

Wegener's Granulomatosis: Survey of 701 Patients in North America. Changes in Outcome in the 1990s

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ABSTRACT. Objective. To study the medical and socioeconomic impact of Wegener's granulomatosis (WG) in a large cohort (n = 701) of patients who are members of the international WG Support Group (WGSG).

Methods. Forty questions designed and validated by one of the authors and reviewed by the medical consultants of the WGSG International were mailed to 1690 patients with WG who are members of the WGSG; 701 (41%) patients returned the questions. Diagnosis of WG was self-reported for purpose of this questionnaire. Study domains included demographic features, education, analysis of categories of medical care providers, organ system involvement, delay in diagnosis, frequency and sites of biopsies to assist in diagnosis, treatment outcome, familial association, disability, and financial effect. We compared some of these features in patients whose diagnosis was made in the 1970s, 1980s, or 1990s.

Results. In our cohort WG was slightly more prevalent in women (56%), particularly if the disease started at a younger age (9–40 years). Peak age period at disease onset was 45–65 years. Ninety-eight percent of patients were Caucasian. Diagnosis of WG was usually made by a specialist, and the majority of patients received subsequent care by specialists. During the past decade only 7% of patients received a diagnosis of WG upon their first visit to a physician. A period of 3–12 months passed from onset of features of WG to achieving a diagnosis in the majority of patients. Compared to the period 1970–90, in recent years fewer patients had biopsies performed for diagnostic purposes. This observation correlated with increased use of antineutrophil cytoplasmic antibodies. In the 1990s the most common reported therapy was combination of corticosteroids and cyclophosphamide (73%). Patients also reported initial therapy with methotrexate (11%), trimethoprim-sulfamethoxazole (32%), and azathioprine (5%). Patients rarely reported other family members with WG. In none of 12 WG patients who had a twin did the twin have WG. The survey did not identify any specific environmental exposure, occupation, or hobby that was overrepresented among patients. One hundred seventy-nine WG patients reported that their disease had a significant financial impact on their lives.

Conclusion. Information from this survey of 701 patients is consistent with physician reported data about organ involvement, initial manifestations and therapy, and outcomes in WG. More WG patients in the 1990s were diagnosed after first physician encounter. This survey did not reveal any predisposing or inducing environmental or familial factors, and showed fewer patients become disabled and more were able to work full time. (J Rheumatol 2002;29:309–16)

Key Indexing Terms:

WEGENER'S GRANULOMATOSIS EPIDEMIOLOGY SURVEY OUTCOME

Wegener's granulomatosis (WG) is an idiopathic multi-system inflammatory disease that has a predilection for the upper and lower airways and kidneys. Histologic features include granuloma formation and vasculitis^{1,2}. The WG Support Group (WGSG) International initiated a study

targeting disease profile and its impact on lifestyle. We report on the data derived from 701 (41%) responses to a questionnaire/survey received from WGSG members. The questionnaire was designed to highlight the differences in disease outcome between the decades of the 1970s and

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Supported by Wegener's Granulomatosis Support Group International, Kansas City, Missouri, and St. Luke's Hospital Foundation.

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Submitted March 13, 2001; revision accepted August 23, 2001.

1990s. WG now has been converted from being almost always fatal to a chronic illness. Nonetheless, morbidity from disease and its treatment remains substantial²⁻⁵. One recent study estimated the medical, socioeconomic, and psychological effects of WG in 60 patients³. However, a large scale national study has not been performed. The WGSg provides an opportunity to undertake a more comprehensive survey on the status of WG in North America. Previous limited and regional surveys have been published⁴⁻⁹.

MATERIALS AND METHODS

The survey was designed by one of the authors (GSH) and has been found to be reliable for content validity, reproducibility, and feasibility³. Additional face validity was derived by consensus of WGSg consultants. This survey had different elements of disease involvement generated from the NIH database of WG; it comprised 40 questions in 4 page section and was mailed to 1690 patients with WG who are members of the WGSg. All recipients were patients who were given the diagnosis of WG by their physicians and subsequently treated for WG accordingly. Forty-one percent (n = 701) of survey forms were returned and data were entered into a Microsoft Access database. Data were analyzed using Microsoft Excel software. Statistical analysis was performed by analysis of variance (ANOVA) and paired t test. The study followed the guidelines of the institutional review board.

