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Wegener granulomatosis in children and young adults

A case study of ten patients

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Abstract This retrospective study reports seven children and three young adults (aged 11–30 years) who suffered from Wegener granulomatosis. Nine represent consecutive patients admitted to the Division of Nephrology over a period of 23 years. All patients had respiratory tract symptoms and renal involvement on admission. In several patients infiltrates on chest X-ray developed within 2 weeks of onset of symptoms. All patients survived. The median observation period was 9 years (range 13 months to 23 years). One patient progressed to end-stage renal disease. Nine patients initially received cyclophosphamide and steroids. After a median period of 9 months (range 6–31 months) the cyclophosphamide was replaced by azathioprine. Relapses occurred after a median of 28 months (range 4–120 months) in 80% of patients, in six of the eight patients causing a definite decrease in kidney function. We believe that early diagnosis and initiation of therapy reduce the extent of organ damage. Since relapses are frequent, these patients should be evaluated frequently.

Key words Wegener granulomatosis · Renal failure · Respiratory failure · Inflammation · Pulmonary infiltrates

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Introduction

When a child presents with respiratory tract symptoms, the usual causes are infections. Inflammatory diseases should be suspected if the symptoms do not resolve spontaneously or with conventional antibiotics. In patients who also have proteinuria and hematuria, the reason may rarely be diseases such as systemic lupus erythematosus (SLE) with glomerulonephritis [1, 2] and Wegener granulomatosis. This necrotizing vasculitis of the upper and lower respiratory tract is often associated with glomerulonephritis [3, 4]. The presence of such vasculitis may be verified by histology of the nasal mucosa or, preferably, by a kidney biopsy. The finding of a pauci-immune, necrotizing and crescentic glomerulonephritis together with antibodies to neutrophils (ANCA) indicate Wegener granulomatosis [5–7]. This disease is rare in childhood [8–12], but awareness is crucial for the prognosis of the child. We report ten children and young adults with Wegener granulomatosis to increase the awareness of this disease in childhood.

Material and methods

The study includes nine Caucasian children and young adults consecutively admitted to one center over a period of 23 years (patients 2–10, northern Sweden) and another 12-year-old girl from the University Children's Hospital in Hamburg, Germany (Tables 1 and 2). Seven of the patients were younger than 19 years at the start of the disease. The median observation time of the disease was 9 years (range 1–23 years). The patients were diagnosed as having Wegener granulomatosis according to the symptom triad of a kidney biopsy demonstrating a rapid progressive crescentic glomerulonephritis, upper and lower respiratory tract disease, and serological findings of raised ANCA.

Serological analyses for proteinase 3 antibodies (denoted c-ANCA) were performed in six and verified in five of the patients before the start of immunosuppressive therapy and plasma exchange, while in four the presence of such antibodies was verified later. These latter patients may have had higher levels before the start of immunosuppression than those given in Table 1. Another patient had myeloperoxidase antibodies (denoted p-ANCA) as well as a clinical picture of both upper and lower airway disease and a crescentic glomerulonephritis with pauci-immune deposits (patient 9).

Antinuclear antibodies (ANA) and anti-glomerular basement membrane (GBM) antibodies were analysed in all. Three patients had a low titer of the Goodpasture IgG antibodies against GBM (patients 4, 6, and 10). The analyses for ANA, anti-GBM, proteinase 3 c-ANCA, and myeloperoxidase p-ANCA were performed according to Wieslab (Lund) [13]. To reduce the extent of complement activation [14], plasma exchange was performed in eight patients by a centrifugation technique (CS 3000, Baxter, Tampa, Fla., USA) by exchange of about 35 ml plasma/kg body weight. Replacement was with an albumin solution containing 50 g albumin/l. Liquid stored plasma (3–4 units, each about 250 g) was used as replacement fluid at the end of the plasma exchange in most exchanges to avoid deficiency of immunoglobulins and factors influencing the coagulation and fibrinolytic systems [15, 16].

Results

Calculation of incidence

Laboratory and demographic data of patients at the time of admission are given in Table 1. Nine patients (nos. 2–10) lived in northern Sweden, and probably represented all young people diagnosed with this disease in this area over a period of 23 years. Due to the policy of centralization of patients with complicated diseases, all younger patients in the area (with a population of 0.96 million inhabitants) presenting with this type of disease would be (sooner or later) admitted to the University Hospital for diagnosis and therapy. All centers responsible for analysis of renal biopsies from this area were asked to check for this diagnosis in all children. No additional child was found. If a child had died of an uncertain disease, the final diagnosis would have been detected at autopsy and thereby known by the clinicians. The incidence of Wegener granulomatosis in children and young adults in this study, therefore, was calculated to be less than 1 per 2 million inhabitants per year. One patient (no. 7) had a heterozygous hereditary deficiency of α_1-antitrypsin (10%).

