

Peripheral Nerve Sheath Tumours: what can we learn from genetic syndromes?

This article provides an overview of peripheral nerve sheath tumours (PNSTs), focusing particularly on the settings in which they occur, their pathology, and underlying genetic basis.

Developmental background

During very early development, a process known as neurulation forms the neural tube. From the posterior aspect of this tube, the neural crest is formed, which maintains its neuroectodermal origin but migrates along segmental paths to form the peripheral nervous system and related structures (including, for example, melanocytes). Within the neural crest population are sensory ganglion neurons that will reach their peripheral targets then send out axons back to synapse with the CNS, and Schwann cells (peripheral glia). Schwann cells differ from CNS glia in three main ways. One Schwann cell myelinates only one axon, while oligodendrocytes myelinate many axons. They contain a different type of myelin, including for example 'protein 0' as opposed to the 'myelin basic protein' of CNS glia; and Schwann cells support axon regrowth, whereas myelin from oligodendrocytes has been shown to inhibit axon regeneration.

What is a peripheral nerve sheath tumour?

A PNST is a tumour composed of cells resembling peripheral nerve sheath elements, primarily Schwann cells, but also perineurial cells and fibroblasts. Most of these tumours are benign and are either schwannomas or neurofibromas.^{1,2} These two tumours are distinct entities with varying clinical pictures, different genetic backgrounds, and contrasting prognoses. While schwannomas are almost always benign in nature, a subtype of neurofibroma is prone to malignant transformation. The vast majority of benign PNST represent sporadic tumours, occurring as single lesions. Neurofibromas and schwannomas also commonly occur within the clinical spectrum of neurofibromatosis type 1 and 2 (NF1 and NF2), respectively. Among the malignant PNSTs (MPNSTs), half occur sporadically and half are linked to NF1. They account for 5% of malignant soft tissue tumours and 10% of tumours have been reported to occur at sites of previous irradiation. This has implications for treatment of incompletely resected neurofibromas in patients with NF1.

Clinical Features of PNSTs

Sporadic neurofibromas usually present as painless, either intraneural or extraneural masses. They occur in 5 different locations (see Table 1). In contrast to schwannomas, they are almost never associated with cranial nerves. Sporadic schwannomas arise from spinal and cranial nerves, also peripheral nerves in the head and neck, and extensor aspects of the extremities. Commonly the VIIIth (vestibular/acoustic) cranial nerve, or occasionally the

Vth cranial nerve is affected. Vestibular (acoustic) schwannomas are commonly known as neuromas, but this is a misnomer as they are tumours of Schwann cells, not neurons. Depending on the location, the symptoms may vary and include hearing difficulties and facial paraesthesias from vestibular schwannomas, or pain and other symptoms from spinal nerve/cord compression. MPNSTs usually present as progressively enlarging masses, often in the extremities, or in a spinal location where they commonly present with pain.

Pathology of PNSTs

Both schwannomas and neurofibromas are benign tumours that by definition are WHO grade I, and thought to arise from mutated Schwann cells. Macroscopically, schwannomas are said to exist as a single mass with peripheral nerve stretched along one aspect, whereas a neurofibroma expands the nerve fascicle and therefore has numerous axons running through it (see Figure 1). Many of the tumour cells stain with antibodies to S-100, which simply reflects their neuroectodermal origin. On closer inspection, these two tumours have many other differences.

Neurofibromas demonstrate uniform histological appearances, featuring a mixture of scattered cell types including neoplastic Schwann cells, perineurial-like cells and fibroblasts, in a matrix of mucoid substances and scattered collagen fibres, typically giving a 'shredded carrots' appearance (Figure 1). Mitotic activity is low.

Schwannomas are usually biphasic in appearance with cellular 'Antoni A' and hypocellular 'Antoni B' areas, palisaded nuclear arrangements into 'Verocay bodies' and a low mitotic rate. Rarer variants include the cellular schwannoma with a higher reported proliferation rate, and others.

