

Chronic demyelinating polyneuropathy associated with eosinophilia-myalgia syndrome

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Abstract

Eosinophilia-myalgia syndrome (EMS) is a newly described syndrome associated with use of L-tryptophan. A neuropathy with features of axonal degeneration has also been described in conjunction with EMS. Demyelinating polyneuropathy is not a well recognised association of the syndrome. The two patients with EMS reported presented with profound weakness and sensory loss and were found to have clinical, electrophysiological and pathological evidence of a chronic demyelinating polyneuropathy. The concurrence of this neuropathy with EMS, as well as several other features of their illness, is suggestive of an immune mediated mechanism in the pathophysiology of EMS.

In the autumn of 1989 the eosinophilia-myalgia syndrome (EMS) was recognised to be associated with the use of L-tryptophan. The key features of this syndrome are a raised peripheral blood eosinophil count (usually > 1000 cells/mm³); severe generalised myalgia; and absence of any infection or neoplasm that could account for the first two.¹ Numerous other features may accompany these signs and symptoms, including sclerodermatous skin changes, dyspnea, cough, and inflammatory infiltrates in skin, muscle, and other tissue.

More than 1200 cases of EMS associated with L-tryptophan have been reported.² The most frequently reported neurological manifestations of EMS are weakness and pain. These symptoms have usually been attributed to myopathy and fasciitis. Several brief statements have suggested that neuropathy may be seen in EMS.^{1,3,4} There are two detailed reports of associated peripheral neuropathy: one suggests a disorder predominantly due to axonal degeneration,⁵ and the other presents electrophysiological data consistent with demyelination but pathological data showing severe axonal degeneration.⁶ We reported two patients with L-tryptophan associated EMS and chronic demyelinating motor and sensory polyneuropathy. The syndrome may easily be mistaken for myopathy associated with EMS. Several clinical and pathological features of EMS associated demyelinating neuropathy suggest an immunopathogenesis.

Case Reports

Case 1

In May 1988 a 45 year old woman was given

L-tryptophan, 3 g nightly, for insomnia and persistent lower back pain. Sixteen months later she developed a macular rash on her forearms, thickening of the skin, and persistent low grade fever associated with increasing fatigue and weakness. In addition, she developed severe lancinating pains in her hands and feet. The peripheral blood eosinophil count was > 4000 cells/mm³. A full thickness skin biopsy showed fasciitis with lymphocytic infiltrates. A diagnosis of tryptophan induced EMS was made, L-tryptophan was discontinued, and prednisone 25 mg daily was started. The rash and fevers abated and the peripheral eosinophilia disappeared; however, the pain persisted, and the weakness progressed such that by December 1989, she was bed bound. Her history revealed hypothyroidism and a remote episode of "fever of unknown origin". The family history was negative for any neuromuscular disease. She was admitted to the Johns Hopkins Hospital in February 1990. On admission she was an ill appearing woman with thickened, leathery skin. Her hands and face were swollen, and her feet and legs were oedematous and discolored. There were flexion contractures at the elbows and knees, and the "groove" sign (branching pattern of collapsed veins, reflecting the absence of dermal fibrosis at venous sites, next to otherwise sclerodermatous skin⁷) was present on her arms. Her lungs were clear to auscultation but breath sounds were diminished. She had mild facial diplegia and ptosis but full extraocular movement. Proximal and distal limb muscles were weak: MRC grade 3 in the arms and proximal muscles of the legs and MRC grade 2 in distal leg muscles. She was unable to walk or sit up independently. Deep tendon reflexes were absent. Plantar responses were flexor. All sensory modalities were diminished in a stocking-glove pattern.

Arterial blood gas analysis showed hypoxia and a partially compensated respiratory acidosis (Pao₂ 71 mm Hg, Paco₂ 74 mm Hg, and pH 7.31). Vital capacity was 1.0 litre. A search for autoantibodies showed that the anti-acetylcholine receptor antibody titre was 1.66×10^9 M (normal $< 0.13 \times 10^9$ M), and the IgG anti-GM1 ganglioside titre was 2216 by ELISA (normal < 60 ; levels > 60 commonly associated with autoimmune disorders^{8,9}). Normal laboratory results included the following: complete blood count, routine serum chemistries, complement, antinuclear antibodies, rheumatoid factor, creatine kinase, vitamin B₁₂, folate, hepatitis B and HIV serologies, and cerebrospinal fluid analysis.

