MRI imaging of thick peripheral nerves and differential diagnosis in adult population

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Learning objectives

In this study, we propose to

- Overview the major diseases which involve the peripheral nerves in adults with regard to MRI findings in review of literature.

- To exemplify some of the frequently encountered diseases and some rare entities that may involve a single peripheral nerve or have a more widespread distribution with multiple nerve tracks.

- To revise the some genetic disorders associated with peripheral nerve pathologies.

Background

Magnetic resonance imaging (MRI) is the modality of choice in evaluating peripheral nerves and soft tissue masses in extremities and also in many cases second after to contrast enhanced computed tomography (CT) for evaluation of thoracic or abdominal cavity masses.

Many diseases that involve peripheral nerves may cause nodular and in some instances diffuse thickening of the involved nerve.

However for generalized conditions, taking the autonomic nervous system into account, as well as the sensory-motor peripheral nerves, there is a wide web of nervous tissue in extremities as well as splanchnic regions, retroperitoneum and thoracic cavity. As a result whether it is congenital or acquired any systemic condition which may involve peripheral and autonomic nervous system may have a different façade according to the presenting symptom.

Findings and procedure details

A) MRI PROTOCOLS
MRI examinations were tailored according to the presenting symptom of the patient. The hospital records and PACS archives were searched retrospectively between January 2012 and August 2014. The MR examinations were conducted on either 1.5 T or 3T scanners.

- Although alterations according to the preliminary diagnosis of the referred case were made with the protocols, generally for the MR imaging of extremities and joints MRI protocol consisted of;

- Fast spin echo (FSE) T1 weighted images in 3 planes (axial, coronal and sagittal)
- Coronal short -tau- inversion recovery (STIR) sequence or T2 - weighted images with and/or without fat suppression
- Sagittal proton density (PD) images with and/or without fat suppression
- Axial fat suppressed T2 images
- Fat suppressed, postgadolinium T1 weighted images (given the patient had had no contraindications)

- In those cases, where the initial purpose of the MRI was not to evaluate a known body mass, but the nerve pathology was discovered incidentally, during another routine MR imaging, the MRI protocol consisted solely of the initially intended purpose.

B) IMAGING FINDINGS

I- True Neoplastic Lesions of Peripheral Nerves

1) Solitary Lesion of a Single Peripheral Nerve

The true tumors of the peripheral nerves are the peripheral nerve sheath tumors (PNST), which can be either benign or malignant.

a) Benign Lesions

Benign PNSTs include schwannomas and neurofibromas.

i) Neurofibromas
Neurofibromas most commonly affect young adults between 20-30 years of age. Neurofibromas are intimately associated with the nerve that they take origin from and are unencapsulated. Consequently they are not usually removable without the compromise of the parent nerve.

Pathologically they have three types: Localized, diffuse and plexiform [1,2].

- The localized type constitutes 90% and are solitary lesions (Fig. 1 on page 10). Localized neurofibromas often arise from cutaneous nerves. However in the setting of neurofibromatosis (NF) they tend to be larger, multiple and deeper in location (Fig. 2 on page 11).

The "split fat" sign represents a rim of fat tissue surrounding the tumor in an intermuscular location [1] (Fig. 3 on page 13).

- Diffuse neurofibromas are common in children and young adults and are located in subcutaneous tissues. They generally grow in a plaque like or infiltrative manner commonly in the head and neck region. They spread along the connective tissue septa rather than destroying the tissue architecture (Fig. 4 on page 13) [3].

- Plexiform neurofibromas are pathognomonic for NF type 1 and they usually involve a long segment of a nerve trunk and its branches diffusely enlarging the involved nerve thus, giving the so-called appearance of "bag of worms" (Fig. 5 on page 14) [1].

