Standardized Neurologic Evaluations of 128 Patients With Wegener Granulomatosis

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Objective: To assess the frequency and type of neurologic involvement in a cohort of patients with generalized Wegener granulomatosis (WG).

Patients and Methods: In a prospective analysis the clinical, electrophysiologic, radiological, and serologic data of 128 patients have been studied over a median observation period of 19 months (range, 1-60 months).

Results: Sixty-four patients (50%) revealed central or peripheral nervous system involvement. Peripheral neuropathy (PN) affected 56 patients, in 9 cases the central nervous system was involved, and in 6 cases the cranial nerves were involved. Thirty-one patients showed a distal symmetrical polyneuropathy, 25 a mononeuritis multiplex. Within the first 2 years of the disease course 47 of the 56 patients had developed their PN, sometimes as the initial symptom of WG. Patients with PN were significantly more often male (34 of 65 patients) than female (22 of 63 patients, \( P = .04 \)), were significantly older at the onset of WG (median age, 53 vs 44 years; \( P = .001 \)), had a significantly larger disease extent (\( P = .001 \)), and had higher classic antineutrophil cytoplasmic antibody titers (\( P = .002 \)) than neurologically unaffected patients. Response to immunosuppression was moderate concerning peripheral nervous system manifestations.

Conclusions: Peripheral neuropathy is frequent in generalized WG, occurring early in the disease course. As PN can be the first and sole symptom of a beginning systemic vasculitis, it is important that in cases of PN of an unclear origin, interdisciplinary investigations are initiated to detect, treat, and closely follow-up a possible underlying WG, especially as these patients seem to have a more severe disease course.

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PATIENTS AND METHODS

One hundred twenty-eight consecutive patients with generalized WG, treated at our center between January 1, 1991, and June 30, 1997, were included in this study. Preconditions for a patient's inclusion in the study were as follows: (1) the fulfillment of the American College of Rheumatology classification criteria\textsuperscript{a} and the international consensus conference definition for WG;\textsuperscript{1} (2) the disease had to be generalized vasculitic at some stage during the observation period; and (3) the patient had to have been seen at least once by the neurologist (A.C.A.) in our center.

All patients underwent a clinical interdisciplinary (internist, ophthalmologist, otolaryngologist, neurologist [A.C.A.])\textsuperscript{2} and serologic-immunologic assessment at the initial visit at our center and at least every 6 months thereafter. Imaging procedures (high-resolution computed tomography of the chest and cranial magnetic resonance imaging)\textsuperscript{8,9} were performed at the initial visit and every 6 to 12 months during the follow-up period, depending on the severity and extent of the disease. Antineutrophil cytoplasmic antibody titers were determined in all patients every 3 months as described elsewhere.\textsuperscript{10-12}

The activity of WG was assessed according to interdisciplinary clinical, serologic-immunologic, and radiological data. The extent of WG was determined using the disease extent index\textsuperscript{13-16} (Table 1).

NEUROLOGIC EVALUATION

Every patient was seen at least once by the same consultant neurologist (A.C.A.). The neurologic assessment was composed of the patient's neurologic history, a complete neurologic examination, completed, at least at the initial visit, and by electroencephalography, concentric needle electromyography, and nerve conduction studies. If available, the cranial magnetic resonance imaging scan was reviewed. On special indications, lumbar puncture or cerebral angiography were performed. When abnormalities were found, the respective examination was repeated at follow-up visits.

Peripheral nerve (n=4), muscle (n=4), or meningeal (n=1) biopsy specimens were obtained in cases, in which the disease was not otherwise confirmed histologically and the differential diagnoses, involving different treatment strategies, needed to be ruled out.

Peripheral neuropathy (PN) was classified according to Kissel et al.\textsuperscript{17} criteria as mononeuritis multiplex when one or more isolated peripheral nerves were involved with ensuing motor and/or sensory deficits in their distribution, or as distal symmetrical sensorimotor polyneuropathy manifesting as symmetrical stocking-glove distribution of sensory and/or motor deficits. Patients displaying characteristics of both PNs were termed to have “overlapping PN.”

To semiquantify the patients' functional incapacities due to vasculitic PN, a functional disability score (DS) as described by Prinças,\textsuperscript{18} using a scale from 0 to 5 points (Figure 1), was applied at every neurologic visit. This was partly done retrospectively on the basis of case record reviews.

