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Case 6-2003: A Nine-Year-Old Girl with Progressive Weakness and Areflexia

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PRESENTATION OF CASE

A nine-year-old right-handed girl from the United Arab Emirates was admitted to the hospital because of progressive weakness and areflexia.

The patient had been well until three months earlier, when a gait difficulty developed. A physician diagnosed a vitamin deficiency, and treatment was instituted but without benefit. One month later, progressive weakness and a slapping gait developed; she was unable to walk on her toes and could barely rise from a full squat. Another physician found that she had both proximal and distal weakness in the arms and legs, that the reflexes were absent throughout, and that the sensation of vibration at the feet was diminished. A lumbar puncture was performed; the level of protein in the cerebrospinal fluid was 48 mg per deciliter, with 3 white cells per cubic millimeter. She received a five-day course of intravenous immune globulin (0.4 g per kilogram of body weight per day).

Four months before admission, the patient had traveled to Egypt with her family, and she had won ribbons at her school's field day. Three and a half months before admission, she had had a "common cold." Her parents had not noticed any diarrhea, fever, rashes, or bowel or bladder dysfunction. Her parents were distant cousins. Her birth and development had been normal, and her medical history was unremarkable. She was the eldest of four children, and the rest of the family was well. She had received all her immunizations.

The girl's condition did not improve, and she was brought to the United States. On admission to this hospital, the temperature was 36.6°C, the pulse was 101, and the respirations were 20. The blood pressure was 107/69 mm Hg, and the weight was 29 kg.

Physical examination showed no abnormalities except for abnormal results on neurologic testing. There was weakness in the arms proximally (strength, 4/5) and distally, in the forearm and intrinsic hand muscles (strength, 4+/5). The strength of the legs was 3/5 proximally and 2/5 distally. The deep-tendon reflexes were absent, with the exception of a trace reflex in the right triceps. The sensation of vibration was diminished greatly at the toes, was abnormal at the knees, and was moderately impaired at the fingers. Proprioception was abnormal in the toes and slightly abnormal in the fingers. The sensation of temperature was preserved. The patient required assistance to walk and had a steppage gait with a wide base. Examination of the cranial nerves showed no abnormalities. She had never been able to whistle.

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Laboratory studies were performed (Table 1). Magnetic resonance imaging (MRI) studies of the brain and entire spine, obtained after the administration of gadolinium, were normal; there was no abnormal parenchymal or leptomeningeal enhancement. The signal intensity and morphologic features of the spinal cord were normal. There was abnormal nodular enhancement along the surface of the conus as well as clumping and enhancement of the nerve roots distally.

Nerve-conduction studies performed in the right arm and in both legs revealed that the sural responses were absent, that the ulnar sensory response was normal, and that the amplitude of the median sensory response was low, with preserved conduction velocity. The motor responses were abnormal throughout, with conduction velocities as slow as 5 m per second and conduction block in the median forearm segment. The F waves were absent throughout, and needle electromyography showed substantial active denervation in the leg, with no recruitment of motor units in the gastrocnemius muscle.

Immune globulin (0.4 mg per kilogram per day) was administered intravenously for five days. The patient was discharged and thereafter underwent daily physical and occupational therapy and weekly clinical examinations. After three weeks, she was readmitted to this hospital. Physical examination revealed that the strength of the arms was 3/5 proximally and 3–/5 distally; on hip flexion the strength was 3+/5, on ankle dorsiflexion 2/5, and on movement of the toes 1/5. The reflexes remained as they had been on admission. The sensation of temperature remained intact, but the sensation of vibration continued to be abnormal, and proprioception was absent in the feet. A third course of intravenous immune globulin was administered, at the same dose as the previous two courses.

A diagnostic procedure was performed, and additional therapy resulted in improvement in the patient's clinical status.