On T2 weighted and proton density images, presence of multiple small ring-like structures with a hyperintense peripheral tissue is called "fascicular" sign and it is another sign for a neurogenic neoplasm. [4] On T2 weighted images in MRI, the "target" sign, which may also be present in other types of peripheral nerve sheath lesions, represents the central area of low signal intensity which corresponds to the fibrocollagenous component of the lesion and the surrounding area of high signal intensity representing the more myxomatous tissue histologically (Fig. 6 on page 14) [1,4-5].

ii) Schwannomas

Also known as neurilemmomas, these lesions tend to occur in 20-40 year old patients. Pathologically they are fusiform masses, composed of Schwann cells, eccentrically located in relation to the involved nerve and are encapsulated unlike neurofibromas. As a result they can be excised without compromising the parent nerve. Like
neurofibromas, split fat sign, target sign and fusiform shape can also be seen in schwannomas. However heterogenous appearance and cystic changes are much more common in schwannomas compared to neurofibromas (Fig. 7 on page 15) [1,4].

b) Malignant Lesions

Because the exact cell of origin is not known, the names "malignant schwannoma" or "neurofibrosarcoma" are being abandoned and the term "malignant peripheral nerve sheath tumor" is preferred to refer to the malignant counterpart of schwannomas and neurofibromas.

They frequently affect patients between 20-50 years of age. Almost 50% of them are associated with NF type 1.

Malignant PNST tend to be larger (>5 cm), exhibit perilesional edema in adjacent tissues and peripheral enhancement pattern and are more heterogeneous with areas central necrosis [1,6]. Also Wasa et al proposed that heterogeneity of the lesion on T1 weighted images in the setting of NF type 1 is also a sign for malignant PNSTs (Fig. 8 on page 16) [6].

Clinically pain at rest and severe motor dysfunction are also signs of malignant nature [6,7].

Metastases most commonly involve lungs, bones, pleura and retroperitoneum with regional lymph node involvement in 9% of cases [4].

Malignant PNSTs may arise at sites of previous irradiation with a latency period of almost 10 years [1, 4, 8-9].

2) Multiple Lesions of a Single Peripheral Nerve Track

Although generally they tend to be solitary lesions, schwannomas may appear as multiple lesions confined to a single nerve anatomy (Fig. 9 on page 17).

3) Widespread Peripheral Nerve Sheath Lesions and Associated Genetic Conditions

Neurofibromatoses
a) Neurofibromatosis Type 1

Also known as von Recklinghausen disease, it is the most common phacomatosis, which is inherited autosomal dominantly. The responsible gene is the NF1 gene located at the 17q11.2 chromosome. Because of many skeletal and dermatological, easily recognizable stigmata, it is generally diagnosed at early childhood.

It is characterized by the presence of numerous neurofibromas, particularly the plexiform type. In this genetic disorder, neurofibromas tend to be aggressive and in approximately 10% of NF type 1 patients malignant PNSTs develop (Fig. 10 on page 18).

In patients with known NF type 1, sudden increase in size of a preexisting neurofibroma should raise suspicion of malignant transformation [4].

It should be noted that, NF type 1 may involve only a single body part with the characteristic skin and peripheral nerve lesions, in which case it is considered as "segmental neurofibromatosis". Although much more rarely, plexiform neurofibromas and malignant PNSTs may arise even in the segmental form of the disease [10].

b) Neurofibromatosis Type 2

It is genetically a totally distinct disorder than NF type 1, with an incidence of 1/25000 or 1/40000.

The hallmark of the disease is bilateral vestibular schwannomas. It is inherited via an autosomal dominant germline mutation of NF-2 gene at the 22q12 chromosome, and usually diagnosed at a later age compared to NF type 1.

Besides central nervous system tumors like meningiomas, schwannomas, ependymomas, neurofibromas, spinal and peripheral nerve schwannomas are also encountered [4, 11].

c) Schwannomatosis

Although more similar to NF type 2 than NF type 1, this condition is considered as a third form of neurofibromatosis. Schwannomatosis, also known as congenital neurilemmomatosis is a rare genetic condition which is characterized by the presence of multiple schwannomas in peripheral nervous system without concomitant vestibular lesions in inner ear. These patients do not show any skin changes, namely the café
au lait spots or freckling as in NF type 1 patients. The genetic mechanism is complex and not yet fully understood, although somatic mutations of NF2 genre are isolated in tumor tissues of these patients.

Radiologists are invited to suggest the diagnosis of schwannomatosis in patients with multiple nonvestibular schwannomas (Fig. 11 on page 19) [11].

II- Non-Neoplastic Diseases of Peripheral Nerves

1) Posttraumatic Conditions

a) Neuromas

Neuromas are pseudotumors that develop after nerve injury or repetitive microtrauma. In the case of a severe nerve trauma with partial avulsion, disruption or total transaction of a nerve lateral or terminal neuromas arise. These lesions are continuous with the normal proximal nerve, arise within 1-12 months after the initial insult and have no malignant potential. On imaging they appear as bulbous shaped masses at the end of the severed nerve.

