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# Giant cell arteritis: Challenges of diagnosis and management in general practice.

1Toby Helliwell PhD, 1Sara Muller PhD, 1,2 Samantha L Hider PhD, 1 James A Prior PhD, 1 Jane C Richardson PhD, 1 Christian D Mallen PhD

1Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Keele Staffordshire ST5 5BG

2Rheumatology Department, Haywood Rheumatology Centre, Staffordshire ST6 7AG

**Address for correspondence:**

Dr Toby Helliwell. Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Keele Staffordshire ST5 5BG.

Email address: t.helliwell@keele.ac.uk

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Background: In the UK, general practitioners (GPs) are usually the first medical contact for patients with suspected giant cell arteritis (GCA). Whilst rare, it is critical not to miss, as delayed treatment can lead to significant complications including permanent visual loss. To date little is known about the approach and challenges to diagnosis and management of GCA by GPs.

Objective: To investigate the diagnosis and management of patients with suspected GCA in UK general practice.

Design and participants: A multi-methods approach was taken, comprising a postal survey of 5000 randomly selected UK GPs and semi-structured telephone interviews of 24 GPs from across the UK.

Setting: UK general practice

Results: 1249 questionnaires were returned. 879 responders (70%) indicated that they had diagnosed and managed a patient with GCA. A variety of clinical features were used to identify GCA. 21.9% suggested that they would exclude GCA as a diagnosis if headache was absent and less than half of GPs routinely initiate glucocorticoid treatment prior to referral. Significant regional variations in referral pathways were reported. Thematic analysis of interview transcripts highlighted fears relating to a missed diagnosis of GCA and the non-specific nature of early GCA presentation. Accessing specialist care was highlighted as challenging by many GPs and that a national standard fast track pathway is lacking to support this patient group. Additionally there were significant concerns regarding potential adverse effects relating to long term treatment with glucocorticoids.

Conclusion: GPs over-rely on headache to identify GCA and marked geographical differences in management, with conflicting referral pathways and difficulties in accessing appropriate services exist in the UK. A national standard for fast-tracking suspected GCA patients to relevant specialists would be beneficial to improve care and outcomes for patients with GCA.



**Strengths**

1. Multi-methods approach, allowing the identification of significant challenges relating to GCA management in primary care and subsequent in depth exploration of those issues.
2. First large study to investigate diagnosis and management of GCA in general practice

**Limitations**

1. Sub-optimal response rate and therefore potential lack of generalisability to findings although responder demographics of the questionnaire study relating to age, gender and GP role were comparable to national GP demographics.
2. Telephone interviews often viewed as inferior to face to face interviews for qualitative studies
3. There is the potential for discrepancies between reported behaviour and actual behaviour, this is inherent in both survey and interview studies

## Background

Giant cell arteritis (GCA) is the most common large/medium vessel vasculitis [1].It is strongly associated with polymyalgia rheumatica (PMR) with an estimated incidence of 1.0 per 10000 patient years [2]. Barraclough (2012) estimated that a full-time general practitioner (GP) will see one new case of GCA every 1-2 years, although this will greatly depend on practice population demographics [3].

Classical presenting features of GCA include new onset headache or head pain (which may be unilateral and often temporal), scalp tenderness, jaw and tongue claudication, constitutional and visual symptoms [1]. Usually there is a significant inflammatory response with raised inflammatory markers. However, it can present atypically which may lead to delays in diagnosis and potentially irreversible complications such as sight loss [4]. Once GCA is suspected, treatment with high dose glucocorticoids (often prednisolone in the UK) should be initiated along with early specialist referral to confirm diagnosis and prevent potential disease complications[1].

Suspected GCA patients are usually identified clinically, followed by specialist referral for temporal artery biopsy (TAB) to confirm diagnosis. Ultrasound scanning however has been shown to be a useful and non-invasive tool to help diagnose GCA [5]. However, the sensitivity of TAB can vary with 13% to 19% of patients with typical features of GCA having a negative temporal artery biopsy [6].

In the UK, GPs are the first point of medical contact for most patients. The role of the GP involves maintaining a high index of suspicion for the disorder, to initiate early therapy and

urgently refer to an appropriate specialist for diagnostic confirmation [1]. Following diagnosis, GPs are often key in tapering glucocorticoid treatment as well as monitoring and management of glucocorticoid related adverse effects and impact on co-morbidity for example osteoporosis, cardiovascular disease, diabetes and development of serious infections [2,7].

The aim of this study was to investigate the diagnostic challenges and initial and on-going management of GCA patients by GPs in the UK.

## Materials and Methods

Given the potential variation in management practices due to multiple influences, such as patient presentation, multi-morbidity, availability of services and variations in practice and local policy, a multi-methods approach was chosen to produce a more complete description of current GP practice[8]. First, a national cross-sectional postal survey of 5000 randomly selected UK GPs was undertaken, followed by a semi-structured telephone interview study with a purposive sample of survey responders to investigate in depth the challenges of diagnosis and management associated with GCA. The cross-sectional postal survey was undertaken first, with the findings used to help develop the topic guide for the interview study.

PMR national cross sectional postal questionnaire survey. A cross sectional survey was mailed to a random sample of 5000 GPs from across the UK identified from the Binley's database. The Binley's database contains the names and addresses of the majority of GPs

working in the UK. It also contains other forms of information including the type of practice, the practice population size, practitioner seniority, and some of the clinical services provided[9]. An online option for survey completion was also available through Survey Monkey [10]. Non-responders were sent a reminder card after 2 weeks and a further survey pack after 4 weeks. The survey was closed 6 weeks after the second survey pack was sent.

No standard survey instrument exists for assessing diagnosis and management of GCA by GPs and so questions were specifically developed using current literature and guidelines for GCA [1]. Questions related to how diagnosis was made (signs and symptoms) and how the GP managed patients with suspected GCA. A mixture of open and closed response questions were used. The questionnaire was piloted amongst GPs, rheumatologists and patients.

Descriptive statistics were generated (mean, standard deviation (SD) and interquartile range (IQR)) using the statistical analysis package SPSS 22 for closed response questions [11]. For open response questions a thematic content analysis was used [12].

The interview study. Participants in the interview study were purposively sampled from responders to the GP survey who had agreed to further contact. To reflect as broad a range of practitioner experience as possible, sampling was based on clinical experience, gender and clinical seniority. The qualitative interview study topic guide which was used as a guide for topics to discuss, was informed by findings from the cross-sectional survey and relevant GCA literature. The topic guide was reviewed and refined with feedback from GPs, rheumatologists and qualitative researchers. As transcripts were reviewed, the topic guide was modified to focus on themes identified from early interviews. The topic guide was

piloted with two GPs and refined within the research team. These interviews were not included in the data analysis.

Interviews were audio recorded and transcribed verbatim using an approved transcription company[13]. The resulting transcripts were screened to remove any identifying information. Thematic analysis, as described by Braun and Clarke, was used to analyse resulting transcript data [14]. Analysis of the transcripts was managed using NVivo (NVivo10) [15]. TH performed the analysis and an inter-rater exercise was undertaken in which three other researchers (SM, SH, JR) were asked to independently analyse and identify general themes relating to a randomly selected interview to compare with findings by TH. No changes resulted from this exercise. Ethical approval for both studies was granted by the Keele University ethics review panel (qualitative study ERP178, survey ERP2206).

**Results**

1249 (25%) completed questionnaires were received and analysed. 879 (70%) GPs had indicated that they had managed a patient with GCA. Responders to the survey had a mean age of 44 years (SD 9.25) and a mean of 13.5 years since qualifying as a GP. 52% were female and the majority were partners (74%), with salaried (21%) and locum GPs (3%) comprising the remainder. For the qualitative study, 24 GP participants were telephone interviewed from various regions across the UK. 16 participants were female and 15 participants were GP partners

Questionnaire survey: Initial diagnosis and management

Free text open response questions in the questionnaire were used to ask all participants to describe how they made a diagnosis of GCA. The results summarised in Table 1.

