Alerts, Notices, and Case Reports

Central Nervous System Polyarteritis Nodosa

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POLYARTERITIS NODOSA is the prototypic necrotizing vasculitis capable of affecting multiple systems. Neurologic involvement occurs in 50% to 75% of patients.[1-9] Peripheral neuropathy is the most frequent form of neurologic involvement. The significance of central nervous system involvement is less appreciated. In this report, two illustrative cases of central nervous system polyarteritis nodosa are described, and the English-language literature describing central nervous system manifestations of the disorder is reviewed. The first case has been reported elsewhere in greater detail.[10]

Report of Cases

Patient 1

The patient, a previously healthy 25-year-old man, was admitted to the hospital because of diffuse abdominal pain for four months and a 12-kg weight loss. He complained that worms were crawling out of his nose and boring into his eyes. Family and friends reported no previous abnormal behavior or ideation. He had a history of intravenous amphetamine abuse but said he had not used any drugs in the three months preceding admission.

On physical examination, the patient was in moderate discomfort. His blood pressure was 150/100 mm of mercury, pulse 128 beats per minute, and temperature 38°C (100.4°F). The heart, lungs, and abdomen were normal. A neurologic examination revealed normal sensory and motor function but abnormal mentation as noted. A hemogram was normal except for a leukocyte count of 18.8×10^9 per liter with a normal differential cell count. The admission chemistry panel results were normal except for an albumin level of 21 grams per liter (2.1 grams per dl). A urinalysis showed rare white cells and a trace amount of protein. The results of a spinal fluid examination were normal. A computed tomographic (CT) scan of the head and the findings of a cerebrospinal fluid (CSF) examination were both normal. Tests for hepatitis B and human immunodeficiency virus antibodies were negative. An abdominal CT scan showed a possible right renal cortical infarct.

During his hospital stay, paresthesias of his right leg developed, followed by a right foot drop and a left wrist drop. Abdominal angiography showed multiple mesenteric, hepatic, and renal aneurysms consistent with polyarteritis nodosa. Extravasation from a ruptured renal artery aneurysm was also noted.

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The treatment consisted of a regimen of prednisone and cyclophosphamide and gelatin sponge (Gelfoam) embolization of the ruptured aneurysm. His abdominal pain lessened and completely resolved a week later at the time of discharge. Active hallucinations had also stopped by that time. Two days later, he had three generalized tonic-clonic seizures in rapid succession. A second evaluation revealed no other cause for the seizures. Treatment with phenytoin sodium was begun, and no additional seizures occurred.

On a regimen of cyclophosphamide and tapering doses of prednisone, there has been no recurrence of his visual hallucinations and there has been a complete return to normal of his mentation. His wrist drop has resolved and the foot drop has lessened. The phenytoin therapy was discontinued at six months with no recurrence of seizures at one year.

Patient 2

The patient, a 31-year-old woman, was seen because she had had left lower quadrant abdominal pain, left flank pain, and fever up to 39°C (102°F) for a week. Treatment of a presumed urinary tract infection was begun with a combination of trimethoprim and sulfamethoxazole, but her symptoms persisted.

During the next week, the patient had persistent elevations of her diastolic blood pressure to levels between 110 and 120 mm of mercury and a left foot drop developed. A renal angiogram showed bilateral aneurysms, and a diagnosis of polyarteritis nodosa was made. The treatment consisted of methylprednisolone sodium succinate, 1 gram given intravenously, and cyclophosphamide, 125 mg given orally, for three consecutive days. A regimen of prednisone, 60 mg a day, was then started, and the cyclophosphamide was continued. Labetalol hydrochloride and nifedipine therapy was used to control her blood pressure.

Five days later she had four generalized tonic-clonic seizures within a four-hour period. A CT scan of her head and the results of a CSF examination were normal. The findings of a chemistry screen were normal except for a blood urea nitrogen level of 12.1 mmol per liter of urea (34 mg per dl; normal, 3.0 to 6.5 mmol per liter) and a creatinine level of 150 μmol per liter (1.7 mg per dl; normal, 50 to 110 μmol per liter). Her seizures were controlled with phenytoin therapy.

Over the ensuing five months, she has been maintained on a regimen of cyclophosphamide and tapered off prednisone and phenytoin. She has remained seizure-free, her foot drop has diminished, and there has been no further evidence of active vasculitis.

