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Clinical Cases in Pediatric Peripheral Neuropathy

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1. Introduction

There are many challenges to diagnosing peripheral neuropathy in children. While the symptoms are similar to those in adults, young children and those with developmental delays pose difficulties in extracting the appropriate history and performing a consistent and careful neurological examination. Neuropathic processes that present in childhood can be divided into those that are progressive and those that will tend improve over time. While there are exceptions, children with the latter category are those that fall into the acquired neuropathies such as vitamin deficiencies, toxicities, some immune mediated, and focal mononeuropathies. Those in the progressive category include the neuropathies that are hereditary/genetic in nature such as the heterogenous group of Hereditary Sensory Motor Neuropathies and some immune mediated neuropathies. In general, when the neuropathies of this group present earlier in childhood, the course and prognosis is worse than if they were to present in adolescence and adulthood. There are exceptions to this as some children who initially present as floppy infants due to a congenital neuropathy with respiratory difficulties can attain the ability to walk independently.

A lot of the entities discussed in this chapter have been discussed in others that are dedicated to their specific mechanisms. What this chapter will try to achieve is to discuss the pediatric presentations of these disorders and to highlight, if present, differences between the adult and pediatric presentations of neuropathies. While this chapter will touch on the pathophysiology, electrodiagnostic findings, and laboratory findings, it will not try to duplicate these areas of discussion found in other chapters of this book. The intent of this chapter is to discuss pediatric presentations of peripheral neuropathy in the context of clinical cases to allow the reader to consider these diagnoses in children.

A mention of performing electrodiagnostic testing is essential in any chapter discussing peripheral neuropathy. The evaluation of weakness often employs using nerve conduction studies and electromyograms. In young children and especially in those who have developmental delays, this can be difficult. In this author's experience, performing these electrodiagnostic studies in children is more time consuming. Frequent coaching and coaxing is often needed. Without sedation available, many studies are truncated due to tolerance, inability to cooperate, and inability to follow commands. A child life specialist can be valuable in utilizing distraction techniques. Certified Child Life Specialists have been used in various clinical settings to help ease the anxiety associated with procedures (McGee, 2003). Also, use of a local anesthetic cream such as topical lidocaine may be helpful in

reducing the amount of discomfort. While most diagnoses can be supported by obtaining 2 motor nerves with F-waves, 2 sensory nerves, and needle examination in one proximal and one distal muscle, some patients will require a more complete study under sedation. It is in this author's opinion that the ability to perform sedated EMGs should be available in facilities that performs these studies on children.

2. Case #1

History: A previously healthy 12 year old boy first started to notice difficulties with tripping while walking. Over the following week, his conditioned worsened and by the time he presented to the emergency room, on day 8 of symptoms, he had difficulty walking. On further questioning, he had a sore throat and runny nose approximately 2 weeks prior to the onset of symptoms.

Examination highlights: 3/5 strength in his anterior tibialis and gastrocnemius muscles bilaterally. Weakness was symmetrical. Hip girdle muscles were nearly normal as was upper extremity strength. Remarkable on his examination were trace to absent reflexes out of proportion to his degree of weakness.

Studies: CT of the head was negative. LP demonstrated a protein of 105 mg/dL with 3 WBC/hpf and no RBCs. CSF glucose was 58 mg/dL (65% of his peripheral glucose). MRI of the brain was normal. MRI of the spine demonstrated enhancing caudal equina roots.

Study	**Findings**
Right Median Motor CMAP	normal
Right Tibial Motor CMAP	normal
Right Radial Sensory SNAP	normal
Right Sural Sensory SNAP	normal
Right Median F-wave	Normal duration, 40% persistence
Right Tibial Motor F-wave	Normal duration, <20% persistence