Clinical manifestation

The female:male ratio was 1:1. The earliest age at onset of disease, 11 years, was in a boy (patient 10) with a history of recurrent laryngitis from the age of 8.5 years (Table 1). The median duration, estimated from the appearance of symptoms relevant for Wegener granulomatosis (e.g., recurrent respiratory tract infection, fatigue) to admission to hospital, was 28 days (range 2–69 days). All patients presented with various upper respiratory tract symptoms that progressed to lower respiratory tract symptoms, verified by X-ray examination in several (Table 2).

Most patients had initially consulted a general practitioner who had prescribed at least one course of antibiotic treatment for a presumed respiratory tract infection. During follow-up, hematuria and proteinuria were detected, which led to admission to hospital and, thereby, further diagnostic work-up. Immunosuppressive treatment was started within 2 months of symptoms in all and within the 2nd week after admission to the hospital in eight patients and the 4th week in two (patient 1 and 10). All patients prior to or on admission had a temperature greater than 38.0°C. The various symptoms of the patients upon presentation are given in Table 2.

All patients had a progressive course of the disease, including impairment of renal function. The progression of respiratory tract impairment was rapid in most patients, and pulmonary dysfunction caused the most-prominent symptoms (patients 2, 3, 4, 7, 8, and 10). Two patients (nos. 3 and 10) needed mechanical ventilation, while two others (nos. 4 and 7) required oxygen by nasal cannulas in the intensive care unit during the period of initiation of immunosuppression. In all patients a crescentic glomerulonephritis was found, verified by renal biopsy (Table 1).

Table 1 Sex, age, and clinical data of the patients on first admission (*c-ANCA* proteinase 3 antineutrophil cytoplasmic autoantibodies, *RPG* rapidly progressive glomerulonephritis, *G* granuloma, *NA* not assessed)

Patient no.	Sex	Age	c-ANCA	Histology (crescents)	Immuno-fluorescence	Chest X-ray	Serum creatinine at start of therapy (μmol/l)[c]
1	F	12	128	RPG, G (90%)	No deposits	Not done	800 (0)
2	F	14	468	RPG (33%)	No deposits	Extensive infiltrates	100 (69)
3	M	17	>25[a]	RPG (95%)	No deposits	Extensive infiltrates	510
4	M	23	>44[a]	RPG (75%)	Moderate IgG,C3	Extensive infiltrates	810
5	F	25	240	RPG (50%)	Pauci IgG, C3	Extensive infiltrates	109
6	M	12	>195[a]	RPG (40%)	Pauci C3	Moderate infiltrates	105
7	F	30	>340	RPG (100%), necrosis	Pauci IgG,IgM, C3	No findings on X-ray	408
8	M	18	>340	RPG (55%)	Pauci C3	Moderate infiltrates	265
9	F	16	<10,160[b]	RPG (24%)	Pauci C3, IgM	Moderate infiltrates	270 (21)
10	M	11	NA[a]	RPG (90%)	Pauci C3	Moderate infiltrates	80

[a] No analyses performed until after start of immunosuppression. Increased titer analyzed later

[b] Myeloperoxidase p-ANCA serology

[c] Glomerular filtration rate (clearance) is given as ml/min per 1.73 m^2 body surface area in parentheses

Table 2 Symptoms present on admission to the University Hospital and X-ray findings of pulmonary infiltrates

Symptoms	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Fatigue	+	+	+	+	+	+	+	+	+	+
Sinusitis	+	+	+	+		+	+	+		+
Otitis media	+	+		+		+				
Mastoditis	+					+				
Hearing loss						+				
Ear ache						+				
Bell palsy						+				
Recurrent nose bleeding									+	
Oral lesion							+			
Pulmonary infiltrates	NA	+	+	+	+	+	–	+	+	+
Hemoptysis			+	+				+		+
Pleural effusion		+								
Bilateral conjunctivitis										
Arthralgia/arthritis			+				+	+	+	+
Skin lesions					+		+		+	+
Head ache					+		+			
Saddle nose					+					+
Proteinuria	+	+	+	+	+	+	+	+	+	+
Hematuria	+	+	+	+	+	+	+	+	+	+

Table 3 Therapy and outcome (*PSt* pulse steroids, *OSt* oral steroids, *Cy* cyclophosphamide, *PE* plasma exchange, *Az* azathioprine, *My* mycophenolate, *ESRD* end-stage renal disease, *Tx* Kidney graft)

