

## Patterns of presentation and diagnosis of patients with Wegener's granulomatosis: ENT aspects

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### Abstract

**Design:** a cross-sectional study.

**Participants:** One hundred and ninety-nine patients with Wegener's granulomatosis belonging to a patient self-help group.

**Main outcome measures:** Mode of initial presentation; diagnosis timescales and delay; rhinologic involvement; and treatment.

**Results:** Sixty-three per cent of patients initially presented with ENT-related symptoms. Ninety-two per cent faced a delay in their diagnosis of more than one month, a pattern which has not improved over the last few decades and which compares unfavourably with North American figures. Rhinologic and otologic symptoms are a common occurrence in up to 85 and 50 per cent of Wegener's granulomatosis patients, respectively, attracting varying degrees of targeted treatment.

**Conclusions:** As sinonasal and other ENT symptoms are so common at the presentation of Wegener's granulomatosis, it is clear that the otolaryngologist has an important role in its diagnosis and treatment. There are long delays in the diagnosis and possible under-treatment of the ENT symptoms of this condition, highlighting the need for greater awareness, particularly in the ENT community.

**Key words:** Wegener's Granulomatosis; Symptoms; Diagnosis; Otorhinolaryngologic Diseases

### Introduction

Wegener's granulomatosis is a rare, multisystem disease with numerous otorhinolaryngological manifestations. More than 80 per cent of patients with this diagnosis experience rhinological morbidity, and 20–40 per cent experience otological morbidity at some point during their life.<sup>1</sup> Furthermore, an increasing number of patients with upper airway disease such as subglottic stenosis are eventually found to have limited forms of Wegener's granulomatosis.<sup>2</sup> Many Wegener's granulomatosis patients will initially present to the physician or otolaryngologist with ENT-related symptoms. Due to the relative rarity of this disease and its presentation in the midst of common ENT pathology, Wegener's granulomatosis patients encounter not only a possible delay in their diagnosis but also variable amounts of therapy directed at their ENT-related morbidities.

One large survey from the United States<sup>3</sup> assessed some of these aspects in general. However, no previous study has investigated such a large group of British Wegener's granulomatosis patients, with a focus on ENT practice.

This study aimed to explore the patterns of presentation and diagnosis of patients with Wegener's granulomatosis. Furthermore, it investigated their ENT symptomatology and the ways in which they were treated.

### Methods

Ethical approval for the study was obtained from the Royal Free Hospital and Medical School research ethics committee.

A postal questionnaire was sent to all members of the Wegener's granulomatosis patients' own UK self-help group, the Stuart Strange Vasculitis Trust. This questionnaire sought basic information from each patient, including the timescale of their diagnosis, their symptoms and their treatment details. The questionnaire had been previously validated with a group of clinically confirmed Wegener's granulomatosis patients, using methodology by Juniper and Guyatt.<sup>4</sup> We excluded from the study those questionnaires in which the patient's age, sex or Wegener's granulomatosis diagnosis were not confirmed. Patients' demographic details were derived from all

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valid responses. The times of symptom onset, presentation to a physician or ENT surgeon, and actual diagnosis of Wegener's granulomatosis were recorded. Delay in diagnosis was calculated from the time of presentation to a specialist.

The questionnaire enquired about any previous or current history of sinonasal morbidity, including a selection of relevant nasal and aural symptoms, and any history of previous nasal surgery. Treatment regimen profiles, including systemic immunosuppressants and any topical nasal treatment, were recorded for each patient.

**Results**

*Population, presentation and diagnosis*

Of all the questionnaires sent to members of the Stuart Strange Vasculitis Trust, 781 were to Wegener's granulomatosis patients. The seven responses received from patients' relatives, and responses missing essential information, were excluded from the study. Valid responses were received from 199 patients with Wegener's granulomatosis (25.5 per cent), and the remainder of the analysis is concerned with these patients. Sixty-five per cent of these respondents were women and 35 per cent were men. Ninety-three per cent of respondents described themselves as white Caucasian. The mean age of Wegener's granulomatosis patients was 58.2 years (median 59, range 17–81 years).

