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CLINICAL MANIFESTATION OF PEDIATRIC GRANULOMATOSIS WITH POLYANGIITIS — THE EXPERIENCE OF TWO REGIONS IN POLAND

Abstract: Background: The purpose of this study was to describe clinical manifestations, laboratory findings and outcome of granulomatosis with polyangiitis (GPA) in pediatric patients living in two regions (Southern and Central) of Poland.
Methods: Retrospective analysis of patient hospital records from four large hospitals during a period from 1995 to 2013. Patients with confirmed diagnosis of GPA according to American College of Rheumatology (*ACR*) and *EULAR/PRINTO/PRES* criteria for GPA were analyzed. All patients were subjected to clinical, laboratory, radiological and immunological assessment.
Results: During this 18-year period only 9 children with confirmed diagnosis of GPA (6 girls, 3 boys) were identified. The average age of the disease onset was 12 years (range: 8–16 years). Average delay between first symptoms and diagnosis was approx. 20 months (range: 0–84 months). Organ system involvement at presentation included: kidneys 88.8% (8/9), lungs 77.7% (7/9), ear/nose/throat 55.5% (5/9), gastrointestinal tract 55.5% (5/9), skin 44.4% (4/9), joints 22.2% (2/9), eyes 11.1% (1/9) and nervous system 11.1% (1/9). In 5 children disease course was progressive (constant progression of sinusitis in one case, end-stage renal disease in two, chronic kidney disease stage IV in one and one child died due to alveolar hemorrhage).
Conclusion: The majority of our patients were females. Clinical features of pediatric GPA were similar to those described in adults. None of our patients developed subglottic stenosis and in only 2 children saddle-nose deformity was observed. Although GPA was treated according to contemporary standards care, disease progression was observed in more than a half of children.

Key words: granulomatosis with polyangiitis, Wegener's granulomatosis, vasculitis, children, childhood.

INTRODUCTION

Granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis) is a systemic, necrotizing vasculitis affecting small and medium-sized blood vessels, associated with granulomatous inflammation [1, 2]. Clinically, this disease manifests itself mainly through constitutional symptoms together with the involvement of respiratory tract and kidneys [3]. The disease was first described in 1936 by

a German pathologist — Friedrich Wegener [4]. Nowadays it was proposed to abandon eponyms and use the name of granulomatosis with polyangiitis [4]. Reported annual incidence of GPA varies between 0.5 and 10 cases per one million [5–7]. This disease usually manifests itself in the 6th and 7th decade of life, with similar frequency between genders in adult age [5]. Its occurrence in childhood has also been reported [2, 8–11], with one case diagnosed as early as in the second week of life [12]. The incidence of pediatric GPA is not well established with boys to girls ratio from 1:1 to 1:4 [9]. Disease course in adulthood and childhood can differ [1]. It was suggested that GPA in childhood is more frequently complicated by a subglottic stenosis and nasal deformity [13]. On the other hand, treatment related morbidity and disease progression might be less common in children [13]. GPA in both children and adults is fatal if left untreated. Induction treatment and chronic therapy is crucial for going into remission and maintaining relapse-free disease. Early medical data, obtained before implementation of effective treatment showed mean survival of about 5 months, with more than 90% of patients dying within the first 2 years after diagnosis [7]. The aim of our study was to provide data on pediatric GPA in four major hospitals from Central and Southern Poland [12] and to compare this experience with the limited (mainly case reports) literature.

PATIENTS AND METHODS

We retrospectively analyzed paper medical records of children hospitalized in two large pediatric hospitals (*Polish-American Children's Hospital and St. Louis Children Hospital, both in Cracow*), one department of internal medicine comprising systemic vasculitis reference center (*2nd Department of Internal Medicine, Jagiellonian University Medical College*) also in Cracow (administrative region of Southern Poland — 3.3 million inhabitants) and one pediatric reference center in a central region of the country (*Nephrology Division, Department of Paediatrics and Immunology Polish Mother Memorial Hospital Research Institute* in Łódź). We systematically collected organ specific clinical, laboratory and imaging features at presentation, and at any time, and measures of outcome, such as remission, progression and refractory disease. Analyzed records came from the period of 1995–2013. Patients were entered into the study, if they had at least 2 out of the 4 criteria according to the *ACR or* at least 3 out of the 6 criteria according to the *EULAR/PRINTO/PRES* [11, 14]. However, there are no precise and unequivocal diagnostic criteria and it's important to base the diagnosis on clinical symptoms (such as epistaxis, haemoptysis with cough and dyspnoe, haematuria, general edema, skin lesions), histopathological picture of affected organ (s) and the presence of anti-neutrophil cytoplasmic antibodies (ANCA) [6, 10–12]. In follow-up these signs can also be observed as indicators of GPA relapse.

