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Proceeding Paper

Neurologic Involvement in Granulomatosis with Polyangiitis: A Comparative Study †

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Abstract: Objective: The aim of this study was to describe the presentation and outcomes of patients with granulomatosis with polyangiitis (GPA) presenting with neurologic involvement according to ACR criteria. Methods: Consecutive newly diagnosed GPA patients who had undergone follow-up for at least six months between 2013 and 2018 at Amir-A'lam hospital, Tehran University of Medical Sciences, were retrospectively analyzed. Results: Patients were divided into two groups: those with nervous system involvement at either disease diagnosis or follow-up (89 patients) and those without neurological symptoms until the last follow-up (131 patients). From all patients reviewed in this study, 68 (30.9%) patients died during the follow-up period. Among the deceased patients, 18 (20.2%) were in the non-neurologic group, and 50 (38.2%) were in the neurologic group. The median (IQR) of BVAS in 220 patients was 11.0 (18.0-8.0) in total: 10.0 (14.5-7.50) and 12.0 (21.0-8.0) in the non-neurologic and the neurologic groups, respectively. The score of BVAS in the neurologic group was significantly higher than in the non-neurologic group ($p = 0.039$). Of 131 patients, sensory neuropathy was found in 99 patients (75.5%). In total, 95 patients (72.5%) complained of hearing loss, which was diagnosed as sensory–neural hearing loss; 27 patients (20.6%) complained of headache; 13 (9.9%) had a history of cerebrovascular events; 5 (3.8%) had an episode of seizure or loss of consciousness (LOC); and 3 (2.3%) had mononeuritis multiplex. Two patients (1.5%) were diagnosed with meningitis and two (1.7%) with encephalitis. Conclusion: According to this study, neurological symptoms are an undeniable part of the disease course for GPA patients, and these symptoms are associated with disease severity, prognosis, and response to treatment.

Keywords: granulomatosis with polyangiitis; central nervous system; neurologic manifestations; ANCA

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1. Introduction

Granulomatosis with polyangiitis (GPA) was first reported in 1936 and was formerly known as Wegener granulomatosis. GPA as vasculitis is small to medium in size and is characterized by granulomas [1].

The pathogenesis of GPA involves an anti-neutrophil cytoplasmic antibody (ANCA) mediated by necrotic vasculitis of small vessels, which is manifested by the production of autoantibodies to neutrophil proteins leukocyte proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). Diagnosis is based on clinical manifestations such as involvement of the throat, nose, lungs, and kidneys. The ACR/European League Against Rheumatism

(EULAR) 2017 Interim Classification Criteria are used to diagnose GPA according to the clinical, pathological, and immunological characteristics of the diagnosis [2].

Neurologic involvement is reported in about 20–50% of patients with GPA [3]. GPA can have a variety of clinical manifestations based on the organs involved. The most common manifestations of GPA are related to the upper respiratory tract and renal and pulmonary systems [4]. However, infrequent symptoms, such as cardiac [5], cutaneous [6], and ocular [7] symptoms, could be observed in patients.

Neurological manifestations of GPA are among the most critical symptoms that necessitate immediate treatment. In fact, all items related to nervous system involvement in the Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS-WG) are considered "major", meaning that these items pose an imminent threat to either the patient's life or their vital organs. The neurological manifestations of GPA are reported in 22% to 54% of patients in their clinical course [3,8–11]. However, these manifestations are commonly not the reason for seeking medical help at the onset of the disease. GPA affects the central nervous system (CNS) and peripheral nervous system (PNS). CNS involvement of GPA can result from spreading granulomatous disease from the ear, nose, and throat to neighboring structures in the brain and cranial nerves or the formation of a granuloma primarily in the nervous system. CNS involvement in GPA occurs often in severe forms and is present in about 10% of patients. Symptoms of CNS involvement in GPA can be headache, sensorineural hearing loss (SNHL), seizure, cranial neuropathy, stroke, meningitis, confusion, or loss of consciousness. On the other hand, PNS involvement in GPA results from vasculitis affecting the PNS structures and usually manifests as peripheral neuropathies and mononeuritis multiplex. In this retrospective study, we aimed to compare patients with and without neurologic involvement in a cohort of 220 patients from a single national center, according to demographical, clinical, and serological features.

