Principles of Peripheral Nerve Pathology

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Pathobiology

The peripheral nervous system (PNS) connects peripheral sensory and motor end organs to the central nervous system and provides the electrophysiological base for conscious and unconscious reactions to the outer environment. As much as the molecular and subcellular equipment of peripheral nerve cell components resemble those of the CNS, the type and composition of their vasculature, immediate (myelin) and peripheral (mesenchymal) sheaths and supporting cells differ.

Hence, the CNS-PNS compound axon, immediately after emergence from the CNS is enwrapped by Schwann cells that in a chain continue down to the terminal muscle junction or sensory end organ. The interface between central oligodendrocyte and peripheral Schwann cell is called transition node (of Ranvier) and marks the origin of the nerve root. Under pathological conditions the CNS-PNS border shifts into one or the other direction.

The peripheral nerve, in a strict sense, arises from the nerve root after the periradicular sheath (meningeal origin) transits into epi- and perineurium and gains lymphatic drainage. Moreover, the PNS contains nerve cell conglomerates (ganglia) for distal autonomic reflexes and for feeding sensory information into the CNS, via centripetal axons of the dorsal root. These nerve cells are supported by peripheral glial cells (satellite cells) but they are not protected by a considerable blood-tissue barrier in contrast to the brain and (to a lesser content) the peripheral nerve trunk. The same holds true for the distal nerve endings.

This varying cellular composition, and hence metabolic demands, exposure, protective and nursing mechanisms already suggest different tissue biologies, disruption of which causes distinct radiculopathy, gangliopathy, neuropathy and junctionopathy.

In contrast to neuronopathies (lower motor neuron disorders, sensory ganglioneuropathy) and junctionopathies (myasthenia), peripheral neuropathies rarely affect one single functional system only. Instead, focal lesions induce mixed deficits and systemic syndromes reflect the fibre type (myelinated vs unmyelinated; large vs small)

independent of their direction of conduction (afferent/sensory; efferent/motor). Hence, large fibre neuropathies affect motor fibres and large fibre senses (pressure, proprioception) whereas small fibre neuropathies involve pinprick or diffuse pain, thermic senses and autonomic nerve function.

Topography & Distribution

Peripheral neuropathies may affect one nerve only in the course of mononeuropathy or monomelic neuropathy, or it can affect multiple nerves in symmetric (polyneuropathy) or asymmetric (multiple mononeuropathy) fashion.

As a matter of fact, systemic disturbances that primarily interfere with the conductive components (axon, myelin sheath) lead to symmetric pictures. Mononeuropathies most commonly arise from focal injury, compression, infiltrative disorders (tumour > inflammation) and occlusive vascular disease. Asymmetric affection of multiple nerves is common in primary inflammatory neuropathies, vasculitis and demyelinating neuropathies with liability to pressure palsy.

Apart from their segmental distribution, neuropathies may be characterized by proximodistal clinical (e.g. distal axonopathy) or electrophysiological (e.g. radiculoneuritis) disease gradients. Typical for so-called dying back neuropathies is the dysfunction of laryngeal abductor muscles, as the recurrent laryngeal nerve is one of the longest nerves of the body.

Electrophysiology and affected functional subunits

Depending on their impact on nerve fibre excitability and continuity, PNS disorders clinically are characterized by functional deficits (motor, sensory) or neuropathic pain. Both denervation of nerve endings and their silencing due to conduction failure convergently lead to end organ dysfunction. Hence, LMN paralysis of a muscle by itself cannot tell at which level of the lower motor unit the failure took place nor what the actual pathomechanism is. At this point, nerve conduction studies (NCS) and electromyography (EMG) come into play, which help to distinguish conduction failures due to loss of insulation (demyelinating neuropathy) or the number of wires (axonal neuropathy), to narrow down the affected nerve region (proximal versus distal) ad conduction blocks and to identify muscle denervation.

Due to differences in their regenerative capabilities, distinction of demyelinating versus axonal disease has been considered to be of prognostic value. Today we know that electrodiagnostic implications are misleading if mixed axon-myelin subunits of the nerve

fibres (node, paranode) are affected or if neutralizing antibodies are involved. That is why nerve biopsies recently went back into focus of advanced neurodiagnostics.

Pathological presentation

Common indications for a surgical approach to peripheral nerves are….

