Acta Neuropathol (1989) 77:514–518

Acta Neuropathologica

Localized hypertrophic neuropathy: possible focal perineurial barrier defect*

P. C. Johnson[1] and D. G. Kline[2]

[1] Division of Neuropathology, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, AZ 85013, USA
[2] Department of Neurosurgery, School of Medicine, Louisiana State University Medical Center, 1542 Tulane Ave., New Orleans, LA 70112-2822, USA

Summary. Localized hypertrophic neuropathy (hypertrophic mononeuropathy) is a rare benign condition that generally occurs in people under 40 years of age. Our immunocytochemical (S-100 protein) study of four new cases confirms previous observations that the cells forming the hypertrophic onion bulb are composed of perineurial cells. These observations and previously published illustrations, reveal a curious hyalinization of the outer perineurium of affected fascicles which suggests the absence of a perineurial barrier. Compartmentation (compartmentalization) of the endoneurium in hypertrophic mononeuropathy closely mimics the transient compartmentation which occurs in the distal nerve stumps of axotomized nerves, particularly in nerves in which re-innervation is prevented. Compartmentalization also can be produced by resection of the perineurial sheath. These findings suggest that hypertrophic mononeuropathy may be a reactive condition due to focal damage to the perineurial barrier.

Key words: Hypertrophic mononeuropathy – Localized hypertrophic neuropathy – Perineurium – Compartmentation

Since the original description in 1964 of localized hypertrophic neuropathy by Imaginario et al. [9], 16 additional cases have been reported and a variety of pathogenic mechanisms have been suggested. Early studies emphasized the histological similarity to systemic hypertrophic neuropathy and considered the disorder to be a form of focal hypertrophic or onion bulb neuropathy [6, 7, 9, 15, 19]. Subsequent studies emphasized the location of the lesions as being sites where nerve entrapment commonly occurs. Localized hypertrophic neuropathy has also been described as a form of neurofibromatosis [10]. Recent studies have demonstrated ultrastructural and immunocytochemical similarities between the cells forming the onion bulbs and perineurial cells [2]. In this study of four additional cases we describe a unique hyalinization of the perineurium. This perineurial sheath alteration may be related to the pathogenesis of this disorder.

Case reports

Case 1

A 12-year-old girl presented with a 1-year history of progressive weakness in dorsiflexion of the right foot. Electromyography showed complete denervation in the distribution of the anterior tibial nerve including the anterior tibialis, extensor halluces longus, and peroneus muscles. It was thought that she might have entrapment of the peroneal nerve at the level of the fibular head. Examination revealed a foot drop with almost complete anterior tibial nerve palsy. There was a mild Tinel's sign over the fibular head. Surgical exploration revealed a firm nerve enlargement just distal to the bifurcation of the sciatic nerve complex and extending to the posterior tibial and anterior tibial nerves. This enlargement was several inches in length. The three atrophic nerves emanating from the mass were thought to be the sural nerve, the superficial, and deep peroneal nerve branches. Internal neurolysis was performed with subsequent placement of interfascicular autologous grafts. The patient was not available for follow-up.

Case 2

A 9-year-old boy had a 13-month history of right foot drop. The symptoms appeared abruptly and were unassociated with recognized trauma. Electromyographically there was denervation in the anterior compartment of the lower leg with rare voluntary motor unit potentials appreciable. The patient had a right foot drop and absence of knee jerk response on the right side. Dorsiflexion and eversion of the right foot and toes were absent. Nerve conduction testing revealed decreased innervation of the medial biceps femoris accompanied by gastrocnemius and soleus atrophy suggesting an involvement of the sciatic nerve. Surgical exploration revealed a sciatic nerve enlargement that began near the sciatic notch. The mass was several inches in length. The lower sciatic nerve branches were atrophic, particu-

* Reported in part at the American Association of Neuropathologists meeting in Minneapolis, MN, 1986

Offprint requests to: P. C. Johnson (address see above)

larly the peroneal and anterior tibial branches. The posterior tibial division found to be functional, was successfully separated and spared. The peroneal and anterior tibial branches had no nerve action potential across the mass lesion; consequently, the mass was resected over a 5 cm length. A sural nerve was then inserted as a graft. There was no evidence of recurrence over the 3-year follow-up.

