

## Wegener's granulomatosis – observation of cases

### *Ziarniniak Wegenera – obserwacja przypadków*

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**Key words:** Wegener's granulomatosis (WG), upper airway involvement, lower airway involvement, renal involvement, ocular signs.

**Słowa kluczowe:** ziarniniak Wegenera (ZW), zajęcie górnych dróg oddechowych, zajęcie dolnych dróg oddechowych, zajęcie nerek, zmiany oczne.

#### Summary

Wegener's granulomatosis (WG) belongs to the group of necrotising granulomatous vasculitides. It affects primarily small and medium size arteries, although the involvement of capillaries and veins is frequent as well. Epidemiological data show increased incidence of Wegener's granulomatosis, particularly in northern Europe during recent years. Early diagnosis of WG is difficult.

We present a retrospective analysis of 7 patients diagnosed with WG and treated at the Central Clinical Hospital in Warsaw in the years 1998–2006. The period of observation was 1–9 years. Changes resolved quickly under standard treatment.

In all patients general symptoms of fever, weight loss and progressive weakness were present. In 4 persons the disease began with arthralgias or arthritis, in 4 with cough or haemoptysis, and in 1 with ocular signs. In our patients upper airway involvement was present in 5 cases (75%) and lower airway involvement in 5 (75%).

All WG cases observed by us were of severe course with renal involvement. Apart from standard treatment in 1 patient with rapidly progressive renal failure dialyses were applied for 2.5 years and kidney transplantation was performed in the 3rd year from diagnosis. Two patients died in the course of observation: 1 from cardiac arrest due to terminal renal failure and 1 from subarachnoid haemorrhage penetrating to brain chambers (III and IV and occipital horns of both lateral chambers). The duration of remission was between 1 and 9 years. Relapses occurred in 3 patients. The prevalence of WG in proportion to all administrations to our hospital, which is a full-scale clinical unit, was 7 cases per 232 591 patients during 9 years.

#### Streszczenie

Ziarniniak Wegenera (ZW) to choroba systemowa należąca do grupy martwiczych ziarniniakowych zapaleń naczyń. Zajmuje głównie naczynia tętnicze małego i średniego kalibru, nie omija jednak żył i naczyń włosowatych. Badania epidemiologiczne ostatnich lat sugerują wzrost zachorowań na tę chorobę zwłaszcza w krajach Europy Północnej.

W niniejszej pracy autorki przedstawiły retrospektywną analizę 7 pacjentów z ziarniniakami Wegenera, leczonych w Centralnym Szpitalu Klinicznym MSWiA w latach 1996–2006. Czas obserwacji wynosił od roku do 9 lat.

U wszystkich obserwowanych chorych występowały objawy ogólne w postaci stanów gorączkowych, utraty masy ciała i narastającego osłabienia. U 4 osób choroba rozpoczęła się bólami i obrzękami stawów, u 2 kaszlem i krwiopluciem, a u 1 osoby zmianami ocznymi. Zajęcie górnych dróg oddechowych było obecne w 5 przypadkach (75%), zajęcie dolnych dróg oddechowych również w 5 (75%). Zmiany ustąpiły szybko po standardowym leczeniu.

Wszystkie obserwowane przez autorki przypadki ziarniniaka Wegenera charakteryzowały się ciężkim przebiegiem z zajęciem nerek. Oprócz standardowego leczenia u 1 chorej z szybko postępującą niewydolnością nerek przez 2,5 roku stosowano leczenie nerkozastępcze w postaci dializ i po 3 latach wykonano przeszczepienie nerki. Dwóch chorych zmarło w trakcie obserwacji – pierwsza osoba z powodu zatrzymania akcji serca w schyłkowej niewydolności nerek, druga – z powodu krwawienia podjąjczyńkowego z przebiegiem do układu komorowego (komora III, IV i rogi potyliczne obu komór bocznych).

Czas remisji wynosił 1–9 lat. Nawroty wystąpiły u 3 chorych. Występowanie przypadków zespołu Wegenera w stosunku do

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Our data confirm the results of previous investigations as regards the aggressive course and the need for aggressive treatment of WG as well as high mortality rate in this disease (28.5% in our patients). Of interest is that we noted relatively short time periods from disease onset to the establishment of diagnosis.

## Introduction

Wegener's granulomatosis was first described as a separate clinical entity by Friedrich Wegener in 1936 [1]. This systemic disease belongs to the group of necrotising granulomatous vasculitides and affects primarily small and medium size arteries, although the involvement of capillaries and veins is frequent as well.