Malignant PNSTs

MPNSTs are relatively rare, clinically aggressive and morphologically variable, with a tendency towards divergent mesenchymal differentiation. As these tumours often arise from a precursor lesion (plexiform neurofibroma) they are also thought to be Schwann cell-derived. They classically have densely cellular fascicles, a high mitotic rate and



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Table 2: A Comparison of NF1 and NF2.

	NF1	NF2
<i>Frequency of disease</i>	<i>Approx. 1 in 3000</i>	<i>Approx. 1 in 40 000</i>
<i>Genetics</i>	<i>AD</i>	<i>AD</i>
<i>Mutated protein</i>	<i>Neurofibromin chr17q11</i>	<i>Merlin/Schwannomin chr22q12</i>
<i>Classical PNST features</i>	<i>Neurofibromas, either multiple, or a single plexiform lesion</i>	<i>Schwannomas, typically of vestibular nerve, and classically bilateral</i>
<i>Propensity for malignant transformation</i>	<i>5% of plexiform neurofibromas; 50% of MPNSTs are linked to NF1</i>	<i>Schwannomas may very rarely undergo malignant transformation.</i>
<i>Other possible Neurological features</i>	<i>Sphenoid wing dysplasia, Macrocephaly, Epilepsy, Glial tumours (optic nerve)</i>	<i>Meningiomas Glial tumours</i>
<i>Other clinical features</i>	<i>Café au lait spots, Axillary freckling, Sarcomas, Lisch nodules in iris</i>	<i>Posterior subcapsular lens opacity, Cerebral calcification</i>
AD = autosomal dominant		

Table 1: Neurofibromas occur in five different locations.

• <i>cutaneous nodule (most common)</i>
• <i>circumscribed mass in a peripheral nerve</i>
• <i>plexiform enlargement of a major nerve trunk (plexiform neurofibroma)</i>
• <i>diffuse but localised involvement of skin and subcutaneous tissue</i>
• <i>extensive involvement of soft tissue of a body area (localised gigantism)</i>