1. Explorative:
   a. Exploration of a suspected focal lesion.
   b. Procurement of nerve biopsy.

2. Interventional/curative:
   a. Decompressive (e.g. neurolysis)
   b. Resection of a focal nerve lesion (e.g. tumour)
   c. Reconstructive (e.g. neurorrhaphy, grafting)
   d. Neuroplastic (e.g. neurotisation)
   e. Vagal nerve stimulator implantation

For both diagnostic and therapeutic approaches (excl. graft excision), the surgeon aims for a diseased nerve prelocalised through neurological findings, imaging and/or electrodiagnostics. On external inspection in situ, normal nerves contain fascicles that are continuous, with distally tapering diameters, whitish, evenly vascularized and present with translucent perineurium that allows for detection of Fontana bands upon oblique illumination.

Loss of Fontana bands indicates loss of myelinated fibres and/or extensive oedema, fibrosis or other types of cellular infiltration.

Focal discolouration or enlargement stand for either nerve injury or other neuropathies with significant interstitial changes. Amongst the latter, peripheral nerve tumours and inflammation predominate but might be imperceptive from neuroma if nodular in appearance. Focal longitudinal enlargement, in particular if plexiform or extending into multiple branches, most often resembles neoplasm. Diffuse enlargement of multiple nerves, on the other hand, requires consideration of neurolymphomatosis, inflammatory nerve diseases and hypertrophic neuropathy, in juvenile pure-bred animals with systemic dysfunction. Notably, nerve root compression results in fascicular enlargement

as well, while in peripheral nerves, it rapidly leads to hour-glass attenuation (demyelinating stage) or distal atrophy (axonal stage). Be aware that it may be a gain of epineurial fat or fibrous tissue that masks fascicular atrophy and that may be taken as biopsy by mistake.

Occasionally, focal nerve enlargement is due to concentric mesenchymal tumours, causing constrictive neuropathy. Depending on the stage of endoneurial compromise, extraneural proliferation may become obvious on neurolysis or transverse sectioning of fascicle. Again in compressive radiculopathy, the periradicular sheath undergoes concentric fibrosis with compression of the endoneurium. Endoneurial types of asymmetric nerve root enlargement, on the other hand, can result from extensive interstitial neuritis in protozoal disease and as a consequence to nucleus pulposus extrusion. Symmetric endoneurial enlargement of roots and plexuses more often arise from recurrent demyelinating autoimmune neuropathy and again from neurolymphomatosis.

Despite these presentations, the majority of inflammatory neuropathies in domestic animals are directed at specific nerve fibre components and rarely go with any macroscopic change of the fascicle. Even though the target epitopes are symmetrically distributed, the lesions may be not. Thus, clinical presentation of these is highly variable. The same holds true for vasculitic neuropathies. They often are part of a systemic connective tissue disorder and non-neural manifestation (e.g. joint involvement) requires specific testing.

Symmetric polyneuropathies (SPN) can be approached diagnostically by obtainment of nerve biopsies (after electrophysiological verification) from well-established sites that harbor low risk of procedural complications. If proximodistal gradients are seen, paired proximal and distal samples facilitate aetiological diagnosis. With the exceptions mentioned above, gross abnormalities are not present in SPN. Instead, they go with microscopic nerve fibre changes accompanied by a variable extent of non-specific endoneurial fibrosis. Therefore, a reliable diagnosis requires specific preservation and visualization of axonal and myelin features. These structures are not adequately preserved in standard FFPE histology and require recruitment of special services.

This is prerequisite, as reaction of the nerve fibre to systemic disturbances manifests in convergent pictures deciphering of which often relies on ultrastructural changes or identification of functional fibre subunits via nerve fibre teasing. Nerve fibres, assessed that way allow for determination of the type and specific distribution of axonal versus myelin sheath impairment and to narrow down differentials according to the VITAMIN D scheme.

After exclusion of immune-mediated events and inherited neuropathy, most SPN are attributable to malnutritive/metabolic/endocrine, toxic and paraneoplastic disorders. As

much as nerve histology can offer surrogates, the definite diagnosis remains a clinical one implementing clinical data from pedigree history, feeding scheme, exposure to toxins, vaccination and infection history, blood work, metabolic screen, genetic testing and response to preceding therapy.

In about 90% of focal neuropathies and 80% of asymmetric polyneuropathies, pathology of the lesions is conclusive of the underlying aetiopathogenesis. In SPN, only 20% of canine and 45% of feline nerve examinations unravel the cause of disease immediately. The rate improves to 50% and 85%, respectively, after implementation of specifically requested clinical data. As SPN diagnoses are based on the context, provide as much relevant information as possible and be available for case discussions after the morphological diagnosis has been issued by the nerve pathologist.