The average time since diagnosis was eight years (range, 1 month to 23 years and 3 months). The average age at diagnosis was 50 years (range 13–78 years). Figure 1 shows the age distribution of the study group at the time of the survey and respondents' ages at diagnosis.

Sixty-three per cent of the Wegener's granulomatosis patients initially presented with an ENT-related symptom: 41 per cent of all presenting symptoms were rhinological; 16 per cent were otological; and 6 per cent related to the pharynx, larynx or trachea. Figure 2 shows respondents' presenting symptoms, by bodily system.

The nose and paranasal sinuses were the commonest presenting systems in all age groups. These were the site of presenting symptoms in 50 per cent of patients diagnosed before the age of 60 years, compared with only 27 per cent of those diagnosed

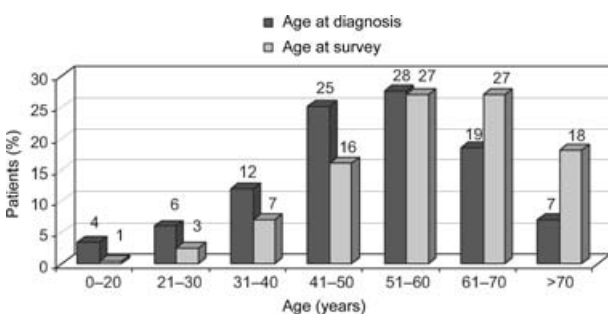


FIG. 1

Respondents' ages at diagnosis and at survey (to nearest whole number).

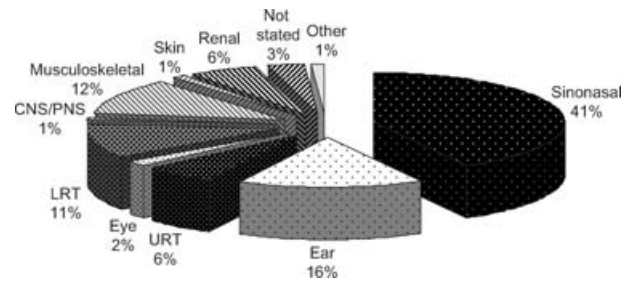


FIG. 2

Respondents' (*n* = 199) initial presenting system. URT = upper respiratory tract; LRT = lower respiratory tract; CNS = central nervous system; PNS = peripheral nervous system

when older than 60 years ( $p = 0.016$  for those each side of 60 years of age at diagnosis (difference in proportions test, Statistica version 6.1 software, Statsoft Inc, Tulsa, Oklahoma, USA)). The younger age groups also had a general predilection to other head and neck related modes of presentation (Figure 3). In comparison, patients diagnosed at a later age (over 60 years) were more likely to initially present with renal, pulmonary and other manifestations than younger patients ( $p < 0.001$ , difference in proportions test).

Diagnosis timescale data (i.e. time of initial presentation to a physician and actual time of diagnosis with Wegener's granulomatosis) was available for 183 patients (92 per cent). Ninety-two per cent of patients reported that their actual diagnosis with Wegener's granulomatosis was delayed by over one month (49 per cent by one to six months, 20 per cent by 6–12 months and 23 per cent by more than 12 months). The overall average delay in diagnosis was as long as seven months.

The average delay in diagnosis was greater for patients presenting with symptoms in the head and neck systems combined (i.e. sinonasal, ear, eye and upper respiratory tract) than in those presenting with non-head and neck systems combined (i.e. lower respiratory tract, renal, nervous system, musculoskeletal, cutaneous and any other presentation). The mean delay was 9.0 months in the