**Table 1**

The predominant reported clinical feature used to diagnose GCA was headache, along with visual disturbance and scalp tenderness. Survey responders indicated that they often used a combination of features when making a new diagnosis. Of particular note however, was that 21.9% of responders indicated that they only use headache to identify GCA.

Management of GCA can be divided into i) initial treatment and referral and ii) long term glucocorticoid reduction and monitoring. For GPs, initial management is intimately associated with diagnosis as suspected GCA patients require urgent specialist referral for definitive diagnosis and treatment. Table 2 summarises the immediate subsequent actions of GPs who have identified patients with suspected GCA.

**Table 2**

Guidance advises that treatment should not be delayed and that appropriate urgent referral for specialist diagnostic confirmation should be made [1]. 445 responders to the survey (35.6%) indicated that they would not routinely initiate treatment prior to referral. However, 78.7% (n=983) reported that if they were to initiate treatment, appropriate doses of between 40 and 60mg of prednisolone would be prescribed. GP responders indicated that they were referring suspected GCA patients to a variety of different specialities using an

assortment of referral pathways, depending on the geographical location in the UK. Table 3 summarises to which speciality survey responders refer suspected GCA patients.

**Table 3**



Themes identified from the qualitative study

**Diagnosis**

The two main themes identified from the interview study related firstly to the presenting features of GCA and secondly to fears of missing a diagnosis of GCA.

Presenting features of GCA

When asked about GCA symptoms in the interviews, participants often gave textbook descriptions of classical features of GCA.

> "H*eadache in someone over 55 you think giant cell arteritis really, that's my mantra, new different headache, classically unilateral but not always, focused around the temple, potentially some tenderness there, possibly protruding temporal artery, classically tender when they're combing their hair, but also looking for things like jaw claudication or tongue symptoms, [.....] and obviously the dread of visual disturbance as well really which can be anything really"*
>
> **GP6 (20, F, P)**

Key: GP identifier [time qualified as a GP (years), gender (male/female), seniority/role (S:salaried, L:locum, P:partner, SP: senior partner)]

While textbook descriptions of classical GCA were given, there was recognition that some of these features may be difficult to recognise or link to GCA.

*"jaw claudication is interesting, because I know at the time, my colleague and myself, kind of, looked a bit more up about GCA and he said, 'I've never heard of jaw claudication.' "*

**GP15 (25, F, P)**

Fear of missing case of GCA

GPs expressed considerable fear about missing a diagnosis of GCA given the potential for irreversible visual loss.

*"I find it, sort of, trickier, I think, to diagnose. I worry about it more. I worry about missing it. And I feel far less confident about treating it. I think when I was first qualified as a GP I think I thought somebody had got it every week. Anybody who'd got a headache, you know"*

**GP 24 (12, F, S)**

Fears surrounding missing a diagnosis of GCA also related to the potential for a wide range of symptoms and atypical presentations.

> *"Just with a vague headache, and hadn't had any visual disturbance at that point in time. And he didn't really have a lot of temporal artery tenderness. [.....] We did some bloods at that point, and the ESR and CRP were normal [.....]… I wrote in the notes at the time, 'Excludes GCA'……which, having read a bit more about it since, after this happened, doesn't totally exclude it."*
>
> **GP 15 (25, F, P)**

**Management**

Two main themes were identified from the interview transcripts. First, initial and on-going treatment and monitoring and second, referral for definitive diagnostic confirmation by a specialist.

Initial and on-going treatment

Most participants indicated that they would initiate suspected GCA patients on appropriate doses of prednisolone.

> *"I think the rheumatologists would say start the 60[mg] and I will see them in clinic."*
>
> ***GP4 (6, M, P)***

However, there was recognition that treatment could impact on the sensitivity of the temporal artery biopsy, especially if it was going to be delayed.

> *"what then happens in secondary care, it's less than ideal, they seem to rotate who might do a temporal artery biopsy between vascular, ophthalmology and general surgery [.....] but the patient generally is having that temporal biopsy before ever seeing a rheumatologist and the timeliness of that temporal artery biopsy is not ideal."*
>
> ***GP6 (20, F, P)***

Local policy also had a significant impact on how suspected GCA patients were initially treated. This, as well as concerns surrounding the impact that treatment could have on biopsy effectiveness, may account for some of the significant number of participants who indicated that they would not initiate treatment prior to referral.

> *"Locally this gets referred to ophthalmology[.....] and our practice is actually within the grounds of the hospital so we've got no issues really in terms of administering steroids you know before they were seen, they would be seen within an hour by an ophthalmologist."*
>
> **GP 7 (10, M, P)**

The principal and over-arching concern relating to long-term management was the potential adverse effects of glucocorticoid treatment.

*"Well, it's a good two years of treatment with steroids and all the complications and side effects that they carry with them. So, yes, and high doses of it, which have been poorly tolerated with the patients. [.....] One patient, she had diabetes, and she was started on the steroids, and she was struggling with awful side effects from the steroids. She developed, well, lots of depressive symptoms. Her blood sugars went all over the place. She got a lot of pitting oedema of the legs, which was hampering her mobility. She got unsteadiness due to the steroids."*

**GP21 (7, F, S)**

Referral for definitive diagnostic confirmation by a specialist

Specialist referral for definitive diagnostic confirmation was a significant issue for GPs, with referral pathways being highly variable across the UK. The speciality to which suspected GCA patients were referred can depend on presenting clinical features; however, some of this variation reflects local policy and also the regional availability of services and specialities.

*"If their history was suspicious and their inflammatory markers were raised, I would then contact…well we've had this issue between rheumatology and ophthalmology and who to contact, and the line seems to be that if they've got any visual symptoms then they go to ophthalmology and if they haven't then they go to rheumatology."*

**GP13 (5, F, S)**

However, in some regions of the UK GPs reported that referral pathways were not clear and that specialist referral can be challenging.

*"But, generally, you speak to the on-call medical team, and they will advise me to speak to someone else. And then they advise me to speak to someone else. So you end up making loads of phone calls to try and find out which route you go in."*

**GP21 (7, F, S)**

Some participants reported that their local policy involved the GP requesting the temporal artery biopsy prior to review by a specialist. This often created challenges in itself.

*"we would try and get a temporal artery biopsy fairly promptly. It has been a bit difficult in the past, and you know, you're supposed to get it done within a day or two. We traipse round the ophthalmologists, who say, 'No, speak to the vascular people.' Who say, 'No, speak to the general surgeons.' Well, we tried, initially, referring to the ophthalmologist, and they just aren't keen at all [.....] at the moment we've had, a general surgery team who have done a temporal artery biopsy for us, and the vascular surgeons have."* **GP15 (25, F, P)**

Further quotations illustrating the two main themes can be seen in Table 4 below.

**Table 4**

## Discussion

This is the first study of its kind to explore diagnosis and a critical aspect of the care pathway for patients with suspected GCA. GCA remains a diagnosis that GPs worry about missing. Whilst GPs were comfortable with classical presentation patterns, an overreliance on headache to trigger consideration of a diagnosis of GCA was evident, with some GPs having limited awareness of the full range of symptoms associated with GCA.

The predominant findings from the cross sectional study, suggest initiation of treatment for suspected GCA patients is not always routine. However a significant finding from both the cross sectional survey and qualitative interview study demonstrated that referral pathways across the UK vary greatly. Additionally GPs have significant concerns relating to treatment with long term glucocorticoids in this patient group, especially in conjunction with co-existing multi-morbidity.

### Recommendations

Early identification, referral and initiation of appropriate treatment for suspected GCA patients in general practice is critical to prevent complications such as irreversible visual loss[1].

GPs responding to the survey seem to be over-relying on headache when diagnosing GCA. Given that almost half of patients do not present with a classical temporal headache and that 24% of patients with proven GCA have no headache symptoms at all [16], excluding GCA on the basis of no headache has the potential to miss a significant proportion of patients with GCA. However symptoms like headache, are common [17] with over half of over 65 year

olds having had a headache in the previous 12 months, [18] yet serious pathology is rare in general practice. Therefore the collective clinical picture needs to be considered and has to include the full range of features of GCA.