Literature Review

A MEDLINE literature search was done for reports of central nervous system manifestations of polyarteritis nodosa published in the English-language literature between January 1965 and May 1988, postdating the modern classification of vasculitis by Zeek.[11] Articles in which Wegener's granulomatosis was identified or where histologic changes of granulomatous vasculitis were found were excluded when calculating the frequency of specific manifestations.

Clinical Manifestations

The association of polyarteritis nodosa and peripheral neuropathy is well established. Peripheral neuropathy de-

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomographic
EEG = electroencephalogram

velops in 30% to 70% of patients with the disorder.[1-9] Central nervous system (CNS) manifestations have been less definitively described. Even the frequency of CNS involvement is controversial. Older studies have found CNS involvement to be infrequent. In an autopsy investigation, Rose and Spencer identified evidence of polyarteritis of the brain in only 4% of 54 patients.[12] Arkin cited CNS involvement in only 8% of cases.[13] In a review of patients with polyarteritis nodosa who were observed at the Mayo Clinic, only 4 of 130 patients had CNS manifestations; all were cerebrovascular accidents.[14] In more recent studies, the frequency of CNS involvement has ranged from 15% to 65% of cases of the disorder.[1-3,6-9] Table 1 summarizes the frequency of CNS involvement in published reports appearing after 1975.[1-9]

Polyarteritis nodosa of the central nervous system differs from peripheral neuropathy in its time of presentation. Peripheral neuropathy is frequently the presenting manifestation. In contrast, CNS disease tends to occur two to three years after the diagnosis of polyarteritis.[3,15,16] Central nervous system disease is evident at presentation in 10% to 28% of patients in whom CNS disease will develop.[3,8] All of these patients had other stigmata of polyarteritis nodosa at the time of presentation. We are not aware of any reported cases of this disorder presenting as isolated CNS disease.

Three major forms of CNS polyarteritis nodosa occur: diffuse encephalopathy, focal neurologic deficits, and seizures. These differ in their frequency, pathogenesis, and natural history. They are discussed individually.

Diffuse Encephalopathy

The most frequent form of CNS dysfunction is a diffuse encephalopathy characterized by the loss of intellectual capacity, disorientation, and occasionally psychosis with visual hallucinations. As in patient 1, the onset of the encephalopathy is often insidious. In an early series of polyarteritis nodosa, 23% of patients without clinically evident neurologic disease had abnormalities identified with formal psychological testing.[15] The incidence of clinically diagnosed encephalopathy has ranged from 8% to 20%.[1-4,6]

Complications of the disorder such as hypertension or uremia must be excluded as causes of an altered mental state associated with polyarteritis nodosa. High-dose corticosteroid administration may contribute to the occurrence of psychosis in these patients. Immunosuppressive therapy may increase the frequency of CNS infection. No consistent laboratory abnormalities are found in the patients with encephalopathy. Computed tomographic scans are normal, CSF examinations are unremarkable except for a mild increase in protein content, and an electroencephalogram (EEG) shows only nonspecific slowing. From our review, it appears that the encephalopathic syndrome resolves more readily and more reliably than other CNS manifestations.[3,16] The identification of a vasculitic cause depends on the exclusion of other treatable causes of encephalopathy in a patient with polyarteritis nodosa.

The pathogenesis of the encephalopathy has not been established. The reversibility of the condition and the normal findings on CT scan, CSF analysis, and an EEG suggest a functional, not a structural cause. Older studies describe perivascular inflammation present at autopsy.[17,18] It is postulated that this inflammatory process leads to neuronal ischemia that results in encephalopathy.

Focal Deficits

The second pattern of CNS involvement is that of focal deficits involving the cerebrum, the cerebellum, or the brain stem. In the studies reviewed, the incidence of focal deficits ranged from 3% to 24%.[1-5] In autopsy series, patients with antemortem focal neurologic findings had evidence of cerebral infarction or hemorrhage at necropsy.[17,18] In the only study that consistently recorded CT findings, three of five patients with focal neurologic deficits had infarction or hemorrhage identified on CT.[3] Although some recovery has been seen in these patients, all have residual deficits. Some authors have noted that cerebrovascular accidents tend to occur late in the course of polyarteritis nodosa and often at a time when the vasculitic process is quiescent.[3,5] They theorize that the cerebrovascular events in these patients result from a weakening of the cerebral vasculature subsequent to earlier acute inflammation.[3,5] Cerebrovascular accident was the cause of 23% of deaths in a recent series of 53 patients with polyarteritis nodosa.[5]

