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Review

# Review and New Insights on Wegener Granulomatosis

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**A B S T R A C T**

*The purpose of this paper is to present Wegener granulomatosis manifesting in its periocular form. Review with new developments in understanding of the etiopathogenesis, clinical and laboratory findings as well as therapy modalities are shown through a series of patients gathered in collaboration with colleagues from UMC Utrecht, Netherlands. In the period from 1992 until 2004 the group of 54 patients with established diagnosis of Mb. Wegener were observed. 13 patients developed periocular form but only 2 presented it as initial symptoms. Lacrimal stenosis and orbital infiltration were predominant periocular symtoms while nasal manifestations were predominant systemic symptoms of the disease. Different treatment modalities were employed showing that orbital disease is difficult to treat in spite of satisfying systemic answer to immunosuppressives which calls for alternative solutions.*

***Key words**: periocular Wegener, ANCA vasculitis, specific immunosuppression*

## Introduction

Wegener granulomatosis is known as primary systemic vasculitis. Vasculitides are heterogenous group of diseases and syndromes and can be of infectious or non-infectious origin, idiopathic or secondary and with systemic or limited presentation.[1] and are defined according to the Chapel Hill Consensus Conference on the basis of the size of the vessels involved, the histopathological findings and characteristic clinical symptoms. The primary systemic vasculitides are characterized by necrotizing inflammation of small blood vessels and ANCA (ant-neutrophil cytoplasmic antibody) laboratory findings and as such are also known as ANCA associated vasculitides (AAV).[1,2]

Wegener granulomatosis as a autoimmune systemic disorder may present itself in various forms and locations but main organic systems involved are upper and lower respiratory tract, vasculatory and renal system.[3,4] Most commonly affected tissues are upper respiratory tract, lung, kidneys, skin, eyes and orbits, ears, joints and lymph nodes.[3] Even though complete etiology of WG is unknown, genetic background is suspected, involving deffects and skewing polymorfism of immune response genes and therefore changing the behavior and creating inbalance between many of immunomodulatory constituents.[1,3,5]

Amongst exogenous factors most commonly suggested to play role in ANCA mediated autoimmunity response are silica and drug exposure and microbial agents, in particular Staphylococcus aureus.[5,6] The disease is more often reported in whites (81%) comparing to other races. 74% of affected are over 40 yrs old and male-female ratio is 1,5–2:1.[3,7] In establishing the diagnosis there are several criteria that should be present. Nowadays if two or more of the following findings: urine sediment abnormalities, abnormal chest radiography, nasal or oral inflamation, granulomatotic infiltrations and positive c-ANCA are present the diagnosis of Mb Wegener is made.[3] The principles of treating Mb Wegener whether it is systemic or limitied form are the same and here we give and overview of standard and some alternative medications used in refractive cases.

## Patients and Methods

From the period of 1992 to 2004 we gathered a group of 54 patient with the diagnosis of Mb. Wegener. The diagnosis was established according to proposed criteria of clinical and laboratory findings. In all patients c-ANCA testing were performed using a combination of

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indirect immunofluorescence (IIF) of normal peripheral blood neutrophils and enzyme-linked immunosorbent assays (ELISAs). Also in all patients sedimenatation rate, C-reactive Protein, white blood count, electrophoresis of the immunoglobulines, TNF, TGF, creatinine clearance, quantitative urine chemistries and urine sediment for blod and protein casts were obtained. Nasal swabs for Staphyloccocus aureus were taken and cultured in all. Biopsy was taken in two patients who presented with skin nodules and dacryoadenitis. The group was comprised of 9 Caucasians and 4 Asians and 9 males and 4 females. Average follow up was 11.3 years (3–22 years).

Different treatment modalities were empolyed in group of 13 patients with periocular Wegener granulomatosis such as standard combination of corticosteroids (prednisolon) and cytostatic drugs (cyclophosphamide) and in refractory cases Cell Cept in combination with standard therapy. Some patient underwent radiotherpy, lacrimal surgery and decompression of the orbit as symptomatic treatement and all was given sulfametoxasol + trimetoprim supportive therapy.