RESULTS

In all four hospitals, during the period of 18 years, diagnosis of GPA was established in only nine children (6 girls and 3 boys). The average age of disease onset was 12 years (range: 8–16 years). The average delay between first symptoms and diagnosis was approx. 20 months (range: 0–84 months) (Table 1). At presentation the most common symptoms were constitutional ones: weight loss, fever or arthralgia. They were presented in all children except for one. Organ involvement at presentation included: kidneys 88.8% (8/9), lungs 77.7% (7/9), ear/nose/sinuses/throat 55.5% (5/9), gastrointestinal tract 55.5% (5/9), skin 44.4% (4/9), joints 22.2% (2/9), eyes 11.1% (1/9) and nervous system 11.1% (1/8) (Table 2). Later, in the course of the disease, upper and lower airway and kidney involvement prevailed (Table 2). Anti-neutrophil cytoplasmic antibodies (ANCA) were positive in all patients. Their presence, however, is not absolutely necessary for a clinical diagnosis of GPA. Other common laboratory abnormalities at diagnosis included: proteinuria 100% (9/9), hematuria 88.8% (8/9) and abnormal chest X-ray 77.7% (7/9) or chest CT scan 77.7% (7/9). Six children reported chronic rhinitis, but sinusitis in CT or X-ray was confirmed in only four. Our analysis included 18 years of medical history. During this time recommendations for GPA treatment have been constantly changing. Moreover, new immunosuppression regimens were invented. For this reason, and due to delayed diagnosis, each child was treated in a different way. All patients received glucocorticosteroids (GCS)

Table 1

Demographic data, delay in diagnosis, treatment at diagnosis of GPA and disease activity score at presentation.

Number	Gender	Age at diagnosis	Age of onset	Diagnosis delay (years)
Patient 1	W	11	11	0
Patient 2	W	20	13	7
Patient 3	W	13	12	1
Patient 4	M	15	15	0
Patient 5	W	11	11	0
Patient 6	M	10	8	2
Patient 7	W	13	9	4
Patient 8	W	16	16	0
Patient 9	M	14	13	1
Average		13.66	12	1.66

Table 2

Clinical manifestation at diagnosis GPA and at any time after diagnosis of GPA.

		At presentation	At any time
Constitutional symptoms		8	9
	Fever	5	7
	Arthralgias	3	3
	Weight loss	5	6
Renal involvement		8	8
	Glomerulonephritis	8	8
	Requirement for dialysis	2	3
	Kidney tranplatation	0	1
Ear, nose, throat involvement		5	8
	Rhinitis	4	6
	Sinusitis	4	4
	Epistaxis	2	2
	Oral ulcers	2	2
	Otitis media	1	3
	Nasal ulcers	0	0
	Conductive/sensorineural deafness	1	1
	Saddle nose	0	2
	Subglottic stenosis	0	0
	Nasal septal perforation	0	4
Pulmonary involvement		7	8
	Alveolar hemorrhage	3	4
	Nodules	3	4
	Fixed infiltrates	2	2
	Required ventilation	0	1
	Pleuritis	2	2
Eye involvement		1	1

		At presentation	At any time
	Conjunctivitis	1	1
	Scleritis/episcleritis	0	0
	Proptosis	0	0
Skin involvement		4	4
	Petechiae/palpable purpura	4	4
	Urticaria	1	1
	Panniculitis/erythematous nodules	1	1
Arthritis		2	3
Hypertension		1	2
Gastrointestinal involvement		5	5
	Abdominal pain	5	5
	Gastrointestinal bleeding	2	3
Venous thrombotic event		1	1
	Deep vein thrombosis	1	1
	Pulmonary embolus	0	0
Nervous system involvement		1	2