Epidemiological data show increased incidence of Wegener's granulomatosis, particularly in northern Europe during recent years [2]. In northern Norway the disease prevalence was 2.7–9.0 per million between 1984 and 1988 and increased to 8.0–17.3 per million in 1994–1998 [3]. A similar increase in frequency was observed in the United Kingdom [4]. The question arises, though, to what extent this is due to amelioration of disease detection methods or to differences among the populations observed (overall or restricted to hospital referrals).

The onset of the disease is often preceded by a protracted infection. Recently, French investigators drew attention to the seasonal fluctuations in incidence [5].

Early diagnosis of WG is difficult. Only in 40% of cases is it established in the first 3 months of the disease [6]. In 5% it is established 3 or more years after the onset of symptoms [6]. There is no specific test for detection of the disease. The criteria of Wegener's granulomatosis were presented at the Chapel Hill Consensus Conference in 1994. The diagnosis is made on a clinical, serological (the presence of c-ANCA antibodies) [7–10] and histopathological basis. In ANCA-positive patients histopathological confirmation is mandatory.

Classification criteria of Wegener's granulomatosis

1. Oral or nasal inflammatory changes – painful or non-painful ulcerations or purulent or blood-containing nasal discharge.
2. Chest X-ray abnormalities – lumps, parenchymal changes or cavities.
3. Urine sediment test abnormalities – erythrocyturia (>5 RBC) or erythrocyte casts.

wszystkich hospitalizowanych w naszym wysokoprofilowym szpitalu stanowiło 7 przypadków na 232 591 chorych hospitalizowanych w ciągu 9 lat. Nasze dane potwierdzają wyniki innych obserwacji o bardzo agresywnym przebiegu i konieczności bardzo agresywnego leczenia oraz o dużym wskaźniku śmiertelności w tej chorobie (28,5% u obserwowanych przez autorki chorych). Na uwagę zasługuje stosunkowo krótki okres choroby do czasu ustalenia rozpoznania u chorych.

4. Granulomatous inflammation in tissue biopsy – granulomatous changes within vessel wall or periarterial/periarteriolar region.

Fulfilling 2 out of 4 criteria is mandatory for diagnosis.

## Main article

We present a retrospective analysis of 7 patients diagnosed with WG and treated at the Central Clinical Hospital in Warsaw in the years 1998–2006. The group consisted of 5 women and 2 men, 33–78 years old. The period of observation was 1–9 years.

In 4 persons the disease began with arthralgias or arthritis, in 2 with cough or haemoptysis, and in 1 with ocular signs. Patients with pulmonary onset visible in chest X-ray and high resolution computer tomography (HRCT) had interstitial changes, infiltrations, fibrosis and signs of bronchial obturation (bronchial wall thickening).

Standard treatment included 3 methylprednisolone pulses of 1000 mg and cyclophosphamide (CYC) pulses of 1000 mg every 4 weeks through the first 6 months. Subsequently patients received 3 pulses of CYC every 8 weeks and 4 pulses every 3 months thereafter (summarized dose amounted to 13 infusions of CYC – 13 g was given under mesna protection). After pulse treatment methylprednisolone prednisone was given at 0.5 mg/kg B.M./day then doses were gradually reduced to 10 or 5 mg per day. Co-trimoxazole treatment (960 mg per day) was subsequently applied for 2 years.

Under standard treatment lung changes resolved and occurred again in flares of the disease.

Renal involvement was present in all patients. In 6 of them kidney biopsy was performed to establish the diagnosis. Apart from standard treatment in 1 patient with rapidly progressive renal failure dialyses were applied for 2.5 years and kidney transplantation was performed in the 3rd year from diagnosis. Four years later the patient developed azotemia. The biopsy of the transplant revealed borderline changes "suspicious of rejection" according to the Banff 97 classification, diffuse fibrosis and tubular atrophy.

In all patients general symptoms of fever, weight loss and progressive weakness were present. Accelerated ESR (often to a 3-digit number), high CRP, normochromic anaemia, proteinuria, erythrocyturia, cylindruria and azotemia (increase in serum creatinine and urea) were noted in each case. All patients were c-ANCA positive.

Two patients died in the course of observation: 1 from cardiac arrest due to terminal renal failure and 1 from subarachnoid haemorrhage penetrating to brain chambers (III and IV and occipital horns of both lateral chambers). The haemorrhage was caused by aneurysm disruption, yet it is uncertain whether the aneurysm was a result of vasculitis or congenital vasculopathy.

The prevalence of WG in proportion to all admissions to our hospital, which is a full-scale clinical unit, was 7 cases per 232 591 patients during 9 years.