## Results

Out of 54 patients 24% (13) subsequently developed symptoms of periocular Wegener granulomatosis while 15% of patients with periocular Wegener presented it as initial symptoms which correllates with published data. The average time elapse from systemic to periocular manifestations was 6.5 years (1–17 years). Average age at onset of the disease was 38.9 years (22–71) with male-female distribution in the group 2,25:1.

In our series the distribution of males and females as well as specific laboratoty findings were consistent with literature. Disease onset age showed skewing towards younger age group while it was in 69.2 % predominant in Caucasians. The predominant periocular presenting symptom in group of 13 patients with periocular Wegener was lacrimal stenosis occuring in 46% while 84.6% patients developed nasal manifestation as systemic symptoms.

69.2% of patients were stable after treatment with combination of immunosuppressive mediacations (coricosteroid+cytostatic drugs) and 30.8 % had frequent relapses including deterioration of visual function, one died and two developed hip necrosis and haemorrhagic cystitis due prolonged use of corticosteroids and cytostatics respectively. The patient with refractive orbital infalamation was given a combination of standard therapy fortified with CellCept but the results are still being monitored.

**TABLE 1**
PERIOCULAR MANIFESTATIONS IN 13 PATIENTS WITH WEGENER GRANULOMATOSIS

| Symptom | N |
|---|---|
| Lacrimal stenosis | 6 |
| Episcleritis | 3 |
| Conjuntivitis | 2 |
| Scleritis | 1 |
| Limbal granuloma | 1 |
| Dacryoadenitis | 1 |
| Orbital infiltration | 5 |

**TABLE 2**
SYSTEMIC MANIFESTATION IN 13 PATIENTS WITH WEGENER GRANULOMATOSIS

| Symptom | N |
|---|---|
| Nose manifestations | 11 |
| Sinuitis | 6 |
| Lung infiltration | 4 |
| Arthralgia | 2 |
| Nephritis | 1 |
| Polychondropathy | 1 |
| Peripheral neuritis | 1 |
| Facialis/reccurens paralysis | 1 |
| Skin nodules | 1 |
| Subglottis stenosis | 1 |
| Otitis | 1 |

## Discussion

Ophtahlmological presentation of Wegener granulomatosis are highly variable and can involve all parts of the, eye and adnexa, orbit and periocular tissues. The damage to the eye and the adnexa are result of focal vasculitis, vascular thrombosis and ischaemia and finally necrotizing granulomatous inflammation with formation of the mass, known as orbital pseudotumor. The orbital tissue can be primariliy affected or its involvement may be the result of the disease spreading from paranasal sinuses or other parts of the upper respiratory system. Ocular and orbital involvement is common in systemic and limited form of the disease, whereas ultimately up to 28%–87% of patients present initially with ophthalmic features.[8]

Most commonnly reported ocular manifestations are orbital inflamation with proptosis and necrotizing keratoscleritis respectively.[9] Other possible manifestation of the ocular disease are eyelid swelling, nasolacrimal duct obstruction, dacryoadenitis, conjunctival injection an ulceration, uveal inflammation, ciliary granuloma, myositis, extraocular muscle palsy, optic nerve compression or neuritis, retinal and choroidal arterial occlusion and vitreous hemorrhage.[10–13]

Only few and not very recent references can be found mentioning ANCA testing in limited form of WG so the value of ANCA testing as disease activity index and relapse predictive factor in limited form of WG are yet to

be determined considering all the breakthroughs made recently.

Other diagnostic tools include biopsy of the involved tissue, standard laboratory testing, MRI – in unenhanced and non-fat-suppresed T1-weighted sequences or CT of head and chest.[14]

Laboratory testing such as sedimentation rate, CRP, white blood count, electrophoresis of the immunoglobulines, levels of TNF and TGF, ceratinin clearance, quantitative urine chemistries, urine sediment for blood and protein casts are of diagnostic values in combination with other clinical and diagnostic findings.