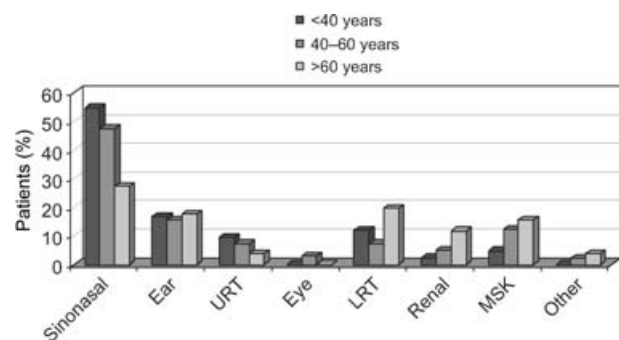


FIG. 3

Presenting system in respondents diagnosed at <40 years (*n* = 191), 40–60 years and >60 years of age. URT = upper respiratory tract (including pharynx, larynx and trachea); LRT = lower respiratory tract; MSK = musculoskeletal system

combined head and neck systems presentation group (standard deviation (SD) 11.0), compared with 5.9 months in the combined non-head and neck systems presentation group (SD 6.1) ( $p = 0.054$ ;  $t$ -test, independent groups) but this was not statistically significant due to the high variability of delay in diagnosis within each system). Figure 4 shows the delay in diagnosis by presenting bodily system. Furthermore, the extent of delay in diagnosis did not seem to improve over the years, as demonstrated by Figure 5. Only a minor negative correlation ( $-0.11$ ) existed between the length of delay and year of diagnosis, indicating little improvement over time.

*ENT symptomatology and treatment*

Twenty per cent (37/183) of the Wegener's granulomatosis patients had never received an ENT consultation. Twenty-three per cent (43/183) had been diagnosed with Wegener's granulomatosis prior to their first ENT consultation. The remaining 56 per cent (103/183) of patients had been seen by otolaryngologists prior to diagnosis with Wegener's granulomatosis. Over 50 per cent of Wegener's granulomatosis patients reported aural fullness and 42 per cent reported dizziness to different degrees. Twenty-nine per cent of the study group also reported otalgia at the time of the survey. Eighty-five per cent of patients reported a history of sinonasal morbidity at some stage during the course of their illness, with 64 per cent reporting active sinonasal involvement at the time of the survey. However, when asked about specific sinonasal symptoms, the patients reported even higher levels of current sinonasal morbidity, as shown by Figure 6. The most prominent symptoms included nasal crusting (affecting 75 per cent of patients), excessive nose-blowing (70 per cent), nasal obstruction (65 per cent) and epistaxis (59 per cent). Twenty-five per cent of patients were unhappy with the shape of their nose.

Treatment profile data were available for 198/199 patients. Eighty-two per cent (163/198) of patients

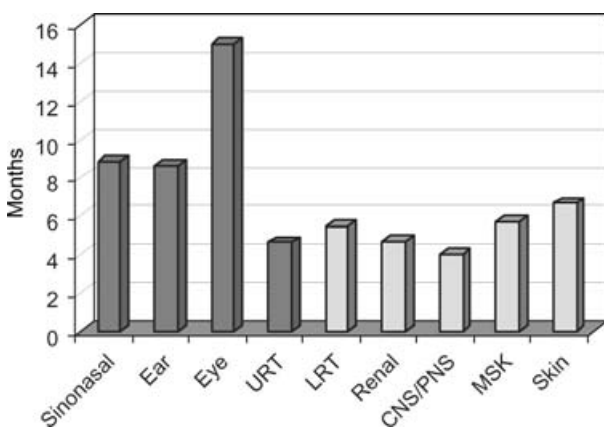


FIG. 4

Respondents' average delay in diagnosis, by presenting system. Dark shading indicates presentation with systems in the head and neck region. URT = upper respiratory tract; LRT = lower respiratory tract; CNS = central nervous system; PNS = peripheral nervous system; MSK = musculoskeletal system