EMG/NCV Findings

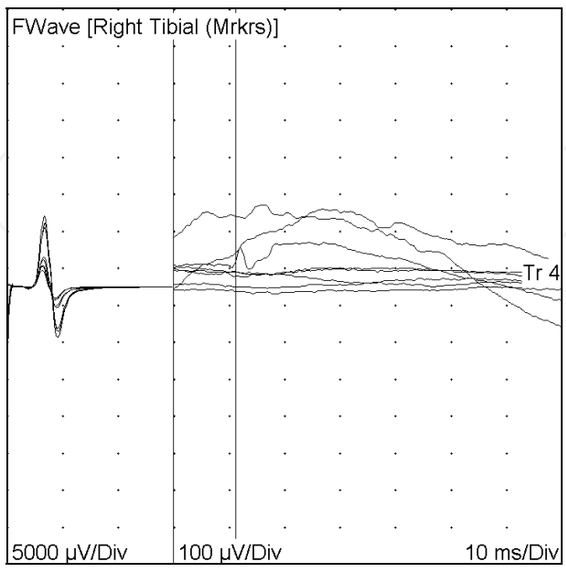


Fig. 1. F-wave persistence <50% in a patient with AIDP



Fig. 2. Enhancing nerve roots of the cauda equine in a patient with AIDP

Clinical Course: The patient received a 5 day course of IVIG (0.4 grams/kg/day) for a total dose of 2 grams/kg. He started to improve on day 3 of treatment. After 4 weeks in the inpatient rehabilitation service, he was discharged home, able to walk, climb stairs, and play basketball.

Diagnosis: Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) also known as the Guillain Barre Syndrome (GBS).

Discussion: In a child that presents with classic ascending paralysis and loss of reflexes, it is important to evaluate for AIDP (Simmons, 2010). The diagnosis of AIDP is mainly clinical with supporting information gathered from laboratory, neurophysiological, and radiological studies. There is little in the differential diagnosis with this history but acute cord lesions should be excluded especially if there is a history of bowel and bladder difficulties. Sensory changes can occur in AIDP. Motor symptoms predominate (Kuwabara, 2004). However, a recent study in adults reported that approximately 70% of AIDP patients had decreased superficial or deep sensation in distal extremities (Kuwabara, 2004). Acute cord lesions tend to be more abrupt (such as an anterior spinal artery syndrome). Arterior spinal artery syndrome has dissociated sensory impairment and sphincter involvement (Servais, 2001). AIDP is difficult to distinguish from the first presentation of CIDP. Especially in younger children where examination can be difficult, other diagnoses to consider include myasthenia gravis (Markowitz, 2008), acute cerebellar ataxia, and other post-infectious disorders such as acute disseminated encephalomyelitis (ADEM). Diminished or absent reflexes, MRI findings, and prolongation F-waves would support AIDP. In this case, a lack of F-wave persistence was seen. Decreased F-wave persistence is seen with AIDP (Frasier, 1992). The lack of fatigueability in this patient would argue against myasthenia gravis. In addition, the majority of patients with myasthenia gravis present with bulbar signs (Andrews, 2003). In these situations, careful examination of DTRs is essential.

The case highlights the clinical features of AIDP: ascending paralysis, association with an inciting infection which is seen in 60-70% of cases, and diminished or absent reflexes. Progressive weakness is seen in more than one limb and progress rapidly over 4 weeks. The nadir is usually reached by 2 weeks. Typically, there is relative symmetry. Sphincters are usually spared but there can be an occasional patient with bladder dysfunction (Asbury, 1990; Cosi, 2006; Agrawal, 2007). A variation that must be mentioned is the Miller Fischer variant. This triad of symptoms includes ophthalmoplegia, ataxia, and areflexia (and an association with the Gq1b antibody (Mori, 2001).

Prolonged F-waves are among the first electrophysiological sign seen in this disease and are suggestive of proximal demyelination even when motor conduction studies are normal. Prolongation of distal latencies is also an early finding (Simmons, 2010). This can be seen in the first week of symptoms. Other features, which are seen later in the course (weeks) include conduction block on nerve conduction studies. 80% of patients who will be eventually diagnosed with AIDP will have abnormalities in their neurophysiological studies upon presentation. In one study, 96% will have abnormal motor responses within 3 weeks. It is also of value to note that 20% will not have abnormalities on their nerve conductions at the time of presentation thus re-enforcing that information gained from neurophysiological studies is supportinve but not diagnostic. Although mild sensory complaints can be an initial feature, approximately 70% can have abnormal sensory responses within 3 weeks of symptom onset. Nerve involvement can be patchy. (Asbury 1990).

Lumbar puncture is needed to exclude infection as well as to evaluate for albuminocytological disassociation which strongly supports the diagnosis of GBS/AIDP (Simmons, 2010). One of the most predictable and consistent early findings in AIDP is enhancement of the nerve roots of the cauda equina. This can be seen within the first 2 weeks of symtoms. Cauda equina root enhancement is 83% sensitive for Guillain Barre Syndrome and is seen in 95% of typical cases (Gorson, 1996).