On MRI lesion demonstrates low to intermediate signal on T1 and T2 weighted images, and after contrast injection little or no enhancement (Fig. 12 on page 20).

If painful, surgical resection may be necessary [4].

- Morton neuroma is an entrapment neuropathy of the interdigital nerve, branch of medial plantar nerve by the distal extent of the transverse intermetatarsal ligament, which produces a perineural fibrosis and enlargement of the involved nerve but it is not a true tumor in nature [4, 12]. It is a spindle neuroma in which the nerve fiber is intact but injured due to chronic irritation [4] Pathologically there is benign fusiform enlargement of the nerve often associated with a perineural fibroma.

Morton’s neuroma is more prevalent in women between 40-60 years of age. Typically the enlargement begins with the 3rd and 4th metatarsal heads.

Fat suppressed contrast enhanced MRI, which is the most sensitive technique, demonstrates a tear drop shaped enhancing mass arising between the metatarsal heads. On fluid sensitive sequences, the lesion appears hyperintense as well as associated intermetatarsal bursitis, if present (Fig. 13 on page 21) [4,12].
b) Neuropathies

i) Mononeuropathy

Mononeuropathy can result from mechanical causes such as nerve entrapment, compression or traction. Imaging findings of an entrapped nerve are focal flattening, proximal swelling and hyperintensity on MRI within the involved nerve. Secondary denervation or fatty atrophy of the relevant muscles may appear on imaging too [13-14].

Although median, ulnar and radial nerves may be entrapped at multiple locations near the elbow joint or wrist, compression of median nerve in the carpal tunnel is the most common entrapment syndrome of upper extremity, followed by ulnar nerve (Fig. 14 on page 21).

Bowler’s thumb is a traumatic neuropathy of the digital nerve of the ulnar side of thumb, almost exclusively seen in bowlers.

Cubital tunnel is the most common location of ulnar nerve entrapment. Fexion of the elbow, valgus stress at the elbow joint as in baseball pitchers, anterior dislocation of the ulnar nerve, accessory muscles at the elbow joint pose a risk of ulnar nerve entrapment (Fig. 15 on page 22 - Fig. 16 on page 23) [13].

For the entrapment neuropathies of lower extremity, starting from the lumbosacal plexuses to the distal individual nerves, many mechanic and anatomic constrictions can cause entrapment neuropathy and individual entrapment neuropathies of each nerve is beyond the scope of this review. Nevertheless common peroneal neuropathy is the most common neuropathy in lower extremity due to its vulnerability to entrapment by its fixed position at the greater sciatic foramen and around the fibular head [15].

Radiation damage can also cause peripheral neuropathy, especially at higher doses of exposure. Peripheral nerves may be damaged following radiotherapy either directly (by the harmful effects of radiation itself) or indirectly (by diffuse fibrosis of tissues surrounding the nerve caused by radiation). Imaging reveals diffuse nerve thickening with no observable mass (Fig. 17 on page 24) [9].

ii) Polyneuropathy
Polyneuropathies are diffuse, symmetrical disorders usually affecting the limbs distally to a greater extent than proximally. Clinically, they are classified as acute or chronic, motor or sensory or mixed and also autonomic.

Although more than 50% of all peripheral neuropathies are idiopathic, some of the major causes can be listed as postinfectious (HIV, leprosy), toxic-metabolic (diabetes, alcohol induced), vitamin deficiencies (B1, B6, B12), vasculitis (rheumatoid arthritis, systemic lupus erythematosus), hereditary (Charcot-Marie-Tooth disease), neoplastic / paraneoplastic (monoclonal gammopathy, carcinomas of lung, breast, ovary), inflammatory (Guillain-Barre Syndrome, chronic inflammatory demyelinating polyradiculoneuropathy).

Although most of the diagnostic work up for peripheral neuropathies constitute of clinical, laboratory and electrophysiological tests, imaging may demonstrate thickening (Fig. 18 on page 25) and enhancement of peripheral nerves in some cases such as chronic inflammatory demyelinating polyradiculoneuropathy [16].