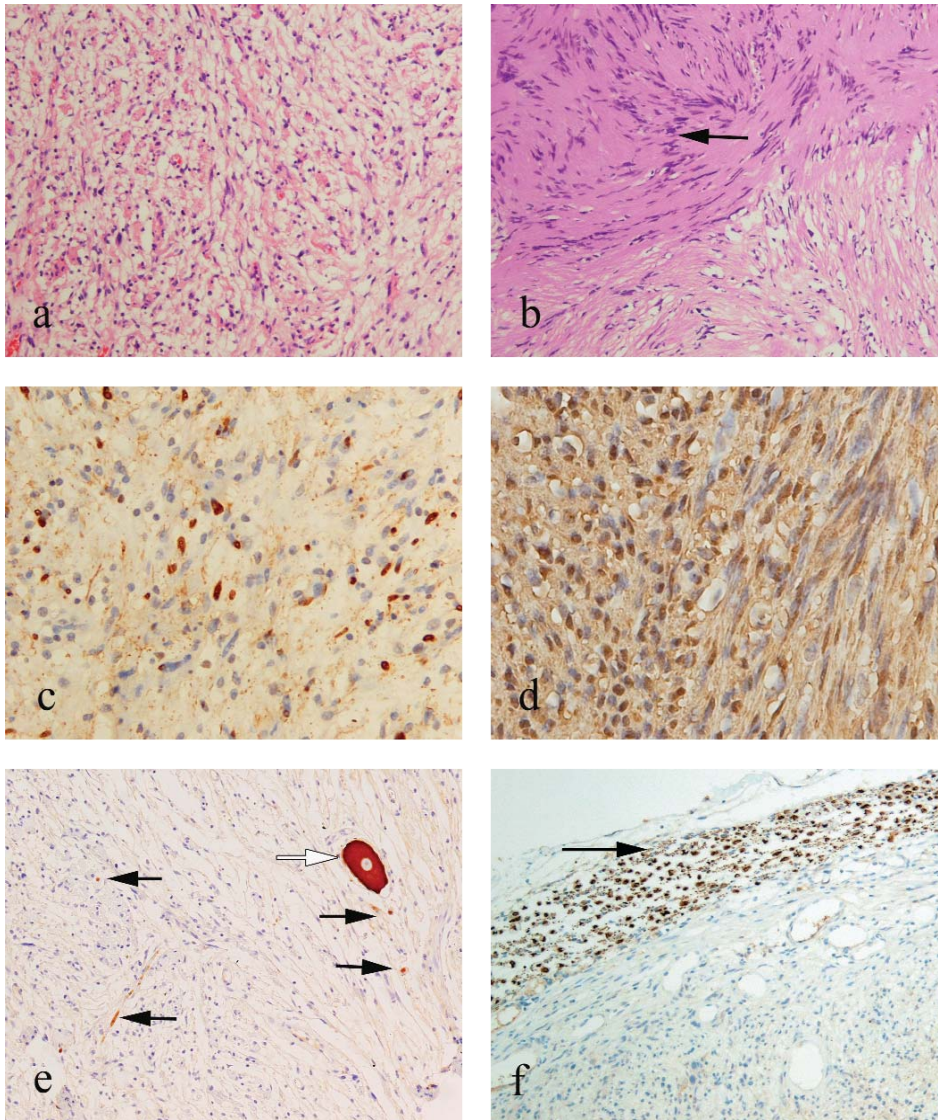


Figure 1: Comparison of typical histological features of neurofibroma (pictures on the left), versus schwannoma (on the right).

- a- Haphazardly arranged cells with wavy nuclei, including neoplastic Schwann cells, perineurial-like cells and fibroblasts on a background of mucoid material and strands of collagen, H&E
- b- Biphasic architecture of a schwannoma with compact Antoni A pattern featuring Verocay bodies (arrow), and loosely textured Antoni B tissue (bottom right), H&E
- c- Neurofibroma showing S-100 reactivity in neoplastic Schwann cells only
- d- Schwannoma showing more widespread S-100 immunopositivity.
- e- Neurofibromas grow within nerves, trapping both axons (black arrows) and an occasional ganglion cell (white arrow), (neurofilament protein, NFP, immunohistochemistry).
- f- Schwannomas displace the nerve containing NFP-positive axons (arrow) towards the periphery.

necrotic areas. Immunohistochemically, the majority (50-70%) of tumours express S-100, but this is only seen in scattered neoplastic cells. A minority of cases demonstrate unusual histological features such as epithelioid morphology (epithelioid MPNST) and divergent differentiation (glandular MPNST, malignant Triton tumour). The WHO classification of tumours assigns a grade III or IV to this neoplasm and its variants. The differential diagnosis for a malignant PNST is wide, including cellular schwannoma/neurofibroma, sarcoma, and, in a gastrointestinal location, gastrointestinal stromal tumour (GIST) or gastrointestinal autonomic nerve tumour (GANT).

Investigations

Depending on the site of the lesion and the overall clinical picture; dermatological, neurological, radiological, pathological and genetic

investigations may be necessary.³ Bilateral vestibular schwannomas are pathognomonic for NF2 (Figure 2), and a number of dermatological lesions are characteristic of NF1 (see Table 2). In both NF1 and NF2, approximately half of all cases are due to newly acquired germline mutations, and there is no family history; however the genetics are largely understood and testing can be performed.

Neurofibromas and NF1

Although any subtype of neurofibroma may be seen, the cutaneous and plexiform types are characteristic of NF1. Within the diagnostic criteria for NF1⁴, a patient has two or more neurofibromas of any type or one plexiform neurofibroma. Although mostly histologically benign, many neurofibromas will grow throughout life and may cause severe disfigurement, sometimes impairing vital functions.

Plexiform neurofibromas have an approximate 5% risk of malignant transformation.