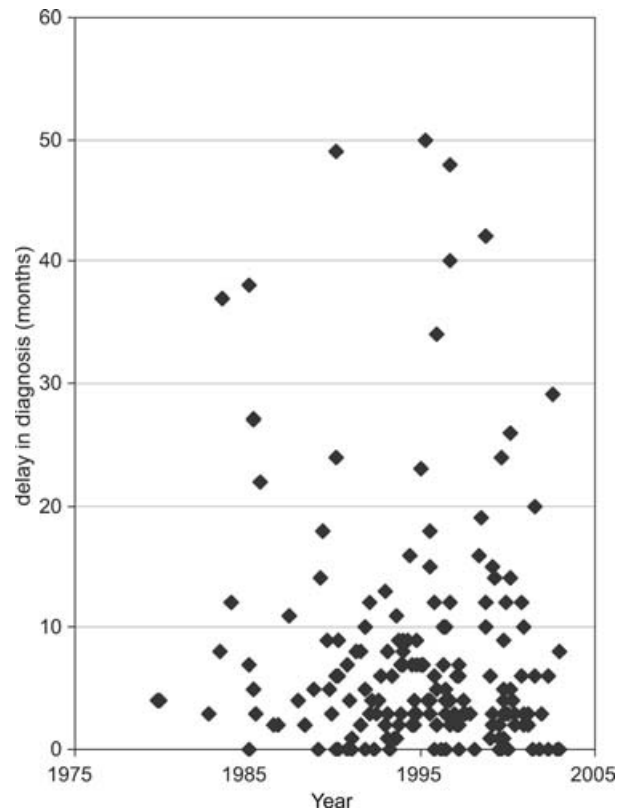


FIG. 5

Respondents' delay in diagnosis, by year of diagnosis, showing no trend in diagnosis delay over the last few decades. ( $n = 183$ , correlation coefficient =  $-0.11$ ).

were receiving systemic immunosuppressant medication to varying degrees, and 53 per cent (105/198) were taking more than one agent. Topical nasal treatment was prescribed to 27 per cent (54/198) of patients, including steroid sprays (22/198; 11.1 per cent), antibiotic creams (19/198; 9.6 per cent) and nasal douches (in as few as 13.1 per cent of patients). Nine patients (4.5 per cent) were receiving both topical steroid spray and nasal douches. Three (1.5 per cent) patients were receiving both a topical cream and a douche. No patient reported receiving all three topical treatments. A breakdown of all treatments is shown in Figure 7.

**Discussion**

Wegener's granulomatosis was named after Frederick Wegener in 1936,<sup>5</sup> but it had probably been described earlier by Heinz Klinger in 1931<sup>6</sup> at the University of Berlin. Up to 1967, 138 unequivocal cases of Wegener's granulomatosis had been reported in the literature.<sup>7</sup> This was at a time when the condition was considered almost invariably fatal within two years, and prior to the advent of immunosuppressant therapy. The condition's aetiology remains obscure, as does its incidence, particularly since the recognition of limited forms of the condition. In some individuals, it may present and remain confined to a particular