There are electrophysiologic criteria for both AIDP and CIDP which includes conduction block in one of more nerves, prolonged late responses, prolonged distal latencies in two or more nerves, and conduction slowing in two or more nerves. Excellent discussions and tables are in various sources. One particularly helpful source is the textbook by Preston and Shapiro. For AIDP, at least one of the following (conduction slowing, prolonged late responses, prolonged distal latencies) in 2 or more nerves within the first 3 weeks of illness (Ho, 1997).

Like most other autoimmune diseases, the pathophysiology lies in molecular mimicry. An inciting infection results in production of antibodies that cross react with myelin components. In some cases, there is axonal involvement such as in those associated with campylobacter infection.

Treatment is not necessary in all cases. Both IVIG and Plasma Exchange are efficacious in the treatment of Guillain Barre Syndrome within 2 and 4 weeks of symptoms. Fewer complications are seen with IVIG. The combination of the two modalities in sequence is not recommended as an initial treatment. There is no benefit from treatment with corticosteroids (Hughes, 2003). An example dose for IVIG is 2 grams per kg and given as 0.4 gram to 1 gram per kg/day for 2 to 5 days. IVIG treatment can be associated with a reduced need for mechanical ventilation (Shanbag, 2003). IVIG treatment is also likely associated with a shorter time to independent ambulation in children (Shaher, 2003; Agrawal, 2007). An example of a plasma exchange schedule is 1 volume plasma exchange every other day for a total of 5 exchanges. Other aspects of treatment include surveillance for and treatment of associated autonomic dysfunction, pain, and respiratory compromise. Rehabilitation services are important in the overall care of a pediatric patient with AIDP.

Patients with preceding *c. jejuni* infection were more likely to have acute axonal neuropathy or axonal degeneration in association with AIDP. This subset of patients is associated with slower recovery, and generally, a worse outcome. Careful history of a preceding gastroenteritis 2-3 weeks before the symptoms of weakness would help in identifying if evaluation for past c. jejuni infection is warranted. In adult studies where c. jejuni infection was associated with the presentation of AIDP, the majority of patients recalled watery diarrhea and a smaller percentage recalled bloody diarrhea. Along with an association with c. jejuni infection, other poor prognostic factors include need for ventillatory support and confinement to a bed within 2 days of neuropathic symptom onset (rapid progression) (Rees, 1995). Also, patients with anti-GM1 antibodies can be associated with poorer prognosis (Van der berg, 1991).
Overall, prognosis is excellent with >80% of patients recovering the ability to ambulate (Simmons 2010). It should be cautioned that (50.00%) of patients who will be eventually diagnosed with CIDP were first diagnosed with AIDP. AIDP can recur in a small percentage of patients. It may also be the first presentation of other autoimmune disorders such as SLE (exceptionally rare, see below). Other associations with AIDP besides viral intections and c. jejuni infection include preceding surgery, vaccinations (although controversial), cancer, and multiple sclerosis (Asbury, 1990).

3. Case # 2

History: A previously healthy 6 year old boy presented with a 3 month history of progressive weakness. Over the course of 3 months, he lost the ability to walk independently.
Examination highlights: He had near normal strength in his bilateral proximal muscles and 4/5 strength distally. He had 2/5 strength in the anterior tibialis bilaterally and 4/5 strength in all remaining muscles. Sensation was preserved grossly. He had no elicitable reflexes.
Studies: Cerebral spinal fluid analysis demonstrated elevated protein at 100 mg/dL with no white blood cells and no red cells. Glucose was 60 mg/dL.

Study	**Findings**
Right Median CMAP	Slowed conduction 38 m/s; preserved amplitude
Left Median CMAP	Slowed conduction 35 m/s; preserved amplitude
Right Ulnar CMAP	Slowed conduction 32 m/s; conductions block with increased temporal dispersion of CMAP
Left Tibial CMAP	Slowed conduction 34 m/s; conduction block with increased temporal dispersion of CMAP
Left Peroneal CMAP	Slowed conduction 38 m/s; preserved amplitude
Left Radial SNAP	Normal conduction and amplitude of SNAP
Right Medial Plantar SNAP	Slowed conduction 35 m/s; preserved amplitude of SNAP
Left Medial Plantar SNAP	Slowed conduction 33 m/s; preserved amplitude of SNAP
EMG Right APB	Large amplitude, long duration, unstable complex MUAPs with decreased recruitment
EMG Right EDC	Large amplitude, long duration, unstable complex MUAPs with decreased recruitment
EMG Right anterior tibialis	Large amplitude, long duration, unstable complex MUAPs with decreased recruitment

EMG/NCV Findings

Clinical Course: He responded partially to IVIG. However, due to ongoing weakness despite a repeat course of IVIG, he was started on prednisone. Due to intolerance and side effects of prednisone (pathological factors, hepatitis, markedly elevated cholesterol levels), he was subsequently started on mycophenylate. 6 months after the initial diagnosis, he is able to walk independently but cannot run. He has trace reflexes. He continues to make improvement with immune suppression.