Case 3

This 12-year-old boy had painless, slowly progressive right foot drop. The duration may have been as long as 3 years. There was no family history of tumors or von Recklinghausen's disease. The patient had a right foot drop but was able to walk on the heel. Severe weakness of the anterior tibial, the extensor halluces, the evertors, and the peroneal muscles were exhibited. The gastrocnemius and soleus strength were slightly diminished. Pin prick and touch sensations over the dorsum of the foot were diminished. Knee and ankle jerk reflexes were also diminished. The right calf was $2^1/_2$ cm smaller than the left. No mass was detected and there was no Tinel's sign. Surgical exploration revealed an 8 cm fusiform enlargement that extended proximally from the sciatic bifurcation.

Case 4

A 35-year-old man presented with a carpal tunnel median nerve palsy with markedly prolonged median nerve sensory latency. At surgery the carpal tunnel was entered and a fusiform mass was found involving the media nerve and its branches (Fig. 1). It was sharply circumscribed and was described as "doughy" and softer than a neurolemoma.

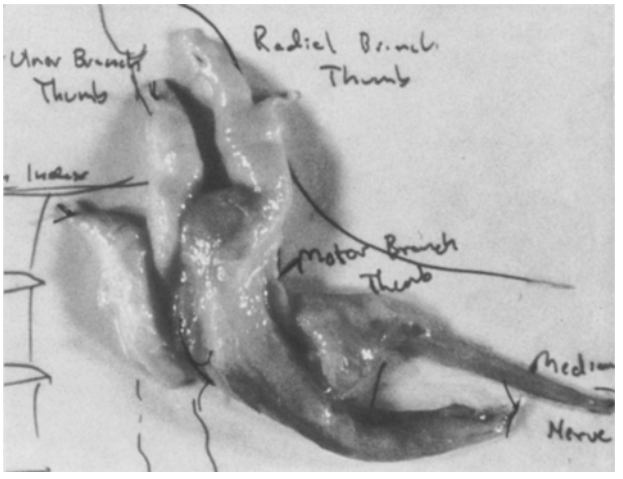

Fig. 1. Surgical specimen of case 4 showing a branched fusiform irregular enlargement of the median nerve and its branches

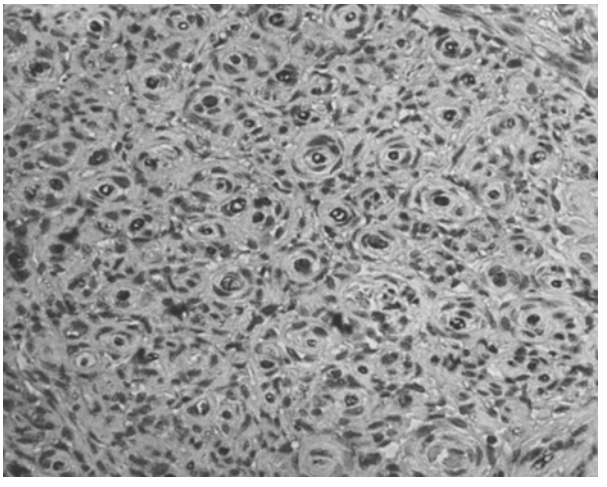

Fig. 2. Endoneurium in hypertrophic mononeuropathy. The compact endoneurium is filled with large onion bulb formations. Only the central sheath of myelin is S-100-protein-(S-100-)positive, × 278

Results

Microscopical finding

Histological characteristics of the nerve lesions from all four patients were essentially identical and will be described together. Nerve lesions were composed of numerous hypertrophic fascicles. Normal fascicles and fascicles in intermediate stages also were identified. Prominent onion bulb formations were evident in hypertrophic fascicles. In cross section, onion bulbs appeared as concentric cellular layers directed circumferentially around a centrally located nerve fiber (Fig. 2). In the longitudinal plane, the circumferentially directed wrapping cells of the onion bulbs appeared as columns of spindle-shaped cells. Onion bulbs were fairly uniform, ranging in size from 100 to 200 μm in diameter. Abundant collagen was interspersed between the onion bulbs. Mast cells were occasionally encountered. Neither edema nor inflammation was identified. Endoneurial blood vessels had hyalinized walls. Case 4 had extensive epineurial fibrosis.