The group of patients with no headache are recognised to be at higher risk of permanent visual loss as a result of delayed diagnosis [4, 19]. Therefore, if alternative presentations are not recognised by GPs they will continue to remain a high risk group. Educating clinicians about other presenting symptoms and atypical presentations is essential to optimise diagnosis and reduce delays in instigating appropriate treatment and referral, which could reduce the potential for visual loss and serious long term complications for this patient group.

A considerable proportion of GPs indicated that they would not initiate treatment prior to referral for specialist review. From the questionnaire responses, current primary care practice would seem to be in line with UK recommendations [1], indicating that appropriate doses of glucocorticoids, when given, are being prescribed at initiation. Additionally there seems to be wide variation in practice across the UK relating to routes of referral and who arranges and performs temporal artery biopsy. Rheumatology remains the predominant speciality to whom GPs refer suspected GCA patients, but a range of different specialities were identified by participants. These findings may in part reflect variations in local policy and the availability of specialities regionally. However, it may also identify a lack of GP awareness of current national GCA guidelines.

Research into conditions such as rheumatoid arthritis highlights that delays in diagnosis can occur at several points in the patient journey. These include the patient recognising that there is a problem requiring consultation (patient level), the patient then getting an appointment with the GP, the GP recognising that referral is needed and making the referral

(GP delay) and the patient getting an appointment with the specialist (specialist delay) [20]. These points of delay are also likely to be relevant to patients with GCA. Health promotion could be used to improve patients' awareness of GCA, but may be of limited value given the rarity of the condition and the wide and non-specific symptoms that patients experience early in the disease course. However, educational strategies for front line clinicians in the early recognition and management of GCA is critical; although some responders indicated that there do not appear to be robust fast track clinical pathways in their local region for patients with suspected GCA . Given the relative rarity of GCA and variation in its early presentation [16], the potential for it not being recognised or for initial misdiagnosis is high. In regions where temporal artery biopsy is arranged by the GP or undertaken before seeing the relevant specialist, there is the possibility that a significant amount of unnecessary biopsies are being performed especially given that there is a great burden of temporal artery biopsies on surgical departments with sometimes low yield rates of positive biopsy [21]. This potentially could be avoided if patients with suspected GCA were carefully selected by a clinician with significant experience in diagnosing and identifying suspected GCA. No participants discussed temporal artery ultrasound which can be used to help identify patients with GCA [5]. Ultrasound techniques may be a preferred option for those with significant co-morbidities or too frail to undergo biopsy. Additionally, it is less invasive and would be more appropriate to being embedded in a care pathway for the rapid assessment of GCA in primary care to streamline patient pathways to help reduce diagnostic confusion, or to better identify patients for temporal artery biopsy [22] thereby improving outcomes for patients with GCA [23, 24]. Further studies are being conducted to determine whether availability and accuracy of temporal artery ultrasound will alter requirements for biopsy [25].

Delays in assessment for definitive diagnosis creates several conundrums surrounding initial treatment. Current guidance is clear that treatment should not be delayed and should be initiated in patients with suspected GCA, although the sensitivity of temporal artery biopsy declines the longer treatment has been given before biopsy [26]. Additionally the American College of Rheumatology criteria for GCA suggests that a positive temporal artery biopsy is not essential to diagnose GCA [27]. High dose glucocorticoid treatment may have a significant impact on symptoms by the time they present to the reviewing specialist and therefore definitive diagnosis for patients who have had a negative biopsy can become extremely challenging. However, an accurate diagnosis is critical and a decision to delay treatment in patients with true GCA could result in visual loss. Equally, a decision to continue treatment in someone who does not truly have GCA will expose that patient to an inappropriate treatment course (and therefore associated potential adverse effects) of glucocorticoids, as treatment often continues for many patients, despite a negative temporal artery biopsy [26].

Our quantitative data suggested that over a third of participants would not initiate treatment prior to referral despite UK national guidance which advises the immediate initiation of high dose glucocorticoids [1]. This represents an area where further education to encourage the immediate initiation of treatment could improve outcomes for patients with GCA. However, not initiating treatment may be in part due to variations in local or practice policy.

Strengths and limitations of this study

The predominant strength of this study is the use of a multi-methods approach, which has allowed the identification of significant challenges relating to GCA management in primary care and subsequent in depth exploration of those issues.

The main weakness in this study was the sub-optimal response rate and therefore the potential lack of generalisability of our findings. However a response rate of 25% is comparable to similar musculoskeletal GP surveys conducted in the same setting [28]. Additionally, while low response rates may increase the possibility of bias, responder demographics of the questionnaire study relating to age, gender and GP role were comparable to national GP demographics [29]. The standard limitations of telephone interviews also apply in this study. While such interviews enabled participants to be interviewed from a wide geographical area and therefore generate rich data on differing local management policies, they may reduce rapport and non-verbal communication. However, the questions used in the topic guide were highly clinical and therefore the lack of rapport building or visual cues is unlikely to have significantly impacted on data quality, as participants were not revealing personal details. TH undertook all of the qualitative data analysis which potentially could impact on theme development due to personal preconceptions and misinterpretations. However, an inter-rater analysis was undertaken to ensure concordance of themes identified. This did not show any difference between raters. Finally, there is the potential for discrepancies between reported behaviour and actual behaviour, this is inherent in both survey and interview studies.

Conclusion

An increased focus on education and awareness of GCA (given its rarity and the range of presenting features) may aid better identification of potential GCA patients. However, significant challenges around GCA remain in primary care, some of which need to be addressed in conjunction with specialist settings. National guidelines suggest that GCA is a medical emergency and so treatment should not be delayed. However, as yet there are no UK national standardised fast track referral/care pathways enabling rapid referral of patients suspected of having GCA yet fast track pathways have been shown to potentially reduce the complication of sight loss in GCA [23]. This study identifies wide variations in the way that patients are initially managed across the UK and therefore adopting standardised fast track services for patients with suspected GCA could enable effective and accurate diagnosis and management and therefore improve outcomes for patients with GCA.

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**Contributorship Statement**

Authors had access to all the study data, take responsibility for the accuracy of the analysis, and had authority over the manuscript and the decision to submit for publication. Guarantor of overall study integrity: TH & CDM. Study concept & design: TH, SM, SLH, JR & CDM. Data collection and interpretation: TH, SM, SLH, JR & CDM. Analyses: TH, SM, SLH, JR & CDM. Manuscript preparation: TH, SM, SLH, JAP JR & CDM. Final approval of manuscript: TH, SM, SLH JAP, JR & CDM

**Conflicts of interest.**

We have no conflicts of interest to report.

## References


1) Dasgupta B, Giant Cell Arteritis Guideline Development Group. Concise guidance: diagnosis and management of giant cell arteritis. Clin Med. 2010;10(4):381-6.
2) Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: data-driven analysis of comorbidities. Arthritis Care Res (Hoboken). 2015;67(3):390-5
3) Barraclough K, Mallen CD, Helliwell T, Hider SL, Dasgupta B. Diagnosis and management of giant cell arteritis. Br J Gen Pract. 2012;62(599):329-30.
4) Ezeonyeji AN, Borg FA, Dasgupta B. Delays in recognition and management of giant cell arteritis: results from a retrospective audit. Clin Rheumatol. 2011;30(2):259-62.
5) Niederkohr RD, Levin LA. A Bayesian analysis of the true sensitivity of a temporal artery biopsy. Invest Ophthalmol Vis Sci. 2007;48(2):675-80.
6) Breuer GS, Nesher R, Nesher G. Negative temporal artery biopsies: eventual diagnoses and features of patients with biopsy-negative giant cell arteritis compared to patients without arteritis. Clinical & Experimental Rheumatology. 2008;26(6):1103-6.
7) Mohammad AJ, Englund M, Turesson C, Tomasson G, Merkel PA. Rate of Comorbidities in Giant Cell Arteritis: A Population-based Study. J Rheumatol. 2017;44(1):84-90
8) Creswell JW, Fetters MD, Ivankova NV. Designing a mixed methods study in primary care. Ann Fam Med. 2004;2(1):7-12.
9) Binleys.com
10) surveymonkey.com

11) IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp

12) Krippendorf K. Content analysis. In: Barbnouw E et al. International encyclopaedia of communication. 1989; 403-407. New York, NY: Oxford University Press.