STATISTICAL ANALYSIS

Data were analyzed using the SPSS statistical package (SPSS, Chicago, Ill). Continuous variables are reported as median values and ranges. The Mann-Whitney test was applied for the analysis of differences in the disease extent index and the patient's age at the initial diagnosis of WG and classic ANCA titer in patients with and without PN, for the comparison between patients with distal symmetrical PN and mononeuritis multiplex, for the comparison of the DS initially and at end of the study, as well as patients with and without vasculitic PN. To determine associations between organ manifestations Spearman correlation coefficients were calculated. The association between the incidence of PN and the patients' sex was analyzed using the $\chi^2$ test.

WG were seen a median of 2 times (range, 1-8 times) by the neurologist (A.C.A.) at a 6-month interval (range, 1-30 times). The median neurologic observation time was 19 months (range, 1-60 months). Six patients died during the observation period. Their deaths were not directly attributable to the neurologic manifestation of WG.

CENTRAL NERVOUS SYSTEM

Only 9 (4 males and 5 females) of the 128 patients suffered from CNS manifestations of WG. The spectrum of findings encompassed continuous granulomatous infiltration of the frontobasal cortex, arising from the adjacent paranasal sinuses, cerebral vasculitis, vascular myeloapathy, and meningeal granulomatosis. In the case of meningeal granulomatosis, the diagnosis of WG was established by meningeal biopsy.

Under immunosuppression with oral continuous or pulsed intravenous cyclophosphamide and corticosteroids, complete remission of CNS involvement could be achieved in 6 of the 9 patients, the remaining 3 patients had a long-standing (median, 43 months) partial remission.

CRANIAL NERVES

One or several cranial nerves were involved in the course of WG in 6 (4.7%) of the 128 patients. The optical nerve was affected 4 times, the oculomotor nerve twice, and the trigeminal and facial nerves were affected once each. One patient had a simultaneous affection of all 4 mentioned cranial nerves unilaterally. In most patients the lesions of the cranial nerves were attributable to contiguous infiltration of granuloma from the paranasal sinuses.

PERIPHERAL NERVOUS SYSTEM

Peripheral neuropathy occurred in 56 (43.8%) of the 128 patients. According to the classification of Kissel et al.\textsuperscript{17} symmetrical sensorimotor polyneuropathy in 31 patients could be distinguished from mononeuritis multi-
plex in 25 patients (55.4% and 44.6% of all patients with PN, respectively). All PNs occurred much more frequently in the lower extremities than in the upper extremities. The distribution of affected nerves from mononeuritis multiplex sums to more than the number of thereby affected patients (n = 25).

Table 3. Survey of Pathophysiologic Characteristics of Peripheral Neuropathy in 56 Patients With Generalized Wegener Granulomatosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of Patients</th>
</tr>
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<tbody>
<tr>
<td>All Patients With Peripheral Neuropathy</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Symmetrical sensorimotor polyneuropathy</td>
<td>31 (55.4)</td>
</tr>
<tr>
<td>Mononeuritis multiplex</td>
<td>25 (44.6)</td>
</tr>
<tr>
<td>Afferent nerves†</td>
<td></td>
</tr>
<tr>
<td>Peroneal</td>
<td>23</td>
</tr>
<tr>
<td>Tibial</td>
<td>6</td>
</tr>
<tr>
<td>Sural</td>
<td>2</td>
</tr>
<tr>
<td>Ulnar</td>
<td>6</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>Radial</td>
<td>2</td>
</tr>
<tr>
<td>Axonal neuropathy</td>
<td>41 (73.2)</td>
</tr>
<tr>
<td>Demyelinating neuropathy</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Both types of lesion present</td>
<td>9 (16.1)</td>
</tr>
<tr>
<td>Acute or subacute onset</td>
<td>25 (44.6)</td>
</tr>
<tr>
<td>Chronic prolonged onset</td>
<td>28 (50.0)</td>
</tr>
</tbody>
</table>

*These characteristics were analyzed as follows: (1) according to the classification by Kissel et al.; (2) according to the functional type of lesion; and (3) according to the time course of peripheral neuropathy development. Percentages do not sum to 100 because some patients’ conditions could not be classified.