- **Leprosy**

Leprosy, which is a chronic infectious disease caused by Mycobacterium leprae is a cause of peripheral neuropathy. It causes "mononeuritis multiplex" in which there is damage of two or more nerve areas by damaging both myelinated and unmyelinated fibers replacing functional tissue by fibrosis. Mononeuritis is the most common presentation of the disease and nerves in the upper limb are more commonly affected than nerves in lower limb. The most commonly involved nerves are ulnar, median, posterior auricular, superficial radial, common fibular, superficial fibular and posterior tibial nerves.

Posterior tibial nerve involvement of leprosy causes anesthesia of the foot sole and may cause neuropathic foot.

On imaging, involved nerves are enlarged and may show calcification, especially at ulnar and peroneal nerves. On MRI, the involved nerves may appear normal, or show enlargement with fascicular abnormalities or loss of fascicular structure (Fig. 19 on page 26) [17].

**III- Rare Proliferative Diseases Involving Peripheral Nerves**

**1) Neural Fibrolipoma**
Also known as "fibrolipomatous hamartoma", "perineural lipoma", fatty infiltration of the nerve and intraneural lipoma, it is a disease where, mature fat and fibroblasts undergo hypertrophy in the epineurium of the nerve. Upper extremity and median nerve are favored sites of involvement. In 27-67% of the cases, macrodactyly accompanies and then the disease is referred to as macrodystrophia lipomatosa. In these patients osseous and soft tissue overgrowth as well as early osteoarthritis may occur. On MRI thick digital nerves are surrounded by fatty tissue (Fig. 20 on page 27) [4].

2) Peripheral Primitive Neuroectodermal Tumor/ Extraskeletal Ewing Sarcoma

Ewing sarcoma of bone, Ewing sarcoma of extraskeletal tissues (EES) and peripheral primitive neuroectodermal tumor (PNET) are considered as a single biologic entity and they have been proposed to belong to the "Ewing sarcoma family of tumors" umbrella (Fig. 21 on page 28) [18]. These tumors share identical morphological, immunohistochemical and cytogenetical features.

3) Perineural Tumor Invasion

Perineural tumor invasion is defined as tumors cells within any of the three layers of the nerve sheath, namely the epineurium, endoneurium and perineurium, from a neoplastic diseases. The process of perineural tumor spread has been well established in many head and neck tumors and mucosal cancers, such as adenoid cystic carcinoma, as well as for biliary tract, rectal, pancreatic, colon and prostate carcinomas (Fig. 22 on page 28) [19,20]

For prostate adenocarcinoma retrograde extension of the tumor within the periprostatic nerves has been demonstrated as the cause of lumbosacral plexopathy [20].

Images for this section:
**Fig. 1:** Axial fast spin echo T1-weighted image just above the tibiotalar joint of the left ankle (a) shows the oval shaped mass (arrow) with intermediate intensity adjacent to the tibialis posterior vessels, representing a solitary neurofibroma. On fat suppressed T2 weighted images (b) from the same plane, the lesion appears hyperintense. Coronal fat suppressed post-gadolinium T1-weighted fast spin echo image (c) demonstrates avid, homogenous contrast enhancement of the lesion. Note that the lesion is within the tibial nerve where the nerve enters and exits through the lesion (arrow heads).
Fig. 2: The coronal single shot fast spin echo fat suppressed T2-weighted image showing the anterior abdominal wall, from the MR-enterography examination of a
case with colon carcinoma reveals the innumerable cutaneous localized neurofibromas (arrows). Later the case was diagnosed with neurofibromatosis type 1.

**Fig. 3:** The split fat sign (red arrows) around the right proximal thigh schwannoma is depicted on the coronal T1-weighted image.
**Fig. 4:** In a patient with a known diagnosis of neurofibromatosis type 1, diffuse neurofibroma on the right side of intergluteal cleft (red circle) is shown. Axial T1-weighted (a) and fat suppressed postgadolinium T1-weighted (b) fast spin echo images and the enlarged view (c) of the lesion in the postcontrast image are shown. Note the marked enhancement and plaque-like morphology of the lesion involving the subcutaneous tissues.