Patient no.	Hospital period					Relapse at month	Latest control				
	Weight (kg)	PSt (mg)	OSt (mg/day)	Cy (mg/day)	PE no.		Months after initial phase	Clearance (ml/min)[a]	Serum creatinine (µmol/l)	c-ANCA (units/l)	Current medication
1	45	0	80	100	10×2	40	144	69	90	30	OSt,Az
2	40	1000	50	1400	3	26	36	96	90	35	OSt,Az
3	57	160	20	100	5	120	132	54	176	40	Ost,Az
4	76	1000	80	100	8	28	120	69	103	20	OSt,Az
5	56	0	120	150	5	72	108	NA	59	<10	OSt,Az
6	31	0	40	75	0	19	156	103	90	195	OSt
7	79	500	30	150	8	4	22	108	80	196	OSt,Az
8	69	500	75	300	5		16	110	95	34	OSt,Az
9	62	1000	50	750	0		25	80	103	<10[b]	OSt,Az
10	38	0	40	0	0[c]	94	276	0	ESRD,Tx	<10	OSt,CyA,My

[a] The clearance is given as corrected for body surface area
[b] p-ANCA also <10
[c] 20 treatments during the relapse period

Serology

c-ANCA were detected in eight (80%) patients; three patients had low titers of IgG antibodies against Goodpasture antigen (nos. 4, 6, and 10) and one had ANA (patient 10). ANCA were not determined until several years later in patient 10, since the technique for their measurement had not been developed. He had already been transplanted and the ANCA titer at this time was negative. He had severe pulmonary involvement, granulomata in the nasal tissue, pauci-immune renal histology, and no linear fluorescence for IgG.

One girl (patient 9) had normal proteinase 3 ANCA (c-ANCA) but increased myeloperoxidase ANCA (p-ANCA). She also displayed the other criteria included in the triad of Wegener granulomatosis, namely, upper and lower respiratory tract inflammation and a crescentic glomerulonephritis. In four patients, ANCA were first measured after the immunosuppression was started. This was due to either lack of suspicion of this diagnosis (in three patients) or lack of methodology at that time (patient 10).

Treatment protocol

The immunosuppressive regimens are shown in Table 3. Nine of the patients received a combination of cyclophosphamide and steroids during the initial phase of the disease. Steroid therapy was given in most by i.v. bolus doses of methylprednisolone that were tapered over 3 consecutive days (the 1st day usually 500 mg, the 2nd day 250 mg, and the 3rd day 125 mg). Then they received oral doses of prednisolone (about 1 mg/kg body

weight tapered to about 0.4 mg/kg body weight at the end of the first 6 months). Thereafter individual doses were administered depending on C-reactive protein (CRP), ANCA titers, and other inflammatory parameters. In two patients (nos. 2 and 9) long-term prednisolone was administered at a dose of 20 mg every other day. Plasma exchanges were performed initially in seven and at relapse in one patient (no. 10, Table 3).

Cyclophosphamide was initially administered either as an i.v. bolus dose (100–750 mg) followed by oral daily doses of about 1–2 mg/kg body weight or, as in two girls (patients 2 and 9), by cyclophosphamide given as intermittent i.v. doses (500–1,400 mg), with the aim of avoiding gonadal side effects. In these the infusions were given weekly for 4 weeks (patient 9) and then monthly (patients 2 and 9) during their menstruation period for 6 months. The doses of cyclophosphamide aimed to maintain the blood leukocyte count at a level of $4.0–8.0\times10^9$/l. After a treatment period of at least 6 months and here a median of 9 months (range 6–31 months), cyclophosphamide was withdrawn to avoid long-term side effects. This was done when the patient was in a stable clinical condition with normalized inflammatory parameters (such as CRP) and stabilized renal function, while the steroids were maintained. In nine patients azathioprine was added at a dose of about 1 mg/kg body weight to suppress immunoactivation and to allow lower doses of steroids. Due to a tendency towards leukopenia and persistent inflammation, cyclosporin A was added at a dose of about 100 mg/day in two patients (nos. 5 and 7). Elevations of the ANCA titers on this therapy were not prevented and cyclosporin A was therefore discontinued. One patient (no. 10) initially received only a pulse dose of steroids and then oral prednisolone for 6 years, because the diagnosis was not established at that time. During a life-threatening relapse 9 years later, he received a combination of steroids, cyclophosphamide, and plasma exchange. These therapeutic efforts improved the clinical condition and inflammatory parameters in all patients and reduced/normalized the c- or p-ANCA levels (Table 3).