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Received 20 November 1990
and in final revision
13 August 1991.
Accepted 21 August 1991

The absolute eosinophil count was 53 cells/mm³. A diagnosis of EMS and demyelinating motor and sensory polyneuropathy was made based on data presented below.

The patient was given prednisone 80 mg daily. Over the following month her skin became softer, less indurated and discolored, and less wooden, but her strength continued to deteriorate, particularly in the hands, and her sensory loss progressed to include the forearms. After she had received high dose steroids for two months her vital capacity was 0.5 litres. Nerve conduction studies showed further reduction in both distal and proximal compound muscle action potential amplitudes. She was readmitted to the hospital and given intravenous gammaglobulin 0.4 g/kg/day for five days while being maintained on high dose steroids. After this treatment was completed her vital capacity improved to 1.1 litres, and her strength improved to the point that she was able to sit up independently and walk short distances with help. Over the ensuing year the patient was maintained on prednisone, 30–50 mg/day, with little functional improvement but no apparent progression of her disease.

Case 2

A 68 year old woman with a history of vitiligo and hypothyroidism had been taking L-tryptophan for insomnia, 1 g nightly, for more than two years. In August 1989 she stopped the medication when she was notified by the manufacturer of potential dangerous side effects. One month later she developed parotid swelling and a dry mouth. An antinuclear antibody titre was 1:160, and a lip biopsy showed sialoadenitis. In October 1989 she noticed dysphagia, limb weakness, and foot pain. She became unable to eat solid foods. In December she was admitted to a local hospital, severely dehydrated and profoundly hypothyroid. She was rehydrated, placed on thyroid replacement, and discharged. She was readmitted in January 1990 because of severe dehydration and a recent 18 kg weight loss. She was able to swallow only clear liquids. Normal laboratory results were obtained for rheumatoid factor, antibodies to double stranded DNA, erythrocyte sedimentation rate, and concentrations of creatine kinase, vitamin B₁₂, and aldolase. Pulmonary function tests showed a restrictive pattern.

In February 1990 she was admitted to the Johns Hopkins Hospital. Examination showed a cachectic, ill appearing woman with patches of hypopigmented skin. Her legs were mildly oedematous and the skin had a leathery quality. Neurological examination showed a distal to proximal gradient of weakness, MRC grade 4 distally and 4+ proximally. Deep tendon reflexes were reduced in the right arm and both legs and absent in the left arm. Plantar responses were flexor. There was a mild sensory loss in a stocking-and-glove distribution.

The following laboratory values were abnormal: antinuclear antibodies, 1:640; absolute eosinophil count, 480 cells/mm³; T4 cells,

2.6 µg/dl (normal, 5.0–13.0 µg/dl); and thyroid stimulating hormone, 32.9 mIU/ml (normal, 0.5–4.5 mIU/ml). IgM anti-GM1 ganglioside titre was 241 (normal, < 50; levels 50–350 commonly associated with autoimmune disorders), and IgG anti-GM1 ganglioside titre was 1612 (normal < 60; levels > 60 commonly associated with autoimmune disorders^{8,9}). Normal results were obtained for analysis cerebrospinal fluid, electrolytes, transaminases, erythrocyte sedimentation rate, creatine kinase, hepatitis B and HIV serology, and antibodies to Ro and thyroglobulin.

A lip biopsy showed severe sclerosing inflammation of the minor salivary glands. There was squamous cell metaplasia of the remaining ducts, and most of the acini were destroyed. In the context of dry mouth, this pathology substantiated a diagnosis of Sjögren's disease.¹⁰ On the basis of electrophysiological and pathological data (presented below), a diagnosis of EMS and chronic demyelinating motor and sensory polyneuropathy was made.

The patient was given prednisone 50 mg daily, which resulted in mild improvement in her skin and her ability to walk. She continued to have difficulty swallowing and felt that her manual dexterity had worsened due to pain and stiffness. A four week course of plasma exchange (40–50 cc/kg twice weekly) was given but there was no measurable improvement. The course was complicated by multiple compression fractures and continued pain. After one year of high dose prednisone, the dose was tapered and azathioprine (2.5 mg/kg) was instituted. After four months her deep tendon reflexes returned, dramatic improvement was noted on quantitative testing of all muscles (particularly in pinch and grip, with grip strength increasing from five to 30 pounds), and all sensory modalities improved.

