Development of a predictive model for temporal artery biopsies

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ABSTRACT ●

Objective: Temporal artery biopsy is a critical, relatively safe, and reliable test in the diagnosis of temporal arteritis. Yet, a clarification of the pre-test probabilities may provide clarity on which patients with suspected giant cell arteritis would benefit from this invasive diagnostic procedure.

Design: A prospective case series

Participants: A consecutive case series of patients referred to the Ophthalmology service for temporal artery biopsy.

Methods: All subjects underwent standardized serum testing, and signs and symptoms assessment. Predictive models were created and evaluated.

Results: 119 patients were analyzed. This exploratory study found that a simple model including platelet count, erythrocyte sedimentation rate, and c-reactive protein was able to define a subset of patients with a pre-test probability of a positive biopsy of 0% or 100%. 40% (95% confidence interval 31%-49%) of patients fell into this category.

Conclusions: Utilizing a simple clinically applicable predictive model of the pretest probability of a temporal artery biopsy in patients with suspected giant cell arteritis, up to 31%-49% of temporal artery biopsies may be avoided. This study was a single site exploratory study with data-driven thresholds - therefore these results need to be validated with an independent sample prior to clinical use.

Giant cell arteritis (GCA) is the most common form of vasculitis in individuals over the age of 50 years, with an estimated annual incidence in the United States of 19 per 100 000 person years.[1] Untreated GCA can lead to vascular compromise, including visual loss, diplopia, and other neurologic and cardiac sequelae, including myocardial infarction, stroke, and aortic dissection.[2–4]

The most common presenting symptom of GCA is headache, which is reported in two-thirds of patients.[5] Other manifestations may include scalp tenderness, jaw claudication, constitutional symptoms, and/or symptoms of polymyalgia rheumatica with shoulder and hip girdle pain and stiffness. Vision loss from ischemia of the optic nerve/eye may occur in 20% of patients.[6–8] The combination of clinical examination, laboratory tests, and histopathology comprises the diagnostic basis for GCA. The American College of Rheumatology proposed classification criteria for GCA in 1990 (see Table 1). The presence of any 3 of the 5 components yields a sensitivity of 93.5% and a specificity of 91.2%.[9] Yet, potentially important factors, such as visual symptoms secondary to vascular occlusion, jaw claudication, C-reactive protein, and platelet count, are not included in these criteria.

Presently, the treatment of GCA comes with significant complications. Systemic corticosteroid therapy remains the mainstay of GCA treatment. The treatment of GCA consists of a prolonged course of glucocorticoids, often for 1–2 years or longer.[10] The frequency of adverse side effects with high-dose steroids is common and can cause significant morbidity.[10] Randomized controlled trials employing steroid sparing agents, namely, methotrexate, have demonstrated efficacy, although the anticipated reduction in steroid-related morbidity was not dramatic.[11–13] Tocilizumab appears to be promising as a steroid-sparing agent for GCA.[14]

Because of the significant morbidity of GCA and its treatment, the threshold for performing a temporal artery biopsy (TAB) as a "definitive" diagnostic tool is appropriately low. Despite the critical role TAB plays in the diagnosis of GCA, false-negative temporal artery biopsies are well documented.[15–18] More specifically, a review of the literature found sensitivities for unilateral biopsy ranging from 58% to 94%, with a mean of 87% (95% CI 83%–91%), whereas sensitivities for bilateral biopsies ranged from 77% to 100%, mean 94.3% (95% CI 90%–98%).[19] Bayesian analysis found very similar sensitivities for unilateral biopsies with a value of 87% (95% CI 81.8%–91.7%).[20] These reported sensitivities are likely overestimates of the true sensitivity because many of the studies defined a positive biopsy result after performing bilateral biopsies as the gold standard for diagnosis of GCA. Reported complications of TAB are rare but include visible scarring, hematoma, wound infection and dehiscence, skin necrosis, facial nerve injury, and, the most

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Table 1—The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis[9]

Variable
Age at disease onset ≥50 years
New headache
Temporal artery tenderness to palpation or decreased pulsation
Erythrocyte sedimentation rate ≥50
Abnormal temporal artery biopsy

If a patient meets ≥3 criteria, they are believed to have a positive test for giant cell arteritis.