DIFFERENTIAL DIAGNOSIS

Dr. Howard W. Sander: The salient clinical features in this case are the stepwise progression of symmetric motor and sensory impairment over a period of approximately four months and the almost complete absence of reflexes. The weakness and sensory changes were more prominent distally than proximally. These clinical findings strongly suggest that the patient has a sensorimotor peripheral polyneuropathy. The presence of weakness in the absence of muscle atrophy suggests that the polyneuropathy is mostly demyelinating. The impairment in proprioception and in the sensation of vibration suggests that there is dysfunction of the large, myelinated, sensory fibers. The conduction block indicates a failure of impulse propagation across a nerve segment with relatively preserved axons. This conduction block, along with the severe, diffuse slowing of motor-nerve conduction velocities, clearly implicates an acquired demyelinating process. The discrepancy between sensory-nerve and motor-nerve conduction velocities also suggests the presence of acquired demyelination.[1]

The protein levels in the cerebrospinal fluid were 48 mg per deciliter two months before admission and 58 mg per deciliter on admission. Normally, cerebrospinal fluid protein levels are high at birth, decline sharply during the first year of life, and then slowly increase. In a nine-year-old child, a conservative upper limit of normal is 33 mg per deciliter.[2] Given the white-cell counts of 3 per cubic millimeter in the cerebrospinal fluid from the first lumbar puncture and 6 per cubic millimeter from the second lumbar puncture, there is clearly a cytoalbuminologic dissociation (an increase in the level of protein in the cerebrospinal fluid that is disproportionate to the increase in the white-cell count in the cerebrospinal fluid).

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

In this case, the patient's history, the findings on physical examination, and the laboratory findings, especially with the history of an antecedent common cold, are consistent with a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy.

The diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy are a subject of debate. In 1991, a set of stringent consensus criteria for the diagnosis of this disease was published to promote consistency in research.[3] The essential clinical criteria include combined motor and sensory dysfunction affecting at least two limbs, with hyporeflexia or areflexia. The dysfunction must occur over a period of at least two months, to rule out the Guillain–Barré syndrome. The course of dysfunction may be progressive or relapsing. Detailed electrodiagnostic criteria ensure documentation of peripheral-nerve demyelination. Pathological criteria include nerve demyelination on electron

microscopy or on teased-nerve studies. The white-cell count in the cerebrospinal fluid should be below 10 per cubic millimeter in patients who are seronegative for the human immunodeficiency virus (HIV).

This patient appears to meet these stringent clinical, electrodiagnostic, and cerebrospinal fluid criteria, although the findings on nerve biopsy are not yet known.[3] In routine practice, chronic inflammatory demyelinating polyradiculoneuropathy may be clinically diagnosed and therapy appropriately administered, even if the research criteria established by the American Academy of Neurology are not met.[3] Furthermore, some autoimmune neuropathies are not accompanied by demonstrable evidence of demyelination.[4,5]

The MRI findings in patients with chronic inflammatory demyelinating polyradiculoneuropathy include enhancement of the cauda equina.[6,7] In some cases, the lesions may enhance after the administration of gadolinium; this enhancement may have a multifocal nodular pattern, as in this case, or it may have a diffuse linear pattern.[6] Nerve-root clumping, however, has not been reported. When MRI scans are evaluated for enhancement of the cauda equina, it should be recalled that the dorsal-root ganglion and the intraforaminal nerve roots are normally enhanced.[6]

The nerve-root enhancement in this case presumably reflects disruption of the blood–nerve barrier at the root level. This finding supports the use of the term "polyradiculoneuropathy" in chronic inflammatory demyelinating polyradiculoneuropathy; the current literature on this disorder often uses the terms "polyneuropathy" and "polyradiculoneuropathy" interchangeably.

Hereditary Causes of Demyelinating Neuropathy

Although this patient appears to have an acquired case of demyelinating neuropathy, several hereditary possibilities in the differential diagnosis should be mentioned. Hereditary neuropathy with a tendency toward pressure palsy, also known as tomaculous neuropathy, is associated with a mutation in the gene encoding peripheral myelin protein 22. In this condition, there is a predisposition for entrapment neuropathy, and there may be features of multifocal demyelination, including conduction block. In the current case, this is an unlikely diagnosis because of the four-month progression to severe quadriparesis, the conduction block at a site not predisposed to entrapment, and the absence of a family history.