Methods

Motor and sensory nerve conduction studies, including late responses and electromyography were performed using standard techniques in our laboratory.

Sural nerve and an adjacent piece of gastrocnemius were biopsied from the midcalf under local anesthesia. Muscle cryosections were prepared routinely. A portion of the nerve was fixed in 5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.2), post-fixed in osmium tetroxide and embedded in Epon. Sections 1 µm thick were stained with toluidine blue for light microscopy. Thin sections were stained with uranyl acetate and lead citrate for electron microscopy.

Another portion of the nerve was snap frozen in isopentane and cryosectioned for immunocytochemistry. Staining of sections was accomplished by using the avidin-biotin-peroxidase method, as previously described.^{11,12} A third portion of nerve was immersion fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.2) for nerve fibre teasing. Using the avidin-biotin-peroxidase complex, nerve bundles were immunostained

Table 1 Motor nerve conduction studies

	Distal latency (ms)	Conduction velocity (m/s)	Baseline to negative peak distal amplitude (μ V)	Baseline to negative peak proximal amplitude (μ V)	Minimum F wave latency (ms)
Peroneal nerve:					
Case 1	5.5	34	1200	900	50.5
Case 2	4.6	33	3500	1000	63.4
Normal	≤ 5.5	≥ 40	≥ 2000	≥ 2000	≤ 55.0
Ulnar nerve:					
Case 1	6.5	18	1200	250	53.7
Case 2	2.8	34	8500	4110	36.6
Normal	≤ 3.4	≥ 50	≥ 4000	≥ 4000	≤ 32.0
Median nerve:					
Case 1	4.5	38	5000	5000	29.0
Case 2	4.7	32	3500	1100	38.6
Normal	≤ 4.2	≥ 50	≥ 4000	≥ 4000	≤ 31.0

for macrophages with EBM/11,¹³ infiltrated with glycerol, and teased with fine needles.

Results

ELECTROPHYSIOLOGICAL STUDIES

Case 1

Electrophysiological studies showed a demyelinating motor and sensory polyneuropathy (tables 1 and 2). Distal latencies were prolonged in five of six motor nerves, as were F wave latencies in two of six nerves. In the left ulnar nerve the forearm conduction velocity was severely reduced (18 m/s). The results of surface recording and stimulation suggested partial motor conduction block in the right ulnar and tibial nerves.¹⁴ In addition, abnormal temporal dispersion was present in the right ulnar and peroneal nerves. Compound muscle action potential amplitudes were reduced in five of six motor nerves.

Electromyography showed myopathic voluntary motor unit potentials without abnormal spontaneous activity in the proximal and distal muscles.

A follow up study was performed five weeks later. In all motor nerves the distal evoked amplitudes were reduced further than in the previous study. Distal latencies were further prolonged in the tibial and ulnar nerves, and conduction velocities were further reduced in all motor nerves. The F wave latency was prolonged in the tibial nerve and absent in the peroneal nerve. The results of surface recordings and stimulation in the left ulnar nerve suggested partial motor conduction block.

Case 2

The nerve conduction studies were interpreted as a demyelinating motor and sensory poly-

neuropathy, (tables 1 and 2). Conduction velocities were reduced and F wave latencies were prolonged in all motor nerves. Distal motor latencies were prolonged in two of three nerves. Partial motor conduction block was suggested by the results of surface recording and stimulation in the right median and ulnar nerves.¹⁴ Abnormal temporal dispersion was present in the right peroneal nerve.

Needle electromyography revealed short duration, low amplitude, polyphasic motor units in proximal muscles. Abnormal spontaneous activity was observed only in distal muscles, where voluntary motor unit potentials were normal. The electromyography findings were consistent with a proximal myopathy and a distal neuropathy.

A follow up study was performed four months later. Further reduction in all motor conduction velocities was seen. F wave latencies were further prolonged or absent. Motor evoked amplitudes were further reduced, with one nerve being 5% of the lower limit of normal.