2. Methods

2.1. Patient Selection and Diagnostic Criteria

Patients who had a clinical and/or histopathologic diagnosis in accordance with the American College of Rheumatology (ACR) criteria and/or the European Medicines Agency (EMA) algorithm and who were diagnosed at the rheumatology clinic, Amir-A'lam hospital, Tehran University of Medical Sciences, from December 2013 to October 2018 were included. All the patients had complete clinical records, including BVAS at the diagnosis and ANCA titer. Demographic data, clinical manifestations, and laboratory results were monitored.

2.2. Clinical and Laboratory Assessments

Patients were divided into two major groups: those with nervous system involvement at either disease diagnosis or follow-up (group 1) and those without neurological symptoms until the last follow-up (group 2). Additionally, patients with neurological symptoms at the diagnosis were distinguished from those who developed symptoms during the disease. Similarly, three significant organs in GPA, including the upper airway, kidney, and lung, were also verified. However, because our hospital is a referral tertiary otorhinolaryngology center, and most patients have otorhinolaryngologic manifestations and the risk of selection bias, upper airway involvement was not included in some analyses. Clinical, serological, radiographic, and, when available, pathological evidence was used to confirm neurological involvement. In this study, cytoplasmic-ANCA below 60 units was considered a negative status, whereas values $\geq$60 units were considered positive. ANCA titers were evaluated by measuring cytoplasmic-ANCA IgG antibody specific to proteinase 3 (PR3) by ELISA.

To evaluate disease severity, the BVAS scoring system was employed. This score was calculated at the disease diagnosis and at each follow-up visit. BVAS scores were also categorized into two groups: total BVAS and specific BVAS scores, which are based on all symptoms of patients regardless of the involved organs and limited scores for neurological symptoms, respectively. Regarding laboratory tests, ANCA was evaluated at time points, if available.

2.3. Statistical Analysis

Descriptive statistics were reported as mean ± standard deviation (SD) for continuous variables and frequency with percentage for categorical variables. Independent t-test and Mann–Whitney U test were used to compare the differences between two continuous variables for normally or not normally distributed variables, respectively. Kruskal–Wallis and One-Way ANOVA tests were also used to compare the difference between more than two groups in variables with normal or not normal distribution, respectively. Pearson's chi-squared test was used to test the relationship between two categorical variables, and the Spearman correlation coefficient was used to evaluate the correlation between two continuous variables. A p-value <0.05 was considered statistically significant, and all statistical tests were two-tailed probability tests. All statistical analyses were conducted using IBM SPSS, Version 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp; Released 2016).

3. Results

Neurological involvement was assessed in 220 patients with a confirmed diagnosis of GPA. In total, 131 patients (76 males and 55 females) presented with neurological manifestations (neurologic group) at initial presentation. The male-to-female ratio was approximately 1:1 in total; it was 1:1.47 in patients with non-neurologic manifestations (non-neurologic group) and 1.38:1 in the neurologic group. The number of male patients in the neurologic group was significantly higher than in the non-neurologic group (Table 1). In the present study, the median (IQR) of follow-up duration was 19.0 (36.0-4.0) months, and 105 patients (47.7%) were followed for more than 24 months.

Table 1. Demographic and characteristics of patients with GPA. Data are shown in number (%). * Chi-square test, ** Mann–Whitney test.