Table 1. Results of Laboratory Tests on Admission.

Variable	Result
Hematologic and blood chemical tests	
Complete blood count	Normal
Electrolytes	Normal
Lactate dehydrogenase (U/liter)	619
Aspartate aminotransferase (U/liter)	70
Alanine aminotransferase (U/liter)	16
Alkaline phosphatase	Normal
Bilirubin	Normal
Creatine kinase (U per liter)	43
Erythrocyte sedimentation rate (mm/hr)	47
Serologic tests	
Antinuclear antibody	Positive (titer, 1:80) with a homogeneous pattern
Rheumatoid factor (IU/ml)	<30
Antibody to heterophil	Negative
Antibody to *Borrelia burgdorferi*	Negative
Antibody to *Campylobacter jejuni*	Negative
Hepatitis C antibody	Negative
Hepatitis B antibody	Consistent with previous immunization
Hepatitis A antibody	Positive, indicating past infection
Antibody to Epstein–Barr virus	Positive, indicating past infection
Serum protein electrophoresis	Normal pattern with a slight, diffuse increase in gamma globulin
Thyrotropin (μU/ml)	2.83
Urinary tests	
Bence Jones protein*	None
Arsenic (μg/liter)†	104
Cerebrospinal fluid	
Total protein (mg/dl)	58
Glucose (mg/dl)‡	73
Cell count (per mm³)	7 red cells and 6 white cells (96% lymphocytes and 4% neutrophils)§
Cultures	No bacteria
Protein electrophoresis¶	No oligoclonal bands

* The study was performed in a specimen concentrated by a factor of 50.
† The study was performed in a 24-hour specimen. The normal range is 0 to 80 μg per liter.
‡ To convert the value for glucose to millimoles per liter, multiply by 0.05551.
§ The measurement was made in the fourth tube of the blood sample.
¶ The study was performed in a specimen concentrated by a factor of 31.

Other hereditary demyelinating neuropathies, such as Charcot–Marie–Tooth disease (type 1, 3, or X) could be considered. However, electrophysiological examination in a patient with Charcot–Marie–Tooth disease would reveal both sensory and motor conduction slowing without demonstrable conduction block. The rapid rate of progression and the absence of a family history in the case under discussion also argue against that disorder. In addition, children with Charcot–Marie–Tooth disease type 3, also known as Dejerine–Sottas disease, usually present by the age of two years.

There are hereditary demyelinating neuropathies that are associated with multiorgan and central nervous system dysfunction. Refsum's disease, which involves phytanic acid storage, usually appears during childhood and can cause demyelinating neuropathy and a cytoalbuminologic dissociation. This diagnosis can be ruled out in the current case because of the absence of pigmentary retinopathy, ataxia, and hearing impairment. Metachromatic leukodystrophy, adrenoleukodystrophy, and adrenomyeloneuropathy are also unlikely diagnoses, given the normal findings on brain and spinal cord imaging, the absence of upper-motor-neuron signs, and the patient's sex.

Vitamin Deficiencies

A deficiency of vitamin E, thiamine, pyridoxine, vitamin B_{12}, or niacin may cause neuropathy, and this patient was initially treated for a vitamin deficiency. However, these deficiencies are unlikely diagnoses in this case: the patient did not have a response to treatment for a vitamin deficiency, and the findings on general physical and cranial-nerve examinations were normal, as were the complete blood count and electrolyte levels. The absence of gastrointestinal and central nervous system signs also argues against a vitamin deficiency. A pyridoxine overdose may cause a predominantly sensory neuropathy, but such an overdose was not a feature of this case.