Diagnosis: Chronic Inflammatory Polyradiculoneuropathy

Discussion: In a child presenting with 3 months of progressive weakness, deciphering the timing and the progression of weakness is needed to aid with the differential diagnosis. AIDP is among the highest on the differential. Had the patient peaked in weakness, and what was presenting 3 months from the onset was improved, then AIDP is a possibility. However, this was not the case in this patient. Hereditary sensory motor neuropathies can also present as progressive weakness, and are a consideration in this patient. Making this diagnosis less likely is that the patient was normal prior to the start of symptoms. In addition, while patients with HSMN can present with elevated protein in the CSF, conduction block is characteristically not a feature. Conudction block is an indication of non-uniform slowing seen on NCV studies along with increased temporal dispersion. HSMN tends to have a more uniform slowing with a few exceptions. As will be discussed in a later section, children with HSMN typically have a history of delayed motor development.

Like in adults, CIDP in children is less likely to have an antecedent event (such as URI symptoms). An antecedent event can be recalled in 20-30% of patients with CIDP. Some studies report up to 57%; but still considerable less than with AIDP (Markowitz, 2008). CIDP presents as a symmetrical predominantly motor polyradiculoneuropathy affecting both proximal and distal muscle groups. Hyporeflexia or areflexia is seen. In adult patients, a predominantly distal course is seen in 17%. A predominantly sensory form is seen in 15% and asymmetry can be seen in just under 10% of patients. Cranial nerves can be involved in 5% of patients and CNS involvement is seen in 8% (Rotta, 2000). The overall course can be relapsing or chronic progressive (Rotta, 2000). The initial presentation in general is typically quite striking in children such as gait disturbance and weakness. Tremor and ataxia are also reported symptoms. This is in contrast to adults who may present with minor complaints such as subtle weakness, mild sensory disturbances or decreased dexterity. Like adults, approximately 50% of children will have sensory discturbances such as parasthesias at the time of diagnosis (Simmons, 1997). Symptoms must be present for at least eight weeks to fit the clinical criteria of CIDP. The incidence of patients younger than 20 diagnosed with CIDP is 0.48 per 100,000 (in contrast to CIDP in adults 1.9 per 100,000) (Markowitz, 2008).

Like with AIDP, neurophysiological studies are supportive of this diagnosis but not diagnostic (see below). Just under 10% of patients will have caudal root enhancement. Elevated protein in the CSF is seen but not all patients have this (Rotta, 2000).

Nearly all CIDP patients will respond to their first treatment within a week. Like adults with CIDP, children will fit electrodiagnostic criteria (Simmons, 1997). Treatment options include IVIG (initially 2 grams per kilogram divided into 4-5 days) with subsequent treatment up to 2 grams/kg every 3 weeks, steroids (prednisone, typically 1-2 mg per kg/day), plasmapharesis for refractory cases, and other immunosuppressive agents such as mycophenilate (Cellcept). Other immunosuppressive agents used include azathioprine, methotrexate, cyclosporine, and interferon therapies (Markowitz, 2008).

In this author's practice, in patients requiring prolonged immune suppression with a combination of medications, it is important to consider prophylaxis with trimethoprim

sulfa. Regular evaluation of potential side effects of these medications and toxicity is essential in the care of patients with CIDP. Routine labs to consider include complete blood counts, chemistry profiles, liver profiles, levels of immunosuppressant agents and their toxic metabolites, lipid panel, vitamin D level, and lipase/amylase. The frequency of surveillance labs will be dictated by the patient's needs.