Fascicles containing onion bulbs consistently exhibited a striking hyaline fibrosis of the perineurium (Fig. 3). The characteristic lamellar appearance of the perineurium was generally replaced by an eosinophilic hyalinized collar. In regions of hyalinization only a few spindle-shaped cells were identified. Some perineurial regions of hypertrophic fascicles appeared relatively normal.

Normal-appearing nerve fascicles were identified in three cases. These fascicles exhibited a normal perineurium and an endoneurium containing the normal complement of myelinated axons. Foci of proliferated minute nerve fascicles within fibrous tissue were identified in cases 1 and 2. The pattern of fascicular proliferation was similar to that found in traumatic neuromas. In case 2, one fascicle was found which appeared intermediate between normal and hypertrophic fascicles. In this there was an eosinophilic collagenous deposition that could be identified multifocally within the perineurium. The endoneurium exhibited hypercellularity and small onion bulb formations.

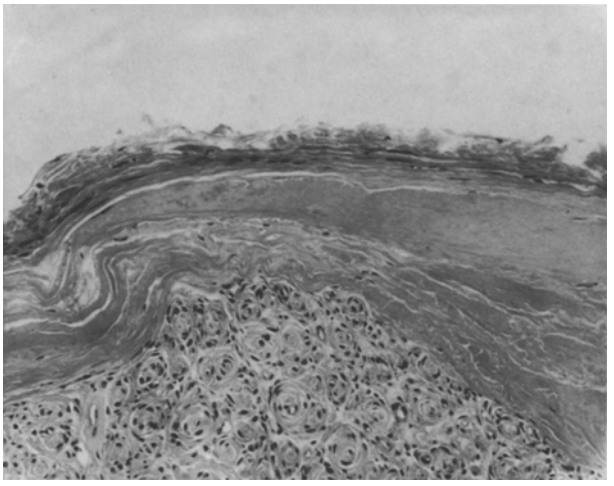

Fig. 3. Periphery of a nerve fascicle in hypertrophic mononeuropathy. The perineurium has been replaced by an irregularly thickened, hyalinized band of collagen containing few cells. Hematoxylin and eosin, ×181

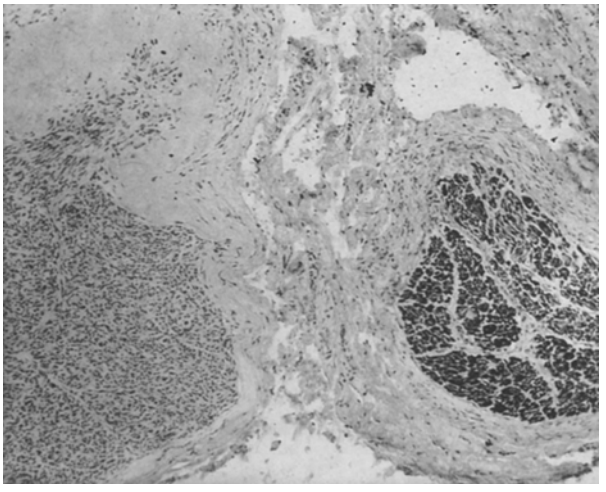

Fig. 4. S-100 reaction product is normal in the normal fascicle on the *right*, while that on the *left* exhibits the hypertrophic change, perineurial hyalinization, and S-100 reaction product restricted to the myelin of the center of each onion bulb, ×70,35

S-100 protein (S-100) immunochemistry

The pattern of S-100 immunocytochemical staining clearly demonstrated that onion bulbs were composed of two distinct cell types. The centrally located structure of the onion bulbs stained positively, while the wrapping cells were negative (Fig. 2). The perineurium of both hypertrophic and normal fascicles was negative. There was positive reaction within the endoneurium of normal-appearing fascicles as well as fascicles which contained traumatic neuroma formations (Fig. 4).

