A probability score to aid the diagnosis of suspected giant cell arteritis

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ABSTRACT

Objective. *We propose a GCA probability score intended to help to risk-stratify patients referred by general practitioners with suspected GCA into those with high probability of GCA versus low probability of GCA. In this pilot study we evaluated the diagnostic accuracy of this proposed scoring system.*

Methods. *A scoring system was proposed based on clinical experience. Retrospective analysis was conducted from clinical notes of consecutive patients presenting to a Fast Track Pathway clinic between August 2016 and August 2017. The GCA Probability Score was calculated for each patient and receiver operating characteristic (ROC) curve plotted.*

Results. *Of 122 consecutive patients, full data were available for calculation of GCA probability score in all patients except one (excluded from this analysis). The area under the ROC curve was 0.953 (95% confidence interval: 0.911, 0.994). The ROC curve showed an optimal cut point of 9.5 out of a possible score of 32. At this cut-point there was a sensitivity of 95.7% and specificity 86.7%, and 88.4% of cases were correctly classified.*

Conclusion. *The GCA Probability Score is a promising and feasible tool for risk stratification of patients referred by general practitioners with suspected GCA. In a fast track clinic setting this aids exclusion of GCA in low probability cases and confirmation of disease in high probability disease. Refinement and subsequent external validation of this score is required.*

Backgroung

Giant cell arteritis (GCA) is the most common primary systemic vasculitis with protean manifestations. Existing classification criteria for GCA are inadequate for clinical diagnosis, partly because the clinical presentation may be highly variable; cranial features may not always be present (1). Rapid specialist evaluation of GCA is required for timely initiation of glucocorticoid therapy in order to prevent ischaemic complications of GCA (2) and to prevent inappropriate GC therapy in those patients who do not have GCA (3), since GC-related side effects affect 85% of patients with GCA (4).

Rapid specialist evaluation may be provided within "fast-track GCA clinics", comprising initial clinical assessment followed by point of care temporal and/or axillary artery colour doppler ultrasound (CDUS) allowing real-time assessment of arterial wall swelling (as assessed by the 'halo sign') (5). The 2018 EULAR Recommendations for imaging in LVV now identify temporal CDUS as the first-choice diagnostic test, provided there is adequate expertise and equipment (6). Efficient care pathways for rapid referral to GCA clinics (Fig. 1) by referring clinicians require risk-stratification to prioritise referrals appropriately, but no validated clinical prediction score has yet been developed for use in this setting.

Methods

A draft GCA Probability Score (GCAPS) (Table I) was generated by two of the authors (BD, SB) based on long-term clinical experience and of running a fast-track service since 2012, supported by the relevant literature cited below.

Baseline demographics*:* GCA is known to occur in older individuals, with the 1990 ACR criteria specifying over the age of 50 (7). Prospective studies have found the mean age of the biopsy positive group to be higher (1). There is typically a female predominance (1, 8).

Clinical presentation

Headache is the most common presenting symptom in GCA, although this should be new and distinct from any

Table I. GCA probability score [GCAPS] proforma.

Weightage	-3	0	+1	+2	+3
Demographics					
Age (years)		≤49	50-60	61-65	≥66
Sex			M	F	
Duration					
Onset of symptoms		>24 weeks	12-24 weeks	6-12 weeks	<6 weeks
Laboratory					
CRP		0-5 mg/L	6-10 mg/L	11-25 mg/L	≥25 mg/L
Symptoms					
Headache		N	Y		
Polymyalgic		N		Y	
Constitutional		N	Single		Combination
Ischaemic		N			Y
Signs					
Visual (AION, CRAO, Field Ioss, RAPD)		N			Y
TA abnormality		N	Tenderness	Thickening	Pulse loss
Extra-cranial artery abnormality		N	Thickening	Bruit	Pulse loss
Cranial nerve paisy		N			Y
Alternative					
Infection	Y				
Cancer	Y				
Systemic Rheumatic diseases	Y				
Head and neck pathology	Y				
Other	Y				
Total score					

prior headache syndromes (9-11). However, headache is also a non-specific symptom and hence given a relatively low weighting The literature consistently highlights ischaemic symptoms of jaw claudication or visual disturbance (unilateral diplopia, blurring or amaurosis fugax) (12) as being significantly associated with increased risk of GCA (8, 10, 13, 14). Constitutional symptoms (fever of unknown origin, night sweats, unintentional weight loss) have been quoted to be as high as 10–20% and particularly suggestive of underlying LVV (10,15). Polymyalgic symptoms are seen in 40-60% of GCA cases at onset, and temporal artery CDUS has shown an increased prevalence of subclinical GCA in this PMR population (16).