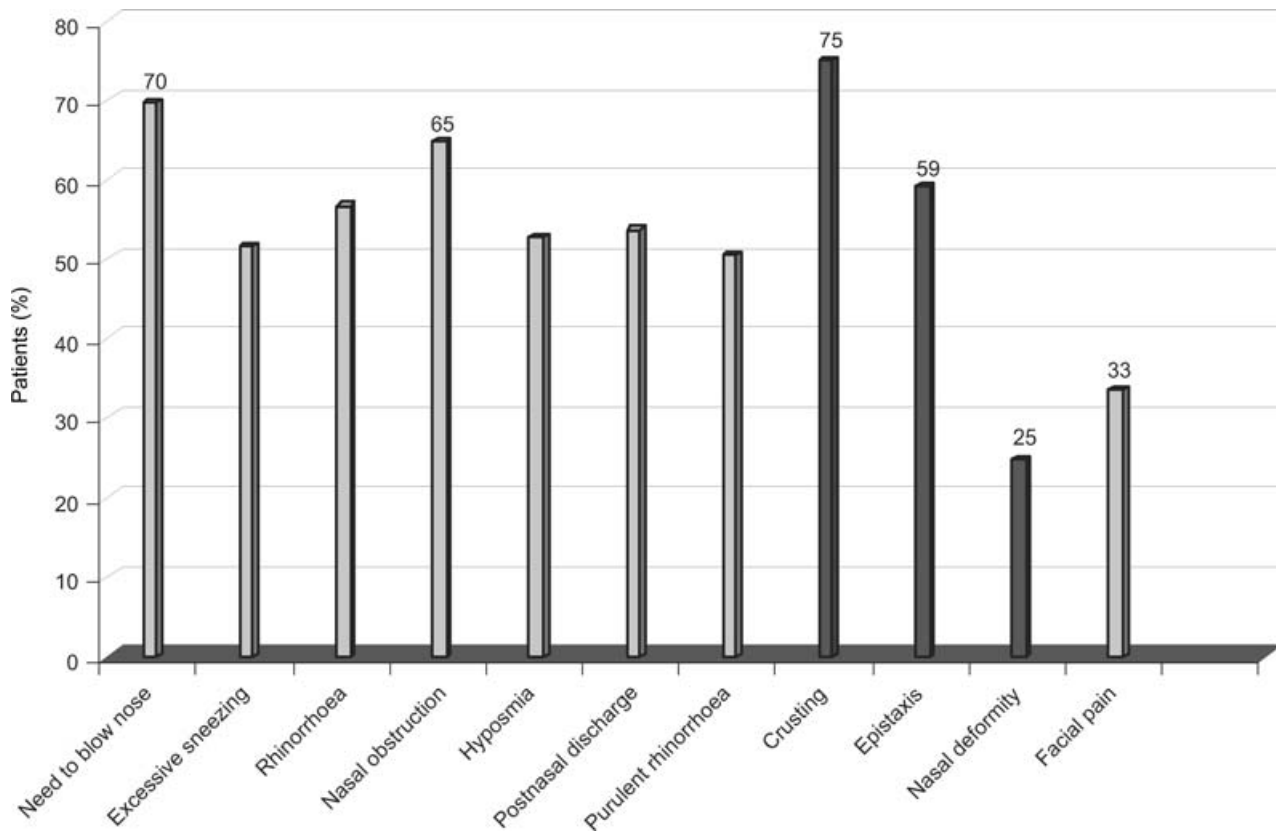


FIG. 6

Respondents' ( $n = 199$ ) sinonasal morbidity. Dark bars = nasal symptoms that are specific to Wegener's granulomatosis.

system for many years, often adding difficulty to an already challenging diagnostic process. It is unknown what proportion of these patients ultimately progress to classical, multisystem disease. The ability to diagnose the condition has been significantly improved by the advent of the

Antineutrophil cytoplasmic antibodies assay in 1987,<sup>8</sup> which has a high specificity (80 per cent) and sensitivity (90 per cent) in multisystem disease. However, the latter may drop to 50–60 per cent in localised forms of the condition.

The average time from diagnosis with Wegener's granulomatosis to questionnaire receipt was quite long – eight years in the studied group (although it ranged widely, from one month to over 23 years). The majority of respondents (53 per cent) were diagnosed in their fifth and sixth decades; at the time of the study, the majority of respondents (52 per cent) were in their sixth and seventh decades. However, it should be noted that patients as young as 13 years and as old as 78 years can present with this condition.<sup>6</sup>

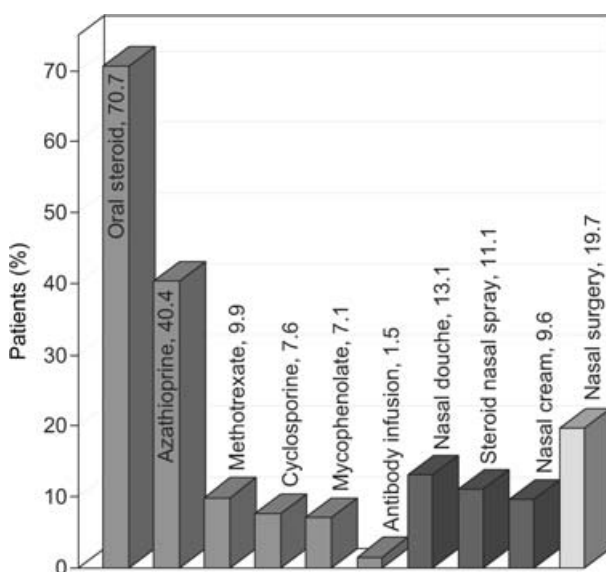


FIG. 7

Respondents' current treatment. Dark bars = nasal symptoms that are specific to Wegener's granulomatosis.