Epidemiology of the WG is very difficult to present unequivocaly as rare disorders are often misdiagnosed and therefore underreported. However, number of studies suggests annual incidence per million varying from 0.5 to 8.5.[3] This results show increased incidence of the disease through last 30 years and could be result of better awareness of the disease as well as advancements made in diagnostic, laboratory procedures. Our series of patients showed also a shift of initial disease onset toward younger age group which could be explained by better medical awareness rather than by an increase of disease incidence. Mortality rate within one year reported in studies until early 1970's were 82% after the diagnosis were made as opposed to recent results of 75% of remissions and 90% of significant improvement of symptoms with standard therapy combination of prednisolon and cyclophosphamide.[15–17] Our results showed the remission rate as high as 60.8% and frequent relapse rate of 39.2%.

The selection of medications in limited form of WG is generally based on the same principles as the treatment of systemic disease.

Yet, several studies suggested that ocular inflammation can be refractory to standard combination of corticosteroids and cyclophosphamide. In such cases some alternative medications have been used to subside the inflamation. Daclizumab, CellCept and ATG (anti-thymocite globulines) in combination with corticosteroids managed to induce remission[16–19]. The studies that reported those results were mainly based on the outcome of a few cases, thus these results needs confirmation through larger series of patients followed for a longer period. The major shortcomings of standard therapy are its toxicity, especially in prolonged use and its inability to substantially reduce the relaps rate after tapering the therapy (relapse over 50% in WG patients). As a critical short-term risk of this therapy, nowadays appears opportunistic infections (54%) especially with Pneumocystis carinii (20%) causing up to 18% of the deaths.[16]

In order to lower this high rate of secondary infections close and regular monitoring of white blood cells levels is recommended as well as regular use of trimethoprim-sulfametoxazol antibiotic.[20] All the drawbecks of standard therapy of WG have encouraged the development of many different supstances which should act selectively on specific component of the immune system with as few negative side effects as possible. Daclizumab as hummanized immunoglobulin G monoclonal antibody inhibiting activated T-cells, CellCept (mycophenolate mofetil) inhibiting B-lymphocites and cytotoxic T-cells, Tacrolimus (FK 506) inhibiting production of cytokines, ATG (antithymocyte globulin), Campath – 1H humanised monoclonal antibody and Etanercept as inhibitor of TNF.[17–20] No ideal drug has been found yet, comprising all: potential to induce and maintain remmision, with no or few minor side effects and with potential in treatment of refractory focal disease manifestations. Without treatment WG is associated with high rate of mortality. The mean survival for typical, fully expressed, untreated cases is cca. 5 months.[16] Considering the chronic course of the disease and possibility of encountering a sight-threatening and even life-threatening condition it is obvious that prompt diagnosis and treatment are warranted.

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## WEGENEROVA GRANULOMATOZA

### S A Ž E T A K

Cilj ovog rada je prikazati oblik Wegenerove granulomatoze koji se manifestira kroz periokularnu lokalizaciju. Pregled literature sa najnovijim spoznajama o etiopatogenezi, kliničkim zapažanjima te laboratorijskim nalazima kao i novim terapijskim modalitetima prikazan je kroz seriju pacijenata skupljenih u suradnji sa kolegama sa Univerzitetske klinike u Utrechtu, Nizozemska. U periodu od 1992. do 2004. praćena je grupa od 54 pacijenata kod kojih je postavljena dijagnoza Wegenerove granulomatoze. 13 pacijenata razvilo je periokularni oblik bolesti, ali samo kod dvoje to je bio inicijalni simptom. Lakrimalna stenoza i orbitalna infiltracija bili su predominantni simptomi kod periokularnog oblika, dok je nazalna infiltracija bila predominantni simptom sistemskog oblika bolesti. U liječenju su korišteni različiti modaliteti terapije što je pokazalo da je periokularni oblik bolesti često refrakteran na liječenje unatoč zadovoljavajućem odgovoru sistemskog oblika bolesti na terapiju imunosupresivima.