TABLE 1.—*Nervous System Involvement of Polyarteritis Nodosa**

Reference	Patients, No.	Peripheral Neuropathy, %	CNS Dysfunction, %	Encephalopathy, %	Focal Deficits, %	Seizures, %
Leavitt and Fauci, 1986[1]†	22	51	23	10	11	4
Duffy et al, 1976[2]	10	30	30	10	10	10
Moore and Fauci, 1981[3]†	25	56	40	20	24	20
Leib et al, 1979[4]†§	64	72	..	11	3	11
Cohen et al, 1980[5]‖	53	60	..	..	6	4
Scott et al, 1982[6]‡‖	37	62	24	8	..	..
Travers et al, 1979[7]‖	17	59	41	..	..	..
Sack et al, 1975[8]‡‖	40	38	28	..	..	..
Guillevin et al, 1988[9]‡‖	165	68	18	..	..	..

CNS = central nervous system

*All reports that included Wegener's granulomatosis were excluded.
†Patients with more than 1 CNS manifestation were counted in each subtype.
‡Includes patients with lung involvement; excludes other types of vasculitis.
§Unable to identify number of individual patients with CNS polyarteritis nodosa.
‖Insufficient detail to identify number of each subtype of CNS involvement.

Seizures

Seizures, either focal or generalized, occur in 4% to 20% of cases of polyarteritis nodosa.[1-5] The seizures may be multiple.[1-5,19] Electroencephalograms are either normal or show nonspecific slowing.[2,3,15,16] The pathogenesis is unclear but is most likely related to the acute inflammatory process, not chronic structural change, since there are no reports of chronic seizure disorder developing as a sequela of polyarteritis nodosa. Therefore, anticonvulsant therapy should be limited to the period of active vasculitis, rather than continued long term.

Treatment

Most polyarteritis nodosa-induced deaths occur in the initial 6 to 12 months of disease.[4-6] This observation has led to the recommendation for early aggressive therapy. Corticosteroid and cytotoxic agents remain the cornerstones in the treatment of the disorder.[1,20-22]

In two retrospective studies, 28 untreated patients with polyarteritis nodosa had a 13% five-year survival, whereas the five-year survival was 50% for the 144 patients who received prednisone.[4,14] Treatment was at the discretion of individual physicians, and comparison of the two groups is difficult. Sack and co-workers noted increased survival for patients treated with prednisone in doses greater than 40 mg compared with patients given less than 20 mg daily.[8]

Whereas corticosteroids are widely thought to be of benefit,[4,6,8,14,22] controversy exists with regard to the optimal role for cytotoxic agents. While several investigators would reserve the use of cytotoxic agents for patients who do not respond adequately to corticosteroid therapy,[5,9] others consider the alkylating agent cyclophosphamide the drug of choice, particularly for patients with severe disease.[6,21,23] Scott and associates reported on 37 patients with polyarteritis nodosa-type vasculitis.[6] The type of therapy in this study was assigned in a nonrandomized manner by the patients' physician. Of patients receiving no therapy, 50% were alive in six months compared with 67% six-month survival for patients given corticosteroids. Of eight patients treated with combined corticosteroid and cyclophosphamide, six were alive and well 1.5 to 6 years following treatment. In a similar nonrandomized study, Leib and colleagues found five-year survival rates of 12% for supportive care, 53% with corticosteroid therapy, and 80% when an immunosuppressive agent was added to the corticosteroid regimen.[4] It is argued that corticosteroids given alone may produce only a partial remission and may mask smoldering disease activity.[22,23] This may result in progressive damage. In an uncontrolled study at the National Institutes of Health, only three patients died from a group of 17 receiving immunosuppressive therapy (cyclophosphamide for 16 and azathioprine for 1).[23] Two of the three deaths were the result of chronic effects of vasculitis, which was active during therapy with prednisone alone. Leavitt and Fauci consider azathioprine to be less effective than cyclophosphamide in inducing remission but note that it may be useful for maintaining remission.[1]