RESULTS

Age and sex of 701 patients. Fifty-six percent of respondents were women. There was a broad age distribution at the time of diagnosis — the peak age distribution was between 45 and 65 years (Figure 1). This sex and age distribution is

similar to that of the current membership in the WGSg International (n = 2737). By comparing the sex of WG patients and age at onset of disease it is clear that more women were seen with WG at an earlier age (age 9–40 years), whereas more men were diagnosed between the ages of 45 and 72 years (Figure 1). Differences in the incidence of WG between women and men in the various age groups were not statistically significant. The youngest patient in the survey was diagnosed at age 9 years and the oldest at age 86.

Race of WG. The survey revealed 97.7% of patients were Caucasian, 0.8% were Hispanic, and 0.8% were Native Americans. There was one each African American, Pacific Islander, and Asian. These figures are similar to previous reports that have emphasized WG is a disease that primarily affects Caucasians³⁻⁶.

Highest education of patients. In education, 44% were college graduates, 38% finished high school, 8% graduate school, 8% trade school, and 2% completed elementary education. The questionnaire was not designed to determine if education played a role in motivating WG patients to answer the survey.

Physicians providing initial care. Forty-six percent of WG patients were first seen by a primary care physician and 20% by an otolaryngologist. Forty-four percent were first seen by an allergist, pulmonologist, rheumatologist, nephrologist, or ophthalmologist. Subsequent first consultations were provided mainly by otolaryngologists (28%), pulmonologists (13%), rheumatologists (9%), and nephrologists (5%).

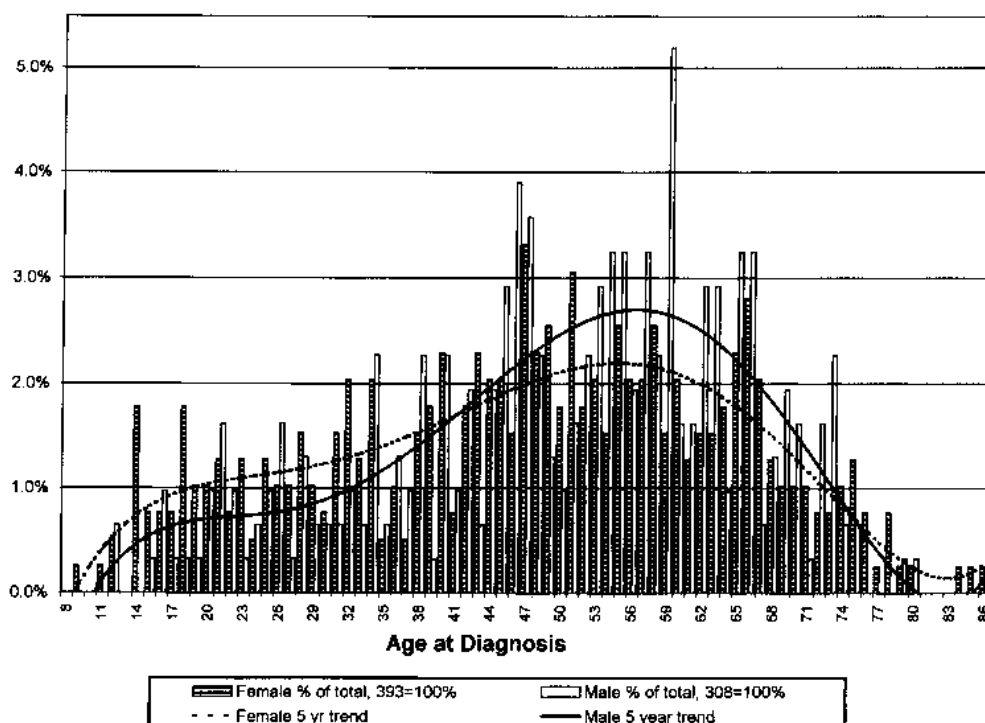


Figure 1. Sex and age distribution at diagnosis of 701 patients with WG. Note more females were diagnosed at an earlier age (9–40 yrs) and more males diagnosed at a later age (45–72 yrs).

