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Adrenal insufficiency in giant cell arteritis

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Abstract

Objectives: To ascertain the frequency of adrenal insufficiency in patients with GCA treated using the Norwich prednisolone regimen.

Methods: Consecutive patients diagnosed with GCA between 1 January 2012 and 31 May 2022 were included. All patients were treated with the Norwich prednisolone regimen, educated about the benefits and risks of long-term prednisolone use and followed up in dedicated vasculitis clinics. When patients contacted the advice line to report being unwell, tests for adrenal function were performed after ruling out relapsing vasculitis or polymyalgia rheumatica. A 9 A.M. serum cortisol was used, providing the daily dose of prednisolone was ≤5 mg, as a gateway to dynamic testing with full-form adrenocorticotrophic hormone (ACTH) stimulation.

Results: A total of 353 consecutive patients with GCA were included. During the prescribed glucocorticoid tapering regimen, 76/353 had a 9 A.M. serum cortisol check after ruling out relapsing disease. Of these, 34/76 had a serum cortisol >350 nmol/l (our laboratory cut-off for adequacy of adrenal reserve); 7/76 had a serum cortisol <100 nmol/l, indicative of insufficient adrenal function and 35/76 had a cortisol level of 100–350 nmol/l. Of the 35 patients who went on to have a standard-dose ACTH stimulation test, 27/35 had an adequate result (i.e. >450 nmol/l at 30 min) and 8/35 had an inadequate result. A total of 15/353 patients required long-term steroids because of adrenal insufficiency and 11/15 patients with adrenal insufficiency were female. The median (IQR) cumulative prednisolone dose at the time of testing was 11.53 grams (7.74) and the median (IQR) duration of prednisolone was 121 weeks (97).

Conclusion: This is the largest study studying the frequency of adrenal insufficiency in patients with GCA treated using the Norwich prednisolone regimen. Adrenal insufficiency requiring long-term steroid replacement therapy is uncommon. Sequential testing using 9 A.M. serum cortisol levels as a gateway to rationalizing the necessity for dynamic testing with standard-dose ACTH stimulation testing is an efficient strategy for this cohort of patients.

Lay Summary

What does this mean for patients?

Patients with giant cell arteritis (GCA) can often take prednisolone for a long period of time—usually starting on a high dose that is gradually reduced. The ideal starting dose and reduction time in patients with GCA is not yet known, but in Norwich a standardized 100-week plan has been used since 2012. Long-term prednisolone can cause adrenal insufficiency in a small number of patients. This means a person does not produce enough of the natural hormone cortisol. Common symptoms of low cortisol can be joint pain, muscle pain, tiredness and loss of appetite. These symptoms can also be mistaken for active GCA. We reviewed 353 of our patients diagnosed with GCA and treated with the Norwich prednisolone regimen to see how many patients developed adrenal insufficiency. We looked at how many patients needed to have a 9 A.M. cortisol blood test followed by a more in-depth 'short synacthen test' if the 9 A.M. cortisol was low. This method showed a small group of our patients are no longer producing enough cortisol. This means a person may need to remain on a small dose of prednisolone long-term. Our findings showed that in our patient group, 15 of 353 patients needed to have long-term steroids.

Keywords: giant cell arteritis, adrenal insufficiency, glucocorticoids, adverse events, Iatrogenic disease.

Key messages

- Patients with giant cell arteritis receiving long-term steroids should be assessed for clinical and biochemical signs of adrenal insufficiency after ruling out relapsing disease.
- Patients should be informed of the risk of developing adrenal insufficiency due to long-term steroid use.
- Sequential testing with 9 A.M. serum cortisol is an effective strategy for triaging the need for dynamic adrenal stimulation testing in the diagnosis of adrenal insufficiency.

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Introduction

GCA is the most common primary systemic vasculitis with an annual incidence of 80–100/million in those >50 years of age in Norfolk, UK [1]. Glucocorticoids have proven efficacy for controlling the disease [2]. Although their use has been enshrined in international treatment recommendations, there is no consensus for the use of a glucocorticoid regimen [3, 4]. We previously published the development of the Norwich prednisolone regimen for the treatment of GCA. The regimen is designed to be a logarithmic taper that starts at 1 mg/kg of lean body mass and is withdrawn in 25 4-week aliquots to deliver 164.64 mg prednisolone/kg lean body mass over 100 weeks [5].

About 1% of the population is thought to be using chronic glucocorticoid therapy [6]. Chronic glucocorticoid use is associated with high morbidity [7]. Long-term suppression of the hypothalamic–pituitary–adrenal axis is known to cause iatrogenic adrenal insufficiency [8]. There are data that the hypothalamic–pituitary–adrenal axis can take a long time to recover in patients with GCA [9]. One study with a mixed population of patients with PMR and GCA reported that 7/47 patients had adrenal insufficiency [10]. But the frequency of adrenal insufficiency in patients with GCA has not been formally explored.