Inflammatory markers

Data from large retrospective studies have shown good correlation between the level of inflammatory response and positive TAB (17). A stronger association with CRP elevation than ESR elevation has also been found (18).

Examination findings

Examination findings of relevance are primarily abnormality of the temporal artery itself. Meta-analysis found a tender or thickened temporal artery was more associated with positive TAB than individual items in the clinical history or inflammatory markers (13). Abnormal fundoscopy is also important (8) as are other ocular features such as relative afferent pupillary defect or visual field defect. The score also includes extracranial artery abnormalities. This important distinction is made due to the increased appreciation of large-vessel GCA, with newer imaging techniques identifying more extensive involvement of the aorta and its proximal branches (4).

Alternative pathology

Mimics of GCA including infections, malignancy, other rheumatological diseases and head and neck pathologies are well documented (13).

Retrospective data was collected in September 2017 for all patients consecutively assessed through our FTP between August 2016 to August 2017. All patients who attended GCA FTP included in our cohort. The GCA probability score thus generated was compared with the final diagnosis as GCA or non-GCA six months after the initial assessment. For GCA, a diagnosis of "definite GCA" was required (defined as: unequivocal positive ultrasound/ TAB without an alternative diagnosis at six months).

Analysis was performed in Stata SE, v. 13.1. The Stata command roctab was used to generate ROC curve and to calculate the area under the ROC curve. 95% confidence intervals were calculated using the bootstrap command in Stata using 1000 replications.

Patient and public involvement

The patients and public were not involved in the design and methodology of this study.

Ethical approval

As per the regulations of the UK Health Departments Governance Arrangements for Research Ethics Committees, the study is limited to a retrospective use of information previously collected during normal clinical care with no patient identifier recorded in the database for analysis. The study therefore, did not require Research Ethics Committee review or formal patient consent.

Results

Of 122 consecutive patients seen, full data for calculation of GCA probability score was available in all cases except one with missing CRP (excluded from this analysis). 23 patients had a confirmed final diagnosis of GCA at 6 months follow up. 75% of patients were reviewed in clinic within one working day and 89% of those were assessed by a specialist within 48hours. Mean age was 70.31 years, median 72 years (STD 10.99years). Our cohort included 96/121 females (79.33%). 71.9% of patients presented with acute (<6 weeks history) and subacute (6–12 weeks) history of symptoms and signs. Out of 121 patients, 113 reported cranial symptoms as scalp pain and headache, 15 constitutional symptoms including drenching night sweats, fever and/or weight loss, 10 polymyalgic symptoms and 15 ischaemic symptoms as unilateral blurring of vision, diplopia, sight loss permanent or transient.

Diagnosis was confirmed for our cohort by using clinical criteria, temporal artery biopsy, Colour Doppler ultrasound (CDUS) and/or PET-CT scan. In our