Later consultations were predominantly by pulmonologists (13%), rheumatologists (12%), otolaryngologists (10%), and nephrologists (8%). Eighty-four percent of patients sought consultations with a specialist to confirm or to make the diagnosis and 59% saw 3 different physicians before the diagnosis was made. As shown in Figure 2, in 32% of WG patients definite diagnosis was made by rheumatologists, followed in frequency by pulmonologists (19%) and nephrologists (16%). Following the initial diagnosis, physicians treating WG patients were predominantly rheumatologists (57%), followed by primary care physicians (33%), pulmonologists (30%), nephrologists (28%), and otolaryngologists (23%). Nineteen percent of patients were followed by more than one specialist (data not shown).

Presenting symptoms at diagnosis (n = 701). As shown in Figure 3, fatigue was the predominant initial complaint in 61% of the patients, followed by joint pain (51%), sinusitis (48%), nasal discharge (43%), cough (39%), and hearing or ear problems (36%). About 95% of patients had more than one complaint at diagnosis and 14% of patients were initially told that symptoms that were later attributed to WG were psychosomatic (not shown in Figure 3). Four percent of patients presented with saddle-shaped nose, and in 12% the disease started with kidney related findings (Figure 3).

Time spent seeking a diagnosis: comparison over sequential decades (1970s–1990s). Only 22% of patients were diagnosed in the first month of illness, and 46% were diagnosed between one and 6 months after their initial symptoms. About 15% and 18% of patients recognized delays of 6–12

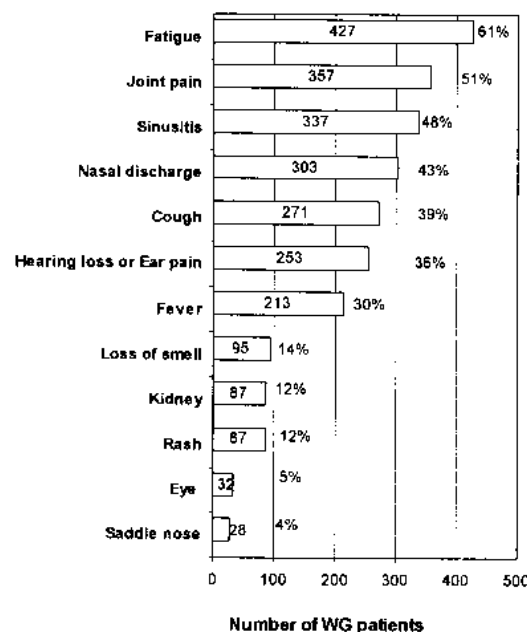


Figure 3. Presenting features of patients at time of diagnosis (n = 701).

months and greater than one year, respectively, before definitive diagnosis. About 7% of the patients spent more than 2 years until their diagnosis was made. Seven percent of patients in the 1990s were diagnosed upon their first visit to a physician. This did not occur in the 1970s or 1980s. The majority of the patients in the 1970s and 1980s had to spend 3 to 6 months before their diagnosis was definitely estab-