Arsenic Poisoning

Arsenic poisoning may mimic chronic inflammatory demyelinating polyradiculoneuropathy in terms of the clinical history and electrophysiological findings, but arsenic poisoning more commonly induces an axonal polyneuropathy. Acute or chronic arsenic-related neuropathy is almost universally associated with nonneurologic signs and symptoms, which include nausea, vomiting, diarrhea, fever, pancytopenia, splenomegaly, renal dysfunction, arrhythmias, desquamation, alopecia, and Mee's lines. This child's weakness progressed during the period when she was being examined weekly by a physician, without observation of any of these systemic signs. In the absence of associated multiorgan dysfunction, arsenic poisoning seems unlikely. The slight elevation in her urinary arsenic level is therefore difficult to interpret. The urinary level of this compound may increase in normal persons after they have eaten a meal containing seafood.[8]

Infections

With regard to primary infectious processes, the case history includes serologic evidence of hepatitis A and Epstein–Barr virus infections at undetermined times. Acute hepatitis A infection is unlikely, however, because the level of alanine aminotransferase was normal. Infection with cytomegalovirus or HIV is associated with chronic inflammatory demyelinating polyradiculoneuropathy. However, there is not enough supporting evidence to diagnose any of these infections. Lyme disease, hepatitis B, and hepatitis C were ruled out by serologic testing. Parasitic infections are unlikely because of the absence of eosinophilia, the normal level of creatine kinase, and the absence of multiorgan involvement. Diphtheria could be considered, because it causes a demyelinating neuropathy and tachycardia. However, this patient had received her immunizations and had no cranial-nerve, upper-airway, or skin changes to support this diagnosis. Infection with human T-cell lymphotrophic virus type I may cause progressive quadriparesis, but such infection is accompanied by upper-motor-neuron signs.

Other Disorders

Some systemic illnesses have uncommon presentations that can mimic that of chronic inflammatory demyelinating polyradiculoneuropathy. These include lymphoma,[9] sarcoidosis,[10] hepatitis A,[11] porphyria,[12] and mitochondrial disorders.[13] However, these illnesses are unlikely as the sole process in the context of severe weakness without multiorgan abnormalities.

CONCURRENT ILLNESSES

The research criteria[3] that I previously mentioned divide chronic inflammatory demyelinating polyradiculoneuropathy into two categories: an idiopathic disorder and a disorder with concurrent illness. Concurrent illnesses that have been reported are listed in Table 2. This patient had several abnormal labo-

ratory values that suggest the presence of a concurrent illness. Her serum lactate dehydrogenase and aspartate aminotransferase levels were elevated, there was a mild polyclonal gammopathy, the titer of antinuclear antibody was abnormal, the erythrocyte sedimentation rate was slightly elevated, and there was mild tachycardia. All of these findings are nonspecific, but taken together they suggest an underlying illness such as a collagen vascular disease, a neoplasm, or a parainfectious or granulomatous process (Table 2).

Among these illnesses, systemic lupus erythematosus seems to be supported by the most evidence: the patient's sex, the abnormal titer of antinuclear antibody, the relatively high incidence of the disease, and the well-described association of lupus with chronic inflammatory demyelinating polyradiculoneuropathy.[14] Cytomegalovirus infection is suggested by the patient's history of an antecedent common cold. In one study, there was a striking 48 percent rate of seropositivity for anticytomegalovirus antibodies in patients with chronic inflammatory demyelinating polyradiculoneuropathy, as compared with 8 percent in control patients. This provides support for the molecular-mimicry hypothesis of chronic inflammatory demyelinating polyradiculoneuropathy.[15]

Table 2. Concurrent Conditions Reported in Association with Chronic Inflammatory Demyelinating Polyradiculoneuropathy.

Diabetes
Human immunodeficiency virus infection or acquired immunodeficiency syndrome
Monoclonal gammopathy of undetermined significance
Monoclonal or biclonal gammopathy (e.g., osteosclerotic myeloma, anti-MAG antibody; plasmacytoid lymphocytic lymphoma, or macroglobulinemia)
Central nervous system demyelination
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective-tissue disorder
Ankylosing spondylitis
Temporal arteritis
Sarcoidosis
Hypothyroidism
Autoimmune thyroiditis
Thyrotoxicosis
Autoimmune hemolytic anemia
Vasculitis
Cryoglobulinemia
Pernicious anemia
Iritis
Eczema
Inflammatory bowel disease
Castleman's disease
Lymphoma
Malignant melanoma
Hodgkin's disease
Squamous-cell carcinoma
Colon cancer
Acute hepatitis A
Chronic hepatitis B
Hepatitis C
Sjögren's syndrome
Celiac disease
Cytomegalovirus
Amyloidosis
Charcot–Marie–Tooth disease
Bone marrow or organ transplant
Gout
Asthma
Addison's disease
Subhepatic abscess
Micronodular cirrhosis
End-stage renal disease
Nephrotic syndrome
Interstitial nephritis