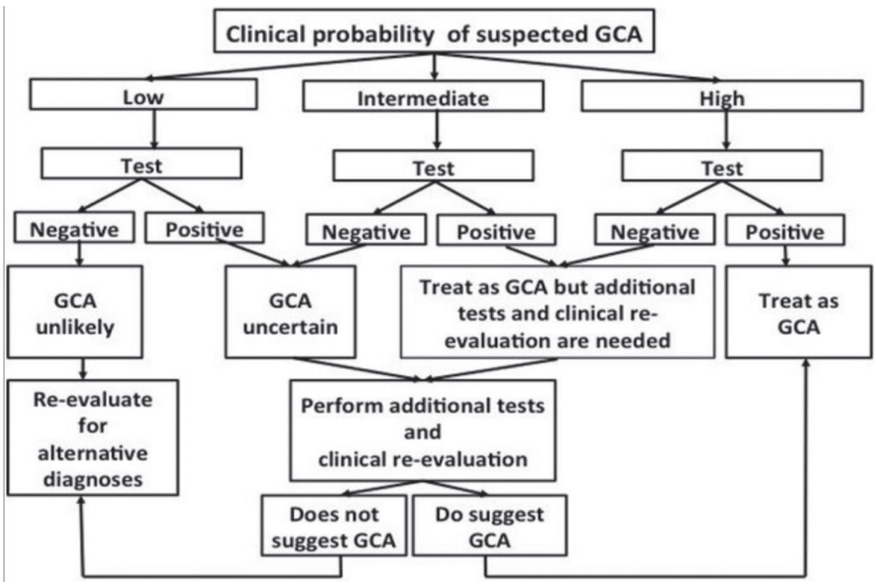

Fig. 1. Clinical diagnostic algorithm for GCA based on the BSR guidelines on GCA.

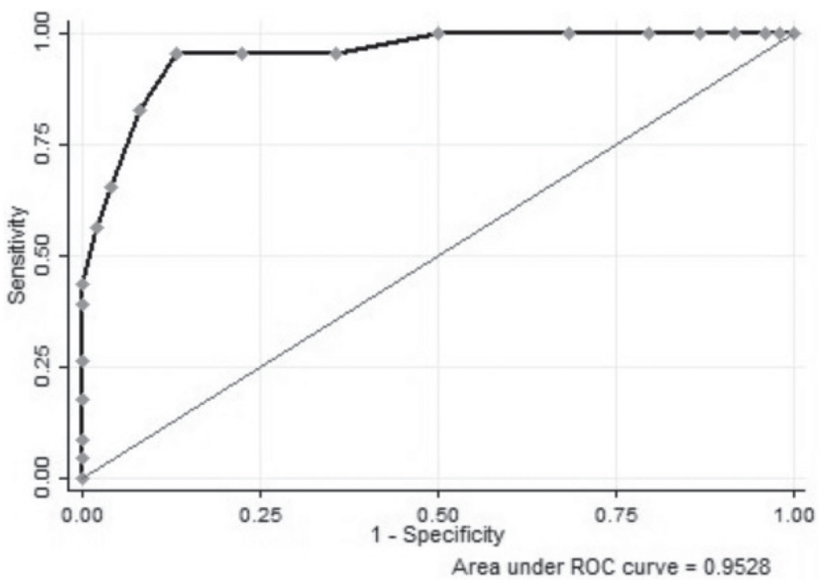

Fig. 2. Receiver operating characteristic curve of the total probability score. The point of inflection [sensitivity, 95.7%, specificity, 86.7%] corresponds to a probability score cut-off of 9.5 [score 9 or below: not GCA; score 10 or above: GCA].

centre, CDUS is the first investigation of choice to exclude or confirm cranial or large-vessel GCA and according to BSR guidelines for suspected GCA (Fig. 1). The gold standard was the diagnosis as ascertained after 6 months follow up. All the diagnoses of GCA were confirmed by vascular ultrasound or by temporal artery biopsy.

Of those 121 patients, 3 were diagnosed with cranial GCA based on their typical clinical picture and their subsequent response to glucocorticosteroids. 4 were diagnosed based on PET-CT scan only as they presented with symptoms which suggested large-vessel vasculitis as polymyalgic and constitutional symptoms. For 3 patients their GCA diagnosis was put based on both positive temporal artery biopsy and CDUS. Only one patient had positive CDUS with negative temporal artery biopsy. Diagnosis was made for the rest of the cohort based on CDUS.

The diagnosis of GCA was reclassified in 2 patients within 6 months from the initial assessment. For the first patient a diagnosis of large-vessel vasculitis was given and initial presented with subacute onset of headache and raised inflammatory markers on a background of recurrent infections, clinical suspicion was low for GCA and initial investigations as CDUS was normal. Probability score was 7 on initial assessment. The second patient, presented with an acute onset headache (<6 weeks) headache, severe constitutional symptoms and raised inflammatory markers. Clinical suspicion was moderate (probability score 11) for suspected GCA, CDUS (temporal and axillary) was normal on repeat scans and a decision was made to review patients within 2 weeks of presentation where the diagnosis was subsequently made for LVV on PET-CT scan.