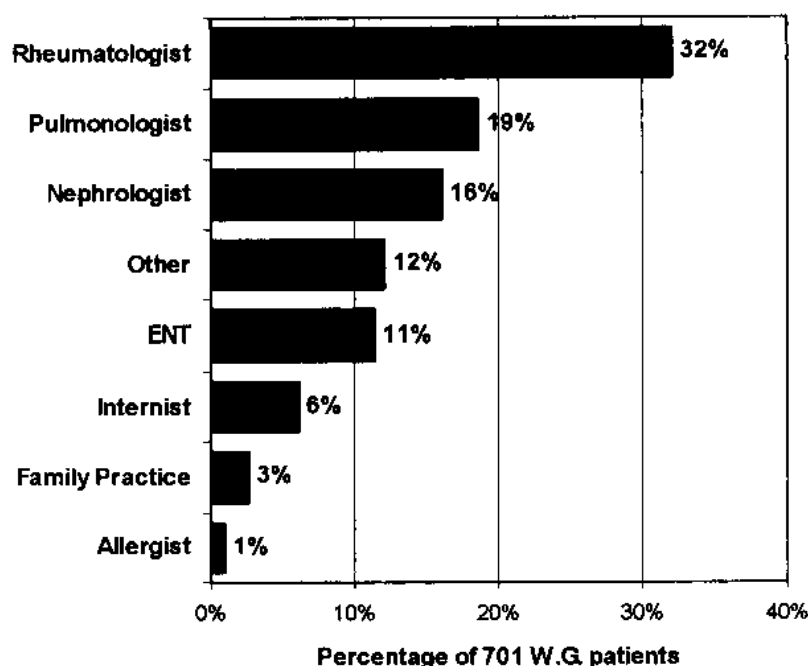


Figure 2. Practitioners who provided the diagnosis of WG, by specialty. Note the majority were rheumatologists, followed by pulmonologists and nephrologists.

lished. In comparing the various decades, patients in the 1990s were diagnosed on average 3 months earlier than patients whose disease started in the 1980s or 1970s.

The number of physicians seen by patients before their diagnosis was confirmed was 5.5 in the 1970s, 4.7 in the 1980s, and 4.4 in the 1990s. These figures represent an encouraging trend, but are not significantly different ($p > 0.05$). Overall, 44% of the patients had seen one to 3 physicians, 45% had seen 4 to 8 physicians, and 11% saw 9 or more physicians before diagnosis.

Organ involvement at time of diagnosis. As shown in Figure 4, the upper and lower respiratory tracts were the predominant organs involved at disease onset; 68% of patients had sinus and 62% lung involvement. Other initial symptoms resulted from joint (57%), nose (51%), ear (43%), or kidney (38%) involvement. Unexplained fever was the first symptom in 33% of cases. Thirty percent of patients had eye complaints and 27% had rashes at the time of diagnosis. Tracheobronchial involvement was less prevalent, affecting 19%. After diagnosis and during the course of the disease, other organs were subsequently involved. As shown in Figure 5, the eye was the most common site of involvement, followed by joints, kidney, and lower and upper respiratory tract. In several patients more than one organ system involvement was reported at the time of diagnosis and in subsequent followup. The average number of organ systems involved was 3.1 per patient (not shown in Figures 4, 5). Moreover, organ involvement shifted in some patients during the course of the disease, as shown by less target organ involvement during the course of the disease when compared to the incidence at the time of diagnosis (Figures 4 and 5).

Incidence of biopsies at time of diagnosis. About 85% of patients had biopsies performed to confirm the diagnosis; 36% of patients reported lung biopsies at the time of diagnosis, 27% had nasal-sinus biopsy, and 23% had kidney biopsy. Skin (7%), trachea (5%), and vocal cords (9%) were biopsied less frequently.

Remission: onset, duration, and disease activation after remission. The 701 patients with WG were asked about the time elapsed between diagnosis and remission. Thirteen percent of patients reported achieving remission in less than 3 months, 30% in 3 to 6 months, and 29% in 6 to 12 months. About 17% of patients achieved remission in one to 2 years, and it took longer than 2 years in 11% of patients. Following the remission, the disease relapsed within 3 months in 14% of patients. In 12% of patients remission lasted longer than 2 years. In the majority of patients, remission lasted from 6 months to 5 years. The survey showed that 50% of the patients are currently in remission, 28% have mildly active disease, and 15% never achieved remission since the diagnosis was established. Not all patients responded to the question in this part of the survey since they did not know about the status of their remission.