severe, cerebral infarction, presumably attributable to dependent collateral bloodflow to the brain via the superficial temporal artery.[17,21–23] Furthermore, organizing urgent biopsies can be logistically difficult, increase medical costs, and result in delays in treatment while awaiting biopsy. Any delay in initiating treatment can increase secondary adverse outcomes, including severe bilateral visual loss.[24]

Because of the limitations and challenges of TAB, further refining of the type of patient who would benefit from this procedure based on the pretest probabilities would be helpful. Patients who are certain to have GCA may benefit from the immediate initiation of treatment without dealing with the downsides, including false negatives, of TAB. Similarly, patients who definitively do not have GCA may benefit from having their practitioners move on to other causes, treatments, or investigations of their symptoms rather than going through an invasive procedure and the accompanying delays and limitations. This conceptual approach is supported quantitatively by a previous decision analysis that demonstrated, in a small proportion of clinical presentation scenarios, bloodwork can rule out GCA, and initiating treatment empirically should be considered if the pretest probability is very high (>90%–95%).[19]

Therefore, our group set out to create a predictive model for TAB results. If one defines the TAB as the "test," our goal was to find a model that could provide very high or very low pretest probabilities in the hopes of defining a subset of patients for whom TAB provides no additional diagnostic information. Ideally, a simple, easy-to-use predictive model would be able to differentiate among 3 categories of patients presenting with possible GCA symptoms: those who will almost certainly have a negative biopsy (pretest probability of 0%), those for whom the biopsy result cannot be predicted beforehand and who require a biopsy (pretest probability of 1%–99%), and those who will almost certainly have a positive biopsy (pretest probability of 100%). If such a model could be built and subsequently validated, only one of these 3 groups would need to undergo a biopsy.

Methods

The detailed methods are described in a previous study.[16] The data and study design were specifically developed to build this predictive model as the primary analysis. A standardized questionnaire assessing the signs, symptoms, and serum markers of GCA was prospectively created based on previously published predictors and the authors' experiences (see the left column of Table 2). All patients who had a suspicion of temporal arteritis and referred for TAB during the study period from 2005 to 2010 were invited to participate. An ophthalmologist involved in the study administered the questionnaire preoperatively. In the case of patients who were treated with steroids before being referred for biopsy and who had improvement of symptoms, clinical symptoms were included if present before steroid treatment. All patients underwent bilateral simultaneous biopsies. Approval from the Ottawa Hospital Ethics Committee was obtained and informed consent was obtained from each patient.

All patients were assessed and biopsied within 7 days of referral, and a minimum 2.5 cm length of specimen was obtained on each side whenever possible. Exclusion criteria included treatment with steroids for greater than 2 weeks before biopsy, or lack of erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and complete blood count (CBC). An experienced pathologist and/or ophthalmic pathologist used accepted histopathologic diagnostic criteria.[17]

Stata XII (StataCorp LLC, College Station, TX) was used for all analysis. Logistic regression was used to compare the baseline characteristics between those patients who were excluded and those who were included in the analysis.

Univariate logistic regression was performed to find the associated signs, symptoms, and serum markers with biopsy as the outcome. Significance in the univariate analysis was defined as $p < 0.1$. Receiver operating characteristic (ROC) curves and the area under the curve (AUROC or concordance statistic) were calculated for all significant predictors from the univariate analysis. The ROC curves were also visually evaluated for any squaring off of the ROC curve, suggesting perfect performance in that range (Fig. 1). The circled zone in the bottom far left represents the section of the graft in which specificity was 100%, and the circled area in the top right of the graph represents the portion of the curve with 100% sensitivity.

A multivariate regression model was built with all the variables from the univariate analysis that had a p-value ≤ 0.1, using stepwise regression with both forward selection and backward elimination. Critical predictors based on previously published data and current practice patterns were kept in the model. Statistical significance for multivariate logistic regression was defined as $p < 0.05$. Various models were created using clinical history, serum markers, and a combined model. Their corresponding ROC curves were compared. A predictive mathematical formula based on the beta coefficients of the multivariate models was created to create risk scores for each model. Sensitivity, specificity, positive predictive values, and negative predictive values were calculated and compared among these