Discussion

Clinical and pathological features of all reported cases of hypertrophic mononeuropathy are listed in Table 1. All but 2 of the 20 patients were under 40 years of age. There was no obvious sex prevalence. The lesions present as a motor deficit involving a large named limb nerve of either the upper or lower extremity. No instances are reported of progressive growth or recurrence which would be suggestive of a true neoplastic lesion. Early studies emphasized the similarity between the onion bulbs of hypertrophic mononeuropathy and the hypertrophic polyneuropathy of Charcot-Marie-Tooth (hereditary sensory motor neuropathy type I) [6, 7, 9, 15, 19]. Lallemand and Weller [10], the first to examine a case with electron microscopy, pointed out features of the wrapping cell which would suggest a perineurial cell origin. These features included the presence of pinocytotic vesicles, cytoplasmic junctions, incomplete basal lamina, and patchy cytoplasmic condensations internal to the plasma membrane. Because the proliferation was within the interstices of the nerve, they concluded that the lesions were neurofibromata despite the absence of other stigmata of von Recklinghausen's disease. Subsequent ultrastructural studies [2, 7, 11] have also identified perineurial features of the wrapping cell but the interpretations have varied. Mitsumoto et al. [11] and Bilbao et al. [2] classified the lesion as a perineurioma, while Hawkes et al. [7] identified it as a form of hypertrophic neuropathy. Bilbao et al. [2] employed S-100 immunocytochemistry and found, as we did, that the wrapping cell which formed the hypertrophic appearance was S-100 negative, while the wrapped cell (i.e., Schwann cell) that immediately surrounded residual myelinated axons was S-100 positive. S-100 immunohistochemistry has been repeatedly used in the study of neurofibromata with the finding of an admixture of S-100-positive and -negative cells. It is thought that they represent Schwann (positive) and perineurial (negative) cells [8].

The main features of hypertrophic mononeuropathy are:

1. A localized enlargement of a large limb nerve accompanied by varying degrees of paresis in the distribution of that nerve.
2. Striking proliferation of perineurial cells surrounding individual myelinated axons accompanied by endoneurial fibrosis.
3. Fibrous replacement of the perineurial sheath.
4. Sparing of some nerve fascicles (our cases and case 1 of Mitsumoto et al. [19]).
5. Benign course with no recurrence following biopsy or resection.

Fibrotic replacement of the perineurium in hypertrophic mononeuropathy apparently has not been previously described, although in an illustration from Mitsumoto et al. (Fig. 1 of [11]) hyalinization of the perineurial sheath can be seen.

Table 1. Reported cases of hypertrophic mononeuropathy

Source, year	Age (years)/sex	Nerve involved	Suggested etiology
Imaginario et al. [9], 1964	27/M	Radial	Hypertrophic neuropathy
Simpson and Fowler [18], 1966			
Case 1	12/M	Common peroneal	Hypertrophic neuropathy
Case 2	11/M	Radial	Hypertrophic neuropathy
Lallemand and Weller [10], 1973	20/F	Posterior interosseous	Neurofibromata
Hawkes et al. [7], 1974	19/F	Posterior interosseous	Hypertrophic neuropathy
Snyder et al. [19], 1977	14/F	Radial	Hypertrophic neuropathy
Mitsumoto et al. [11], 1980			
Case 1	17/M	Lateral cord of brachial plexus	Perineurioma
Case 2	13/F	Posterior interosseous	Perineurioma
Case 3	40/F	Tibial	Perineurioma
Grossiord et al. [6], 1980	20/M	Upper trunk of brachial plexus	Hypertrophic neuropathy
de los Reyes et al. [5], 1981	19/F	Posterior cord	Hypertrophic neuropathy
Peckham et al. [15], 1982			
Case 1	17/F	Median	Hypertrophic neuropathy
Case 2	42/M	Digital	Hypertrophic neuropathy
Bilbao et al. [2], 1984			
Case 1	35/M	Posterior interosseous	Perineurioma
Case 2	30/M	Sciatic	Perineurioma
Case 3	25/M	Median	Perineurioma
Boker et al. [3], 1984	73/F	Radial	Microtraumata
This report, 1988			
Case 1	12/F	Tibial	Perineurial hyperplasia
Case 2	9/M	Sciatic	Perineurial hyperplasia
Case 3	12/M	Sciatic	Perineurial hyperplasia
Case 4	35/M	Median	Perineurial hyperplasia