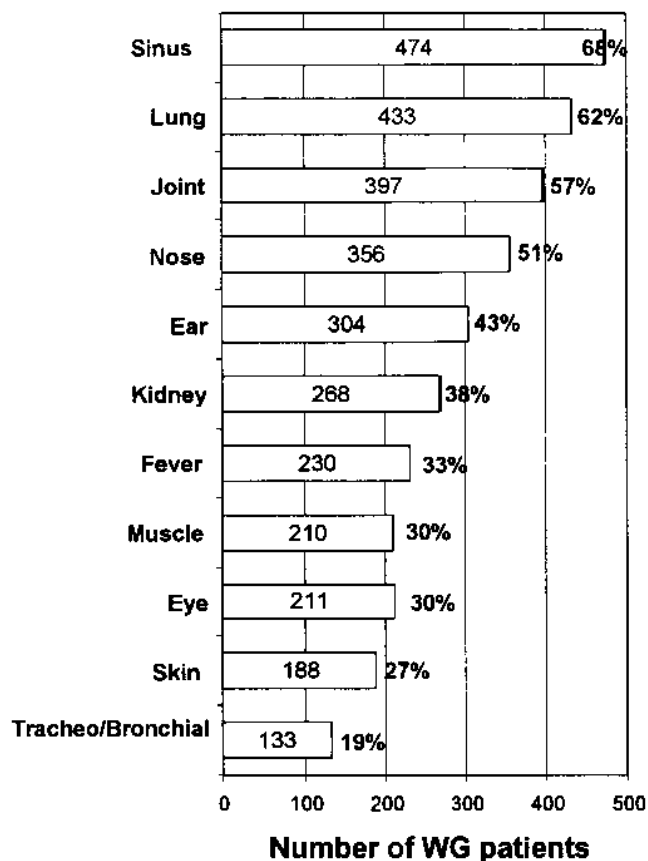


Figure 4. Predominant organ system involvement at diagnosis of WG (n = 701). Note predominant upper and lower respiratory tract involvement at diagnosis. Several patients had more than one organ system involvement at diagnosis.

Therapy reported by patients. Initial medications after diagnosis: The majority of patients (73%) initially received both prednisone and cyclophosphamide (CYC). Other cytotoxic drugs used at diagnosis were methotrexate (MTX) (11%) or azathioprine (5%). Trimethoprim-sulfamethoxazole (TS) was given to 32% of patients. Medications for maintenance were prednisone in 56% of patients, CYC in 33%, MTX in 15%, and TS in 28%. Only 5% of patients were maintained with azathioprine, and 1% are being treated with mycophenolate mofetil. The prednisone dose varied; initially it was 40–60 mg per day in 39% of the patients, and 2% of patients received < 10 mg prednisone initially. The maintenance dose of prednisone after the initial high dose was < 10 mg per day. The duration of therapy with prednisone after diagnosis was more than one year in 18% of patients. About 28% of patients received prednisone for less than 3 months.

Use of cytotoxic agents and TS: The majority of patients received 100 to 200 mg CYC daily, and only 4% received the drug by intravenous pulse. Initially 8% of patients received < 100 mg CYC per day. Duration of therapy with CYC varied; 22% of patients who received CYC took the

