Indian Journal of Anatomy
Volume 6 Number 1, January - March 2017

Ultrastructural Characteristics of Peripheral Nerves in Diabetic Peripheral Neuropathy: Is There a Structure-Function Inter-Relationship

Senthil P. Kumar

Abstract

This letter to editor is aimed at re-exploring the structure-function inter-relationship from an evidence-informed bench-to-bedside perspective for ultrastructural characteristics of peripheral nerves in diabetic peripheral neuropathy (DPN) and its implications for assessment and management of patients. Ultrastructural changes occurred in all parts of the peripheral nerves- axons, cell bodies, dendrites, myelin sheath and endplates.The ultrastructural changes were reported in both sympathetic and parasympathetic fibers, and occurred in both myelinated and unmyelinated nerve fibers. The ultrastructural changes responded to treatment by ponalrestat, an aldose reductase inhibitor. These findings from experimental studies on diabetic rats indicate that the peripheral nerve lesions in human diabetics were mainly due to metabolic impairment of nerve fibers, accompanying dysmetabolism of Schwann cells and diabetic microangiopathy.

Keywords: Ultrastructure; Morphometry; Histochemical Study; Neuroanatomy; Diabetic Neuropathy.

Dear Sir,

This letter to editor is aimed at re-exploring the structure-function inter-relationship from an evidence-informed bench-to-bedside perspective for ultrastructural characteristics of peripheral nerves in diabetic peripheral neuropathy (DPN) and its implications for assessment and management of patients.

Ultrastructural changes occurred in all parts of the peripheral nerves- axons, cell bodies, dendrites, myelin sheath and endplates. Carson et al [1] found axonal degeneration, disruption of myelin, accumulation of electro-dense material in axons, satellite cells and Schwann cells, increased frequency of pi granules of Reich in Schwann cells, enlarged mitochondria, and proliferated and thickened Schwann cell basal laminae in peripheral nerves of rats which correlated with degenerative and regenerative changes secondary to alterations in lipid metabolism.

The ultrastructural alterations in Schwann cells were reported by Sima [2] who found conspisuousearly changes of mitochondrial accumulation of glycogen in the axons and the development of honey-combed Schwann cell-axon networks in peripheral nerves of diabetic insulin-dependent BB-Wistar-rats which later showed axonal dwindling and disintegration in both myelinated and unmyelinated fibers; and by Sima and Robertson [3] who found development of honeycombed Schwann cell-axon networks followed by axonal atrophy in both myelinated and unmyelinated fibers of axons, later accompanied by secondary corrugated myelin breakdown in mutant diabetic mice.

The ultrastructural changes were found in both sympathetic and parasympathetic fibers as shown by Yagihashi and Sima [4] who studied parasympathetic fibers using electron-microscopic and morphometric studies and found increased numbers of axonal glycogenosomes and axonal sequestration in unmyelinated fibers of the diabetic vagus nerve and myelinated fibers of the penile nerve, with diminished fiber size; and by Yagihashi and

Author's Affiliation: Professor and Head, Department of Physiotherapy, School of Allied Health Science and Research, Sharda university, Plot No. 32-34, Knowledge Park III, Greater Noida, Uttar Pradesh 201306.

Corresponding Author: Senthil P. Kumar, Professor and Head, Department of Physiotherapy, School of Allied Health Science and Research, Sharda University, Plot No. 32-34, Knowledge Park III, Greater Noida, Uttar Pradesh 201306.

E-mail: senthilparamasivamkumar@gmail.com

Received | 17.12.2016, **Accepted** | 28.12.2016

Sima [5] who studied sympathetic nerves (paravertebral thoracic ganglion cells, preganglionic myelinated fibers of the white ramus, and postganglionic unmyelinated fibers of the gray ramus communicans) using ultrastructural and morphometric techniques and found pre-ganglionic axonal dystrophy, the ganglionic cells had decreased number of synapses, and the postganglionic fibers in the gray ramus had an increased number of glycogenosomes, axonal sequestration, and reduction in axonal size, accompanied bydegenerative changes of myelin sheaths, various kinds of cytoplasmic inclusion bodies (crystalloid, lamellar inclusion bodies and lipids-like droplets), aggregates of glycogen particles in the Schwann cell cytoplasm and basement membrane hyperplasia of Schwann cells.