		Non-Neurologic (N = 89)	Neurologic (N = 131)	Total (N = 220)	*p*-Value
Gender	Female Male	53 (59.6) 36 (40.4)	55 (42.0) 76 (58.0)	108 (49.1) 112 (50.9)	0.013 *
Median (IQR) of Age, year	At onset At diagnosis	35.0 (44.0-29.0) 38.0 (46.0-30.0)	44.0 (61.0-32.0) 47.0 (62.0-35.0)	39.0 (57.0-31.0) 43.0 (57.0-32.0)	0.001 ** 0.001 **
Diagnostic delay, year	Median (IQR) Mean (SEM)	1.0 (3.0-0.0) 2.15 (0.30)	1.0 (2.0-0.0) 1.84 (0.31)	1.0 (2.0-0.0) 1.97 (0.22)	0.053 **
Death during follow-up		18/89 (20.2)	50/131 (38.2)	68/220 (30.9)	0.005 *
Time to death, month	Median (IQR) Mean (SEM)	11.0 (45.0-3.0) 25.94 (7.75)	6.0 (16.0-1.0) 17.88 (3.72)	6.0 (36.0-2.0) 19.92 (3.40)	0.164 **
Time to first relapse, month	Median (IQR) Mean (SEM)	6.0 (10.0-3.25) 9.63 (1.78)	8.0 (14.25-3.0) 10.77 (1.39)	6.5 (12.0-3.0) 10.34 (1.09)	0.475 **
BVAS at diagnosis	Median (IQR) Mean (SEM)	10.0 (14.5-7.50) 11.87 (0.66)	12.0 (21.0-8.0) 14.69 (0.73)	11.0 (18.0-8.0) 13.54 (0.51)	0.039 **
PGA at diagnosis	Median (IQR) Mean (SEM)	5.0 (7.0-4.0) 5.14 (0.18)	6.0 (8.0-5.0) 6.29 (0.15)	6.0 (7.0-5.0) 5.94 (0.12)	<0.001 **

The median (IQR) age of patients at the onset of the disease was 39.0 (57.0-31.0) in total: 35.0 (44.0-29.0), and 44.0 (61.0-32.0) years in the non-neurologic and neurologic groups, respectively. Moreover, age at the time of the diagnosis was 43.0 (57.0-32.0) in total: 38.0 (46.0-30.0) and 47.0 (62.0-35.0) years in the non-neurologic and neurologic groups, respectively. The age of patients, both at the onset of symptoms and at the time of diagnosis, was significantly higher in the neurologic group (p = 0.001 and p = 0.001, respectively, Table 1).

There was a delay between the first presentation of the disease, which was reported by the patient, and a definite diagnosis by the clinician. The duration of the diagnostic delay was not significantly different between groups ($p = 0.053$, Table 1). We also compared the delay time between deceased and alive patients in each group and found no significant differences (Table 2).

Table 2. Clinical characteristics comparison between deceased and alive cases of the two groups; * Mann–Whitney test.

		Non-Neurologic (N = 89)			Neurologic (N = 131)		
		Median (IQR)	**Mean (SEM)**	***p*-Value ***	**Median (IQR)**	**Mean (SEM)**	***p*-Value ***
Diagnostic delay, year	Alive Deceased	1.0 (2.0-0.0) 2.0 (4.75-0.0)	1.90 (0.30) 3.16 (0.89)	0.306	1.0 (1.0-0.0) 1.0 (2.0-0.0)	1.81 (0.40) 1.90 (0.52)	0.116
Time to first relapse, month	Alive Deceased	6.0 (11.50-4.0) 5.0 (9.25-3.0)	10.12 (1.98) 5.75 (1.70)	0.631	8.0 (15.25-3.75) 7.0 (9.0-3.0)	11.71 (1.79) 8.31 (1.77)	0.458
BVAS at diagnosis	Alive Deceased	10.0 (14.0-8.0) 10.0 (16.0-6.75)	11.71 (0.69) 12.50 (1.80)	0.959	12.0 (18.0-7.0) 16.0 (26.25-8.0)	13.11 (0.77) 17.22 (1.39)	0.024
PGA	Alive Deceased	5.0 (7.0-4.0) 5.0 (6.25-4.75)	5.39 (0.21) 5.50 (0.38)	0.686	6.0 (6.0-5.0) 8.0 (8.0-6.0)	5.71 (0.17) 7.24 (0.26)	<0.001

From a total of 220 patients reviewed in this study, 68 (30.9%) patients died during the period of follow-up. Among deceased patients, 18 (20.2%) were in the non-neurologic group, and 50 (38.2%) were in the neurologic group. The frequency of death during this follow-up was significantly higher in the neurologic group than in the non-neurologic group ($p = 0.005$). The median (IQR) duration from diagnosis to death was 11.0 (45.0-3.0) and 6.0 (16.0-1.0) months for the non-neurologic group and the neurologic group, respectively. Although this duration was lower for the neurologic group, the difference was insignificant ($p = 0.164$, Table 1).

