The pathological diagnosis of nerve biopsies: a practical approach

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Abstract

The approach to the neuropathological assessment of nerve biopsies is the main focus of this review. Nerve biopsies are invasive diagnostic procedures resulting in a permanent neurological deficit, and are therefore carried out only following an in-depth clinical assessment including laboratory, imaging, electrophysiological, and where appropriate also genetic studies. This review will outline the key diagnostic approaches and will discuss neuropathies relevant in clinical practice, caused by vasculitis, inflammatory demyelination, dysproteinaemic, amyloid, toxic agents, and neuropathies due to genetic conditions.

Keywords amyloid neuropathy; axonal; demyelination; dysproteinaemic neuropathy; genetic neuropathy; inflammatory neuropathy; neuropathy; vasculitis

Introduction

This review considers nerve pathology in the context of diagnostic nerve biopsies as part of the clinical workup. Therefore, the focus of this review is the diagnostic approach with practical considerations for the preparation, processing and staining of samples and an appraisal of the use of different techniques to achieve a clinically relevant and meaningful diagnosis. An overview of the pathology of the most common peripheral neuropathies will be provided.

Peripheral neuropathies can be acquired or genetic, and have an acute, subacute or insidious (chronic) onset. They can present at any age with no gender predilection. Whilst nerve conduction studies (NCS) are helpful in differentiating axonal from demyelinating neuropathies in most instances, occasionally the interpretation can be difficult. Furthermore, NCS do not inform about the underlying cause of either axonal or demyelinating neuropathy. Laboratory tests, such as assessment of antibody titres can suggest inflammatory, dysproteinaemic or infiltrative processes, but are not confirmatory on their own. The treatment options vary depending on the underlying pathology, hence the necessity of a nerve biopsy.

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Indication for nerve biopsies

The ENMC International workshop[1] defined the following for patients groups in an attempt to define indications for nerve biopsies:

1) Patients in whom sural nerve biopsy will be diagnostically helpful
2) Patients in whom sural nerve biopsy will have therapeutic implications
3) Patients who are at risk for complications from sural nerve biopsy
4) Patients who will definitely not benefit from sural nerve biopsy.

Sural nerve biopsy is helpful in inflammatory and dysimmune neuropathies, specifically vasculitis and chronic inflammatory demyelinating neuropathy, possibly in leprosy and some forms of genetic neuropathies (which over time are increasingly replaced by genetic testing of the patient). A nerve biopsy is more often diagnostic in acute and subacute forms than chronic forms.

The indication for the biopsy of a peripheral nerve can vary according to the clinical context and is strongly indicated in many conditions such as acute or subacute multiple mononeuropathies, subacute, or chronic axonal sensory motor polyneuropathies with rapid evolution, in CIDP where clinical and electrophysiological features are compatible with this diagnosis but where additional clinical symptoms raise the possibility of additional diseases, and in the final step in the diagnostic workup of a neuropathy of unknown origin.

Acquisition and preparation of samples

The specimen should be obtained from an affected nerve. The most common biopsy site is the sural nerve, as it is relatively easy to access surgically. The sural nerve is purely sensory in more than 90% of patients and contains only few motor fibres in the remaining patients.[2] A biopsy of the sural nerve will result in a permanent deficit, which is independent of the length of the specimen and therefore at least 4 cm should be obtained. Because nerve biopsy is invasive, costly and associated with possible morbidity, it is highly recommended that sufficient tissue is taken so that multiple blocks of tissue can be embedded. Removal of shorter segments will be less useful diagnostically and may limit the diagnostic value. After excision, the biopsy has to be handled with care in order to minimise mechanical injury to the sample.

The nerve biopsy should be divided (transversely) and one part should be formalin-fixed and another glutaraldehyde fixed. The formalin-fixed and paraffin processed specimen should contain representative longitudinal and transverse sections. A portion of the glutaraldehyde fixed nerve will be processed into resin for the preparation of semithin resin sections (Figure 1) and optional subsequent electron microscopy. A further proportion should be kept for optional subsequent preparation of teased fibres.