The symptoms of adrenal insufficiency may include fatigue, nausea, anorexia and diffuse aches and pains and can be easily overlooked or mistaken for a PMR relapse of GCA [9]. Patients may not be fully aware of the possibility of adrenal insufficiency [11]. Anecdotally, the combination of a lack of awareness and the mimicking of PMR may result in arbitrary escalation of the dose of prednisolone, which may further compound the problem.

The tetracosactide test (also known as the co-syntropin or short synacthen test) has been used for almost 60 years as a rapid way of assessing adrenal reserve [12]. Because it is faster and safer than the insulin tolerance test for primary adrenal insufficiency, the administration of synthetic adrenocorticotrophic hormone (ACTH) has also been used to assess secondary adrenal insufficiency. In primary and secondary adrenal insufficiency, the 30-min and/or 60-min cortisol values in response to a 250 μg intravenous or intramuscular dose of synthetic ACTH would be suboptimal.

Our aim here is to report the frequency of symptomatic adrenal insufficiency in patients treated with the Norwich prednisolone regimen for GCA.

Methods

Ethics

No ethics approval was sought. All the patients were under our care and the data were collected to submit quarterly returns to NHS England. Consent was not needed because no experimental interventions were performed and no patient-identifiable data were needed for this work.

Centre

Our centre is recognized to provide specialized care for adult rheumatology services, including primary systemic vasculitis. We have previously published how nationally acclaimed services for GCA were developed in our centre [13].

Patients

Consecutive patients diagnosed with GCA between 1 January 2012 and 31 May 2022 were included. The diagnosis was established using either ultrasonography, temporal artery biopsy or PET [14].

Triage

All patients with GCA have access to the vasculitis advice line for support. They are educated to inform us if either they or another healthcare professional feels that they may be relapsing or have an iatrogenic problem. They are systematically assessed for relapsing disease. If a combination of tests, including CRP and ultrasonography, for relapsing large vessel vasculitis and PMR do not suggest relapse, and if the prednisolone dose is ≤5 mg/day, we test for adrenal insufficiency.

Adrenal testing

Our strategy for testing for adrenal insufficiency includes checking serum cortisol at 9 A.M. Practically, we advise patients to have blood drawn between 8 A.M. and 10 A.M. They are instructed to not take their daily dose of prednisolone until after the blood has been drawn. A serum cortisol >350 nmol/l makes adrenal insufficiency unlikely and prednisolone can be stopped safely with immediate effect. A serum cortisol <100 nmol/l is diagnostic for adrenal insufficiency. Based on local data, these patients will not have a positive ACTH test, making further testing unnecessary before initiating steroid replacement therapy. A serum cortisol of 100–350 nmol/l was considered indeterminate, necessitating further testing in the form of a standard-dose ACTH stimulation test. The Alinity immunoassay (Abbott Labs, Abbott Park, IL, USA) is used in our centre for checking 9 A.M. cortisol. The cut-off values mentioned are based on local validation. The ACTH test is done by placing an intravenous cannula into a hand or arm vein. After a few minutes, blood is taken for baseline measurement of cortisol. A 250-μg dose of synthetic ACTH is given intravenously and blood is taken at 30 and 60 min to measure serum cortisol concentrations.

Results

Between 1 January 2012 and 31 May 2022, 353 patients were diagnosed with GCA and treated with the Norwich prednisolone regimen. A total of 234 were female and the median (IQR) age was of 75.3 years (10.0).

A total of 76 patients were clinically suspected to have adrenal insufficiency after ruling out relapsing disease (Fig. 1). A total of 52 were female and the median (IQR) age was 75 years (10). Fig. 1 shows the testing journey of 76 patients suspected of adrenal insufficiency in whom the serum cortisol levels were checked around 9 A.M. Of the 76 patients, 34 had a serum cortisol >350 nmol/l, 7 had a serum cortisol <100 nmol/l and 35 had a serum cortisol of 100–350 nmol/l and proceeded to a standard-dose ACTH challenge test. Of these 35 patients, 8 had a post-injection serum cortisol <450 nmol/l.

A total of 15/353 (4.3%) patients were found to have adrenal insufficiency due to long-term glucocorticoid use, not a relapse of GCA. They had been treated with prednisolone for a median of 121 weeks (IQR 97). Their cumulative prednisolone exposure at the time of adrenal testing was a median of 11.53 g (IQR 7.74).