NEUROPATHOLOGY

Case 1

A biopsy of sural nerve showed enlargement of the nerve with extensive epineurial thickening as a result of collagen deposition (fig 1). Both epineurium and endoneurium had scattered inflammation, and there was rimming of the perineurium with mononuclear cells. The density of large and small myelinated fibres was noticeably reduced. Many thinly myelinated fibres were seen, suggesting remyelination. One fascicle (fig 1B) was extensively demyelinated, illustrating the inhomogeneous pattern of these changes. The epineurial and endoneurial blood vessel walls were thickened. Electron microscopy (fig 1C, D) showed evidence of prior and active demyelination; some fibres had intratubal macrophages splitting myelin lamellae.

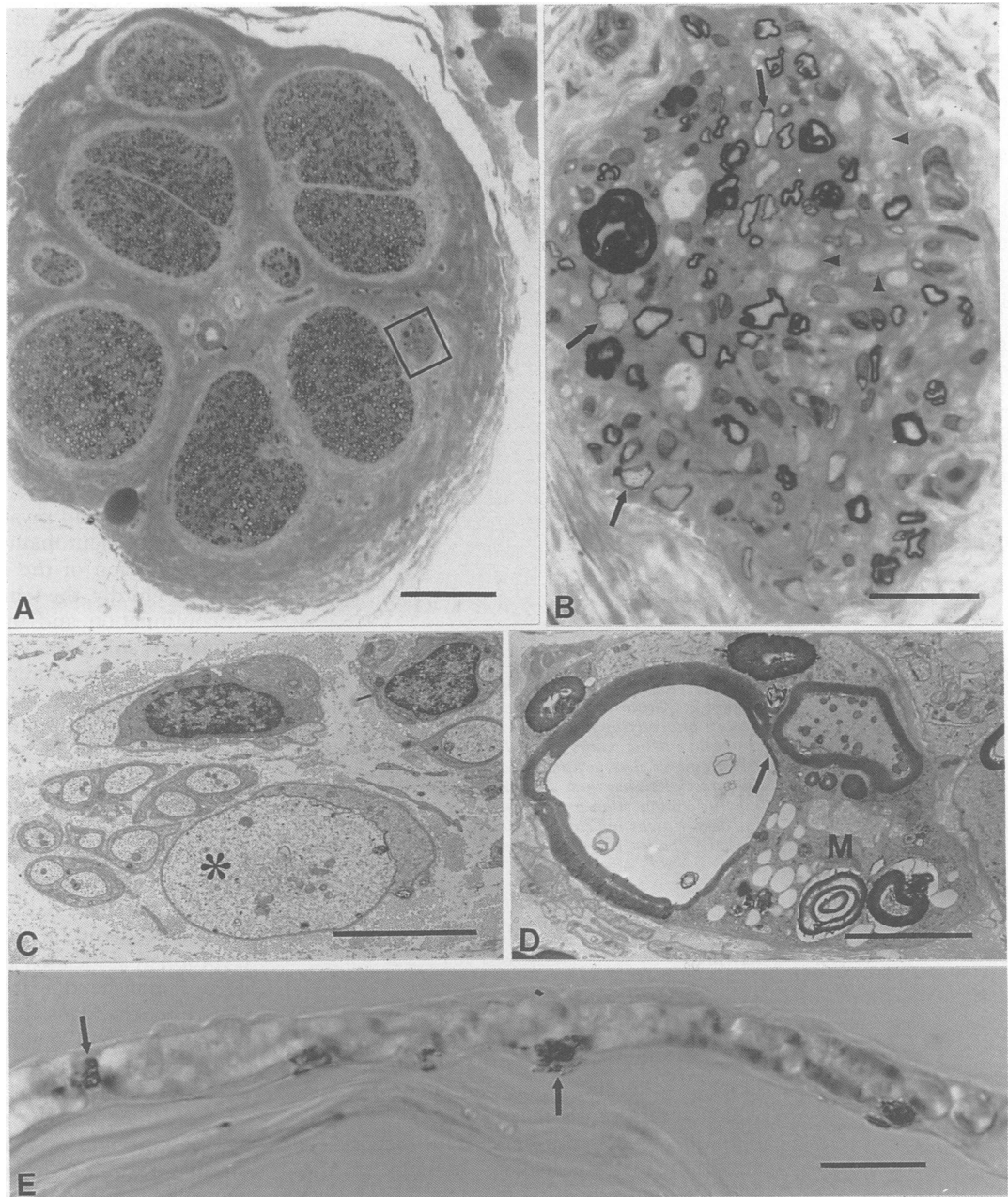
Examination of teased fibres confirmed extensive demyelination and remyelination; in one fascicle, 38% of fibres had demyelinated or demyelinating internodes; in a second fascicle, 8% of fibres were affected. By immunostaining for macrophage markers, the demyelinating fibres had adherent and intratubal macrophages (fig 1E). Remyelinated fibres and fibres undergoing active Wallerian-like degeneration were also identified. Immunostaining of frozen