The pulmonary infiltrates disappeared or were considerably reduced within 3 weeks of initiation of immunosuppression. Azoospermia has been verified in three men (patients 4, 6, and 10). One woman suffers from amenorrhea (patient 7). No other severe side effects (due to immunosuppression), such as agranulocytosis, cystitis, malignancies, cataracts, or aseptic necrosis, have been recorded.

Relapse

After a median of 28 months (range 4–120 months), eight patients had a relapse of the disease. In two (nos. 5 and 7) this was manifested by increased fatigue and raised c-ANCA titers, while in the others a more-generalized relapse occurred, including impaired renal function (patients 1, 2, 3, 4, 6, and 10). These relapses prompted either initiation of cyclophosphamide and steroids (patient 10), an increase of the dose of cyclophosphamide (patient 7), resumption of cyclophosphamide (patients 1, 2, and 4), or recycling of steroids and azathioprine (patient 3) or steroids alone (patient 6). Trimethoprimsulfate was given to one patient with consistently high titers of c-ANCA (no. 7).

Two years after discontinuing immunosuppression, patient 10 had a severe relapse necessitating mechanical ventilation and dialysis. His primary diagnosis had been wrongly interpreted as a mild vasculitic disease such as SLE. Clinical findings and histological findings in renal and nasal (granuloma) biopsies were now consistent with Wegener granulomatosis. He received combination therapy with cyclophosphamide and steroids, and a total of 20 plasma exchanges, which improved his overall condition but did not improve the renal failure. He was treated with dialysis and, later, kidney transplantation. His first transplanted kidney rejected after 5 years. The loss of this graft was due to chronic rejection with which he had massive proteinuria. He now has a new well-functioning kidney graft and is working full time. His immunosuppression regimen consists of prednisolone, cyclosporin A, and mycophenolate mofetil.

Outcome of therapy, including renal function

The therapeutic efforts in all patients reduced the c- or p-ANCA levels (patients 5 and 10 normalized their levels). During the relapses glomerular clearance rates were permanently decreased in six patients [a decrease from a median of 87 (range 50–110) to 69.5 (0–115) ml/min per 1.73 m^2 (–27%).] The pulmonary infiltrates verified by X-ray disappeared in six patients within 4 weeks (patients 2, 5, 6, 8, 9, and 10) of initiation of immunosuppression, and respiratory function was normalized in nine, graded subjectively (verified by pulmonary function test in patient 2). One patient (no. 10) has a permanently decreased respiratory function and saddle nose. All have returned to "normal life," including three who actively participate in competitive sports (patients 2, 3, and 4).

Discussion

This study shows that Wegener granulomatosis may be easily overlooked in young patients by misinterpreting the symptoms as an infectious disease of the respiratory tract. Having a high index of suspicion, especially when the disease does not respond to early antibiotics or is especially protracted, is helpful. In addition, laboratory tests such as CRP-measurement, leukocyte count, sedimentation rate, urinalysis for hematuria and proteinuria, and serology for detection of antibodies against GBM and ANCA may be particularly helpful in hastening the diagnosis.

Early treatment of the disease may improve the prognosis. In a study of adults with various types of rapidly progressive glomerulonephritis [17], renal recovery was

more likely if treatment was started before dialysis-dependent renal dysfunction developed. This is substantiated with the favorable recovery of kidney function in our patients who were treated before they developed end-stage renal disease. The one exception was one patient whose severe relapse led to end-stage disease. Since the prognosis is less favorable once the kidneys are affected [18], we felt it reasonable to treat this patient with plasma exchange, since ANCA levels were high and the disease active in most of the patients during the acute phase of the disease. The procedure not only lowered the concentration of antibodies quickly but, since we used liquid-stored plasma from healthy donors [15], it replenished lost proteins, such as protease inhibitors, fibrinolytic factors, and α_1-antitrypsin. α_1-Antitrypsin seems to be an important factor for scavenging antibodies [19].

Continuous administration of steroids and cyclophosphamide is purported to be a favorable initial immunosuppressive regimen for the early stage of the disease in adults. This is reported to be more advantageous than pulse doses, stage-adapted treatment, or cyclosporin A [18, 20–25], but there are also data favoring pulse doses of steroid [26] or cyclophosphamide [27]. Our study does not support one or the other, except that addition of cyclosporin A, at a dose of 100 mg daily, to steroids and azathioprine was not effective in suppressing the rise of c-ANCA.