†In several patients more than 1 nerve was affected, therefore, the number of affected nerves by mononeuritis multiplex sums to more than the number of thereby affected patients (n = 25).

lesions were seen. The condition of 4 patients could not be classified, owing to conflicting data.

At diagnosis of PN, 46 of the 56 patients showed symptoms due to peripheral nerve lesions: paresthesia, numbness, burning pain, and paresis. The remaining 10 patients did not display any symptoms, their PN was solely diagnosed by clinical and electrophysiologic assessment. The clinical findings of the neurologic examination at diagnosis of PN are summarized in Table 4. The most common findings were impairment of touch sensation and loss of tendon reflexes, which usually occurred very early. The median time span between the first symptoms from PN and the diagnosis of PN was 3 months (range, 1-251 months).
At the time of diagnosis of WG, 31 (55.4%) of the 56 patients who eventually developed PN had already had a manifested neuropathy. Twenty-four months after diagnosis of WG, the PN had emerged in 47 (85.2%) of the 56 patients (Figure 2). From the second year after diagnosis of WG onward, the incidence of a PN decreased to 1 patient per year. In 11 patients the PN was one of the first symptoms indicative of generalized WG. In another 2 cases PN was the only initial symptom of WG followed by other organ manifestations. In 1 case PN preceded other organ manifestations by 3 years.

The functional impairment by PN was assessed by DS18 (Figure 1). At the initial visit the median DS was 2 points (range, 1-5 points). Patients with mononeuritis multiplex at the diagnosis of vasculitic PN displayed higher DS values (median, 3 points; range, 1-5 points), compared with patients with symmetrical polyneuropathy (median, 2 points; range, 1-3 points; \( P = .004 \)). There was a statistically significant positive correlation of the disease extent (disease extent index) with the severity of the PN as expressed by the DS \( (r = 0.4, \ P = .004) \).

All patients received immunosuppressive treatment, also with regard to the severity of all other vasculitic organ manifestations. Therapy for induction of remission consisted of either daily oral (48 of 56 patients) or 3, weekly pulsed (4 of 56 patients) cyclophosphamide or low-dose methotrexate (4 of 56 patients) plus corticosteroids, respectively.

At the end of the follow-up period, the neurologic examination revealed a decline of motor defects and to a lesser extent of sensory defects (Table 4). The mean DS score declined significantly from 2.36 points at the start of the study to 2.04 points at the end of the study \( (P = .001) \) (Figure 1), whereas the median DS remained at 2 points throughout the study. There was a statistically significant positive correlation between the DS at the initial and final presentations \( (r = 0.6, \ P = .001) \). Patients with mononeuritis multiplex experienced a more marked functional recovery (decline of median DS from 3 points to 2 points, \( P = .001) \), especially of motor impairment, eg, quadriplegia, at the end of the study than did patients with symmetrical polyneuropathy (no statistically significant reduction in DS). Only 1 patient achieved complete clinical and electrophysiologic reconstitution \( (DS=0 \) points) at the end of the study.

**CHARACTERISTICS OF THE PATIENTS WITH PN AS OPPOSED TO THE PATIENTS WITHOUT PN**

Men were significantly more often affected than women from vasculitic PN (34 of 65 men vs 22 of 63 women, male-female ratio=1.55/1, \( P = .04 \)), although the male-female ratio in the entire cohort of 128 patients was almost equal (65:63). The relative risk to develop PN in the course of generalized WG was 1.5 for male (95% confidence interval, 1.04-2.07) and 0.7 for female patients (95% confidence interval, 0.46-0.98). At the diagnosis of WG, patients with PN were significantly older than patients without PN (53 vs 44 years, \( P = .001 \)) (Table 5).

Patients with PN showed a significantly greater disease extent of WG than patients without PN (disease extent index, 11 vs 7, \( P = .001 \)), even after correcting the number of affected organs for the presence of PN. Figure 3 shows the different organ manifestations in the patients with and without PN. The median of the maximal classic ANCA titer within the study period was significantly higher in patients with PN than without PN (1:256 vs 1:128, \( P = .002 \)).
the end of the study: (1) patient age 50 years or older at the diagnosis of WG (P<.001); and (2) renal (P<.001), skin (P<.001), or cardiac (P=.005) involvement within WG. The relative risk for a patient with glomerulonephritis from WG to also develop PN was 1.6 (95% confidence interval, 1.32-2.22).