Table 2 Sensory nerve conduction studies

	Conduction velocity (m/s)	Peak to peak amplitude (μ V)
Sural nerve:		
Case 1	NR	
Case 2	46	8
Normal	≥ 40	≥ 10
Median nerve:		
Case 1	38	6
Case 2	48	9
Normal	≥ 50	≥ 10
Ulnar nerve:		
Case 1	NR	
Case 2	48	4
Normal	≥ 50	≥ 10

NR = no response.

Figure 1 Sural nerve from patient 1. (A) Light photomicrograph shows extensive thickening of both epineurium and perineurium (bar = 200 μ m). (B) One fascicle (box in A) shows features of active demyelinating neuropathy, including naked axons (arrowheads) and large thinly myelinated fibres that imply remyelination (arrows) (bar = 40 μ m). (C) Electron micrograph showing completely demyelinated axon (asterisk) (bar = 5 μ m). (D) Macrophage (M) is actively stripping myelin from axon. Note tongue of macrophage cytoplasm interdigitating between myelin lamellae (arrow) (bar = 5 μ m). (E) Teased fibre immunostained with EBM11, an antibody to macrophages, showing adherence of macrophages to nerve fibre (arrows) (bar = 20 μ m).



sections with a T cell marker showed scattered T cells throughout the perineurium.

A biopsy of gastrocnemius muscle (fig 2) showed widespread fibrosis of the overlying fascia and endomysial connective tissue. Close to the fascial plane the muscle fibres were atrophic and basophilic, often distorted and embedded in collagen. Split fibres and fibres with abnormal internal architectural changes also occurred. In a gradient farther from the fascial plane these changes became milder. Throughout the biopsy, focal grouped atrophy, fibre type grouping, and pyknotic nuclear clumps were seen. The intramuscular capillary walls were thickened and fibrotic. No inflammatory infiltrates were seen. These findings were interpreted as consistent with denervation and coexisting fasciopathy, which was a likely residue of severe fasciitis.

Case 2

A biopsy of the sural nerve showed thickening

of both the epineurium and perineurium, with particularly dramatic rimming with mononuclear cells, indicating active perineuritis (figs 3A, B). Ongoing demyelination as well as Wallerian-like degeneration were apparent. The density of large and small myelinated fibres was slightly reduced. Electron microscopy showed scattered demyelinated fibres and some remyelinating fibres, along with frequent endoneurial inflammatory cells (fig 3C). Immunostaining of frozen sections with Leu4 and Dako antibodies showed prominent rimming of the perineurium with T cell lymphocytes (figs 3D, E) and macrophages.

The gastrocnemius muscle biopsy showed diffuse thickening of the fascial plane and endomysial connective tissue. There were changes consistent with a neuropathic process, including fibre type grouping and small angular fibres. In addition, a gradient of myopathic changes, including rounded atrophic fibres, central nuclei, and split fibres, extended from

