Case Report

# Isoniazid intoxication

## Light and electron microscopic findings in muscle and sural nerve biopsies

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## ABSTRACT

This study indicates the cellular and ultrastructural changes of the thigh muscle and sural nerve biopsies of a patient intoxicated as a result of isoniazid intake for tuberculosis treatment. The observation of the relative degradation of myelination and fibre type II groups was apparent. The regular concentric layers of the myelin sheath were destroyed. There was a consistent increase in irregular vacuolization and membranous structures in the axon and the cytoplasm of the Schwan cells. It is concluded that poisoning cannot be attributed solely to the axonal degradation but also to the direct toxic effect of the drug.

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The toxic effect of chemicals and drugs on the peripheral nervous system and skeletal muscle fibers is of major importance in estimating and judging the vast effects of medicinal, occupational, and environmental exposure. One of the most common systemic diseases to cause peripheral neuropathy is treatment with steroids and cytotoxic agents.[1,2] Treatment with isoniazid (INH) has been advocated in tuberculosis (TB) subjects.[3,4] In this paper, we report an incidence of both sural neuropathy and myopathy in a patient with TB receiving steroid treatment. Furthermore, this study aims to investigate changes in axonal degeneration and muscle fiber types affected by INH treatment.

Case Report. The patient aged 70 years, was found to have mild weakness of both hip flexions; subsequently he was admitted to hospital where a lymph node biopsy revealed caseating granuloma. All of the biopsies were processed in full according to current standard methodologies in nerve and muscle biopsies using frozen sections for enzyme histochemistry and fresh samples for electron microscopy.[5,6]

***Light microscopy.*** Frozen sections stained with hematoxylin and eosin show muscle fibers with marked variation in muscle fiber size (**Figure 1**). There was no muscular degeneration, fat replacement, fibrosis, or increased endomysial connective tissue. Fiber atrophy in between hypertrophied muscle fibers with many angulated fibers was seen. Internalization of nuclei was noted in 20% of the fibers. Sections stained for myofibrillar adenosine triphosphatase (pH 9.4) showed fibers committed to type II with strong staining in 40% of the fibers. Type I fibers comprised 60% with atrophied fibers of 2 groups. There were grouping of type II fibers.

***Electron microscopy.*** Sections of the long and cross sections of the nerve show areas of myelin interruption with lysis and fragmentation into small ovoids and zebra like bodies. Edema was seen between the nerve fibers. Vesicles were seen in the

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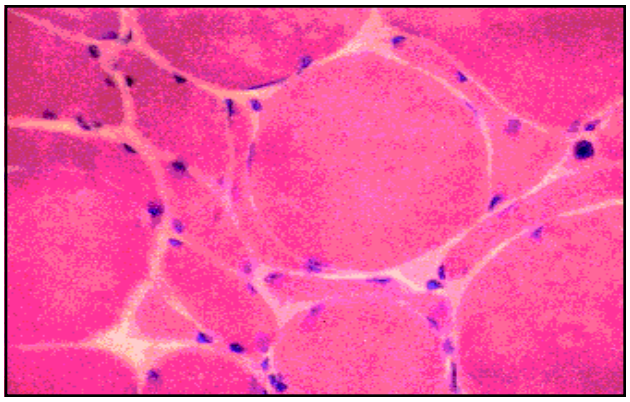

Figure 1 - Muscle biopsy from a patient aged 70 years, showing increased variation in fiber size and shape (Hematoxylin and Eosin x 300).

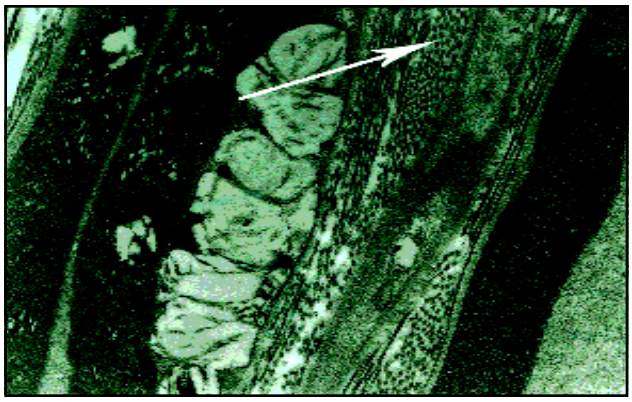

Figure 2 - Isoniazid neuropathy, one year after onset of isoniazid-application. Unusual myelinated axon with focal accumulation of inclusions. Electron optically empty vacuoles with an axon and accumulation of collagen fibers seen in the stroma of nerve fibers (arrow) (x 18500).

mitochondria of the axon and collagen fibers were seen in the stroma between the nerve fibers. Schmidt Lanterman incisura were obliterated in some areas (**Figure 2**).

Discussion. The case reported in this study showed distinctive features of muscle weakness, loss of knee jerks and numbness of both lower limbs which together with the progressive nature of these symptoms, were highly suggestive of axonal neuropathy and muscle fiber changes. The axonal neuropathy with secondary myelination degradation and type II fiber grouping confirmed by a muscle biopsy analysis were consistent with toxic effect of INH. This information will have considerable implications for patients with anti-TB treatment in terms of prognostic advice and counseling, and will help to identify the true impact of anti-TB drugs without pyridoxine coverage as reported in this case. We have been able to show that the selective pattern of muscle fiber changes described in this patient is a distinctive feature for INH effect on peripheral neuropathy and skeletal muscle fiber distribution.[7]

It is reported that INH produces a characteristic pattern of axonal degeneration involving selectively the sensory component of the sural nerve.[8] This axonal degeneration is expressed clinically as a symmetric, distal, sensorimotor polyneuropathy resulting from myelin degradation showing manifold forms of lysis and fragmentation into small ovoids.

In most of the micrographs, numerous degenerated nerve fibers, unstructured myelin sheaths and myelin ovoids were observed. The particular effect of INH on muscle fiber types has also been reported.[9,10] In our light microscopic examination, grouping of type II muscle fibers was apparent in muscle biopsies. The structural changes characterized by variation in muscle fiber size and presence of angulated muscle fibers express a probable functional abnormality due to INH intoxication. These pathologic changes can be attributed to both the axonal degeneration and INH toxicity. As a result, it can be concluded that the muscle degenerations in INH intoxication can not be attributed to the axonal degeneration, but to the direct toxic effects of INH on muscle fibers as well.

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