This study on the incidence and further course of neurologic manifestations within generalized WG showed that half (50%) of the patient cohort (N=128) displayed nervous system involvement. Peripheral neuropathy was by far the most frequent finding (43.8% of the total cohort), occurring rather early in the disease course. In a surprising number of cases, PN was the first or even the sole symptom of generalized WG.

In accordance with the literature19 (Table 6), CNS involvement of WG was rare in our cohort, but if present, it can cause severe impairment. Central nervous system vasculitis is still a diagnostic challenge, as no reliable factors of differentiation from other vascular lesions, such as artherosclerosis, are available. Contrarily, contiguous or de novo cerebral granulomatous masses are reliably disclosed by imaging procedures.

Cranial nerve affection was also scarce in our cohort (6 [4.7%] of the 128 patients), supporting the findings of Nishino et al5 (Table 6). Contrarily, in earlier reports cranial nerve affection, if at all differentiated from CNS involvement, occurred much more frequently (26% in the cohort studied by Anderson et al23). Mostly, contiguously spreading granulomatous masses rather than vasculitic lesions account for this lesion.

The relative infrequency of CNS and cranial nerve manifestations in our cohort is most likely explained by the use of systematic interdisciplinary diagnostic procedures including cranial magnetic resonance imaging that allow early detection and treatment of any vasculitic and/or granulomatous lesions, thus preventing advanced CNS and cranial nerve affection.

Vasculitic PN, which was the main interest in this study, occurred considerably more frequent in our cohort than reported by others (Table 6). Furthermore, as opposed to previous reports, describing mainly mononeuritis multiplex,5,23-26 most PNs in our cohort (31 of 56 patients) were classified as having distal symmetrical polyneuropathies. This again may be a result of systematic neurologic and electrophysiologic investigations, enabling the detection of vasculitic PN at a stage where it does not yet produce impressive clinical signs and symptoms. This may especially apply to early distal symmetrical polyneuropathy. Peripheral neuropathy may, thus, not have been recognized, unless patients are subjected to systematic neurologic investigation, as was the case in our cohort.

The pathogenic mechanism of vasculitic PN is an occlusion of nutrient blood vessels resulting in hypoxic ischemic injury of the thereby supplied peripheral nerves.27 Depending on the size and number of vessels affected, the following 3 patterns of peripheral nerve damage can be distinguished: (1) mononeuritis multiplex, due to large vessel affection and subsequent whole nerve trunk infarction; (2) asymmetrical sensorimotor neuropathy, caused by smaller vessel involvement leading to discrete fascicular infarction; and (3) distal symmetrical sensorimotor neuropathy, caused by diffuse peripheral nerve ischemia,27 eg, through necrotizing capillaritis in the course of WG.

The main functional result of the ischemic nerve lesion is axonal degeneration. Progressing damage results in segmental loss of the myelin sheath.25 Accordingly, in

![Figure 3. Spectrum of organ manifestations in the patient group with peripheral neuropathy (PN) (n=56) and without PN (n=72). Single asterisk indicates patients with PN who displayed more frequent renal involvement (K) (r=0.30, P<.001); double asterisks, cardiac involvement (H) (r=0.21, P=.001); E, ears, nose, and throat; L, lung; K, kidney; EY, eye; A, arthralgias and/or arthritides; B, constitutional symptoms; H, heart; S, skin; GI, gastrointestinal tract; P, peripheral nervous system; and C, central nervous system.](image-url)