13) http://thetranscription.co.uk/

14) Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2), pp. 77-101.

15) NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 10, 2012

16) Smetana GW, Shmerling RH. Does this patient have temporal arteritis? JAMA. 2002;287(1):92-101.

17) Boardman HF, Thomas E, Milson DS, Croft PR. One-year follow-up of headache in an adult general population. Headache. 2005;45(4):337-345.

18) Prencipe M, Casini AR, Ferretti C, Santini M, Pezzella F, Scaldaferri N, Culosso F,. Prevalence of headache in an elderly population: attack frequency, disability, and use of medication. Journal of neurology, neurosurgery, and psychiatry. 2001;70(3):377-381.

19) Prior JA, Ranjbar H, Belcher J, Mackie SL, Helliwell T, Liddle J, et al. Diagnostic delay for giant cell arteritis - a systematic review and meta-analysis. BMC Med. 2017 Jun 28;15(1):120,017-0871-z.

20) Raza K, Stack R, Kumar K, Filer A, Detert J, Bastian H, et al. Delays in assessment of patients with rheumatoid arthritis: variations across Europe. Ann Rheum Dis. 2011;70(10):1822-5.

21) Cristaudo AT, Mizumoto R, Hendahewa R. The impact of temporal artery biopsy on surgical practice. Ann Med Surg (Lond). 2016 ;11:47-51.

22) Ball EL, Walsh SR, Tang TY, Gohil R, Clarke JM. Role of ultrasonography in the diagnosis of temporal arteritis. Br J Surg. 2010;97(12):1765-71.

23) Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015;33(2 Suppl 89):S,103-6.

24) Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatology (Oxford). 2016;55(1):66-70.

25) Luqmani R, Lee E, Singh S, Gillett M, Schmidt WA, Bradburn M, et al. The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess. 2016;20(90):1-238.

26) Pieri A, Milligan R, Hegde V, Hennessy C. Temporal artery biopsy: are we doing it right? Int J Health Care Qual Assur. 2013;26(6):559-63.

27) Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33(8):1122-8

28) Clarson LE, Nicholl BI, Bishop A, Edwards JJ, Daniel R, Mallen CD. Monitoring Osteoarthritis: A Cross-sectional Survey in General Practice. Clin Med Insights Arthritis Musculoskelet Disord. 2013;6:85-91.

29) http://content.digital.nhs.uk/

Table 1 Table demonstrating the features used by responders to identify GCA

| GCA Feature | Theme Frequency |
|---|---|
| Headache/Head Symptoms | 1071 |
| Visual disturbances | 671 |
| Scalp Tenderness | 468 |
| Jaw Symptoms | 420 |
| PMR symptoms | 69 |
| Systemic Symptoms | 65 |
| Fatigue | 29 |
| Joint/Muscle symptoms | 20 |
| Tongue symptoms | 12 |

Table 2. Actions undertaken by GPs with patients with suspected GCA

| Action | n | (%) |
|---|---|---|
| Urgent blood tests, initiate treatment and refer for out-patient review urgently, if blood tests positive | 554 | 44.4 |
| Refer to hospital immediately without investigation | 244 | 19.5 |
| Urgent blood tests and refer to hospital immediately if positive | 201 | 16.1 |
| Urgent blood tests, initiate treatment and refer for out-patients review routinely | 66 | 5.3 |

Table 3 Specialties to which GCA patients are referred

| Speciality | Frequency | (%) |
|---|---|---|
| Rheumatology | 478 | 38.3 |
| Ophthalmology | 366 | 29.3 |
| General Medicine | 144 | 11.5 |
| Accident and Emergency | 35 | 2.8 |
| Neurology | 12 | 1.0 |
| Elderly Care | 9 | 0.7 |
| Other | 41 | 3.3 |
| Missing | 164 | 13.1 |

Table 4. Verbatim quotations from the qualitative study and open responses from the cross-sectional survey

| Theme | Sub-theme | Verbatim quotation |
|---|---|---|
| Challenges of diagnosis | Fear of Missing GCA and non-specific presentation | "an elderly lady who was having headaches and kind of pain around her eyes and I'm trying to think what other symptoms she had, general misery really. And it sort of came and went and came and went and she didn't really have any visual problems which is good and when you said to her, "Does it hurt to chew?" she'd say, "Oh yes I think it does". And so yes all of that so in the end I started, I did discuss it with our local physicians because just in that situation where you don't want to miss it but on the other hand it doesn't seem like it's probably the most likely diagnosis. And we got as far as them saying, "Well if it's maybe a possibility then go ahead and treat with steroids", at which point she said, "No I'm feeling much better thank you". And that was that until she started complaining about it again another few months later" GP17 (11, F, P) |
| Initial and on-going | Starting treatment | "And, certainly, in the past couple of years, we've started them on steroids first, because, kind of, getting anybody |

| | | |
|---|---|---|
| treatment and monitoring | | to see them quickly, you know, within a day or two, not been possible, which doesn't seem very ideal to me. And we've taken the view if it turns out to be wrong, we can stop it, but if we don't start it, there might be a problem before they get the biopsy. So that's, kind of, what we've done here."<br>GP15 (25, F, P) |
| | | "Yes again just I think in terms of the ongoing management really because my experience with another patient, the one that ended up with visual disturbance, she sort of then fell between ophthalmology and rheumatology without either necessarily taking full responsibility for her and actually she was a patient of a partner of mine so he was kind of following her up but his experience was that he was piggy in the middle really"<br>GP 6 (20, F, P) |
| | Expediency of review | "you refer them under a two-week wait, and it's not that much of an emergency, whereas we all thought you referred them acutely, because it was that much of an emergency. So there was a big discrepancy of views between what we felt we'd been taught about it, and |

| | | |
|---|---|---|
| | | what other people were now doing."<br><br>GP23 (12, F, S) |
| | | "I know we, kind of, all get it drummed into us, you know, we should all get these things sent in on the day. But I think, well, one of them was hanging round for a year, and he didn't really come to any harm, except undue pain and distress that he had. And the other one was hanging round for a couple of months, you know. And they were both proved – as I say, I'm turning the clock back 15 years - but I think they were both proven to be temporal arteritis. It maybe isn't that, kind of, you know, you must get them in on the day, as I thought as a medical student, you know"<br><br>GP22 (15, M, P) |
| Challenges with referral for definitive diagnostic confirmation by specialist | Delays in temporal artery biopsy | "The patient that I referred on the NHS, she ended up having a biopsy before she saw a consultant rheumatologist. So, yes, it was done that way round. The biopsy, of course, came back negative because the two week delay before getting it done meant the steroids had treated it." **GP21 (7, F, S)** |
| | | "Local issue regarding whether ophthalmology or vascular |

| | |
|---|---|
| | surgery will perform temporal artery biopsy, reliability of this procedure and steroid response whilst waiting for the biopsy" |
| | Participant 2506 (4, 2, P) |

Key to participant demographic: GP (n) (qualitative study identifier), Participant (n) (survey identifier) [time qualified as a GP (years), gender (Male/Female), seniority/role (S:salaried, L:locum, P:partner)]

BMJ Open

# The challenges of diagnosis and management of giant cell arteritis in general practice: a multi-methods study

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# The challenges of diagnosis and management of giant cell arteritis in general practice: a multi-methods study

1Toby Helliwell PhD, 1Sara Muller PhD, 1,2 Samantha L Hider PhD, 1 James A Prior PhD, 1 Jane C Richardson PhD, 1 Christian D Mallen PhD

1Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Keele Staffordshire ST5 5BG

2Rheumatology Department, Haywood Rheumatology Centre, Staffordshire ST6 7AG

**Address for correspondence:**

Dr Toby Helliwell. Arthritis Research UK Primary Care Centre, Primary Care Sciences, Keele University, Keele Staffordshire ST5 5BG.

