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Low diagnostic yield of sural nerve biopsy in patients with peripheral neuropathy and primary amyloidosis

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Summary

Patients with primary amyloidosis may develop peripheral neuropathy as an early feature Sural nerve biopsy is reported to be a sensitive method for diagnosing amyloidosis in such patients. We identified nine patients, ultimately diagnosed as having amyloidosis, who were referred for peripheral neuropathy of undetermined etiology. In six, a sural nerve biopsy demonstrated no amyloid Subsequent examination of other tissue or of the contralateral sural nerve eventually resulted in the correct diagnosis. We conclude that sural nerve biopsy may be less sensitive than previously believed for the diagnosis of amyloidosis in patients with peripheral neuropathy secondary to amyloid. When the clinical suspicion of amyloidosis is high, a nondiagnostic sural nerve biopsy should not discourage the performance of further investigative studies

Introduction

Primary amyloidosis is a disorder in which the fibrous protein amyloid may be deposited in virtually any tissue (Kyle and Greipp 1983; Cohen 1991). Since peripheral neuropathy is frequently an early or presenting feature of amyloidosis (Kyle and Bayrd 1975; Kyle and Greipp 1983; Duston et al. 1989), the neurologist may be called upon to evaluate patients who are ultimately found to have amyloidosis, but in whom this diagnosis has not yet been established. Previous series (Kelly et al. 1979; Kyle and Greipp 1983; Janssen et al. 1986) have indicated a high diagnostic yield from sural nerve biopsy in patients with primary amyloidosis and peripheral neuropathy. We have recently evaluated 9 patients for peripheral neuropathy of unclear etiology who were eventually diagnosed as having amyloidosis. In 6 of these patients, Congo red or crystal violet staining of sural nerve biopsy sections as well as electron microscopy failed to show amyloid deposits. This raises questions regarding the sensitivity of routine sural nerve biopsy in the diagnosis of amyloidosis, and emphasizes the need for further diagnostic workup of patients with neuropathy whose clinical presentations and laboratory studies suggest amyloidosis, but in whom routine studies of sural nerve are nondiagnostic.

Materials and methods

We reviewed records of the University of Michigan Neuromuscular Clinic and the Geisinger Medical Center Department of Neurology for the past 6 years, and identified 9 patients referred for peripheral neuropathy of undetermined etiology who were eventually diagnosed as having amyloidosis. Amyloid was demonstrated in the initial rectal biopsy in 2 patients and the initial sural nerve biopsy in one. The remaining 6 patients are the subjects of this report

None of the patients had systemic cancer, a history of excessive alcohol use, or other disorders known to cause neuropathy except for one patient (patient 3),

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who had mild diabetes mellitus which was controlled by diet alone. All had undergone comprehensive evaluations to rule out other causes of neuropathy, including physical examination, complete blood count, Westergren sedimentation rate, ANA, glucose, electrolytes, BUN, creatinine, liver function tests, T4, TSH, vitamin B_{12} level, VDRL or RPR, and chest X-ray. High resolution agarose gel serum electrophoresis, immunoglobulin quantification, determination of kappa: lambda light chain ratio, and if necessary immunofixation of serum (Keren et al. 1988) were performed in 5 of the patients, while one underwent serum immunoelectrophoresis.

Sural nerve biopsies, taken at the level of the ankle, were divided into 2 sections immediately after surgery The portion for light microscopy was fixed in 10% formalin. One longitudinal and 1–3 cross-sections were then obtained and embedded in paraffin. These blocks were then cut at 2 or more levels. All were stained with hematoxylin-eosin and with a stain for amyloid (crystal violet in patient 4, Congo red in the others). Trichrome staining was also employed in all except patient 6. For all patients, another portion of nerve was fixed in glutaraldehyde and divided into 2 sections. One section was minced and the pieces embedded in Epon, and the other was processed in glycerol for teasing. At least 10 blocks of epon-embedded material were examined on multiple 1 micron thick toluidine-stained sections, and one or two of them were selected for electron microscopy All biopsies were reviewed by a neuropathologist (M.B. or J.T.)

Case reports

Two illustrative cases are described.

Patient 2

An 83-year-old man was admitted with a 6-month history of bilateral hand pain and arm weakness He had surgical treatment for bilateral carpal tunnel syndromes 3 years previously and a cholecystectomy for abdominal pain 2 years previously On examination, there was diffuse mild upper and lower extremity weakness Achilles reflexes were absent Pinprick and vibration were decreased distally Serum protein electrophoresis and immunofixation revealed an IgM lambda monoclonal gammopathy Bone marrow biopsy was normal