TREATMENT OF CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Controlled trials have shown the efficacy of corticosteroids, plasma exchange, and intravenously administered immune globulin.[16-19] Uncontrolled studies have also suggested the efficacy of cyclosporin, interferon alfa, azathioprine, and cyclophosphamide.[20-27] The rate of response to therapy has ranged from 30 to 80 percent. Maintenance therapy is often required. A relatively good prognosis is reported in children, but progression of the disease for more than three months is thought to indicate a worse prognosis.[28,29] Corticosteroid administration is usually the treatment of choice.[30]

No large series of nerve-biopsy studies have been reported in childhood chronic inflammatory demyelinating polyradiculoneuropathy. However, in three small studies, demyelination was seen in every nerve.[7,28,29] I assume that a sural-nerve biopsy was performed in this case to establish a diagnosis and to assess the possibility of a concurrent illness.

Additional therapy in this case probably consisted of an immunomodulating agent, which would treat both the chronic inflammatory demyelinating polyradiculoneuropathy and the possible concurrent illness. Of the available therapies, corticosteroids were probably chosen because of the ease of administration and relatively lower potential for side effects.

Dr. E. Tessa Hedley-Whyte: Dr. Dawson will present the electromyographic findings.

Dr. Katherine T. Dawson (Neurology): The electromyographic findings indicated the presence of an acquired demyelinating polyneuropathy and met the stringent research criteria for chronic inflammatory demyelinating polyradiculoneuropathy.[3]

The first electromyographic study revealed a severe conduction block of the right median nerve (85 percent), with temporal dispersion, and severe conduction slowing in the forearm (25 m per second). The median distal latency was prolonged in comparison with the ipsilateral ulnar distal latency.[31] The conduction velocity was normal in the ulnar forearm segment (60 m per second) but was very slow in the elbow segment (20 m per second). Because the ulnar groove is a potential site of mechanical entrapment, this focal slowing cannot be used as a definitive criterion for a generalized acquired demyelinating process. There is also temporal dispersion of the proximal ulnar waveforms. Both tibial-nerve motor-response amplitudes were very low and showed marked temporal dispersion. On the right side, stimulation at the knee did not evoke a recordable tibial response, and the tibial F waves were absent.

Sensory-nerve conduction studies revealed that the sural responses were absent bilaterally, that the right ulnar response was normal, and that the amplitude of the right median response was slightly decreased. The discrepancy between the relatively normal right median sensory response and the severely affected right median motor response, with conduction block, indicates the presence of a nonuniform, demyelinating, neuropathic pathophysiologic process.

Needle electromyography revealed prominent fibrillations in the tibialis anterior and gastrocnemius muscles. In the right gastrocnemius, voluntary motor-unit potentials were not recordable. This finding, combined with the presence of a recordable tibial motor-nerve conduction response after ankle stimulation, suggests the presence of a conduction block in the axons serving the gastrocnemius muscle.

CLINICAL DIAGNOSIS

Chronic inflammatory demyelinating polyradiculoneuropathy.

DR. HOWARD W. SANDER'S DIAGNOSES

Chronic inflammatory demyelinating polyradiculoneuropathy.

? Concurrent collagen vascular disease, such as systemic lupus erythematosus.