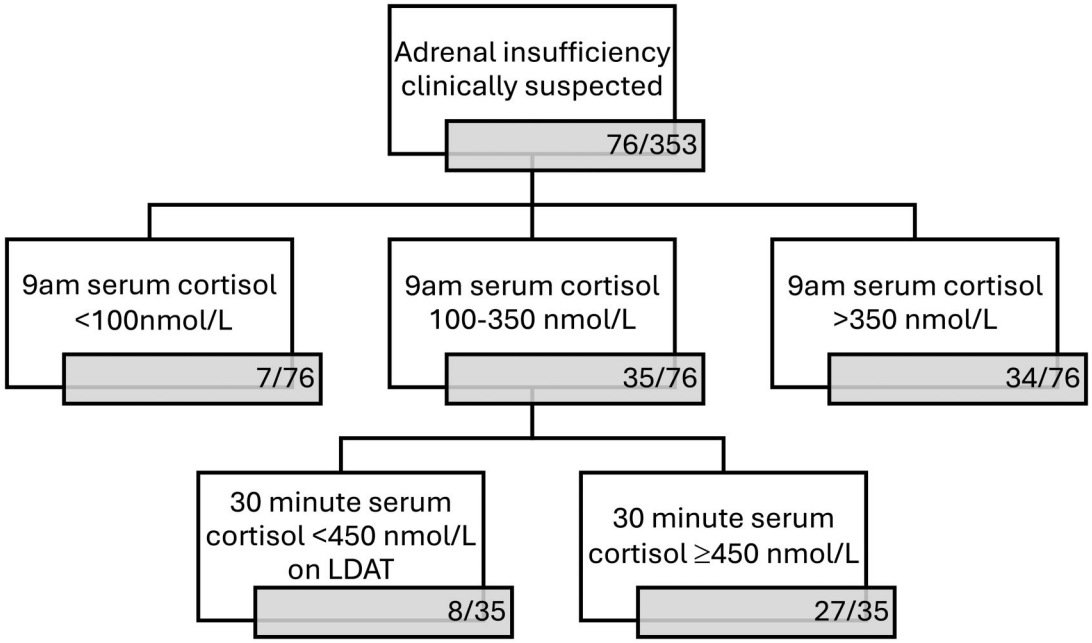

Figure 1. Flow diagram demonstrating the testing journey of patients with suspected adrenal insufficiency (i.e. a pre-prednisolone 9 A.M. cortisol concentration of 100–350 nmol/l)

Discussion

This is the largest cohort in the world of consecutively diagnosed patients with GCA treated in a homogeneous way. We have shown that the incidence of secondary adrenal insufficiency is 4.3%. There are very few data on this subject. Jamilloux *et al.* [9] reported the time to recovery of adrenal function in patients with GCA. They used classification criteria for establishing the diagnosis and checked adrenal function with a low-dose ACTH stimulation test in all patients who reached a daily prednisolone dose of 5 mg. A total of 49% of patients appeared to have adrenal insufficiency [9]. The high incidence of adrenal insufficiency may be related to their use of the low-dose ACTH stimulation test. Borresen *et al.* [14] studied a mixed cohort of 47 patients with PMR and GCA and reported a 15% incidence of adrenal insufficiency.

Our study has many strengths. Every patient was diagnosed using an objective test—ultrasonography, temporal artery biopsy or PET and each patient has been treated with a prednisolone regimen tailored to their lean body mass [5]. At diagnosis, every patient is handed a printed regimen with clear dates for dose changes, allowing us to clearly record the cumulative prednisolone exposure. The data presented here are real-life clinic data that represent the efficiency of algorithmic testing within a resource-constrained public healthcare system.

We acknowledge that our study has the limitation that all patients did not routinely have 9 A.M. serum cortisol checks when they reached a threshold prednisolone dose. This may lead to an underestimation of the true frequency of adrenal insufficiency, and we accept that the true incidence may be between 15/353 (4%) and 15/76 (20%). Jamilloux *et al.* [9] routinely tested for adrenal insufficiency and found that repeated testing did improve adrenal function. Routine testing in all patients is feasible in our centre and this may lead to additional discoveries of silent adrenal insufficiency. The clinical utility and cost efficiency of this method in the absence of clinical manifestations is unclear. We have not performed dynamic ACTH testing on all patients. This is a pragmatic study that is supported by international recommendations that recommend using the 9 A.M. serum cortisol as a gateway to the more intensive standard-dose ACTH stimulation test [6].

All our patients were followed up throughout the prednisolone taper. Routine care includes an enquiry and clinical examination to assess for ischaemic and constitutional manifestations associated with active large vessel vasculitis, as well as adverse effects of corticosteroids, including the routine testing of glycated haemoglobin. Our patients receive education from a vasculitis specialist nurse (G.D.) on glucocorticoid therapy and its potential side effects. This is multimodal education provided at the initial diagnosis, with ongoing clinical support via a dedicated advice line and cohorted vasculitis clinics. This provides additional opportunities for patient contact to monitor steroid reduction, assessing for any new or worsening symptoms related to GCA and its treatment.

Healthcare registry data demonstrate that patients with GCA have an odds ratio of 4.95 (95% CI 4.13, 5.93) for developing adrenal insufficiency over the general population [15]. In summary, we have shown that sequential testing using serum 9 A.M. cortisol as a gateway to dynamic testing using standard-dose ACTH stimulation can be recommended as a strategy to diagnose secondary adrenal insufficiency in this cohort of patients.

Data availability

All reasonable requests for data will be entertained for future collaborative work.

Authors' contributions

G.D.: conceived original idea, collected and analysed data, drafted original manuscript; K.D.: contributed to the review of the manuscript and expert critical feedback; C.B.M.: provided supervision with review and editing of manuscript; All authors contributed to the final version of the manuscript.

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