We suggest that the pathogenesis of this lesion is an exaggerated proliferative response on the part of the perineurium, a phenomenon called intrafascicular compartmentalization (or compartmentation) which may occur whenever the perineurial barrier is breached. Cajal [4] illustrates and discusses this phenomenon in nerve regeneration following transection. He termed the phenomenon "fasciculation" in which regenerating axons with their investment of Schwann cells receive an encapsulating perineurial membrane. While Cajal's illustration is a drawing, that of Seddon [17] is a photomicrograph of the appearance of a nerve following transection. The endoneurium appears strikingly similar to those seen in hypertrophic mononeuropathy. Thomas and Jones [21] illustrated these changes by electron microscopy. In an ultrastructural study by Morris et al. [12], the sequential changes that occurred in the distal portion of the proximal stump following nerve transection were illustrated. They introduced the term "compartmentalization" for those changes in which there was a proliferation of the endoneurial fibroblasts which resulted in their forming cellular tubes which surrounded the endoneurial Schwann cells and axons. The ultrastructural features of these investing cells evolve from those characteristic of fibroblasts to features typical of perineurial cells. This response on the part of the endoneurial fibroblast was regarded as a response to the changes induced in the endoneurial environment following the transection. Compartmentalization was also illustrated by Spencer et al. [20] in an experimental model in which a "window" of perineurium was removed from a nerve fascicle. Compartmentalization occurred below this window, which had allowed the endoneurial contents to herniate and exposed the endoneurium to the epineurial extracellular space. Nesbitt and Acland [13] studied the phenomenon further by analyzing changes that occurred in rats following resection of the perineurial sheath over a length of a fascicle. Their ultrastructural studies demonstrated that compartmentalization was transient. When the perineurium regenerated in its normal position, the cells responsible for the fascicular compartmentalization appeared to regress and a more normal endoneurial septation resulted. Weinberg and Spencer [22] (rats and rabbits) and Roytta et al. [16] (rats) have demonstrated that extensive compartmentalization by perineurial-like

cells derived from endoneurial fibroblasts occurred in axotomized rat nerves in which reinnervation was prevented.

Pearson and Weddell [14] noted compartmentalization (their term was compartmentation) in some cases of human leprosy. They concluded that compartmentation was a response to leprous damage of the perineurium and its barrier function and termed it a perineuropathy. We have observed compartmentalization in sural nerves and dermal nerves from patients with diabetes and one patient with sarcoid neuropathy (Johnson, unpublished observation), both conditions with perineurial injury [1].

We conclude that, for unknown reasons, the perineurial barrier of some fascicles in solitary limb nerves is rendered incompetent for a distance, resulting in compartmentalization from the proliferation of endoneurial fibroblasts and their transformation into perineurial cells. This proliferation proceeds to the extent that an onion bulb of perineurial cells surround individual myelinated nerve fibers, resulting in a mass lesion. Nerve trauma may be a contributing mechanism to the development of this lesion, since compartmentation develops in clinical and experimental nerve injuries. Also, we found traumatic neuroma foci in two of our cases. An alternative explanation for the presence of neuromatous foci may be that the expanding mass of the hypertrophic nerve may in itself be the injuring entity. In any event, there is a reactive proliferation resulting in a lengthy scar. The resulting mass effects produce nerve fiber injury such that paresis in the distribution of the nerve ensues. Since localized nerve hypertrophy is a reactive rather than true neoplastic condition, regrowth following partial removal has not been recorded.

Acknowledgements. The authors would like to acknowledge Teri Heiskell for secretarial assistance, Gist Farr, MD, for referring cases 1, 2, and 3, and Drs. John Kaiser and John McGill for referring case 4.