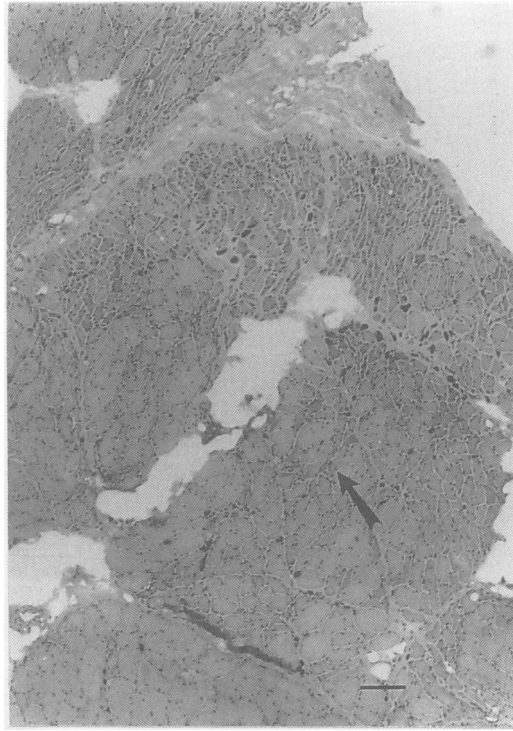


Figure 2 Gastrocnemius muscle from patient 1. Marked fibrosis of overlying fascia and all layers of investing connective tissue occurs in gradient from surface inward. Muscle fibres close to fascial plane are distorted; farther from fascial plane, these changes are less severe. Pyknotic nuclear clumps (thin arrow) and grouped atrophy seen in the deeper areas indicate coexistent denervation atrophy (H&E) (bar = 100 μ m).

the muscle fibres adjacent to the fascia inward.

Discussion

These two patients show the symptoms, signs, laboratory findings, and pathological changes which comprise the recently described eosinophilia-myalgia syndrome.¹ This report calls attention to two striking findings in these patients: demyelinating neuropathy and severe perineuritis. Unlike the vast majority of patients with EMS, these two patients developed rapidly progressive weakness. The weakness occurred with a distal to proximal gradient, accompanied by mild wasting and moderate sensory loss. Reflexes were reduced or absent. Nerve conduction studies showed a severe demyelinating motor and sensory polyneuropathy. The nerve biopsies confirmed ongoing demyelination and remyelination and active inflammation. This constellation of findings suggests an acquired demyelinating polyneuropathy. Such neuropathies are postulated to be immunopathogenic.¹⁵

The eosinophilia-myalgia syndrome appeared as an epidemic in 1989.^{1 2 16-18} The syndrome is characterised physically by the acute onset of pain, oedema, and induration of the legs, arms, and trunk. Other prominent features may include weakness, cough, and dyspnea. Pathological findings in the skin include perivascular collections of lymphocytes, eosinophils, and plasma cells and excessive collagen deposition. EMS has been linked

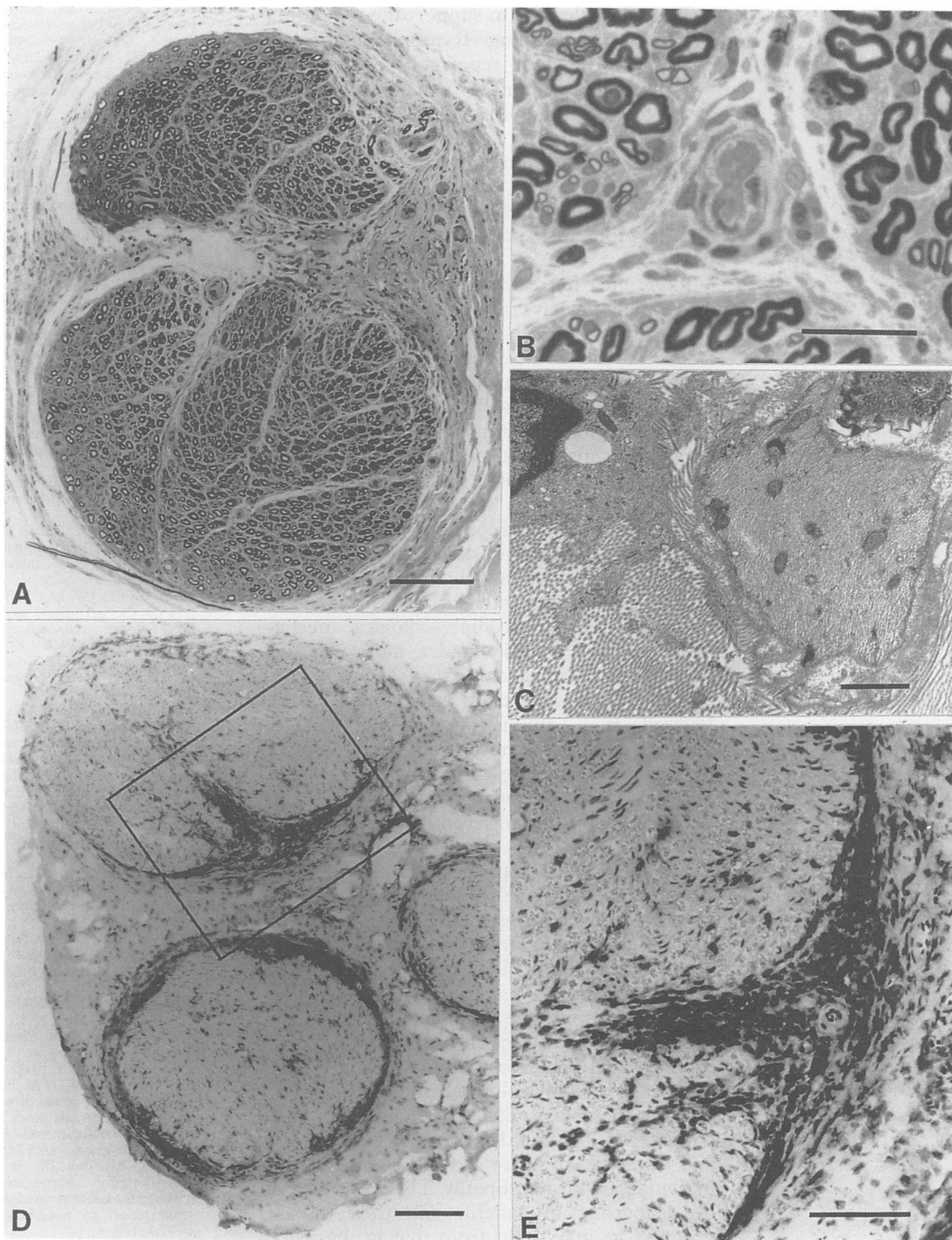
to the chronic use of L-tryptophan, but the exact pathophysiology is unknown. Speculation has centred on three hypotheses: (a) L-tryptophan may trigger an autoimmune response in some susceptible individuals;^{1 16} (b) EMS is due to a contaminant of some preparations of the drug; or (c) EMS may be due to faulty tryptophan metabolism.