Prognosis for patients with CIDP is variable. Some patients remit after the first treatment and most patients have improvement after the first treatment. 60% of patients will respond to IVIG, 70% to steroids, 50% to plasma exchange, and 36% to cytotoxic agents. However, it is not well delineated which of the pediatric patients will have a course of frequent relapsing and partial remitting with treatment (Rotta, 2000). It must be highlighted that early treatment will provide the best opportunity for improvement. Pediatric patients tend to have more of a remitting-relapsing course and not typically have a progressive decline. Those patients that have a more insidious, slower onset are more likely to be associated with disease that is more difficult to treat. Pediatric patients with CIDP are less likely to need ventillatory support compared to those with AIDP, and adults with CIDP (although it has been reported). Long term treatment with IVIG has been demonstrated to be beneficial in patients with CIDP. Relapses can correlate with tapering of treatment (Simmons, 1997). Adults with an associated IgM monoglonal gammoathy and predominanrly sensory symptoms with or without serum anti-MAG antibodies have a poorer response to treatment. Further studies in children regarding positive antibody subsets are needed. One study comparing treatment of CIDP with high dose intermittent IV methylprednisolone demonstrated no difference in outcome between those treated with oral steroids and IVIG (Lopate, 2005). This study was in adults. Intermittent high dose IV methyprednisolone may be a lower cost, lower side effects treatment option. Further studies, particularly in children, are needed.

4. Case #3

History: A 7 year old boy did not start walking until he was 2 years of age. His parents report that although he has maintained the ability to walk, he has been tripping more as if he cannot pick up his feet. He cannot keep up with the other children when playing although cognitively, he is at grade level, if not advanced. His mother was able to play basketball and soccer in high school. She still helps with coaching their other children in soccer. Family history is notable for three of his father's siblings with muscular dystrophy. Two of his father's brothers died in their 30s after being wheelchair bound in their teens. His older sister is in her 50s and is wheelchair bound. His father is healthy. On his mother's side, multiple family members needed special shoes for their high arches. Although ambulatory into their 60s, several of his mother's relative had feet that started to turn in and toes to claw. One relative had to use a wheelchair.

Examination highlights: Negative Gower maneuver. Proximally, he has full strength. In his hands, he had 4/5 strength in his intraossei and FDI. Although he has full strength in the hip girdle muscles, he has 3/5 strength in the anterior tibialis and 4/5 strength in the gastrocnemius muscles bilaterally. He has absent reflexes and no fasciculations. His calves are thin and he has high arches in his lower extremities. He has a high steppage gait and bilateral foot drop. The patient has a pes cavus. His mother similarly has high arches and absent reflexes in the lower extremities. Strength is normal in her proximal muscles of her upper and lower extremities. She has minimal weakness in bilateral ankle dorsiflexion.

Study	Findings
Right Median CMAP	Prolonged distal latency >8 seconds Slowed conduction velocity <30 m/s Normal CMAP amplitude No conduction block
Right Ulnar CMAP	Prolonged distal latency >8 seconds Slowed conduction velocity <30 m/s Normal CMAP amplitude No conduction block
Left Tibial CMAP	Prolonged distal latency >8 seconds Slowed conduction velocity <30 m/s Normal CMAP amplitude No conduction block
Left Peroneal CMAP	Prolonged distal latency >8 seconds Slowed conduction velocity <30 m/s Normal CMAP amplitude No conduction block
Right Median SNAP	Slowed conduction velocity <40 m/s Normal SNAP amplitude
Right Radial SNAP	Slowed conduction velocity <40 m/s Normal SNAP amplitude
Left Sural SNAP	Slowed conduction velocity <35 m/s Normal SNAP amplitude
Left Medial Plantar SNAP	Slowed conduction velocity <35 m/s Normal SNAP amplitude
Mother's Right Median CMAP	Prolonged distal latency >8 seconds Slowed conduction velocity <30 m/s Normal CMAP amplitude No conduction block

EMG/NCV Findings

Other Studies: CPK is normal. Genetic testing confirms that the patient and his mother are positive for duplication in the PM22 gene.

Diagnosis: Hereditary Motor Sensory Neuropathy – CMT1a

Discussion: Especially in a young boy who presents with progressive weakness, the differential diagnosis must include muscular dystrophy such as a dystrophinopathy. In general, the distribution of weakness and the reflexes in comparison to the degree of weakness help to separate myopathic from neuropathic processes. In general, myopathic processes involve proximal muscles first and neuropathic processes involve distal muscles initially. Reflexes that are proportionate to the degree of weakness are consistent with a myopathic process and that are out of proportion (much less than expected) to the degree of weakness are consistent with a neuropathic process. A negative Gower's sign, normal CPK, and thin calves make a diagnosis of a dystrophinopathy not likely. A dystrophinopathy classically presents with a Gower maneuver, toe walking (rather than foot drop), large, firm (pseudohypertrophied calves), and markedly elevated CPK. What may be confusing is that the patient has uncles with muscular dystrophy. It should be observed that the uncles who were affected were paternal relatives. Although some sporadic occurrence can happen, the typical inheritance pattern for a dystrophinopathy (the most common type of muscular dystrophy in boys), is X-linked (maternally inherited).