In addition, Schmidt et al [6] studied prevertebral and paravertebral sympathetic and vagal parasympathetic structures in hamsters and found large numbers of markedly dilated axons, suggestive of neuroaxonal dystrophy. Dystrophic axons were also found to contain substance P- and gastrin-releasing peptide (gastrin-releasing peptide/ bombesin)-like staining but were not found to be labeled by antisera directed against vasoactive intestinal peptide, dynorphin-B, somatostatin, leu- and met-enkephalin and neuropeptide tyrosine; and Schmidt and Plurad [7] examined Ileal mesenteric nerves of streptozotocin(STZ) diabetic rats and found neuroaxonal dystrophy with dystrophic axons present in superior mesenteric gangliawhich also had increased number of postsynaptic dendritic processes dilated by unusual tubular profiles.

The ultrastructural changes occurred in both myelinated and unmyelinated nerve fibersas shown by Yagihashiand Matsunaga [8] who found axonal degeneration in sural nerves of diabetic rats, with following structural changes of the axons: axonal dwindling, depletion of axoplasmic organelles, vacuolarization and an increase in neurofilaments.

Treatment-induced ultrastructural effects were reported by Yagihashiet al [9] who found beneficial effects of ponalrestat, an aldose reductase inhibitor in STZ-induced diabetic rats, by reduced sorbitol and fructose levels, normalizing myo-Inositol levels andmyelinated nerve fiber size and fiber occupancy of sural nerves.

The findingsfrom experimental studies on diabetic rats indicate that the peripheral nerve lesions in human diabetics were mainly due to metabolic impairment of nerve fibers, accompanying dysmetabolism of Schwann cells and diabetic microangiopathy. Can future randomized clinical trials examine the therapeutic effects in terms of changes in ultrastructural characteristics so that a bench-to-bedside translation of evidence into practice could be implemented in diabetes care?

References

1. Carson KA, Bossen EH, Hanker JS.Peripheral neuropathy in mouse hereditary diabetes mellitus. II. Ultrastructural correlates of degenerative and regenerative changes.NeuropatholApplNeurobiol. 1980; 6(5):361-74.
2. Sima AA.Peripheral neuropathy in the spontaneously diabetic BB-Wistar-rat.An ultrastructural study.ActaNeuropathol. 1980; 51(3): 223-7.
3. Sima AA, Robertson DM.Peripheral neuropathy in the diabetic mutant mouse. An ultrastructural study.Lab Invest. 1979; 40(6):627-32.
4. Yagihashi S, Sima AA.Diabetic autonomic neuropathy in BB rat.Ultrastructural and morphometric changes in parasympathetic nerves. Diabetes. 1986; 35(7):733-43.
5. Yagihashi S, Sima AA.Diabetic autonomic neuropathy in the BB rat.Ultrastructural and morphometric changes in sympathetic nerves. Diabetes. 1985; 34(6):558-64.
6. Schmidt RE, Plurad DA, Plurad SB, Cogswell BE, Diani AR, Roth KA.Ultrastructural and immunohistochemical characterization of autonomic neuropathy in genetically diabetic Chinese hamsters. Lab Invest. 1989; 61(1):77-92.
7. Schmidt RE, Plurad SB.Ultrastructural and biochemical characterization of autonomic neuropathy in rats with chronic streptozotocin diabetes.J NeuropatholExp Neurol. 1986; 45(5):525-44.
8. Yagihashi S, Matsunaga M.Ultrastructural pathology of peripheral nerves in patients with diabetic neuropathy. Tohoku J Exp Med. 1979; 129(4):357-66.
9. Agihashi S, Kamijo M, Ido Y, Mirrlees DJ.Effects of long-term aldose reductase inhibition on development of experimental diabetic neuropathy. Ultrastructural and morphometric studies of sural nerve in streptozocin-induced diabetic rats. Diabetes. 1990; 39(6):690-6.