**Fig. 5:** The three consecutive coronal short-tau inversion recovery (STIR) images (a-c), of an adult patient who was referred for MR urography to investigate the etiology of bilateral hydronephrosis, show the incidental finding of typical "bag of worms" pattern of plexiform neurofibromas (blue arrows) in the lumbar spinal nerve roots and branches of lumbar nerve plexuses bilaterally. Note the right sided renal collecting system dilatation (red arrows).
**Fig. 6:** Coronal single shot fast spin echo fat suppressed T2- weighted image of the same patient as in figure 2, with colon carcinoma demonstrates two incidentally discovered neurofibromas in the right presacral region (red arrow) showing the typical target sign and on the left subcostal region (blue arrow) with the characteristic fascicular sign.
**Fig. 7:** The axial T1-weighted fast spin echo (a), T2-weighted fast spin echo (b) and postgadolinium fat suppressed T1-weighted fast spin echo (c) images demonstrate a small superficial schwannoma (thick red arrows) with the typical target sign in T2 weighted and postcontrast images similar to neurofibromas. In another patient axial fast spin echo T1-weighted (d), short tau inversion recovery (STIR) (e) and, fat suppressed postgadolinium T1-weighted fast spin echo images (f) of the right mid-thigh depicting the small cystic areas within a schwannoma (red arrows) involving the sciatic nerve are shown. Note that the sciatic nerve fasicles are pushed laterally and the lesion is somewhat eccentrically located with respect to the parent nerve (blue arrows). The arrow head in image (a) indicates the thin capsule of the lesion which in this case is best appreciated on T1 weighted images.
Fig. 8: Sagittal (a) and axial (b) T1 weighted fast spin echo images of a malignant peripheral nerve sheath tumor in right pulmonary apex in a case with known neurofibromatosis type 1. Note the heterogenous intensity of the lesion in unenhanced T1-weighted images. Postgadolinium T1-weighted sagittal image (c) shows diffuse enhancement and axial T2-weighted fast spin echo image (d) of the same lesion demonstrates heterogenous high signal intensity. The pleural effusion and seeding are appreciated in axial T1 (b) and T2-weighted (d)images (arrows).
**Fig. 9:** Sagittal T1 weighted fast spin echo image (a) of distal left thigh shows the "beaded" appearance of the multiple schwannomas in the tibial nerve and posterior cutaneous nerve of thigh. Note the presence of the target sign (arrows) in the coronal T2- weighted fast spin echo image (b).
**Fig. 10:** Axial T1-weighted fast spin echo (a) and postgadolinium fat suppressed T1-weighted images (b) show the large left sacral neurofibroma (red arrows) of a case with neurofibromatosis type 1. Note how expansile the lesion is, destroying the bony structures of the left hemisacrum. Coronal T1 weighted (c) and short-tau inversion recovery (STIR) image (d) of the same lesion demonstrate the true size of the lesion extending below the bony sacrum and involving the left sacral plexus. Note that there is a right sciatic neurofibroma (blue arrows) with the typical split fat sign on T1 weighted coronal image.
Fig. 11: Sagittal T1 weighted fast spin echo (a), coronal short-tau inversion recovery (STIR) (b) and coronal postgadolinium fat suppressed T1-weighted (c) images of a case with multiple schwannomas of the right sciatic nerve. The patient presented neither the other findings of neurofibromatosis type 1, nor vestibular schwannomas as expected in neurofibromatosis type 2. Schwannomatosis was suggested based upon the imaging findings.
**Fig. 12:** Sagittal T1- weighted fast spin echo (a) and fat suppressed proton density (b) images of the left thigh of a case with above the knee amputation shows the fusiform swelling at the end of the transected sciatic nerve, representing a terminal neuroma (arrows). Axial T1 (c) and T2- weighted images (d) of the lesion show intermediate signal intensity and postgadolinium fat- suppressed T1-weighted image (e) shows that the lesion does not enhance.