and cyclophosphamide (CTX). In addition, mycophenolate mofetil was used in four children and cyclosporine in one. In four children plasmapheresis was used and two children required chronic hemodialysis. In five patients disease course was progressive in spite of treatment with cyclophosphamide and corticosteroids (constant progression of sinusitis in one case, end-stage renal disease in two, chronic kidney disease stage IV in one, one child died due to alveolar hemorrhage). The child, who died was the youngest of our patients at the time of the first GPA symptoms (8 years of age with 2 years delay in diagnosis). In all five children progression was observed after steroid withdrawal. Progression of sinusitis was mainly a consequence of delayed diagnosis and a very low maintenance dose of corticosteroid (on average 0.1 mg per kg every other day). In one child progression (renal failure) developed on mycophenolate mofetil combined with low-dose steroids. Three (out of four) children who achieved stable and long lasting disease remission were diagnosed and treated without delay. Their remission induction treatment included oral prednisone (0.5 mg/per kg/per day), or periodic infusion

of intravenous high-doses of methylprednisolone, and intravenous cyclophosphamide. In our group of patients, apart from increased risk of infections, no other important clinical side effects of immunosuppressive therapy were observed.

DISCUSSION

Based on our material we are not able to precisely specify the prevalence of pediatric GPA in Poland. Our estimation, however, indicates approximate frequency of about 0.05 per 100 000 children per year in analysed region, which is probably less than the real. In the available literature GPA incidence among children is also not well established, but estimated between 0.03 and 3.2 per 100 000 children per year, with boys to girls ratio from 1:1 to 1:4 [9, 7, 12, 15]. Recently, the number of newly diagnosed cases of GPA constantly increases. This is possibly due to increased awareness of its existence [6, 7, 9]. The median of age at first symptoms in our study was 12 years (range: 8–16 years); higher than that reported by Belostotsky *et al.* (6 years) [12], but lower than those published by Stegmayr *et al.* (17.8 years) [16], Akikusa *et al.* (14.5 years) [2] and Cabral *et al.* (13.975 years) [11]. The adult literature and pediatric study performed by Stegmayr *et al.* suggested an equal male/female ratio or male predominance [16]. However, in our study, similarly to those performed by Belostotsky *et al.* [16], Cabral *et al.* [11] and Akikusa *et al.* [2] predominance of girls was evident. Clinical manifestations of pediatric GPA is usually different than that observed in adults and this is probably the most important reason for delayed diagnosis [1]. In our group of patients the diagnosis was also significantly delayed (by 20 months on average) even though 7 of 9 children at presentation had coexistence of symptoms from upper and/or lower airways and kidneys. This relates to poor awareness of this disease in children among family doctors and pediatricians in the Polish health system, probably because of its rarity in children. Other reasons may include variable course, sometimes limited to constitutional symptoms only [17], which may lead to wrong diagnosis and mistreatment of GPA in children. As an example — two of our patients were initially diagnosed with Schoenlein-Henoch purpura. This caused a substantial delay in the institution of a proper immunosuppressive therapy and in effect in severe and irreversible organ damage (kidney failure and destruction of parasinusal bones, respectively). Constitutional symptoms in children GPA are always presented at the time of diagnosis, accompanied by rhinitis (87%) and kidney involvement (86%) [2, 17]. Frequency of rhinitis and sinusitis may continue to grow during the further course of the disease [2, 12]. Based on the data from 23 GPA children Rottem *et al.* reported that this form of disease is five times more often complicated by subglottic stenosis and two times more often by nasal deformity. Belostotsky *et al.* made a similar observation in their group of 17 children with GPA [12]. In con-

trast, none of our patients developed subglottic stenosis and only in two children saddle-nose deformity was observed. A reason for rare occurrence of above-mentioned symptoms lies probably in a higher age at first symptoms. Ophthalmologic complications and peripheral neuropathy was presented in 11% and 22% of our patients, respectively. This roughly corresponds to the available literature [13].

In summary, even though GPA affects mainly adult patients, pediatricians must be aware of this possibility. Diagnosis should be made as quickly as possible to avoid irreversible organ damage or even death. Especially, when there are symptoms from upper and/or lower respiratory tract and kidneys, GPA should be always considered. We can describe these signs as a diagnostic "red flag".

ABBREVIATIONS AND ACRONYMS

ACR	— American College of Rheumatology
ANCA	— anti-neutrophil cytoplasmic antibodies
EULAR/PRINTO/PRES	— European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society
CTX	— cyclophosphamide
GCS	— glucocorticosteroids
GPA	— granulomatosis with polyangiitis
MMF	— mycophenolate mofetil
WG	— Wegener's granulomatosis

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