Schwannomas and NF2

NF2 associated vestibular schwannomas tend to differ from sporadic schwannomas by way of their early age of presentation, lobulation and classical eventual bilaterality. They show similar clinical presentations to sporadic schwannomas, namely hearing difficulties, or spinal symptoms. Apart from the common type, the variant of plexiform schwannoma is typically seen in NF2. Recently, the diagnostic criteria for NF2 have been revised: while the original criteria for NF2 required a family history of the disease or bilateral vestibular schwannomas,⁵ the current diagnostic criteria are based on the facts that other lesions often precede vestibular schwannomas, and that a family history is lacking in 50% of cases.⁶

Schwannomatosis

Schwannomatosis is a recently recognised third major form of neurofibromatosis that causes multiple schwannomas without vestibular schwannomas.⁷ Patients with schwannomatosis represent 2.4 to 5% of all patients requiring schwannoma resection and approximately one third of patients with schwannomatosis have tumours limited to a single limb or segment of spine. Epidemiologic studies suggest that schwannomatosis is as common as NF2, but that familial occurrence is rare. Patients with schwannomatosis present with pain which remains the primary clinical problem and indication for surgery. Revised diagnostic criteria have recently been published.⁸

Genetic background Neurofibromas

The NF1 gene encodes the protein neurofibromin, which is highly expressed in the nervous system. It reduces cell proliferation via both the inactivation of the proto-oncogene p21/Ras, and the control of a kinase (serine/threonine kinase mTOR).⁹

Both sporadic and NF1-associated neurofibromas have been shown to harbour mutations in the NF1 gene or carry deletions affecting the gene.¹⁰ There is no hot-spot mutation in the gene, and numerous mutations have been identified. Interestingly, significant differences in gene expression were found between dermal and plexiform neurofibromas.¹¹

Schwannomas

Mutations in the NF2 gene are implicated in the formation of sporadic and NF2-linked schwannomas. In most cases, loss of the remaining wild-type allele of the gene on chromosome 22 is associated with the NF2 mutation (akin to Knudson's two-hit hypothesis¹²). Loss of the NF2 protein merlin/schwannomin appears to be the majority feature of schwannomas, strongly suggesting this as a critical event in schwannoma formation. Merlin is linked to the actin cytoskeleton and has several functions, including inhibition of proliferation.¹³ Similar to NF1, the NF2 gene has not demonstrated hot-spot mutations, and sporadic lesions cannot be genetically differentiated from NF2-linked cases.

Familial Schwannomatosis

This is not linked to NF2 mutations but has recently been reported to be associated with germline mutations of INI1/SMARCB1.^{14,15}

MPNST

The mutations seen in NF1-associated benign neurofibromas are also seen in MPNSTs in patients with NF1. Sporadic MPNSTs also have NF1 gene mutations, probably due to their origin. Genetic events implicated in malignant transformation from neurofibroma to MPNST include mutations of p53 and CDKN2A, genes which are involved in cell cycle control. Unlike other sarcomas, no specific chromosomal changes have been demonstrated. Recently, expression array studies have revealed differentially regulated genes ('signatures') for MPNST versus neurofibromas, but again no differences between those that were sporadic and those that were linked to NF1.^{11,16}

Summary

Peripheral nerve sheath tumours are common, mostly benign and usually sporadic tumours with considerable clinical significance due to their association with the neurofibromatoses (NF1, NF2 and the more recently recognised familial schwannomatosis). The most frequent PNSTs are schwannomas and neurofibromas, the latter of which can show malignant transformation (plexiform subtype). Malignant PNSTs are strongly linked to NF1 (50%). The genetic background of PNSTs is largely known, and while genetic testing is possible for all neurofibromatoses, the specific clinical presentation of neurofibromatosis 1 or 2, or even schwannomatosis, is often pathognomonic. Diagnostic criteria for NF2 and schwannomatosis have recently been revised.

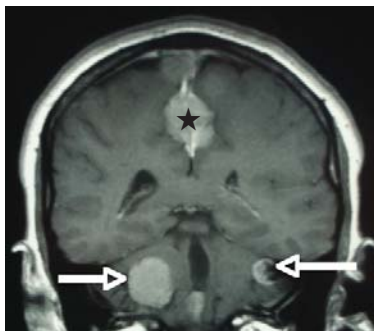


Figure 2: T1-weighted, contrast-enhanced MRI showing coronal section of brain (hemispheres, cerebellum/brain stem). The two arrowed lesions are bilateral vestibular schwannomas. A parasagittal meningioma (star) is also seen. This combination is characteristic of NF2 (picture kindly provided by Mr JR Pollock, Consultant Neurosurgeon, Queen's Hospital).

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