**Fig. 13:** Coronal T1- weighted fast spin echo (a), coronal short tau inversion recovery (STIR) (b), coronal fat suppressed postgadolinium T1- weighted fast spin echo (c) and axial fat suppressed postgadolinium T1- weighted fast spin echo (d) images of the right foot in a middle aged female patient shows the classical "tear drop" shaped mass between second and third metatarsal heads (arrows). Note that the lesion is hypointense on T1- weighted images, heterogenously hyperintense on STIR images and diffusely enhances after contrast administration.
Fig. 14: Axial T1- weighted fast spin echo (a) and fat suppressed T2- weighted image (b) of the wrist of a patient with rheumatoid arthritis show the apparent enlargement of the median nerve (red arrows). Note that there is tenosynovitis of the flexor tendons within the carpal tunnel, somewhat narrowing the space and constricting the median nerve. In another patient with the clinical diagnosis of carpal tunnel syndrome, axial fat suppressed T2-weighted image (c) at the level of the carpal tunnel demonstrates that the median nerve has a relatively higher signal intensity and is also mildly flattened (blue arrow) by a ganglion cyst (arrow head) which extends underneath the flexor retinaculum.
Fig. 15: Coronal T1-weighted fast spin echo (a) and fat suppressed proton density image (b) of a case with cubital tunnel syndrome. Note the generalized thickening of the ulnar nerve (red arrows) just behind the medial epicondyle. The accessory anconeus muscle (blue arrows), which is well appreciated in axial T1-weighted (c) and fat suppressed T2-weighted fast spin echo (d) images, is most likely the cause of the clinical picture in this case.
Fig. 16: Dislocated ulnar nerve (arrows) at the level of medial epicondyle is depicted in axial T1-weighted fast spin echo (a), fat suppressed proton density (b) and coronal T1-weighted (c) images. Note the thickening and increased intensity within the nerve, along with the soft tissue stranding around it.
Fig. 17: Axial fat suppressed postgadolinium T1- weighted fast spin echo (a) and short-tau inversion recovery (STIR) (b) images of a case with post-irradiation sciatic neuropathy for treatment of squamous cell carcinoma of the skin in left gluteal region. Note the enlargement and increased signal intensity of the nerve (red circle) with very mild enhancement.
Fig. 18: Reformatted coronal short-tau inversion recovery (STIR) (a) and T1-weighted fast spin echo image (b) of a patient with bilateral lower extremity polyneuropathy reveal diffusely and regularly thickened sciatic and tibial nerves (red arrows). Axial T1-weighted fast spin echo image (c) and fat suppressed T2-weighted fast spin echo image (d) show a closer look at the hyperintense and thick sciatic nerves. The patient had had a motor vehicle accident and polyneuropathy was attributed to viral infection during his stay in intensive care unit. Note the bilateral femoral intramedullary rods on the axial images (blue arrows).
**Fig. 19:** Two consecutive axial T1 weighted fast spin echo images (a-b) from right ankle of a case with inactive leprosy demonstrate the thick tibial nerve (red arrows). Note the loss of fasicular pattern and the increased size of the nerve relative to the adjacent vessels. Coronal T1 weighted fast spin echo image (c) shows the muscle atrophy (blue arrow) as well as the thick and slightly irregular tibial nerve (red arrow).
**Fig. 20:** In a case with macrodystrophia lipomatosi, the thickened digital branches of the median nerve on both radial and ulnar sides of the third finger are shown on consecutive coronal (a-b) and axial (c) T1- weighted fast spin echo images. Note the hypertrophy of the lipomatous tissue around the digital nerves as well as the macrodactyly in the third digit.

![Fig. 20](image)

**Fig. 21:** Pretreatment axial T1- weighted fast spin echo (a) and fat suppressed postgadolinium T1- weighted images (b) of extraskeletal Ewing sarcoma/ peripheral neuroectodermal tumor of the sciatic nerve are shown. Note that the T1 intensity of the tumor is heterogenous with slightly increased areas (arrow). The enhancement pattern is heterogenous and in the corresponding post-chemotherapy images (c-d) it is well established that the enhancing solid component has shrunk. Note the close association of the mass to the sciatic nerve in the sagittal fat suppressed T2 weighted image (e) from the pretreatment imaging.

![Fig. 21](image)
Fig. 22: Bilateral masses in the obturator and right sciatic foramina in a case with advanced prostate adenocarcinoma are depicted on the axial fat suppressed postgadolinium T1-weighted image of the pelvis (a). The periprostatic nerves are also involved (yellow arrows) in this case. Note the muscle atrophy of the obturator externus and adductor longus and brevis muscles (blue arrows) on the T1-weighted axial image of the pelvic floor.
Conclusion

It is important to know the radiologic findings in peripheral nerve disorders to be able to characterize their masses as well as to insinuate some important genetic conditions or systemic disorders which may involve peripheral nerves in adulthood as these disorders may have late onset of symptoms or delayed diagnosis.

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