The autoimmune hypothesis may be supported by several notable features of these cases. Firstly, both patients, before being exposed to L-tryptophan, had a strong history of other disorders thought to be autoimmune. Secondly, after exposure to L-tryptophan both patients also had high concentrations of several autoantibodies in their serum samples. The presence of anti-acetylcholine receptor antibodies in patient 1 and anti-GM1 antibodies in both patients does not necessarily imply that these patients had myasthenia gravis or multifocal motor neuropathy^{8 9}; rather, it suggests that regulation of the immune system is disturbed. Thirdly, the temporal lag between drug discontinuation and the onset of the disease suggests an intervening mechanism (for example, autoimmunity) rather than a direct toxic mechanism. A fourth clinical feature that supports the autoimmune hypothesis is the apparent improvement of patient 1 after one course of intravenous gammaglobulin¹⁹⁻²² and the dramatic improvement of patient 2 after four months of azathioprine treatment. Finally, inflammation was a prominent part of the neuropathology in both cases.

What is the pathophysiological relation between a demyelinating polyneuropathy and tryptophan associated EMS? While their coexistence may be due to chance, several speculative mechanisms may be considered. EMS or L-tryptophan might trigger a widespread autoimmune response, as suggested above. Or, as the morphological data presented here suggest, there may be more specific targeting by the immune system of peripheral nerve myelin, resulting in macrophage mediated demyelination. Perhaps L-tryptophan or a contaminant serves as an antigen or antigenic modifier (adjuvant), stimulating the immune system to recognise self antigens in peripheral nerve myelin. Those patients with EMS who developed demyelinating polyneuropathy may have a latent hypersensitivity to nerve antigen that is activated by the L-tryptophan preparation. Both our patients had a strong history of immune dysfunction which may have predisposed them to develop either demyelinating neuropathy or EMS. A similar mechanism was proposed in a patient with procainamide induced polyradiculopathy who showed lymphocyte sensitisation to peripheral nerve myelin and procainamide.²³

The similarities between the neuropathy described in this paper and chronic inflammatory demyelinating polyradiculopathy (CIDP) should be noted because CIDP is generally considered to be a disorder of the immune system.^{23 24} Electrophysiologically, our patients' neuropathy was indistinguishable from CIDP.¹⁵ Clinically, both present with predominantly motor dysfunction and hypore-