PATHOLOGICAL DISCUSSION

Dr. Hedley-Whyte: A sural-nerve biopsy was performed. Examination of the biopsy specimen revealed accumulations of chronic inflammatory cells, mainly lymphocytes and occasional plasma cells,

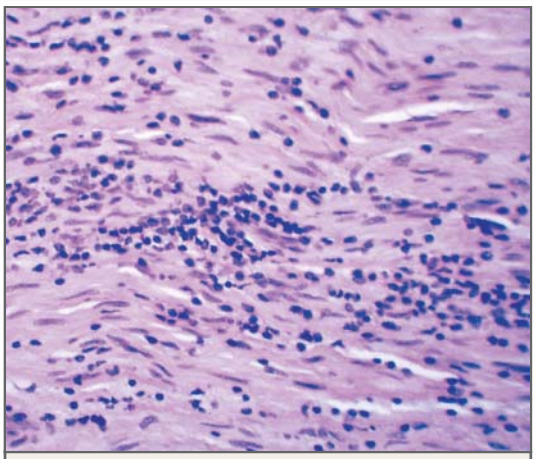

Figure 1. Longitudinal Section of a Sural-Nerve Biopsy Specimen (Hematoxylin and Eosin, ×250).
There is diffuse infiltration of lymphocytes and plasma cells.

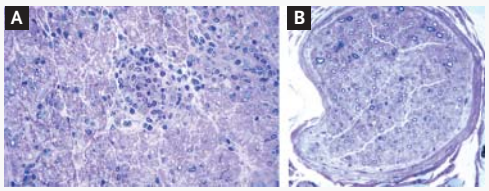

Figure 2. Cross Section of Adjacent Nerve Fascicles (Toluidine Blue Stain, ×250).
One fascicle has almost total loss of myelinated fibers (Panel A); others have an overall decrease in myelinated fibers, particularly the fascicles that are thickly myelinated (Panel B). Perivascular inflammatory cells are visible in Panel A. The section, 1 μm in thickness, was embedded in Epon resin.

throughout the nerve (Fig. 1). Special stains for tubercle bacilli, fungi, and other organisms were all negative. Myelin sheaths were virtually absent from most of the fascicles. There was no evidence of vasculitis. In Epon-embedded sections that were 1 μm thick, some fascicles were devoid of myelinated fibers; other fascicles were less badly damaged (Fig. 2). Although this distribution suggests ischemia as a cause, immunohistochemical staining for neurofilament revealed many axons in a segment of the nerve (Fig. 3) that had no apparent myelin on Luxol fast blue staining, a finding indicating a demyelinating process. In addition, examination of teased-nerve preparations revealed numerous myelin ovoids, which indicate axonal degeneration as well as demyelination (Fig. 4). The teased-nerve preparation did not disclose evidence of either segmental demyelination or remyelination.

Electron-microscopical examination of the nerve revealed almost no normally myelinated fibers. Some axons were thinly myelinated for their size (Fig. 5A), and there were Schwann cells filled with myelin debris (Fig. 5B). Although many normally unmyelinated axons (C fibers) were still visible, the presence of collapsed Schwann-cell lamellae indicates that there was a loss of unmyelinated fibers in

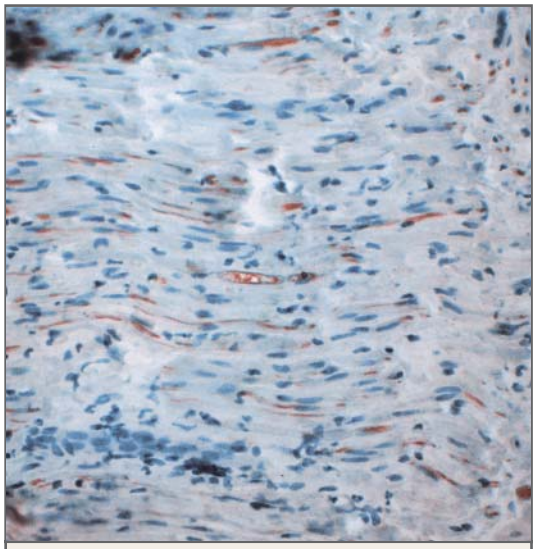

Figure 3. Immunoperoxidase Reaction for Neurofilament on a Longitudinal Section of a Sural-Nerve Biopsy Specimen (×230).