The area under the ROC curve for the 121 cases with full data was 0.953 (95% CI: 0.911, 0.994) (Fig. 2). At the point of inflection of the ROC curve, corresponding to a cut point of 9.5, sensitivity was 95.7%, and specificity was 86.7%; the likelihood ratio for a positive test was 7.2 and the likelihood ratio for a negative test, 0.050. At this cut point, 88.4% cases were correctly classified.

Conclusion

This single centre cohort study suggests that the GCA probability score may be a useful tool for rating the pre-test probability for GCA. There was a high level of data completeness, supporting the feasibility of this score in clinical practice. It does not require an app, calculator or spreadsheet making it suitable for point-of-care use. This also has the advantage of standardisation that may reduce variation in clinical assessment and aid decision-making.

Fast-track pathways for GCA diagnosis have been introduced to prevent irreversible sight loss, but practical implementation is not always feasible because of a lack of a feasible scoring system to prioritise referrals. In addition to its potential use in prioritising referrals, the proposed score could also be tested for its ability to support clinical decisions where the initial confirmatory test (CDUS or biopsy) is negative. A high sensitivity GCAPS based on initial assessment, could be used

as a decision aid to refer appropriately and would avoid the need for referral to a FTP clinic if the score was low. Among referred cases, those with probability score (<9.5) could be assessed by CDUS. A negative CDUS would exclude GCA whereupon the clinician could stop GC and reassure the patient. Conversely, a patient with high GCAPS (since it has high specificity as well) and positive CDUS could have the diagnosis definitively confirmed and treated with appropriate doses of GC. Patients with intermediate scores, those with conflicting GCAPS and CDUS findings or those with equivocal CDUS results would require additional investigations including TAB and/or other imaging scans.

Other prediction algorithms for GCA diagnosis have been published from ophthalmology settings, focusing on patient selection for TAB (10, 14, 19-24). Limitations of these previous studies include misclassification rate, poor area under ROC curve, circularity with use of TAB to aid diagnosis, lack of appreciation of key predictors such as constitutional and polymyalgic symptoms, and absence of negative weightings given to competing diagnosis. In addition, the clinical spectrum of patients presenting to ophthalmology services is likely to differ significantly from referrals from UK general practitioners to a fast-track clinic, and this would be expected to affect the ability to generalise to our setting.

Physicians are already trained in using pre-test probability scores. The score was developed based on clinical experience, but this is because of absence of longitudinal inception cohort studies of unselected suspected GCA referrals. BVAS and Wells score are examples of other scores that have been developed based on clinical experience and currently being used world wide. The 'Wells Score' for venous thromboembolism (VTE) (20) is in widespread use. Like our proposal, the score is derived from aspects of initial assessment. A low score in combination with a negative initial test (d-dimer) allows the clinician to confidently rule out (VTE). A high score, or low score in combination with a positive initial test, would prompt further evaluation.

This was a pragmatic single-centre study and we cannot exclude bias arising from the clinician/sonographer being aware of the GCA probability score when undertaking and reporting the CDUS. Future validation of the GCAPS should require the sonographer and imaging assessor to be blinded to the pre-test probability and clinical features of the individual patient. Selection of predictors and their weightings was clinically-informed rather than data-driven. The predictors and weightings could be refined in a separate, larger dataset with external validation.

The GCA Probability Score is a promising and feasible tool for risk stratification of patients referred by general practitioners with suspected GCA. In a fast track clinic setting this aids exclusion of GCA in low probability cases and confirmation of disease in high probability disease. We are indeed aware that these results are based currently on a single centre experience and we have sent the score to different expert units in Europe with a request of feedback based on their individual experience. The score was discussed at the 6th International ultrasound workshop held in Southend in April 2018 as well as in the GCA masterclass held in London July 2018. All attendees and delegates as well as the faculty members were given a copy of our probability score with a request to validate locally. One problem is that fast track clinics (such as at Southend) accepting unselected suspected GCA referrals are still quite low in number – hence experience in external validation cohorts will be slow to accrue but we do emphasise the need for refinement and subsequent external validation of this score.

We believe that this score will be primarily used by rheumatologists staffing fast track rapid access clinics for suspected GCA referrals. However, the clear majority of our referrals were from GP's and hence our score largely reflects the referral pattern of GPs in our area. It would be necessary to get a validation cohort study in primary care suspected GCA patients – however we feel that all suspected GCA should be referred to secondary care for confirmation of diagnosis.

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