Comparison of the time to first relapse between two groups and deceased and alive cases during follow-up in non-neurologic and neurologic groups demonstrated no significant differences ($p = 0.475$, $p = 0.631$, and $p = 0.458$, respectively; Tables 1 and 2).

We evaluated the clinical condition based on BVAS and PGA at the time of diagnosis. The median (IQR) of BVAS in 220 patients was 11.0 (18.0-8.0) in total: 10.0 (14.5-7.50) and 12.0 (21.0-8.0) in the non-neurologic and neurologic groups, respectively. The score of BVAS in the neurologic group was significantly higher than in the non-neurologic group ($p = 0.039$). Furthermore, the BVAS score was significantly higher in deceased patients of the neurologic group during follow-up but not in the non-neurologic group ($p = 0.024$ and $p = 0.959$, respectively, Tables 1 and 2).

The median (IQR) of PGA at the time of diagnosis was 6.0 (7.0-5.0) in total and was 5.0 (7.0-4.0) and 6.0 (8.0-5.0) in the non-neurologic and neurologic groups, respectively, but it was significantly higher in the neurologic group ($p < 0.001$, Table 1). Furthermore, the score of PGA in patients in the neurologic group who died from the disease was significantly higher than in alive patients ($p < 0.0001$), but not in the non-neurologic group ($p = 0.686$, Table 2).

Neurologic manifestations are summarized in Table 3. Of 131 patients, 95 patients (72.5%) complained of hearing loss, which is diagnosed as sensory–neural hearing loss (SNHL). Headache was present in 27 patients (20.6%); 13 patients (9.9%) had cerebrovascular events; 5 (3.8%) had an episode of seizure or loss of consciousness (LOC); 3 (2.3%) had mononeuritis multiplex; 2 (1.5%) were diagnosed with meningitis; and 2 (1.7%) with encephalitis (Table 3). However, 114 of 131 (87.0%) patients had one or more cranial nerve involvement, as shown in Table 3.

Table 3. Summary of neurologic manifestations frequency.

Neurologic Manifestation	N (%) N = 131
Hearing loss (SNHL)	95 (72.5)
Headache	27 (20.6)
Cerebrovascular events (vasculitis, thrombosis)	13 (9.9)
Seizure or LOC	5 (3.8)
Mononeuritis multiplex	3 (2.3)
Sensory neuropathy	99 (75.5)
Meningitis	2 (1.5)
Encephalitis	2 (1.5)
Cranial nerve (CN) involvement	114 (87.0)
CN I	4 (3.0)
CN II	2 (1.5)
CN III	7 (5.3)
CN IV	2 (1.5)
CN V	12 (9.0)
CN VI	4 (3.0)
CN VII	39 (29.7)
CN VIII	95 (72.5)
CN IX, X, XI	6 (4.5)
Spinal Cord lesion	0 (0)