An assessment of the benefits of therapy for CNS polyarteritis nodosa is complicated by an absence of controlled studies. Also, because CNS involvement usually does not lead directly to death, benefits of therapy must be measured by less definitive end points. At this time, the relative merits of treatment with steroids alone versus steroids combined with cyclophosphamide in CNS involvement can be assessed only on the basis of anecdotal reports. In a report of the clinical course of 25 patients with polyarteritis nodosa, Moore and Fauci describe five patients in whom encephalopathy developed.[3] Encephalopathy developed in four of these patients while they were on steroid therapy. The encephalopathy cleared completely in all five patients when cyclophosphamide was added to their regimen. In the same report, five patients had cerebrovascular accidents while receiving corticosteroids. In contrast, no progression of disease activity was noted once cyclophosphamide was added to the therapeutic regimen. Based on this favorable experience and because of the gravity of neurologic complications as well as the limited healing capacity of the nervous system, these authors recommend limited courses of early aggressive therapy, to include cyclophosphamide, for patients with neurologic polyarteritis nodosa.

The usual oral dose of cyclophosphamide is 2 mg per kg of body weight in conjunction with prednisone, 60 mg daily. The combination is necessary initially because the maximal effect of the cyclophosphamide occurs only after two weeks. The prednisone therapy should be converted to an every-other-day regimen and tapered within the first few months of treatment. Doses of cyclophosphamide should be adjusted so that the leukocyte count remains greater than 3×10^9 per liter and the neutrophil count greater than 1.5×10^9 per liter.[22] After a year of remission, tapering of cyclophosphamide may be attempted.[1]

Only anecdotal information supports the parenteral use of "pulse" steroids or cyclophosphamide or of plasma exchange. Necrotizing vasculitis and acute renal failure were recently reported in a single patient who had reversal of his renal insufficiency by initial treatment with intravenous pulses of both methylprednisolone and cyclophosphamide.[24] There have also been reports on the response and safety of using plasma exchange in the treatment of polyarteritis nodosa.[25-27]

The choice of therapy must be based on considerations of toxicity as well as efficacy. The considerable long-term morbidity of prednisone therapy is well known and will not be detailed.[21,23] Cyclophosphamide therapy may lead to life-threatening infection, acute nonlymphocytic leukemia, and infertility.[28,29] Hemorrhagic cystitis occurs in about 15% of patients.[30] The cumulative risk of bladder cancer in a group of patients with non-Hodgkin's lymphoma treated long term with cyclophosphamide was 10.7% 12 years after the initiation of therapy.[31] The bladder cancer may develop years after the cessation of the cyclophosphamide administration, and long-term surveillance has been recommended.[30,31]

The potential benefits of combined prednisone and cyclophosphamide outweigh the corresponding risks for patients with CNS polyarteritis nodosa. Until further information is available regarding the efficacy of intermittent bolus steroid and cyclophosphamide therapy, we recommend a daily regimen of this combination.

In addition to treating the vasculitic process, clinicians must aggressively detect and manage general medical problems that may occur in these patients. Blood pressures should be followed closely and hypertension treated appropriately. Infections may occur in acutely ill patients as a result of immunosuppressive therapy and the invasive procedures to which they may be subjected.[29] Close surveillance and timely therapy are crucial.

Limitations of Review

It is clear more information needs to be gathered about CNS involvement in patients with polyarteritis nodosa. Articles vary in their method of patient selection.[32-35] The final

diagnosis and listing of clinical manifestations are dependent on physicians' clinical acumen and the degree of diagnostic intervention. Authors may have included patients who would now be classified as having Wegener's granulomatosis, Churg-Strauss vasculitis, or hypersensitivity vasculitis. Case reports may be published because of unusual manifestations and may not accurately reflect the spectrum of the disorder.[36] Thus, certain clinical features may be overestimated. In addition, reports from major academic centers may suffer from referral bias—that is, the most complex of cases are disproportionately represented. Review articles may provide qualitative rather than quantitative information.[16,37] Most critical, no well-controlled randomized studies have evaluated the relative merits of the various therapeutic options.

A prospective series that incorporates modern diagnostic criteria, includes a standardized clinical evaluation, and makes use of newer diagnostic modalities, such as magnetic resonance imaging, would add much to our knowledge of CNS polyarteritis nodosa. Similarly, a prospective randomized therapeutic trial comparing corticosteroid therapy with a regimen of corticosteroids combined with cyclophosphamide would greatly clarify the optimal approach to treating this form of the disease.

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