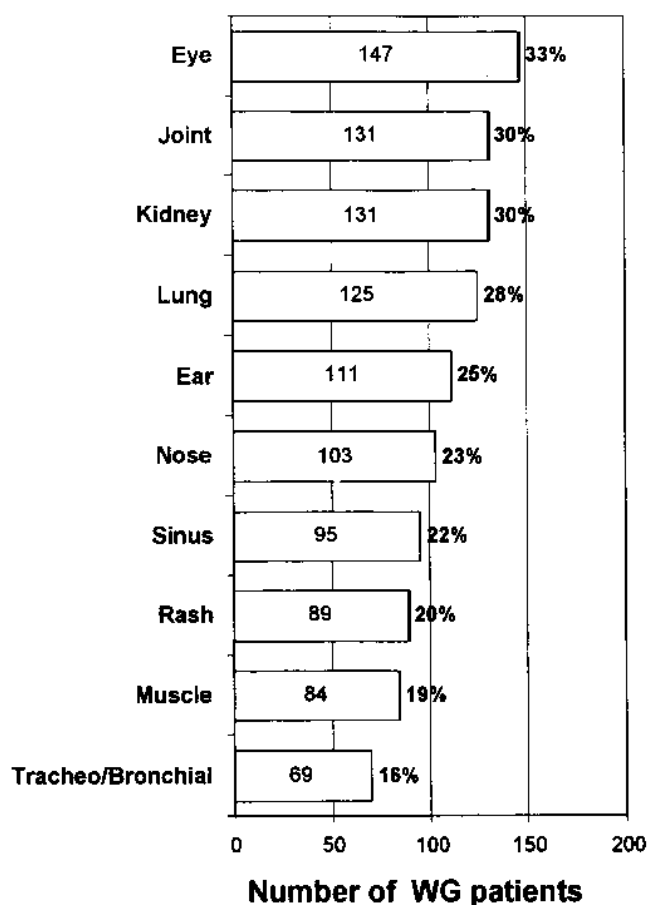


Figure 5. Organ system involvement during the course of the disease and after initial diagnosis with WG. Several patients had more (3.1) than one organ system involvement. Note that certain organs affected during course of the disease were less than incidence at time of diagnosis due to shift of organ involvement during the course of the disease.

drug for more than one year, 13% for 6 months to one year, 11% for 3 to 6 months, and about 6% for less than 3 months. About 20% of patients received CYC subsequently, but not at the time of diagnosis. About 4.3% of patients had been taking MTX for one year or less, and 1.4% for more than one year. Initial therapy with azathioprine was reported by 5.4% of the patients, and subsequent use by 5.1%. About 2.6% of patients were kept on azathioprine for less than one year and 1% for more than one year. About 32% of patients reported receiving TS during the course of their illness. Only 5% of patients had been taking TS for less than one year and 4.4% for more than one year from the time of diagnosis. Subsequent therapy with TS after the initial diagnosis occurred in 27% of patients.

Combination therapy. About 73% of the patients started taking prednisone and CYC at the time of diagnosis; 50% of them reported marked improvement, 29% slight improvement, and about 8% were worse. Thirteen percent of the patients were not able to tell if they were better or worse since their diagnosis. We compared this group of patients to

those that started triple therapy, namely, prednisone, CYC, and TS. About 19% of the patients started such combination; 52% of those have markedly improved, 28% are slightly better, and about 11% were worse. About 4.3% were not able to tell if they are better or worse. Combination therapy with prednisone, CYC, and TS was not significantly different compared to CYC and prednisone without TS. Prednisone was the only drug used in 6% of patients. Of those, 38.6% reported marked improvement and 34% slight improvement and 13.6% are worse. These results were significantly worse ($p < 0.05$) compared to patients who received a drug regimen featuring CYC. Use of CYC alone occurred in 2% of the patients, and 1% of the patients started taking TS alone. The efficacy of these drugs could not be analyzed statistically due to the small number of patients given a single drug for therapy.

Maintenance therapy. The majority (76%) of the patients were taking a combination of prednisone and CYC therapy, 10% prednisone only, 5% TS only, 4% MTX only, and about 2% CYC only. The large number of patients taking maintenance CYC is probably due to the traditional use of the drug in the 1990s. We expect that, as information about MTX and anti-tumor necrosis factor usage becomes available and accepted to maintain remission, there will be fewer patients taking CYC after the active phase of the disease is controlled.

Medical problems prior to diagnosis. The majority of patients had shortness of breath, hearing loss, arthritis, or hypertension prior to diagnosis of WG. Saddle-shaped nose and subglottic stenosis amounted to about 2% each prior to diagnosis. The incidence of allergies, sinus surgery, allergic reactions, and fungal infections was not elevated in patients prior to their diagnosis with WG.

Patients' complaints after diagnosis. As shown in Figure 6, about 39% of patients who had the disease less than 5 years reported shortness of breath as their main complaint. The percentage of patients with dyspnea increased to 46% if they had the disease for 5 to 10 years, and to 49% if they had the disease more than 10 years. Other common complaints are hearing loss, arthritis, and hypertension. Figure 6 illustrates the percentage of patients with the various complaints based on the duration of their illness. It is notable from Figure 6 that 15% of patients are undergoing dialysis if they had the disease more than 10 years. Among patients on dialysis 8% had the disease for 5–10 years and 7% for less than 5 years. The incidence of saddle-nose dramatically increased to 23% if patients had the disease for more than 10 years since the diagnosis (Figure 6).