References

1. Asbury AK, Johnson PC (1978) Pathology of peripheral nerve. Saunders, New York, pp 190–193
2. Bilbao JM, Khoury NJS, Hudson AR, Briggs J (1984) Perineurioma (localized hypertrophic neuropathy). Arch Pathol Lab Med 108:557–560
3. Boker DK, Schoenber F, Gullotta F (1984) Localized hypertrophic neuropathy – A rare, clinically almost unknown syndrome. Clin Neuropathol 3:228–230
4. Cajal SRY (1959) Degeneration and regeneration of the nervous system, vol 1. Hafner Publishing, New York, pp 198–204
5. de los Reyes RA, Chason JL, Rogers JS, Ausman JI (1982) Hypertrophic neurofibrosis with onion bulb formation in an isolated element of the brachial plexus. Neurosurgery 8:397–399
6. Grossiord A, Lapresle J, Lacert P, Appeloig E (1968) A propos d'une forme localisée de nevrite hypertrophique. Rev Neurol (Paris) 119:248–252
7. Hawkes CH, Jefferson JM, Jones EL, Smith WT (1974) Hypertrophic mononeuropathy. J Neurol Neurosurg Psychiatry 37:76–81
8. Hirose T, Sano T, Hizawa K (1986) Ultrastructural localization of S-100 protein in neurofibroma. Acta Neuropathol (Berl) 69:103–110
9. Imaginario JDG, Coelho B, Tome F, Luis MLS (1964) Nevrite interstitielle hypertrophique monosymptomatique. J Neurol Sci 1:340–347
10. Lallemand RC, Weller RO (1973) Intraneural neurofibromas involving the posterior interosseous nerve. J Neurol Neurosurg Psychiatry 36:991–996
11. Mitsumoto H, Wilbourn AJ, Goren H (1980) Perineuroma as the cause of localized hypertrophic neuropathy. Muscle Nerve 3:403–412
12. Morris JH, Hudson AR, Weddell G (1972) A study of degeneration and regeneration in the divided rat sciatic nerve based on electron microscopy. IV. Changes in fascicular microtopography, perineurium and endoneurial fibroblasts. Z Zellforsch 124:165–203
13. Nesbitt JA, Acland RD (1980) Histopathological changes following removal of the perineurium. J Neurosurg 53:233–238
14. Pearson JMG, Weddell AGM (1975) Perineurial changes in leprosy. Lepr Rev 46:51–67
15. Peckham NH, O'Boynick PL, Meneses A, Kepes J (1982) Hypertrophic mononeuropathy. Arch Pathol Lab Med 106:534–537
16. Roytta M, Salonen V, Pettonen J (1987) Reversible endoneurial changes after nerve injury. Acta Neuropathol (Berl) 73:323–329
17. Seddon HJ (1943) Three types of nerve injury. Brain 66:237–288
18. Simpson DA, Fowler M (1966) Two cases of localized hypertrophic neurofibrosis. J Neurol Neurosurg Psychiatry 29:80–84
19. Snyder M, Cancilla PA, Batzdorf U (1977) Hypertrophic neuropathy simulating a neoplasm of the brachial plexus. Surg Neurol 7:131–134
20. Spencer PS, Weinber HJ, Raine CS, Prineas W (1975) The perineurial window – A new model of focal demyelination and remyelination. Brain Res 96:323–329
21. Thomas PK, Jones DG (1967) The cellular response to nerve injury. 2. Regeneration of the perineurium after nerve section. J Anat 101:45–55
22. Weinberg HJ, Spencer PS (1976) The fate of Schwann cells isolated from axonal contact. J Neurocytol 7:555–569

Received October 5, 1987/Revised July 22, 1988/
Accepted September 29, 1988

Note added in proof. We tested for the presence of epithelial membrane antigen using immunocytochemistry in Cases 1 and 2 and found that there was positive reaction on the outer most cells of the individual hypertrophic onion bulb formations. The perineurium of fascicles without hyalinization and with the hypertrophic onion bulb formations failed to show positive reaction product while those of the intact fascicles exhibited reaction product. Epithelial membrane antigen positivity has been reported as a feature of perineurium [Theaker JM, Gillet MB, Fleming KA, Gatter KC (1987). Epithelial membrane antigen expression by meningiomas, and the perineurium of peripheral nerve. Arch Pathol Lab Med 111:409]. These findings further support the perineurial character of the wrapping cells.