurate than CRP for diagnosis and follow-up of GCA but it is not widely available in clinical practice [26,27].

The preponderance of data suggests that CRP is slightly superior to ESR in the diagnosis of GCA. Using both tests further increases the specificity of diagnosis and increases the odds of a positive TAB. The CRP may be more useful for monitoring patient progress than for making a definitive diagnosis based on absolute CRP values. A rise in CRP during treatment with glucocorticoids should alert the clinician to the possibility of early relapse, treatment failure, overt tissue damage from a superinfecting pathogen, or patient noncompliance.

No laboratory test alone can substitute for a careful history and physical examination to initially characterize GCA, nor does it provide sufficient information to direct optimum management. CRP, therefore, should be used in conjunction with other clinical and laboratory data to make decisions about care. It remains a nonspecific marker for GCA diagnosis and activity assessment. Clearly, better biomarkers are needed for these purposes.

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