This study confirms the frequency of sinonasal symptoms at the presentation of Wegener's granulomatosis; this was notably higher in younger patients. Of the nasal symptoms, nasal crusting, discharge, blockage and bleeding were the most prominent, as anticipated. As we have previously reported, Wegener's granulomatosis patients may present with various otologic symptoms (16 per cent; e.g. persistent otitis media, sensorineural deafness and vertigo), upper aerodigestive tract symptoms (6 per cent; e.g. gingivitis and ulceration, which may lead to oro-antral fistula), and laryngeal symptoms (e.g. hoarseness and dyspnoea, which may be associated with cranial nerve palsies or isolated sub-glottic stenosis).



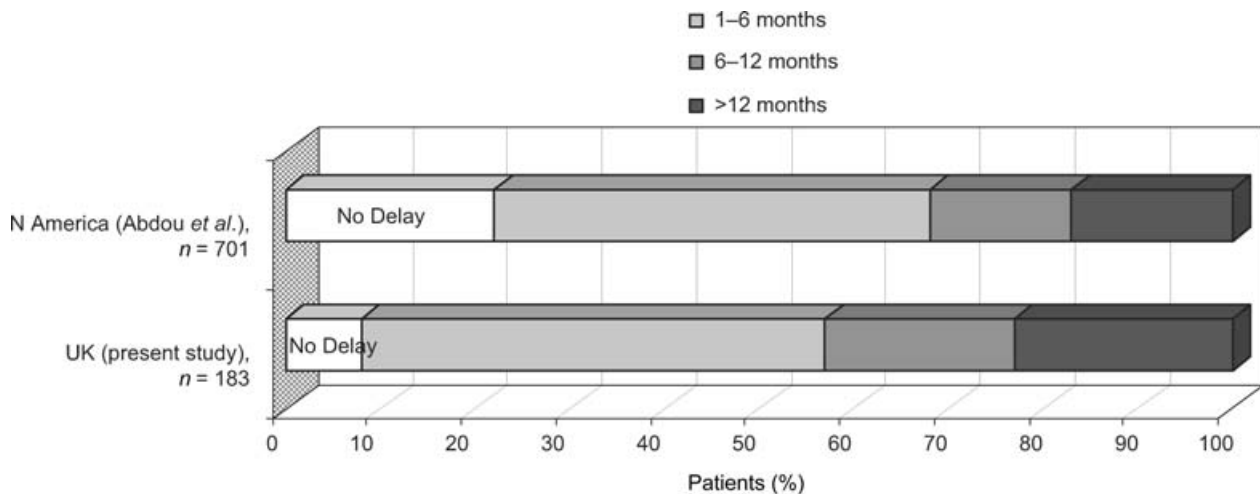


FIG. 8

Comparison of delay in diagnosis, between patients in the present study (UK) and those in the study by Abdou *et al.* 2002 (North America).<sup>3</sup>

The majority of Wegener's granulomatosis patients reported receiving systemic immunosuppressants, suggesting that they had active disease. Prednisolone was the most popular (71 per cent), followed by azathioprine (41 per cent), with fewer patients taking methotrexate, cyclophosphamide or mycophenolate mofetil. This range reflects the broad spectrum of physicians managing Wegener's granulomatosis throughout the United Kingdom. Despite active nasal symptoms in 63 per cent of respondents, a relatively small number were receiving topical treatment (see Figure 7). This is an important finding in the light of theories implicating nasal bacterial carriage in the exacerbation and relapse of controlled Wegener's granulomatosis.<sup>9</sup>

The reported significant delay in diagnosis is disturbing, given that the majority of the Wegener's granulomatosis patients (63 per cent) first presented with ENT symptoms. Intriguingly, the delay was greater for those with head and neck system involvement at initial presentation. It is also very noteworthy that 56 per cent of these individuals had been seen by ENT surgeons prior to diagnosis, some of whom by inference had failed to recognise the condition. Furthermore, awareness of Wegener's granulomatosis in the UK has not increased over the last three decades, as evidenced by consistent periods of delay, including delays of more than 6–12 months for one-fifth of respondents and delays of more than 12 months in another 23 per cent. This is despite improvements in diagnostic tests.