First symptoms of the disease developed in 1 case in spring, 4 cases in autumn and in 2 cases in winter.

The duration of remissions lasted from 1 to 9 years. Relapses occurred in 3 patients (Tab. I).

## Discussion

Wegener's granulomatosis can affect any organ and its course is unpredictable. Clinical remissions induced by aggressive treatment, suddenly interrupted by severe flares, not infrequently fatal, are typical for

the disease. Relapses can occur at any time of even a long-standing remission and are often due to infection or cessation of treatment.

The disease most frequently affects upper and lower airways and kidneys. Head and neck structures are involved in up to 95%, and the lower airways in 85–100% of patients [11].

In our patients upper airway involvement was present in 5 cases (75%) and lower airway involvement in 5 (75%). The changes resolved quickly under standard treatment.

The clinical picture of lung involvement is miscellaneous. Patients often complain of dyspnoea and haemoptysis. In CT [12] and the less sensitive chest X-ray asymptomatic nodules, interstitial infiltrations, circular shadows prone to lysis, often complicated by bacterial or fungal infection [13], hilar and sometimes mediastinal adenopathy [14] or alveolitis caused by small vessel inflammation can be seen. Pleural effusions occur sometimes as well. Lung disease in Wegener's granulomatosis must be differentiated from lung neoplasms, lymphomas (e.g. midline lymphoma), Hodgkin's disease, Castleman's disease, tuberculosis and tuberculoma, sarcoidosis, actinomycosis, borreliosis, recurrent polycondritis and alveolar haemorrhage in different forms of primary systemic vasculitis [15, 16].

**Table I.** Data of patients with Wegener's granulomatosis  
*Tabela I. Dane chorych z ziarniniakiem Wegenera*

Gender and age	Organ involvement	c-ANCA	Histopathology	Time to diagnosis	Time remission (years)	Relapse	Treatment Outcome
F, 59	right orbital cavity, sinuses, kidneys	1:320	OB granuloma vasculitis	1 year	6	no	M+C cotrimoxazole CR
F, 33	lungs (haemorrhage, PI), kidneys (RPGN)	1:320	RB vasculitis CG	4 months	2,5	yes	M+C dialysis renal transplant CR
F, 76	lungs (PI), orbit, kidneys (RPGN)	1:320	RB vasculitis CG	3 months	4	no	M+C cotrimoxazole CR
F, 49	ethmoid sinuses, M.P., middle ear, kidneys	1:320	RB focal segmental glomerulonephritis	6 months	3	no	M+C plasmapheresis 7x CR
M, 68	nose, throat, lungs (PI, pleuritis), kidneys	1:160	RB focal segmental glomerulonephritis	1 year	4	yes	M+C cotrimoxazole Death
F, 78	sinuses, lungs (PI), kidneys	1:160	RB focal segmental glomerulonephritis	2 months	9	no	M+C cotrimoxazole CR
M, 59	ear, sinuses, lungs (PI), kidneys (RPGN)	1:320	RB Vasculitis CG	2 months	2	yes	M+C cotrimoxazole Death

PI – parenchymal infiltrations; MP – mastoid processes; OB – orbital biopsy; RB – renal biopsy; RPGN – rapidly progressive glomerulonephritis; M+C – pulse methylprednisolone and cyclophosphamide; CR – clinical remission; CG – crescentic glomerulonephritis

All WG cases observed by us were of severe course with renal involvement, which occurred at presentation in about 25% of patients. In the general population it is observed in the course of the disease in up to 80% of cases. The biopsy reveals a focal segmental necrotizing glomerulonephritis, which we also found in our patients. Clinical signs comprise proteinuria, erythrocyturia, cylindruria and nephritic syndrome. Patients may present with life-threatening acute renal failure due to rapidly progressive glomerulonephritis. This we observed in one of our patients who further underwent kidney transplantation. Kidney disease is a factor of poor prognosis, yet early application of aggressive standard treatment gives a chance to obtain remission. Dialyses and renal transplantation increase the survival time, which was short before the introduction of immunosuppressive treatment (glucocorticoids, cytotoxic agents: cyclophosphamide as the drug of choice). Walton [17] reported 5-month survival in renal involvement and overall 1-year survival in 82% of patients in the past. At present the 10-year survival rate for patients is 58%, the dialysis-free survival rate is 51% and the mortality rate is 41% [18]. The most frequent complications of standard treatment are superimposed infections.

Our data confirm the results of previous investigations as regards the aggressive course and the need for aggressive treatment of WG as well as high mortality rate in this disease (28.5% in our patients). Of interest is that we noted relatively short time periods from disease onset to the establishment of diagnosis.

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