ANCA in WG diagnosis and followup. At the time of diagnosis, 77% of the patients had a blood test for antineutrophil cytoplasmic antibody. The use of ANCA results could not be analyzed because the ANCA test was not available when some patients were diagnosed. Moreover, the quality of the

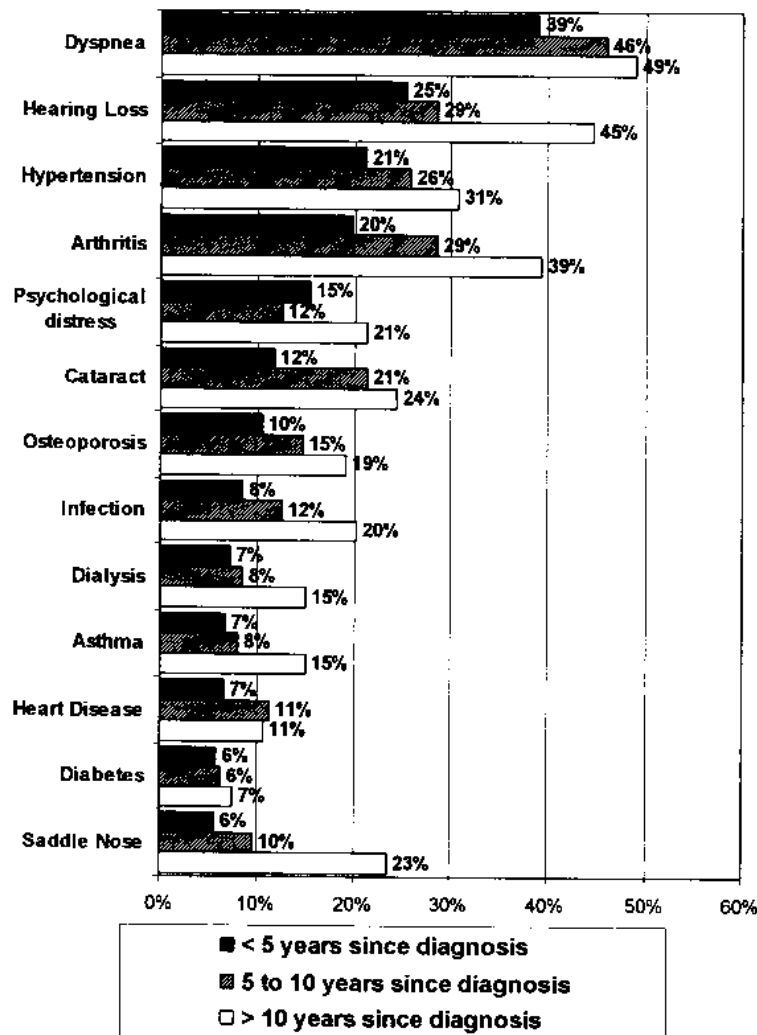


Figure 6. Major complaints — problems patients had during the course of their illness. Effect of duration of WG.

laboratory performing the ANCA testing and the titers used for cutoff were unknown to the authors, and we were unable to relate the frequency of ANCA testing that was ordered to the duration of the disease or to disease activity.

Family history of WG or autoimmune diseases. Twelve patients with WG were twins, and no twin of a patient had WG. Duration of the disease in the affected twin was 3.5–12 years. Prevalence rates of autoimmune diseases in other family members of patients were rheumatoid arthritis in 3.9%, lupus in 2.7%, and insulin dependent diabetes mellitus 1.4%. This was significantly higher ($p < 0.01$) than the reported prevalence of these diseases in the general population and would raise the question that genetic influences in WG may be polygenic in contrast to there being a “Wegener’s gene” per se.

Financial effects on patients. Four hundred ninety-two patients (70% of those who completed the survey) responded to financial impact questions. Of these, 9%

reported that they spent less than \$1,000, 35% spent \$1,000 to \$10,000, 49% spent \$10,000 to \$100,000, and 7% spent more than \$100,000 on their therapy and diagnosis. It is not clear from this survey if patients’ expenses were for medications, medical insurance, physician visits, or hospitalization. Future surveys will clarify the actual expenditure for each category. We also surveyed income losses due to WG illness. About 26% of patients reported loss of less than 25% of their income; 54% reported losses of 25% to 75%, and 20% lost more than 75% of their income. One hundred thirty-five (19%) WG patients were receiving social security disability income. Of those, 46% were receiving less than \$600 a month, 40% from \$600 to \$1,200, 14% more than \$1,200. Eight percent of patients with WG who applied for social security were denied.