Table 4 depicts the status of serologic markers evaluated in patients at the diagnosis of GPA and the comparison between the two groups. In our study, 75.2% of all patients were ANCA (either PR3- or MPO-ANCA)-positive, and this portion was nearly the same for non-neurologic and neurologic patients (Table 4). As shown in Table 4, the frequency of positive PR3-ANCA was higher than MPO-ANCA. The frequency of positive PR3-ANCA and MPO-ANCA was 138/218 (62.7%) and 29/216 (13.2%), respectively. There was no significant difference between the non-neurologic and neurologic groups regarding positive or negative ANCA (Table 4). The median (IQR) of PR3-ANCA was 34.5 (89.0-1.97) in total: 22.0 (73.5-0.0) and 48.0 (99.65-3.95) in the non-neurologic and neurologic group, respectively, which was significantly higher in the neurologic group ($p = 0.029$, Table 4). In contrast to PR3-ANCA, there was no significant difference between the two groups regarding MPO-ANCA titer ($p = 0.079$, Table 4). As expected, the median (IQR) of both ESR and CRP were above the normal range in all patients, and their values were significantly higher in the neurologic group compared to the non-neurologic group ($p < 0.001$ and $p = 0.023$, respectively, Table 4).

We classified patients with one or multiple neurologic manifestations into three groups (Tables 5 and 6). The BVAS score was calculated for each group, and a comparison was performed using the Kruskal–Wallis test (Table 5). There were statistically significant differences between these groups ($\chi^2 = 12.206$, $p < 0.001$), with a mean rank BVAS score of 55.82 for one, 75.66 for two, and 82.63 for more than two neurologic manifestation groups. To find out which groups have a significant difference, we performed a post hoc method to clarify the significant difference between each paired group. Pairwise comparison showed that the differences between one and two neurologic manifestation groups and one and more than one neurologic manifestation group were significant ($p = 0.040$ and $p = 0.007$, respectively, Table 5). Spearman's correlation was used to determine the relationship between the number of neurologic manifestations and BVAS and PR3-ANCA. There was a positive correlation between the number of neurologic manifestations and the BVAS score ($p < 0.001$, $r_s = 0.307$).

Table 4. Serologic markers in patients with GPA, and comparison between non-neurologic and neurologic groups; data are shown in number/total (% of N). * Chi-square test.

		Non-Neurologic (N = 89)	Neurologic (N = 131)	Total (N = 220)	*p*-Value
ANCA	Positive Negative	67/89 (75.3) 22/89 (24.7)	97/129 (74.0) 32/129 (24.4)	164/218 (75.2) 54/218 (24.5)	0.559 *
PR3-ANCA	Positive Negative	51/89 (57.3) 38/89 (42.7)	87/129 (66.4) 42/129 (32.1)	138/218 (62.7) 80/218 (36.4)	0.083 *
MPO-ANCA	Positive Negative	17/87 (19.1) 70/87 (78.7)	12/129 (9.3) 117/129 (89.3)	29/216 (13.2) 187/216 (85.0)	0.026 *
PR3-ANCA	Median (IQR) Mean (SEM)	22.0 (73.5-0.0) 49.03 (6.91)	48.0 (99.65-3.95) 68.81 (7.77)	34.5 (89.0-1.97) 60.73 (5.42)	0.029 *
MPO-ANCA	Median (IQR) Mean (SEM)	0.1 (8.5-0.0) 16.55 (3.93)	0.0 (2.0-0.0) 7.68 (2.33)	0.0 (3.22-0.0) 11.25 (2.12)	0.079 *
ESR	Median (IQR) Mean (SEM)	28.0 (53.0-10.5) 36.94 (3.30)	54.0 (90.0-19.0) 57.73 (3.72)	42.0 (78.0-15.0) 49.24 (2.67)	<0.001 *
CRP	Median (IQR) Mean (SEM)	16.0 (63.0-3.0) 34.56 (4.38)	47.0 (96.0-7.0) 52.87 (4.67)	23.0 (86.0-5.0) 45.45 (3.35)	0.023 *

ANCA: antineutrophil cytoplasmic antibodies, PR3: Proteinase 3, MPO: myeloperoxidase, ESR: erythrocyte sedimentation rate, CRP: C-reactive-protein, IQR: interquartile range, SEM: standard error of the mean.

Table 5. Comparison between BVAS score and number of neurologic manifestations; * Kruskal–Wallis test.