Email address: t.helliwell@keele.ac.uk

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**Keywords:** Giant cell arteritis, general practice, diagnosis, management

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Background: In the UK, general practitioners (GPs) are usually the first medical contact for patients with suspected giant cell arteritis (GCA). Whilst rare, it is critical not to miss, as delayed treatment can lead to significant complications including permanent visual loss. To date little is known about the approach and challenges to diagnosis and management of GCA by GPs.

Objective: To investigate the diagnosis and management of patients with suspected GCA in UK general practice.

Design and participants: A multi-methods approach was taken, comprising a postal survey of 5000 randomly selected UK GPs and semi-structured telephone interviews of 24 GPs from across the UK.

Setting: UK general practice

Results: 1249 questionnaires were returned. 879 responders (70%) indicated that they had diagnosed and managed a patient with GCA. A variety of clinical features were used to identify GCA. 21.9% suggested that they would exclude GCA as a diagnosis if headache was absent and around one third do not routinely initiate glucocorticoid treatment prior to referral. Significant regional variations in referral pathways were reported. Thematic analysis of interview transcripts highlighted fears relating to a missed diagnosis of GCA and the non-specific nature of early GCA presentation. Accessing specialist care was highlighted as challenging by many GPs and that a national standard fast track pathway is lacking to support this patient group. Additionally there were significant concerns regarding potential adverse effects relating to long term treatment with glucocorticoids.

Conclusion: GPs appear to over-rely on headache to identify GCA and marked geographical differences in management, with conflicting referral pathways and difficulties in accessing appropriate services exist in the UK. A national standard for fast-tracking suspected GCA patients to relevant specialists would be beneficial to improve care and outcomes for patients with GCA.



**Strengths**

1. Multi-methods approach, allowing the identification of significant challenges relating to GCA management in primary care and subsequent in depth exploration of those issues.
2. First large study to investigate diagnosis and management of GCA in general practice

**Limitations**

1. Sub-optimal response rate and therefore potential lack of generalisability of findings although responder demographics of the questionnaire study relating to age, gender and GP role were comparable to national GP demographics.
2. Telephone interviews often viewed as inferior to face to face interviews for qualitative studies
3. There is the potential for discrepancies between reported behaviour and actual behaviour, this is inherent in both survey and interview studies

**Background**

Giant cell arteritis (GCA) is the most common large/medium vessel vasculitis [1]. It is strongly associated with polymyalgia rheumatica (PMR) with an estimated incidence of 1.0 per 10000 patient years [2]. Barraclough (2012) estimated that a full-time general practitioner (GP) will see one new case of GCA every 1-2 years, although this will greatly depend on practice population demographics [3].

Classical presenting features of GCA include new onset headache or head pain (which may be unilateral and often temporal), scalp tenderness, jaw and tongue claudication, constitutional and visual symptoms [1]. Usually there is a significant inflammatory response with raised inflammatory markers. However, it can present atypically which may lead to delays in diagnosis and potentially irreversible complications such as sight loss [4]. Once GCA is suspected, treatment with high dose glucocorticoids (often prednisolone in the UK) should be initiated along with early specialist referral to confirm diagnosis and prevent potential disease complications[1].

Suspected GCA patients are usually identified clinically, followed by specialist referral for temporal artery biopsy (TAB) to confirm diagnosis. Ultrasound scanning however has been shown to be a useful and non-invasive tool to help diagnose GCA [5] although typical ultrasound features of GCA may diminish after just a few days of glucocorticoid treatment, whereas histological features of GCA may still be evident on TAB several months after initiation of treatment [6]. However, the sensitivity of TAB can vary with 13% to 19% of patients with typical features of GCA having a negative temporal artery biopsy [7].

In the UK, GPs are the first point of medical contact for most patients. The role of the GP involves maintaining a high index of suspicion for the disorder, to initiate early therapy and urgently refer to an appropriate specialist for diagnostic confirmation [1]. Following diagnosis, GPs are often key in tapering glucocorticoid treatment as well as monitoring and management of glucocorticoid related adverse effects and impact on co-morbidity for example osteoporosis, cardiovascular disease, diabetes and development of serious infections [2,8].

The aim of this study was to investigate the diagnostic challenges and initial and on-going management of GCA patients by GPs in the UK.

**Materials and Methods**

Given the potential variation in management practices due to multiple influences, such as patient presentation, multi-morbidity, availability of services and variations in practice and local policy, a multi-methods approach combining two study methodologies was chosen to produce a more complete overall description of current GP diagnostic and management practices for GCA [9]. First, a national cross-sectional postal survey of 5000 randomly selected UK GPs was undertaken to investigate PMR and its closely associated illness of GCA, followed by a semi-structured telephone interview study with a purposive sample of survey responders to investigate in depth the challenges of diagnosis and management associated with GCA and PMR. The cross-sectional postal survey was undertaken first, with the findings used to help develop the topic guide for the interview study. This paper presents the combined findings from the two studies relating to GCA.

PMR national cross sectional postal questionnaire survey. A cross sectional survey was mailed to a random sample of 5000 GPs from across the UK identified from the Binley's database. The Binley's database contains the names and addresses of the majority of GPs working in the UK. It also contains other forms of information including the type of practice, the practice population size, practitioner seniority, and some of the clinical services provided[10]. An online option for survey completion was also available through Survey Monkey [11]. Non-responders were sent a reminder card after 2 weeks and a further survey pack after 4 weeks. The survey was closed 6 weeks after the second survey pack was sent.

No standard survey instrument exists for assessing diagnosis and management of GCA by GPs and so questions were specifically developed using current literature and guidelines for GCA [1]. Questions related to how diagnosis was made (signs and symptoms) and how the GP managed patients with suspected GCA. A mixture of open and closed response questions were used. The questionnaire was piloted amongst GPs, rheumatologists and patients.

Descriptive statistics were generated (mean, standard deviation (SD) and interquartile range (IQR)) using the statistical analysis package SPSS 22 for closed response questions [12]. For open response questions a thematic content analysis was used [13].

The interview study. Participants in the interview study were purposively sampled from responders to the GP survey who had agreed to further contact. To reflect as broad a range of practitioner experience as possible, sampling was based on clinical experience, gender and clinical seniority. The qualitative interview study topic guide which was used as a guide for topics to discuss, was informed by findings from the cross-sectional survey and relevant

GCA literature. The topic guide was reviewed and refined with feedback from GPs, rheumatologists and qualitative researchers. As transcripts were reviewed, the topic guide was modified to focus on themes identified from early interviews. The topic guide was piloted with two GPs and refined within the research team. These interviews were not included in the data analysis.

Interviews were audio recorded and transcribed verbatim using an approved transcription company[14]. The resulting transcripts were screened to remove any identifying information. Thematic analysis, as described by Braun and Clarke, was used to analyse resulting transcript data [15]. Analysis of the transcripts was managed using NVivo (NVivo10) [16]. TH performed the analysis and an inter-rater exercise was undertaken in which three other researchers (SM, SH, JR) were asked to independently analyse and identify general themes relating to a randomly selected interview to compare with findings by TH. No changes resulted from this exercise. Ethical approval for both studies was granted by the Keele University ethics review panel (qualitative study ERP178, survey ERP2206).

**Results**

1249 (25%) completed questionnaires were received and analysed. 879 (70%) GPs had indicated that they had managed a patient with GCA. Responders to the survey had a mean age of 44 years (SD 9.25) and a mean of 13.5 years since qualifying as a GP. 52% were female and the majority were partners (74%), with salaried (21%) and locum GPs (3%) comprising the remainder. For the qualitative study, 24 GP participants were telephone interviewed

from various regions across the UK. 16 participants were female and 15 participants were GP partners.

Questionnaire survey: Initial diagnosis and management

Free text open response questions in the questionnaire were used to ask all participants to describe how they made a diagnosis of GCA. The results summarised in Table 1.