TABLE 1

CLINICAL AND HISTOLOGICAL FINDINGS IN PATIENTS WITH POLYNEUROPATHY AND AMYLOIDOSIS

Patient No	Age at onset/sex	Sural nerve biopsy			Other tissue studied		
		Symptom duration at biopsy	Biopsy findings	Amyloid (Congo red and EM)	Type of tissue	Time after sural nerve biopsy	Amyloid (Congo red)
1	62/F	10 months	Severe loss of small > large myelinated axons	Negative	Rectal biopsy	1 month	Positive
2	82/M	36 months	Moderate loss of small > large myelinated axons	Negative	Transbronchial biopsy of lung mass	5 months	Positive
3	64/M	15 months	Severe loss of all myelinated axons	Negative	Contralateral sural nerve	4 months	Negative (Positive by EM)
					Ileum from ileostomy	See text	Positive
4	66/M	16 months	Moderate loss of all myelinated axons	Negative *	First rectal biopsy	13 months	Negative
					Second rectal biopsy	16 months	Positive
					Autopsy brachial plexus, femoral nerve, phrenic nerve, dorsal root ganglion	21 months	All positive
5	66/M	6 months	Moderate loss of small > large myelinated axons	Negative	Autopsy brachial plexus	10 months	Positive
6	68/M	5 months	Marked loss of small > large myelinated axons	Negative	Autopsy obturator nerve, anterior and posterior roots, heart	11 months	All positive

EM = electron microscopy,

* Crystal violet and electron microscopy

Two skeletal surveys showed no bone lesions Electrodiagnostic studies revealed an axonal polyradiculoneuropathy Sural nerve biopsy was negative for amyloid by Congo red staining and by electron microscopy A lung mass was identified, and he underwent transbronchial biopsy which demonstrated amyloid

Patient 6

A 68-year-old man presented with a 4-month history of burning paresthesias of the distal lower extremities and fingertips, accompanied by midline abdominal numbness. Examination revealed mild weakness of foot dorsiflexors and toe extensors Patellar reflexes were depressed, and Achilles reflexes were absent These was decreased sensation to pin, light touch, and vibration in the distal lower extremities, and decreased pin and light touch sensation in the midline abdomen Serum and urine immunoelectrophoreses were normal Electrodiagnostic studies revealed an axonal polyneuropathy Sural nerve biopsy was negative for amyloid by Congo red staining and by electron microscopy Sensory and motor deficits progressed and he died suddenly At autopsy, amyloid deposition was demonstrated in obturator nerve, anterior and posterior nerve roots, and heart

Results

Data from the 6 patients studied are presented in Table 1. The youngest was 62 years old and 5 were male. All presented with dysesthetic limb pain and numbness. Strength varied from normal to severely impaired, and sensory loss was present in all. Four had monoclonal heavy or light chains in serum or urine. None was known to have amyloidosis at the time of presentation, and none had features of other organ involvement at that time

The presence of a painful sensorimotor neuropathy, often with a monoclonal gammopathy, led to consideration of amyloid neuropathy in all patients. Sural nerve was the first tissue evaluated for amyloid in all. The time from onset of symptoms to sural nerve biopsy varied from 5 to 36 months. All biopsies revealed an axonal neuropathy, and none demonstrated amyloid.

After the nondiagnostic sural nerve biopsy, amyloid was eventually identified in all patients by biopsy of other tissue or at autopsy 1 to 21 months after the initial sural nerve biopsy. Patient 3 was the only one to undergo a second sural nerve biopsy. While the first one was negative for amyloid, the second one, obtained 4 months later, contained very small amounts of amyloid on electron microscopy Patient 3 also was unique in that one other tissue which eventually was found to stain positive for amyloid (ileum) was actually obtained at another institution 2 months prior to the first sural nerve biopsy (13 months after onset of symptoms), but was not stained for amyloid at that time. Once we suspected amyloidosis but were unable to demonstrate it on sural nerve biopsy, the ileal tissue previously removed was obtained and stained with Congo red, resulting in a diagnosis of amyloidosis

Discussion

Peripheral neuropathy occurs in 13–35% of patients with primary amyloidosis, may be the presenting symptom of the disease, and may be present for months to years before the diagnosis of amyloidosis is established (Kyle and Bayrd 1975; Kyle and Greipp 1983; Duston et al. 1989). Our patients possessed clinical features consistent with amyloid polyneuropathy, and some had monoclonal gammopathies. In such patients, a sural nerve biopsy frequently is performed to look for amyloid deposits

The yield of sural nerve biopsy in patients with primary amyloidosis and peripheral neuropathy is said to be high. One small series (14 patients) cited a yield of 86% (Kyle and Dyck 1993). A figure of over 90% has also been cited (Kelly 1985). Review of other data suggests that the yield may even approach 100% (Kelly et al. 1979; Kyle and Greipp 1983, Janssen et al. 1986). However, such data are derived from small numbers of patients.