Occupations and hobbies of patients. No unusual or environmental exposures were noted in the survey either before or after diagnosis of WG. In reviewing the patients’ profes-

sions we found no predominant careers patients are pursuing. Nineteen percent of patients were doing office/secretarial work, 12% were in sales, 4% performed computer and technical work, and 6.6% were in management.

Effect of WG on the lifestyle of patients. Stress from the disease was a major problem in 51% of patients with WG. Sixty-nine percent of patients worked an average of 42.8 hours per week prior to diagnosis. After diagnosis 44% of patients continued to work an average of 35.2 hours per week and 14% retired because of their illness.

DISCUSSION

This study describes the largest survey of patients with WG; it illustrates the improved outcome in the 1990s, the earlier diagnosis and remission, less invasive procedures for diagnosis, and the changes in drug combinations used for therapy. One survey previously reported the effect of WG on health, disability, relationships, and income³. Other studies have focused on efficacy of drugs⁴, longterm survival⁶, prevalence, distribution, morbidity and mortality^{3,7-9}, and longterm outcome by an interdisciplinary approach¹⁰.

We cannot unequivocally verify the diagnosis of WG in all our respondents, and the data need to be viewed with that uncertainty in mind. Moreover, overlap with microscopic polyangiitis cannot be excluded²; and only 41% of patients returned the questions, which could subject the results to selection bias. Despite these limitations, our survey has confirmed previous single institution and regional surveys and added new information with respect to (1) lack of family history in patients with WG; (2) probable lack of specific environmental factors or exposures that could predispose patients to the disease¹¹; and (3) a trend toward improvement in timely diagnosis, i.e., in the 1990s, patients were diagnosed earlier and required fewer consults and biopsies before diagnosis.

There is no significant sex difference in patients with WG (56% were female), which is different from other autoimmune diseases with marked female predominance, such as systemic lupus erythematosus, Sjögren's syndrome, or Hashimoto thyroiditis¹². In our survey, however, there was a trend of female predominance in younger WG patients and male predominance when the disease started after age 45 years. There was an increase of autoimmune diseases in other family members with WG. This observation supports the notion that WG may be an autoimmune disease¹³. Progress in pursuing the autoimmune pathogenesis of WG is still hampered by the lack of animal models of the disease and the lack of definitive information on the *in vivo* role of ANCA^{14,15}.

It is impossible to give accurate data on the prevalence of WG due to the lack of national registries for the disease. Studies have estimated the prevalence of WG to be 30 per million per year in the US^{7,8}, compared to an annual preva-

lence of 20 per million in eastern England⁹. A recent report indicated increased prevalence of WG in northern Norway in the last 15 years¹⁶.

Our survey seems to confirm the value of ANCA in diagnosis. Several newly diagnosed patients in the late 1990s reportedly did not require invasive biopsies because their diagnosis was established by highly suspect clinical characteristics in the setting of a positive C-ANCA. The utility of ANCA in followup of the disease and in making therapeutic decisions still remains controversial¹⁴. Improvement in the overall quality of ANCA testing throughout North America is an ongoing effort of the College of American Pathologists Survey Program, with one of the WSGS consultants (JAG) heading this effort. It is anticipated that a positive influence on ANCA testing will result from this, as well as steady improvements in assay technology¹⁴.

Although WG has an effect on income of patients and families³, we were encouraged to see that significant numbers of patients in our survey are working full time and earning their living. The future, we believe, is brighter for patients with WG because information about the disease is spreading to primary care physicians, particularly via the efforts of WSGS International (1500 professionals in the medical field receiving regular information), and because there is interest from dedicated medical centers in understanding the pathogenesis of WG and finding new therapeutic modalities.

ACKNOWLEDGMENT

The authors thank Joyce Kullman and Iva N. Roe of WSGS for their encouragement and support, and Hope Schreck for manuscript preparation.

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