**Table 1**

The predominant reported clinical feature used to diagnose GCA was headache, along with visual disturbance and scalp tenderness. Survey responders indicated that they often used a combination of features when making a new diagnosis. Of particular note however, was that 21.9% of responders indicated that they only use headache to identify GCA.

Management of GCA can be divided into i) initial treatment and referral and ii) long term glucocorticoid reduction and monitoring. For GPs, initial management is intimately associated with diagnosis as suspected GCA patients require urgent specialist referral for definitive diagnosis and treatment. Table 2 summarises the immediate subsequent actions of GPs who have identified patients with suspected GCA.

**Table 2**

Guidance advises that treatment should not be delayed and that appropriate urgent referral for specialist diagnostic confirmation should be made [1]. 445 responders to the survey (35.6%) indicated that they would not routinely initiate glucocorticoid treatment prior to

referral. However, 78.7% (n=983) reported that if they were to initiate treatment, appropriate doses of between 40 and 60mg of prednisolone would be prescribed. GP responders indicated that they were referring suspected GCA patients to a variety of different specialities using an assortment of referral pathways, depending on the geographical location in the UK. Table 3 summarises to which speciality survey responders refer suspected GCA patients.

**Table 3**



Themes identified from the qualitative study

**Diagnosis**

The two main themes identified from the interview study related firstly to the presenting features of GCA and secondly to fears of missing a diagnosis of GCA.

Presenting features of GCA

When asked about GCA symptoms in the interviews, participants often gave textbook descriptions of classical features of GCA.

> "H*eadache in someone over 55 you think giant cell arteritis really, that's my mantra, new different headache, classically unilateral but not always, focused around the temple, potentially some tenderness there, possibly protruding temporal artery, classically tender when they're combing their hair, but also looking for things like*

*jaw claudication or tongue symptoms, [.....] and obviously the dread of visual disturbance as well really which can be anything really"*

**GP6 (20, F, P)**

Key: GP identifier [time qualified as a GP (years), gender (male/female), seniority/role (S:salaried, L:locum, P:partner, SP: senior partner)]

While textbook descriptions of classical GCA were given, there was recognition that some of these features may be difficult to recognise or link to GCA.

*"jaw claudication is interesting, because I know at the time, my colleague and myself, kind of, looked a bit more up about GCA and he said, 'I've never heard of jaw claudication.' "*

**GP15 (25, F, P)**

Fear of missing case of GCA

GPs expressed considerable fear about missing a diagnosis of GCA given the potential for irreversible visual loss.

*"I find it, sort of, trickier, I think, to diagnose. I worry about it more. I worry about missing it. And I feel far less confident about treating it. I think when I was first*

*qualified as a GP I think I thought somebody had got it every week. Anybody who'd got a headache, you know"*

**GP 24 (12, F, S)**

Fears surrounding missing a diagnosis of GCA also related to the potential for a wide range of symptoms and atypical presentations.

*"Just with a vague headache, and hadn't had any visual disturbance at that point in time. And he didn't really have a lot of temporal artery tenderness. [.....] We did some bloods at that point, and the ESR and CRP were normal [.....]… I wrote in the notes at the time, 'Excludes GCA'……which, having read a bit more about it since, after this happened, doesn't totally exclude it."*

**GP 15 (25, F, P)**

**Management**

Two main themes were identified from the interview transcripts. First, initial and on-going treatment and monitoring and second, referral for definitive diagnostic confirmation by a specialist.

Initial and on-going treatment

Most participants indicated that they would initiate suspected GCA patients on appropriate doses of prednisolone.

> *"I think the rheumatologists would say start the 60[mg] and I will see them in clinic."*
>
> ***GP4 (6, M, P)***

However, there was recognition that treatment could impact on the sensitivity of the temporal artery biopsy, especially if it was going to be delayed.

> *"what then happens in secondary care, it's less than ideal, they seem to rotate who might do a temporal artery biopsy between vascular, ophthalmology and general surgery [.....] but the patient generally is having that temporal biopsy before ever seeing a rheumatologist and the timeliness of that temporal artery biopsy is not ideal."*
>
> ***GP6 (20, F, P)***

Local policy also had a significant impact on how suspected GCA patients were initially treated. This, as well as concerns surrounding the impact that treatment could have on biopsy effectiveness, may account for some of the significant number of participants who indicated that they would not initiate treatment prior to referral.

*"Locally this gets referred to ophthalmology[.....] and our practice is actually within the grounds of the hospital so we've got no issues really in terms of administering steroids you know before they were seen, they would be seen within an hour by an ophthalmologist."*

**GP 7 (10, M, P)**

The principal and over-arching concern relating to long-term management was the potential adverse effects of glucocorticoid treatment.

*"Well, it's a good two years of treatment with steroids and all the complications and side effects that they carry with them. So, yes, and high doses of it, which have been poorly tolerated with the patients. [.....] One patient, she had diabetes, and she was started on the steroids, and she was struggling with awful side effects from the steroids. She developed, well, lots of depressive symptoms. Her blood sugars went all over the place. She got a lot of pitting oedema of the legs, which was hampering her mobility. She got unsteadiness due to the steroids."*

**GP21 (7, F, S)**

<u>Referral for definitive diagnostic confirmation by a specialist</u>

Specialist referral for definitive diagnostic confirmation was a significant issue for GPs, with referral pathways being highly variable across the UK. The speciality to which suspected GCA

patients were referred can depend on presenting clinical features; however, some of this variation reflects local policy and also the regional availability of services and specialities.

> *"If their history was suspicious and their inflammatory markers were raised, I would then contact…well we've had this issue between rheumatology and ophthalmology and who to contact, and the line seems to be that if they've got any visual symptoms then they go to ophthalmology and if they haven't then they go to rheumatology."*
>
> **GP13 (5, F, S)**

However, in some regions of the UK GPs reported that referral pathways were not clear and that specialist referral can be challenging.

> *"But, generally, you speak to the on-call medical team, and they will advise me to speak to someone else. And then they advise me to speak to someone else. So you end up making loads of phone calls to try and find out which route you go in."*
>
> **GP21 (7, F, S)**

Some participants reported that their local policy involved the GP requesting the temporal artery biopsy prior to review by a specialist. This often created challenges in itself.

> *"we would try and get a temporal artery biopsy fairly promptly. It has been a bit difficult in the past, and you know, you're supposed to get it done within a day or two. We traipse round the ophthalmologists, who say, 'No, speak to the vascular people.' Who say, 'No, speak to the general surgeons.' Well, we tried, initially, referring to the ophthalmologist, and they just aren't keen at all [.....] at the moment we've had, a*

*general surgery team who have done a temporal artery biopsy for us, and the vascular surgeons have."* **GP15 (25, F, P)**

Further quotations illustrating the two main themes can be seen in Table 4 below.

**Table 4**



## Discussion

This is the first study of its kind to explore diagnosis and a critical aspect of the care pathway for patients with suspected GCA. GCA remains a diagnosis that GPs worry about missing. Whilst GPs were comfortable with classical presentation patterns, an overreliance on headache to trigger consideration of a diagnosis of GCA was evident, with some GPs having limited awareness of the full range of symptoms associated with GCA.

The predominant findings from the cross sectional study, suggest initiation of treatment for suspected GCA patients is not always routine. However a significant finding from both the cross sectional survey and qualitative interview study demonstrated that referral pathways across the UK vary greatly. Additionally GPs have significant concerns relating to treatment with long term glucocorticoids in this patient group, especially in conjunction with co-existing multi-morbidity.

Recommendations

Early identification, referral and initiation of appropriate treatment for suspected GCA patients in general practice is critical to prevent complications such as irreversible visual loss[1].

GPs responding to the survey seem to be over-relying on headache when diagnosing GCA. Given that almost half of patients do not present with a classical temporal headache and that 24% of patients with proven GCA have no headache symptoms at all [17], excluding GCA on the basis of no headache has the potential to miss a significant proportion of patients with GCA. However symptoms like headache, are common [18] with over half of over 65 year olds having had a headache in the previous 12 months, [19] yet serious pathology is rare in general practice. Therefore the collective clinical picture needs to be considered and has to include the full range of features of GCA.