A normal sural nerve usually comprises between five and ten nerve fascicles. In a large autopsy study, 3300–8000 myelinated and 10,500–45,500 unmyelinated nerve fibres were found in subjects without history of disease or ingestion of drugs known to affect peripheral nerve.[3]

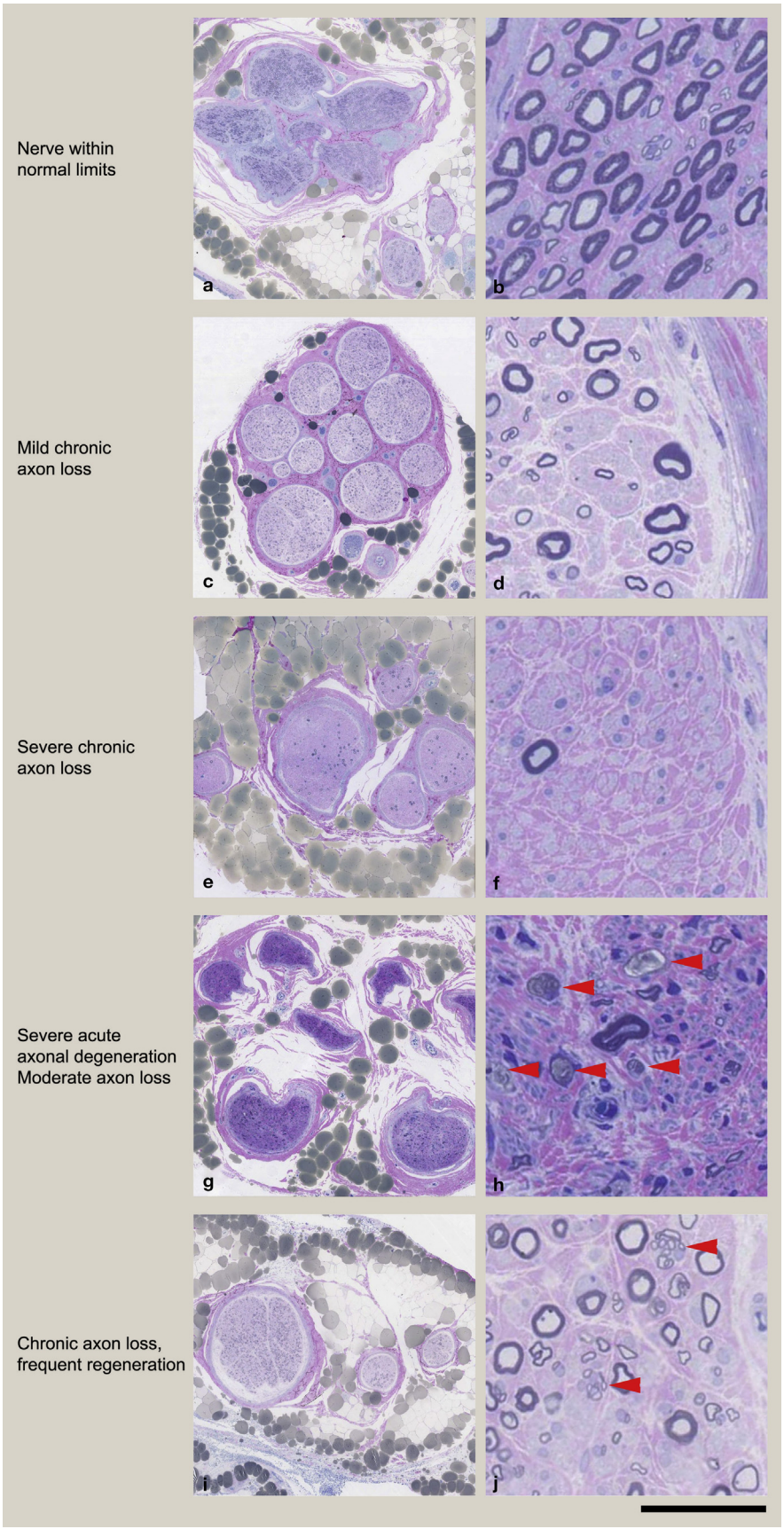

Figure 1 Neuropathological features of axonal neuropathies: cross sections of nerve biopsies on resin semithin sections stained with MBA-BF. The left column shows an overview (equivalent to the 5× objective) and the right column the same nerve at high magnification (equivalent to the 40× objective). (**a**, **b**): nerve within normal limits, showing a population of large and small myelinated fibres. (**c**, **d**): this nerve biopsy shows a mild loss of axons with no visible degenerating fibres. (**e**, **f**): this nerve biopsy shows a very severe chronic axon loss with only rare myelinating fibres remaining. No profiles of degenerating axons are seen. (**g**, **h**): this nerve biopsy shows an ongoing (active) axon degeneration. Arrowheads in (**h**) indicate degenerating axon profiles. (**i**, **j**), this nerve with a moderately severe axon loss shows several regeneration clusters (arrowheads in **j**).