The tendency towards head and neck involvement in younger patients and non-ENT involvement in older patients is in agreement with previously published findings.<sup>10</sup> Interestingly, our community-based study showed an even higher prevalence of nasal blockage, crusting, bleeding and hyposmia than that found in a previously published, clinically selected rhinology-immunology study group.<sup>11</sup>

Figure 8 compares our findings for delay in diagnosis with those of a previously published North

American study.<sup>3</sup> It can be seen that a significantly larger proportion of UK than US Wegener's granulomatosis patients faced a diagnosis delay of more than one month (92 per cent compared with 79 per cent, respectively;  $p < 0.001$ , difference of proportions test) as well as delays of other durations.

- **ENT involvement is common in Wegener's granulomatosis, but most existing figures are from tertiary care units, with their associated specialty-related bias**
- **This community-based study confirms not only the high prevalence of ENT involvement but also its frequency at the initial presentation of Wegener's granulomatosis, highlighting the important role of otolaryngologists in the diagnosis of this condition**
- **There were significant delays in the diagnosis of Wegener's granulomatosis patients, particularly when presenting with symptoms in the head and neck region, demonstrating the need for greater awareness of the condition within the ENT community**
- **Wegener's granulomatosis patients showed a sinonasal symptom pattern, with under-treatment of significant, Wegener's granulomatosis-related nasal symptoms**

In the literature, the reported incidence of system involvement in Wegener's granulomatosis is influenced by the speciality of the reporting unit. The present study was conducted on a relatively large cohort of patients who had been diagnosed and were being treated for Wegener's granulomatosis. Sourcing these patients via a self-help organisation avoided any selection bias, as their diagnosis and care were being undertaken by a wide range of

clinicians. However, the study was liable to detection bias in that it relied on the patients' confirmation of their diagnosis, history and treatment, without the possibility of clinical verification. Nonetheless, for a disease of such potential seriousness, in patients motivated enough to belong to a self-help organisation, this information is likely to be as accurate, if not more so, than a retrospective assessment of medical notes, with all its intrinsic limitations.

The survey response rate of just over 26 per cent seems modest but should be considered as a minimum; as some of the excluded survey questionnaires were returned by patient's relatives, it is unknown how many unreturned questionnaires were not actually received by Wegener's granulomatosis patients. For this reason, the true return rate is likely to be significantly higher than the above figure. In addition, when considering such a rare condition as Wegener's granulomatosis (UK incidence of 10.2/million/year and prevalence of 25/100 000),<sup>12</sup> our sample size of 199 Wegener's granulomatosis patients would, by extrapolation, be comparable to a sample group of 30 000 patients in a study of nasal polyps (prevalence of 4.2 per cent of adult population).<sup>13</sup>

### Conclusion

This study clearly demonstrates the need for greater awareness of Wegener's granulomatosis, particularly in the ENT community. It also highlights the fact that particular symptoms (such as nasal crusting and bleeding, and indeed a range of other ENT symptoms which do not respond to conventional treatment) should raise the possibility of this diagnosis. A diagnosis of Wegener's granulomatosis should be especially considered in patients who report levels of malaise which are disproportionate to their ENT symptoms and clinical findings.

We also hope that this study will raise otolaryngologists' awareness of the Stuart Strange Trust, the UK's patient help group for Wegener's granulomatosis patients as well as for those suffering from any of the associated vasculitides (e.g. Churg–Strauss syndrome and microscopic polyangiitis). The trust was established in 1992 by family and friends in memory of Stuart Strange, a Wegener's granulomatosis patient who had started raising money for research into Wegener's granulomatosis but who tragically succumbed to his disease. The trust publishes a newsletter at least twice a year and provides support to patients and their families. Referring patients to such self-help groups can help ease the tremendous isolation many feel when

diagnosed with a rare condition such as Wegener's granulomatosis.

### Acknowledgements

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Mr I A Srouji takes responsibility for the integrity of the content of the paper.  
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