The group of patients with no headache are recognised to be at higher risk of permanent visual loss as a result of delayed diagnosis [4, 20]. Therefore, if alternative presentations are not recognised by GPs they will continue to remain a high risk group. Educating clinicians about other presenting symptoms and atypical presentations is essential to optimise diagnosis and reduce delays in instigating appropriate treatment and referral, which could reduce the potential for visual loss and serious long term complications for this patient group.

A considerable proportion of GPs indicated that they would not initiate treatment prior to referral for specialist review. From the questionnaire responses, current primary care practice would seem to be in line with UK recommendations [1], indicating that appropriate doses of glucocorticoids, when given, are being prescribed at initiation. Additionally there

seems to be wide variation in practice across the UK relating to routes of referral and who arranges and performs temporal artery biopsy. Rheumatology remains the predominant speciality to whom GPs refer suspected GCA patients, but a range of different specialities were identified by participants. These findings may in part reflect variations in local policy and the availability of specialities regionally. However, it may also identify a lack of GP awareness of current national GCA guidelines.

Research into conditions such as rheumatoid arthritis highlights that delays in diagnosis can occur at several points in the patient journey. These include the patient recognising that there is a problem requiring consultation (patient level), the patient then getting an appointment with the GP, the GP recognising that referral is needed and making the referral (GP delay) and the patient getting an appointment with the specialist (specialist delay) [21]. These points of delay are also likely to be relevant to patients with GCA. Health promotion could be used to improve patients' awareness of GCA, but may be of limited value given the rarity of the condition and the wide and non-specific symptoms that patients experience early in the disease course. However, educational strategies for front line clinicians in the early recognition and management of GCA is critical; although some responders indicated that there do not appear to be robust fast track clinical pathways in their local region for patients with suspected GCA . Given the relative rarity of GCA and variation in its early presentation [17], the potential for it not being recognised or for initial misdiagnosis is high. In regions where temporal artery biopsy is arranged by the GP or undertaken before seeing the relevant specialist, there is the possibility that a significant amount of unnecessary biopsies are being performed especially given that there is a great burden of temporal artery biopsies on surgical departments with sometimes low yield rates of positive biopsy [22]. This potentially could be avoided if patients with suspected GCA were carefully selected by a clinician with

significant experience in diagnosing and identifying suspected GCA. No participants discussed temporal artery ultrasound which can be used to help identify patients with GCA [5] and this may be because this imaging modality where available, is requested by the treating specialist and not the GP. Ultrasound techniques may be a preferred option for those with significant co-morbidities or too frail to undergo biopsy but will have to be rapidly available to clinicians given the importance of starting glucocorticoid treatment in GCA and the rapid effects treatment has on typical ultrasound features [6]. It is however, less invasive and could be appropriate to being embedded in a care pathway for the rapid assessment of GCA in primary care to streamline patient pathways to help reduce diagnostic confusion, or to better identify patients for temporal artery biopsy [23] thereby improving outcomes for patients with GCA [24, 25]. Further studies are being conducted to determine whether availability and accuracy of temporal artery ultrasound will alter requirements for biopsy [26].

Delays in assessment for definitive diagnosis creates several conundrums surrounding initial treatment. Current guidance is clear that treatment should not be delayed and should be initiated in patients with suspected GCA, although the sensitivity of temporal artery biopsy declines the longer treatment has been given before biopsy [27]. High dose glucocorticoid treatment may have a significant impact on symptoms by the time they present to the reviewing specialist and therefore definitive diagnosis for patients who have had a negative biopsy can become extremely challenging. However, an accurate diagnosis is critical and a decision to delay treatment in patients with true GCA could result in visual loss. Equally, a decision to continue treatment in someone who does not truly have GCA will expose that patient to an inappropriate treatment course (and therefore associated potential adverse effects) of glucocorticoids, as treatment often continues for many patients, despite a negative temporal artery biopsy [27].

Our quantitative data suggested that over a third of participants would not initiate treatment prior to referral despite UK national guidance which advises the immediate initiation of high dose glucocorticoids [1]. This represents an area where further education to encourage the immediate initiation of treatment could improve outcomes for patients with GCA. However, not initiating treatment may be in part due to variations in local or practice policy.

Strengths and limitations of this study

The predominant strength of this study is the use of a multi-methods approach, which has allowed the identification of significant challenges relating to GCA management in primary care and subsequent in depth exploration of those issues.

The main weakness in this study was the sub-optimal response rate and therefore the potential lack of generalisability of our findings. However a response rate of 25% is comparable to similar musculoskeletal GP surveys conducted in the same setting [28]. Additionally, while low response rates may increase the possibility of bias, responder demographics of the questionnaire study relating to age, gender and GP role were comparable to national GP demographics [29]. The standard limitations of telephone interviews also apply in this study. While such interviews enabled participants to be interviewed from a wide geographical area and therefore generate rich data on differing local management policies, they may reduce rapport and non-verbal communication. However, the questions used in the topic guide were highly clinical and therefore the lack of rapport building or visual cues is unlikely to have significantly impacted on data quality, as participants were not revealing personal details. TH undertook all of the qualitative data

analysis which potentially could impact on theme development due to personal preconceptions and misinterpretations. However, an inter-rater analysis was undertaken to ensure concordance of themes identified. This did not show any difference between raters. Finally, there is the potential for discrepancies between reported behaviour and actual behaviour, this is inherent in both survey and interview studies.

## Conclusion

An increased focus on education and awareness of GCA (given its rarity and the range of presenting features including more subtle features such as limb claudication, constitutional symptoms, vascular bruits, asymmetry of pulses and or blood pressure, anaemia[1]) may aid better identification of potential GCA patients. However, significant challenges around GCA remain in primary care, some of which need to be addressed in conjunction with specialist settings. National guidelines suggest that GCA is a medical emergency and so treatment should not be delayed. However, as yet there are no UK national standardised fast track referral/care pathways enabling rapid referral of patients suspected of having GCA yet fast track pathways have been shown to potentially reduce the complication of sight loss in GCA [24]. This study identifies wide variations in the way that patients are initially managed across the UK and therefore adopting standardised fast track services for patients with suspected GCA could enable effective and accurate diagnosis and management and therefore improve outcomes for patients with GCA.

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**Contributorship Statement**

Authors had access to all the study data, take responsibility for the accuracy of the analysis, and had authority over the manuscript and the decision to submit for publication. Guarantor of overall study integrity: TH & CDM. Study concept & design: TH, SM, SLH, JR & CDM. Data collection and interpretation: TH, SM, SLH, JR & CDM. Analyses: TH, SM, SLH, JR & CDM. Manuscript preparation: TH, SM, SLH, JAP JR & CDM. Final approval of manuscript: TH, SM, SLH JAP, JR & CDM

**Conflicts of interest.**

We have no conflicts of interest to report.

**References**


1) Dasgupta B, Giant Cell Arteritis Guideline Development Group. BSR and BHPR guidelines for the management of giant cell arteritis. Rheumatology 2010;49(8):1594–1597
2) Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: data-driven analysis of comorbidities. Arthritis Care Res (Hoboken). 2015;67(3):390-5
3) Barraclough K, Mallen CD, Helliwell T, Hider SL, Dasgupta B. Diagnosis and management of giant cell arteritis. Br J Gen Pract. 2012;62(599):329-30.
4) Ezeonyeji AN, Borg FA, Dasgupta B. Delays in recognition and management of giant cell arteritis: results from a retrospective audit. Clin Rheumatol. 2011;30(2):259-62.
5) Niederkohr RD, Levin LA. A Bayesian analysis of the true sensitivity of a temporal artery biopsy. Invest Ophthalmol Vis Sci. 2007;48(2):675-80.
6) Schmidt WA. Role of ultrasound in the understanding and management of vasculitis. Ther Adv Musculoskelet Dis. 2014;6(2):39–47.
7) Breuer GS, Nesher R, Nesher G. Negative temporal artery biopsies: eventual diagnoses and features of patients with biopsy-negative giant cell arteritis compared to patients without arteritis. Clinical & Experimental Rheumatology. 2008;26(6):1103-6.