Figure 3 Sural nerve from patient 2. (A) Light photomicrograph showing thickening of epineurium and perineurium and active perineurial inflammation (toluidine blue) (bar = 100 μ m). (B) Blood vessel typical of those seen throughout the biopsy shows perivascular mononuclear cells (toluidine blue) (bar = 35 μ m). (C) Completely demyelinated axon (EM, bar = 1 μ m). (D) Frozen section of nerve immunostained with Leu4, an antibody to CD3 antigens on T cells, showing extensive rimming of all fascicles with T cells (bar = 200 μ m). (E) Boxed area (from D) is shown at higher power and shows intensity of inflammatory infiltrate (bar = 60 μ m).



flexia. Our patients differed from those with CIDP pathologically because there was pronounced fibrosis and perineuritis in our patients. In addition, the abnormalities of muscle are not found in patients with CIDP.

One final analogy that suggests an autoimmune mechanism is the remarkable resemblance of EMS to eosinophilic fasciitis (EF), first described by Shulman in 1975. Patients with EF develop cutaneous lesions similar to those described in EMS, as well as fascial inflammation, weakness, and peripheral eosinophilia.^{25 26} The aetiology of EF is unclear, but EF has occurred in association with hypergammaglobulinaemia and in association with autoimmune syndromes such as vitiligo,

thyroid disease, and Sjögren's syndrome. To date, there is no strong evidence to link EF with L-tryptophan.²

In favour of a toxic substance causing EMS is the presence of an unidentified chemical found in some retail lots of L-tryptophan which were consumed by patients who developed EMS.²⁷ Perhaps this "toxin" triggers the eosinophilic proliferation in EMS. The subsequent nerve damage could then be due to eosinophil derived neurotoxins.^{5 28-30} This might explain why the polyneuropathy most commonly seen in EMS is predominantly due to axonal degeneration; however, this would not account for the inflammation, demyelination, and other features seen in our patients.

There is little data to support the remaining hypothesis concerning tryptophan and its metabolism. Recent reports have suggested that levels of kynurenine, a major product of L-tryptophan metabolism, are increased in patients with EMS compared with control patients.¹⁶ In addition, two patients with EMS and neuropathy had raised concentrations of the excitotoxin quinolinic acid, a final product of L-tryptophan metabolism, in cerebrospinal fluid.

Experience in treating EMS is limited. While some patients have responded to corticosteroids, those patients with the more severe forms of the disease, including the neuropathies and pulmonary disease, may not. One of our patients improved clinically after receiving gammaglobulin, but she continues to have debilitating pain and weakness. The other patient remained stable on long term, high dose prednisone and has shown considerable improvement on azathioprine. Other immune treatments have been tried, including cyclosporin, plasmapheresis, hydroxychloroquine, and methotrexate, with variable success.^{31,32} Perhaps when the pathophysiological mechanism of EMS is delineated a more effective treatment will be developed.

Although L-tryptophan was banned by the Federal Drug Administration in March 1990, patients with this syndrome may continue to present to neurologists and rheumatologists for several reasons. Firstly, symptoms may not become apparent until several months after the discontinuation of the drug. Secondly, although both our patients had long since discontinued the medication, they continued to show disease progression. Lastly, although L-tryptophan is no longer available in stores, it may remain in medicine cabinets for many years.

In conclusion, we draw attention to the important association of demyelinating neuropathy with the eosinophilia-myalgia syndrome. Electrophysiological studies are important in patients with EMS, particularly in those patients with a rapidly progressive proximal and distal weakness, in order to identify those individuals with neuropathy. The treatment of this subgroup of patients and their disease progression may differ from that in the usual EMS patient.

This work was supported by The Muscular Dystrophy Association (MLF), The Jay Slotkin Fund for Neuromuscular Research (RWK), and National Institutes of Health grants PO1 NS26643 (WRT) and NS 07179 (JDG). We thank Dr Ronenn Roubenoff and Dr William Ravich for referring their patients; Dr Mohammed Lehar for technical assistance; and Dr Chun Yan Li for preparation of teased fibres. Rod Graham prepared the manuscript and offered editorial assistance.

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