Our yield, while also based on a small number of patients, is strikingly lower. One factor which may account for this is the timing of the biopsy relative to the pattern of amyloid deposition within the peripheral nervous system. Proximal portions of the peripheral nervous system are thought to be involved first, followed by breakdown of the blood–nerve barrier and distal amyloid deposition (De Navasquez and Treble 1938; Verghese et al. 1983, Hanyu et al. 1989; Sobue et al. 1990; Antoine et al. 1991). Thus, a patient studied early in the course of amyloidosis may show amyloid deposition only in the proximal peripheral nervous system. A study later in the illness may demonstrate amyloid more distally. Such a pattern of amyloid deposition would explain not only our initial nondiagnostic sural nerve biopsy results, but also the presence of amyloid in the contralateral sural nerve of patient 3 several months later and the presence of amyloid in proximal nerve of two of our patients at autopsy. The high yield of sural nerve biopsies previously reported in amyloidosis (Kelly et al 1979; Kyle and Greipp 1983, Janssen et al. 1986; Kyle and Dyck 1993) may have resulted from a longer duration of peripheral nervous system involvement prior to the time of nerve biopsy, although such data cannot be extracted from those reports. The duration of symptoms in our patients at the time of sural nerve biopsy varied from 5 to 36 months, which we believe is representative of the time a sural nerve biopsy usually would be obtained in such patients.

Technical factors must be considered when comparing our low yield of sural nerve biopsy to the higher values previously published. Techniques for evaluating sural nerve biopsies vary from institution to institution. Because this was a retrospective study, control for

biopsy technique and specimen handling was not possible Amyloid deposition within a nerve may be patchy, and possibly our yield could have been increased by the use of very large numbers of sections per nerve or staining for both Congo red and crystal violet. However, this is often not practical in the usual clinical setting, and there is no data to indicate how helpful this might be We believe that our protocol for the processing and study of sural nerve biopsies, resulting in the review of cross and longitudinal Congo red or crystal violet sections as well as multiple sections for electron microscopy, reflects the type of evaluation performed routinely in large institutions, so that our figures are of interest to clinicians and neuropathologists involved in the management of such patients A prospective study comparing techniques such as ours to other means of processing sural nerve biopsies would be helpful to address this issue.

Although our series is small, these cases suggest the need for persistence in diagnostic workup if amyloidosis is strongly suspected as the cause of peripheral neuropathy, since the yield of routinely processed sural nerve biopsies in the diagnosis of amyloidosis may be lower than previously believed When patients, particularly older males, present with a painful neuropathy and a monoclonal protein in the serum or urine, the sural nerve biopsy may show only nerve fiber loss. In such cases, biopsy of additional tissue or eventually of the contralateral sural nerve may lead to an accurate diagnosis.

References

Antoine, J C , Baril, A , Guettier, C , Barral, F.G , Bady, B , Convers, P and Michel, D (1991) Unusual amyloid polyneuropathy with predominant lumbosacral nerve roots and plexus involvement Neurology, 41 206–208

Cohen, A S (1990) Amyloidosis In Williams, W J , Beutler, E , Erslev, A J. and Lichtman, M A (Eds.), Hematology, 4th ed., McGraw-Hill, New York, pp 1148–1157

De Navasquez, S and Treble, H.A (1938) A case of primary generalized amyloid disease with involvement of the nerves Brain, 61 116–128

Duston, M A , Skinner, M , Anderson, J and Cohen, A S (1989) Peripheral neuropathy as an early marker of AL amyloidosis Arch Intern Med., 149. 358–360

Hanyu, N , Ikeda, S , Nakadai, A , Yanagisawa, N and Powell, H (1989) Peripheral nerve pathological findings in familial amyloid polyneuropathy a correlative study of proximal sciatic nerve and sural nerve lesions Ann Neurol , 25 340–350

Janssen, S , Van Rijswijk, M H , Meijer, S , Ruinen, L. and Van Der Hem, G K (1986) Systemic amyloidosis a clinical survey of 144 cases Neth J Med , 29 376–385.

Kelly, J J (1985) Peripheral neuropathies associated with monoclonal proteins a clinical review Muscle Nerve, 8 138–150

Kelly, J J , Kyle, R A , O'Brien, P C and Dyck, P J (1979) The natural history of peripheral neuropathy in primary systemic amyloidosis Ann Neurol , 6 1–7

Keren, D F , Warren, J S and Lowe, J B (1988) Strategy to diagnose monoclonal gammopathies in serum high-resolution electrophoresis, immunofixation, and k/l quantification Clin Chem , 34 2196–2201

Kyle, R A and Bayrd, E D (1975) Amyloidosis review of 236 cases Medicine, 54 271–299.

Kyle, R A and Dyck, P J (1993) Amyloidosis and neuropathy In Dyck, P J , Thomas, P K , Griffin, J W , Low, P.A and Poduslo, J F (Eds), Peripheral Neuropathy, W B Saunders, Philadelphia, PA, pp 1294–1309.

Kyle, R A and Greipp, P R (1983) Amyloidosis (AL) Clinical and laboratory features in 229 cases Mayo Clin Proc , 58: 665–683

Sobue, G , Naoki, N , Murakami, K , Yasuda, T , Sahashi, K., Mitsuma, T , Sasaki, H , Sasaki, Y. and Takahashi, A (1990) Type I familial amyloid polyneuropathy Brain, 113 903–919

Verghese, J P , Bradley, W G , Nemni, R and McAdam, K P W J (1983) Amyloid neuropathy in multiple myeloma and other plasma cell dyscrasias J. Neurol Sci , 59 237–246.