8) Mohammad AJ, Englund M, Turesson C, Tomasson G, Merkel PA. Rate of Comorbidities in Giant Cell Arteritis: A Population-based Study. J Rheumatol. 2017;44(1):84-90

9) Creswell JW, Fetters MD, Ivankova NV. Designing a mixed methods study in primary care. Ann Fam Med. 2004;2(1):7-12.

10) Binleys.com

11) surveymonkey.com

12) IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp

13) Krippendorf K. Content analysis. In: Barbnouw E et al. International encyclopaedia of communication. 1989; 403-407. New York, NY: Oxford University Press.

14) http://thetranscription.co.uk/

15) Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2), pp. 77-101.

16) NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 10, 2012

17) Smetana GW, Shmerling RH. Does this patient have temporal arteritis? JAMA. 2002;287(1):92-101.

18) Boardman HF, Thomas E, Milson DS, Croft PR. One-year follow-up of headache in an adult general population. Headache. 2005;45(4):337-345.

19) Prencipe M, Casini AR, Ferretti C, Santini M, Pezzella F, Scaldaferri N, Culosso F,. Prevalence of headache in an elderly population: attack frequency, disability, and use of medication. Journal of neurology, neurosurgery, and psychiatry. 2001;70(3):377-381.

20) Prior JA, Ranjbar H, Belcher J, Mackie SL, Helliwell T, Liddle J, et al. Diagnostic delay for giant cell arteritis - a systematic review and meta-analysis. BMC Med. 2017 Jun 28;15(1):120,017-0871-z.

21) Raza K, Stack R, Kumar K, Filer A, Detert J, Bastian H, et al. Delays in assessment of patients with rheumatoid arthritis: variations across Europe. Ann Rheum Dis. 2011;70(10):1822-5.

22) Cristaudo AT, Mizumoto R, Hendahewa R. The impact of temporal artery biopsy on surgical practice. Ann Med Surg (Lond). 2016 ;11:47-51.

23) Ball EL, Walsh SR, Tang TY, Gohil R, Clarke JM. Role of ultrasonography in the diagnosis of temporal arteritis. Br J Surg. 2010;97(12):1765-71.

24) Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015;33(2 Suppl 89):S,103-6.

25) Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatology (Oxford). 2016;55(1):66-70.

26) Luqmani R, Lee E, Singh S, Gillett M, Schmidt WA, Bradburn M, et al. The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess. 2016;20(90):1-238.

27) Pieri A, Milligan R, Hegde V, Hennessy C. Temporal artery biopsy: are we doing it right? Int J Health Care Qual Assur. 2013;26(6):559-63.

28) Clarson LE, Nicholl BI, Bishop A, Edwards JJ, Daniel R, Mallen CD. Monitoring Osteoarthritis: A Cross-sectional Survey in General Practice. Clin Med Insights Arthritis Musculoskelet Disord. 2013;6:85-91.

29) NHS Digital [Internet]. UK national information, data and IT systems for health and care services [cited 2017 Aug 25]. Available from: http://digital.nhs.uk/catalogue/PUB21772

Table 1 Table demonstrating the features used by responders to identify GCA

| GCA Feature | Theme Frequency |
|---|---|
| Headache/Head Symptoms | 1071 |
| Visual disturbances | 671 |
| Scalp (including temporal artery tenderness) | 468 |
| Jaw Symptoms | 420 |
| PMR symptoms | 69 |
| Systemic Symptoms | 65 |
| Fatigue | 29 |
| Joint/Muscle symptoms | 20 |
| Tongue symptoms | 12 |

Table 2. Actions undertaken by GPs with patients with suspected GCA

| Action | n | (%) |
|---|---|---|
| Urgent blood tests, initiate treatment and refer for out-patient review urgently, if blood tests positive | 554 | 44.4 |
| Refer to hospital immediately without investigation | 244 | 19.5 |
| Urgent blood tests and refer to hospital immediately if positive | 201 | 16.1 |
| Urgent blood tests, initiate treatment and refer for out-patients review routinely | 66 | 5.3 |

Table 3 Specialties to which GCA patients are referred

| **Speciality** | **Frequency** | **(%)** |
|---|---|---|
| Rheumatology | 478 | 38.3 |
| Ophthalmology | 366 | 29.3 |
| General Medicine | 144 | 11.5 |
| Accident and Emergency | 35 | 2.8 |
| Neurology | 12 | 1.0 |
| Elderly Care | 9 | 0.7 |
| Other | 41 | 3.3 |
| Missing | 164 | 13.1 |

Table 4. Verbatim quotations from the qualitative study and open responses from the cross-sectional survey

| Theme | Sub-theme | Verbatim quotation |
|---|---|---|
| Challenges of diagnosis | Fear of Missing GCA and non-specific presentation | "an elderly lady who was having headaches and kind of pain around her eyes and I'm trying to think what other symptoms she had, general misery really. And it sort of came and went and came and went and she didn't really have any visual problems which is good and when you said to her, "Does it hurt to chew?" she'd say, "Oh yes I think it does". And so yes all of that so in the end I started, I did discuss it with our local physicians because just in that situation where you don't want to miss it but on the other hand it doesn't seem like it's probably the most likely diagnosis. And we got as far as them saying, "Well if it's maybe a possibility then go ahead and treat with steroids", at which point she said, "No I'm feeling much better thank you". And that was that until she started complaining about it again another few months later" GP17 (11, F, P) |
| Initial and on-going treatment and | Starting treatment | "And, certainly, in the past couple of years, we've started them on steroids first, because, kind of, getting anybody to see them quickly, you know, within a day or two, not been possible, which doesn't seem very ideal to me. And |

| | | |
|---|---|---|
| monitoring | | we've taken the view if it turns out to be wrong, we can stop it, but if we don't start it, there might be a problem before they get the biopsy. So that's, kind of, what we've done here."<br>GP15 (25, F, P) |
| | | "Yes again just I think in terms of the ongoing management really because my experience with another patient, the one that ended up with visual disturbance, she sort of then fell between ophthalmology and rheumatology without either necessarily taking full responsibility for her and actually she was a patient of a partner of mine so he was kind of following her up but his experience was that he was piggy in the middle really"<br>GP 6 (20, F, P) |
| | Expediency of review | "you refer them under a two-week wait, and it's not that much of an emergency, whereas we all thought you referred them acutely, because it was that much of an emergency. So there was a big discrepancy of views between what we felt we'd been taught about it, and what other people were now doing."<br>GP23 (12, F, S) |

| | | |
|---|---|---|
| | | "I know we, kind of, all get it drummed into us, you know, we should all get these things sent in on the day. But I think, well, one of them was hanging round for a year, and he didn't really come to any harm, except undue pain and distress that he had. And the other one was hanging round for a couple of months, you know. And they were both proved – as I say, I'm turning the clock back 15 years - but I think they were both proven to be temporal arteritis. It maybe isn't that, kind of, you know, you must get them in on the day, as I thought as a medical student, you know" GP22 (15, M, P) |
| Challenges with referral for definitive diagnostic confirmation by specialist | Delays in temporal artery biopsy | "The patient that I referred on the NHS, she ended up having a biopsy before she saw a consultant rheumatologist. So, yes, it was done that way round. The biopsy, of course, came back negative because the two week delay before getting it done meant the steroids had treated it." **GP21 (7, F, S)** |
| | | "Local issue regarding whether ophthalmology or vascular surgery will perform temporal artery biopsy, reliability of this procedure and steroid response whilst waiting for the |

biopsy”

Participant 2506 (4, 2, P)

Key to participant demographic: GP (n) (qualitative study identifier), Participant (n) (survey identifier) [time qualified as a GP (years), gender (Male/Female), seniority/role (S:salaried, L:locum, P:partner)]