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Patients</th>
<th>Patients With Neurologic Involvement, No. (%)†</th>
<th>Patients With CNS Involvement, No. (%)</th>
<th>Patients With Cranial Nerve Affection, No. (%)</th>
<th>Patients With Peripheral Neuropathy, No. (%)</th>
<th>Patients With Distal Symmetrical Polyneuropathy, No. (%)</th>
<th>Patients With Mononeuritis Multiplex, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walton,21 1958</td>
<td>56</td>
<td>ND</td>
<td>4 (7 necropsy)‡</td>
<td>ND</td>
<td>16 (29)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Drachman,4 1963</td>
<td>104</td>
<td>56 (54)</td>
<td>ND</td>
<td>27 (26)</td>
<td>ND</td>
<td>14 (14)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Anderson et al,5 1975</td>
<td>249</td>
<td>64 (26)</td>
<td>44 (18)§</td>
<td>ND</td>
<td>65 (26)</td>
<td>27 (11)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Nishino et al,5 1993</td>
<td>324</td>
<td>109 (34)</td>
<td>13 (4)</td>
<td>ND</td>
<td>21 (7)</td>
<td>53 (16)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Hoffman et al,22 1992</td>
<td>158</td>
<td>36 (23)</td>
<td>13 (8)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>24 (15)</td>
</tr>
<tr>
<td>This study</td>
<td>128</td>
<td>64 (50)</td>
<td>9 (7)</td>
<td>2 (2)</td>
<td>6 (5)</td>
<td>56 (44)</td>
<td>31 (24)</td>
</tr>
</tbody>
</table>

*ND indicates data not available; CNS, central nervous system; and PNP, polyneuropathy.
†If the numbers in subsequent columns sum more than in this column, it is because some patients have more than 1 neurologic abnormality.
‡n = 54.
§Number includes patients with cranial nerve affection.
our cohort, axonal lesions were found much more frequently than demyelinating ones (Table 3).

Variability in clinical expression depends on the acute-ness of the onset of ischemia, the extent of collateral circulation, and the degree of tissue sensitivity to ischemia.3 Fujimura et al28 found that myelinated nerves of a large diameter are more vulnerable to ischemia than smaller and unmyelinated nerves. This is the correlate of mononeuritis multiplex, mainly affecting larger myelinated nerve trunks as the peroneal, ulnar, and median nerve.24,26

In a great proportion of patients with WG, PN was one of the first symptoms or even the sole presenting symptom of generalized WG, occurring probably even months before the diagnosis of WG was made. Early manifestation of peripheral nerve involvement in the course of necrotizing vasculitides has also been observed by others.5,10,20 Early detection of PN in our cohort is reflected by only moderate neuropathic symptoms, expressed by a rather low median DS of 2 points. It must also be realized, that there may be no other symptoms of WG when PN is first diagnosed. This warrants a careful assessment of patients seen with PN of unknown origin beyond the neurologic field, such as interdisciplinary clinical examination and autoimmune serologic studies, including ANCA testing, to detect potential other vasculitic organ involvement. This is important for the appropriate and timely treatment of the PN and other potential vasculitic organ manifestations.

Unexpectedly, elderly male patients were preponderantly affected by vasculitic PN. The regenerative capacity of their peripheral nerves may be expected to be naturally reduced and additional atherosclerotic vasculopathy of their peripheral nerves may be expected to be partly explained by the concept of "subinfarctive ischemic damage," suggesting that vasculitis can produce demyelination or functional disruption of conduction without necessarily resulting in axonal infarction.33

Davies and colleagues20,24 confirmed the persistence of mainly sensory symptoms despite of clinical and electrophysiologic amelioration of neuropathic signs in a patient cohort of mixed vasculitic PN. As recovery of vasculitic PN is a result of immunosuppression of vasculitic activity and inevitable subsequent suppression of regenerative capacity of the affected nerve,25 it is conceivable that reconstitution of peripheral nerve function is time-consuming and not always complete.

Tailoring the duration of immunosuppression according to the patient's symptoms and reports of vasculitic PN is difficult, as the symptoms do not always allow the physician to distinguish between residual defects and still ongoing vasculitic activity. Nerve conduction studies and concentric needle electromyography are helpful concerning this problem since in vasculitic PN remission does not necessarily mean clinical reconstitution of nerve function. However, a decision on continuation or cessation of therapy should never depend on the picture of vasculitic PN alone but must consider the course of all other disease manifestations.

Despite the rare achievement of complete remission in vasculitic PN, prompt initiation of immunosuppression is warranted, to prevent the disease from spreading further within the nervous system and toward other organ systems. This is important, as we could demonstrate that patients with PN suffer from a significantly greater disease extent, more severe organ manifestations (1.6-fold elevated risk for glomerulonephritis) paralleled by a higher ANCA titer than patients without vasculitic PN. Therefore, patients with vasculitic PN need close interdisciplinary surveillance of their disease course and adaptation 50 years or older of treatment.

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