There are intact axons (brown) in a demyelinated area.

Figure 4. Preparation of Teased-Nerve Fibers, Showing Myelin Ovoids, Indicative of Axonal Degeneration (Black Granules) (×230).

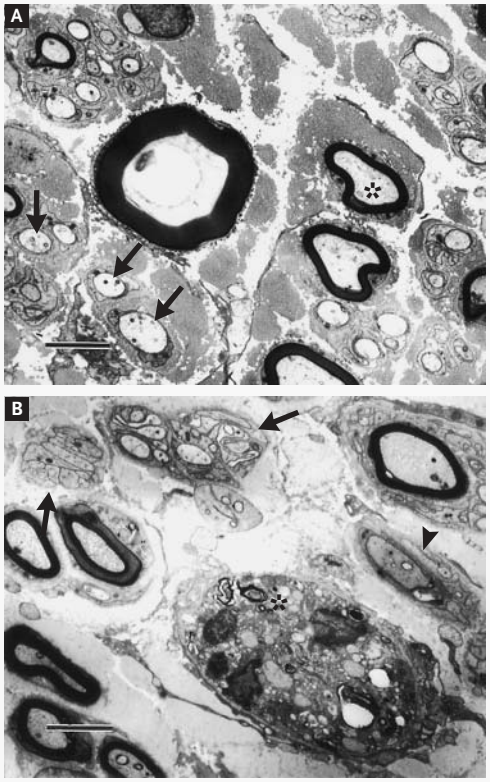

Figure 5. Electron Micrographs of the Sural-Nerve Biopsy Specimen (×2870).

The micrograph in Panel A shows that the axons have relatively thin myelin sheaths (asterisk), a finding suggesting remyelination. Some relatively large, unmyelinated axons, indicative of demyelination (arrows), are also visible. Panel B shows a Schwann cell filled with myelin debris (asterisk). Stacks of cytoplasmic lamellae (arrows) indicate a loss of unmyelinated axons and myelinated axons. There is an "onion bulb" (arrowhead) surrounding an unmyelinated axon, a finding indicating demyelination. The bars represent 3.48 μm.

addition to a loss of myelinated fibers. There was also early onion-bulb formation (i.e., formation of layers of Schwann cells around an unmyelinated axon), with a central unmyelinated axon that was too large to be a C fiber, suggesting that it was a demyelinated axon.

This is a mixed picture in which demyelination with inflammation is the predominant characteristic, fulfilling the criteria for chronic idiopathic demyelinating polyradiculoneuropathy in a subacute phase.[32] The degree of inflammation in this case is unusual for chronic idiopathic demyelinating polyradiculoneuropathy. We did not see any evidence of vascular abnormalities.

Dr. Dawson: After the biopsy, corticosteroid therapy was initiated. Within four days, a beneficial response was observed, and the patient was transferred to the rehabilitation service. She was discharged after one month, while still receiving corticosteroids. Several weeks later, the results of a neurologic examination were essentially unchanged, but Cushing's syndrome had developed. A repeated electrodiagnostic study revealed further deterioration. The median and ulnar motor amplitudes, which initially had been nearly normal, were now very low. The conduction velocities had decreased to 6 m per second. The tibial-nerve motor responses were no longer elicitable. The minimal latency of the ulnar F wave was very prolonged (63 msec).

Intravenous immune globulin therapy was reinstituted, with a loading dose of 2 g per kilogram over a period of five days, followed by weekly maintenance infusions. Corticosteroid therapy has been continued, despite concerns about side effects, since the patient is still very severely affected clinically and since she had an initial response to the administration of corticosteroids.

Dr. Sander: When axon loss is noted in a specimen from a sural-nerve biopsy, it should be recalled that the site of original injury is unknown. Injury to the nerve at the level of the root, plexus, or proximal nerve trunk may lead to Wallerian degeneration of the distal axon segment. The observed distal axon loss may therefore be related to either a local process or a more proximal site of injury.

ANATOMICAL DIAGNOSIS

Chronic inflammatory demyelinating polyradiculoneuropathy.

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