Number of Neurologic Manifestations	N (%) N = 131	BVAS at Diagnosis		*p*-Value *
		Median (IQR)	Mean (SEM)	
One	76 (34.4)	10.0 (18.0-7.0)	12.70 (0.92)	0.002
Two	31 (14.1)	15.0 (22.0-10.0)	16.51 (1.37)	
More than two	24 (10.9)	17.5 (25.5-10.0)	18.54 (1.77)	

Table 6. Comparison between PR3-ANCA titer and number of neurologic manifestations; * Kruskal–Wallis test, corrected *p*-value.

Number of Neurologic Manifestations	N (%) N = 131	PR3-ANCA		*p*-Value *
		Median (IQR)	Mean (SEM)	
One	76 (34.4)	56.0 (100.0-3.5)	78.28 (11.79)	0.531
Two	31 (14.1)	25.0 (68.75-6.55)	56.29 (13.81)	
More than two	24 (10.9)	54.0 (94.92-6.07)	54.89 (8.78)	

Moreover, the PR3-ANCA titer was compared between the neurologic manifestation groups via the Kruskal–Wallis test. A titer above 20 is considered positive. The result revealed no statistically significant difference between the three groups regarding PR3-ANCA titers ($\chi^2 = 1.266$, $p = 0.531$, Table 6). Additionally, there was no correlation between neurologic manifestation and PR3-ANCA titer using Spearman's correlation ($p = 0.47$, $r_s = -0.064$).

4. Discussion

This study shows that 59.5% of patients had at least one neurological symptom during the mean follow-up of nearly two years. This percentage is high compared to the previous studies [3,8–11]. This might be explained by either otorhinolaryngologic involvement in almost all of the included patients or a higher prevalence of nervous system involvement among the Iranian patients with GPA. Although neurological symptoms are less frequently observed among GPA patients, especially at the disease onset, 42.5% of our patients had nervous system involvement when the disease was diagnosed. As previously reported [11–13],

we did not find any gender predilection regarding the presence of neurological involvement or any other evaluated variable.

Diagnostic delay was shorter in patients with neurological involvement, although it did not reach statistical significance. The more severe disease might explain this in such patients. Indeed, those with neurologic symptoms had a significantly more severe disease than those in the other group according to the BVAS score (14.69 vs. 11.87).

Regarding serologic markers, it was found that inflammatory markers (both ESR and CRP) are significantly higher in patients with neurologic manifestations. Furthermore, mean anti-PR3 was higher in the neurologic patients. This serologic test was not only associated with disease severity but also predicted a poor treatment outcome regardless of the specific organ involvement in our GPA patients.

Regarding the frequency of neurological symptoms, cranial neuropathy (especially vestibulocochlear and facial nerves) and headache were the most frequent. Interestingly, all of these were also associated with more severe disease at the diagnosis, and patients with cranial neuropathy had higher c-ANCA titers at the baseline. Previous studies have reported that headache and sensory dysfunction were the most frequent symptoms in GPA patients with neurological involvement [13]. Increasing BVAS could be due to higher scores as the result of neurological symptoms, but c-ANCA titers and the ability of facial nerve involvement to predict the prognosis of patients are interesting findings. In contrast to the previous studies, which found optic nerves to be the most frequently affected, we found the eighth (vestibulocochlear) and the seventh (facial) carinal nerves to be the most common cranial nerves affected [14]. However, these results might be due to the patient's recruitment from a tertiary otorhinolaryngology center.

This study has limitations, such as otorhinolaryngologic involvement in almost all the included patients. Because this involvement is widespread among GPA patients, this might not render our results incorrect. However, considering this limitation, the results of this study seem to be true for GPA patients with otorhinolaryngologic involvement, which also might be true for the other patients. Other limitations are that patients were not followed for further relapses and that only the three common organs (upper airway, kidney, and lung) were considered in our analyses, along with nervous system involvement.

In conclusion, we have found that neurological symptoms are an undeniable part of the experiences of GPA patients; these neurological symptoms are associated with disease severity, prognosis, and response to treatment. To better understand the importance of neurological symptoms in GPA patients, designing prospective and case/control studies with a larger number of patients is required.

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