Relapses are common in this disease. Our data indicate that relapses occurred in most patients when they had stopped cyclophosphamide therapy and were on low-dose or no azathioprine and steroids (azathioprine of less than 0.5 mg/kg body weight per day and less than 0.1 mg/kg body weight per day of prednisolone). However, in another study of childhood-onset Wegener granulomatosis by Rottem et al. [11], several patients were off steroids for a median time of 10 months. In that study only 61% suffered from glomerulonephritis. Symptoms were similar to our patients, except that 39% of their patients had hearing loss, 48% eye disease, 78% arthralgia/arthritis, and 48% subglottic stenosis.

We found that serum ANCA were especially increased in the early phase of the disease. In three patients, ANCA normalized with treatment. No relapses have occurred in these patients, although they are still on immunosuppression. In the other patients ANCA are still present. Since the antibodies may be predictors of a relapse [28], this indicates the need for more-frequent evaluations.

The risk of long-term side effects with cyclophosphamide may be a reason to convert patients to azathioprine within 1 year, depending on clinical and laboratory findings, although the risk of relapse should be borne in mind. Cyclophosphamide is likely the preferred re-treatment medication. In the study of Rottem et al. [11], the risk for secondary infections was emphasized. We have had a few such episodes. No malignancies occurred either in their patients or in ours.

Although the inheritance of reduced α_1-antitrypsin production is said to increase the risk for development of vasculitic diseases and yield a worse prognosis [19], only one of our patients suffered from this deficiency. This patient has retained higher titers of ANCA than the others, although the clinical outcome to date has not been worse.

To detect relapses early, we suggest that clinical and laboratory analyses should be performed at least every 3rd month when the patient is in a stable condition. We advocate frequent urinalyses and measurement of serum ANCA levels as part of their assessment. These patients should be followed by physicians specializing in the treatment of immunological diseases.

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LITERATURE ABSTRACTS

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Increased serum and urinary neopterin in nephrotic syndrome indicate cell-mediated immune dysfunction

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T-cell-mediated immune disturbances are likely but not certain to cause the nephrotic syndrome. Because neopterin (NP) production is closely related to activation of cell-mediated immunity, we addressed the question by measuring serum NP concentrations and urinary NP/creatinine (Cr) ratios, as well as by assessing interstitial lymphocyte and monocyte infiltration in the kidney and activation of the same cell types in peripheral blood. Finally, we observed whether urinary NP/Cr ratios in nephrotic syndrome are changed by steroid therapy. Seventy-four patients with primary glomerulonephritis were divided into 4 groups based on presence or absence of nephrotic syndrome and presence or absence of mesangial proliferation and expansion. Serum and urinary NP concentrations were measured chromatographically. Infiltrating cells in the kidney were identified by immunohistochemistry, and activation of peripheral blood cells was examined by fluorescent surface marker antibodies and flow cytometry. Irrespective of the pathohistology of glomeruli, nephrotic groups showed significantly higher urinary NP/Cr ratios and serum NP concentrations. Nephrotic groups also exhibited more activation of T cells in peripheral blood than did nonnephrotic groups or a healthy control group. Serum NP did not correlate with extent of interstitial renal infiltrates. Steroid therapy decreased urinary NP/Cr ratios in steroid-responsive patients, but not in steroid-resistant patients. Increased serum NP concentrations and urinary NP/Cr ratios may reflect disordered cell-mediated immunity in the nephrotic syndrome, irrespective of glomerular histology or interstitial cell infiltration.

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Prothrombin gene expression in rat kidneys provides an opportunity to examine its role in urinary stone pathogenesis

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Urinary form of prothrombin (PT) fragment 1 is the most abundant protein in calcium oxalate crystals generated in human urine. The protein has also been detected in human calcium-containing stones. In its purified form, the protein inhibits calcium oxalate crystal growth and, more importantly, aggregation in aqueous inorganic solutions and undiluted human urine. Recently, PT gene expression has been reported in human kidneys. However, access to human renal tissue for studies is limited, and it is not possible to easily manipulate PT biosynthesis in human subjects. The aim of this investigation, therefore, was to determine whether PT gene expression is present in rat kidneys. Samples of total RNA were isolated from the kidneys, and livers (positive controls) of 12 male hooded Wistar rats. Using reverse transcription-PCR, mRNA corresponding to the thrombin and F1+2 regions of PT was analyzed by agarose gel electrophoresis. The expression of the "housekeeping" gene glyceraldehyde-3-phosphate dehydrogenase was also examined, to determine the availability of amplifiable sustrate in each specimen. The amplified products were also sequenced, to determine their identities. All rat kidneys displayed evidence of expression of the thrombin and F1+2 domains of the PT gene. This similarity between human and rat kidneys allows the possibility of using established rat models of stone disease to evaluate therapeutic strategies to reduce stone formation.