Hereditary Sensory Motor Neuropathy is a heterogenous group of disorders affecting the peripheral nerves and affects 1:2500 people. It is characterized by atrophy in the distal extremities (anterior tibialis often affected early) and diminished or absent deep tendon reflexes. Associated features include a high steppage gait, impaired sensation, high arches of the feet, and pes cavus (Antonellis, 2003). It was first described in 1886 by the physicians whose names bear the eponym. Duplications in the PMP22 gene lead to the most common type of CMT, CMT1a (as is the case in our patient). This is located on chromosome 17 p11.2. CMT1b is associated with an abnormality mapping to chromosome 1 resulting in abnormal P0 protein (involved with the compaction of peripheral myelin) (Kulkens, 1993). What appears to be recurring a theme in the majority of demyelinating Charcot Marie Tooth Disease, is that they are the result of abnormal function in the Schwan cell.

In general, HSMN can be divided into demyelinating forms (designated as CMT 1) and axonal forms (designated as CMT 2). Nerve conduction studies can help with the distinction between the two. If the underlying process is predominantly a demyelinating abnormality, prolonged distal latencies and slowed conductions will be seen with relatively preserved amplitudes. If the underlying process is axonal, then conduction velocity will be relatively preserved, but CMAP and SNAP amplitudes will be small. NCS can also help with distinguishing HSMN from CIDP when the history may not be as clear. As described above, one of the electrodiagnostic features of CIDP is conduction block. In type 1 CMTs, slowing typically is uniform.

Symptoms of patients with CMT1 usually begin in childhood. Progression is generally slow but progressive. Symptoms include inability to keep up with other children, clumsiness, tripping, and foot drop (typically, the muscles of the anterior compartment of the legs are affected first and most noticeably). Reflexes tend to be trace at best but will most likely be absent.

It is not uncommon for the family history to have multiple relatives presenting with various degrees of weakness severity. The disease of most HSMN patients is inherited in an autosomal dominant pattern, although inheritance can also be autosomal recessive, X-linked, and sporadic. There are many mutations seen in X-linked CMT. However, these mutations are all associated with various Connexin 32 mutations (Cxn 32 is a gene responsible for encoding gap junctions, mapped to Xq13) (Oh, 1997). X-linked CMT is the second most frequent in the HSMN demeyelinating category. As with other X-linked disorders, males are much more affected than females with respect to clinical presentation as well as from a neurophysiological standpoint. However, as is the trend in patients with HSMN, there is a spectrum of clinical presentations. Most females with X-linked CMT are asymptomatic (Dubourg, 2001). As in this case, it is not uncommon for parents of affected children to be unaware that they are also affected; albeit to a lesser degree.

CMT2, the heterogenous group of disorders characterized by their predominantly axonal involvement also is autosomal dominant in inheritance (although, sporadic forms do occur). In the author's experience with children, this is much more of a rarity. The age of onset is older;- usually young adulthood. There are now 8 subtypes of CMT-2 (and designated as A-I) (NINDS, 2011). Molecular biology has allowed for the identification of the genes associated with these phenotypes including CMT2A associated with a mutation in KIF1B, CMT2B with the RAS-related GTP binding protein, CMT2E with the neurofilament light chain gene (NEFL), and a mutation in glycyl trNA synthase mapped to chromosome 7p in CMT 2D (Antonellis, 2003). CMT2F is characterized by a symmetrical distal limb weakness and subsequent atrophy. There are multiple genes that can be associated with this

phenotype including one mapping to chromosome 7q11-q21. Other mutations in small heat shock protein 27 have been reported to cause this phenotype (Evgrafov, 2004).
Dejerine Sottas Disease is also known as CMT3 or HSMN 3. It presents in infancy and is a severe peripheral neuropathy. Nerve conduction studies demonstrate markedly slowed velocities, generally less than 12 m/s. CSF protein can be elevated. Inheritance can be dominant, recessive, or sporadic. Genes affected include the PMP22, P0, EGR2, and PRX. The same abnormality that causes CMT1a in one family member can be associated with DSD in another. Patients are slow to make motor milestones and some do eventually achieve the ability to walk.
The course of disease varies depending on the type of abnormality (hence the type of CMT). Families with the same mutation can have variable courses as do individual members within the same family, as seen in our case presentation.
There is no cure for CMT. Treatment of the patient is supportive. Braces may help with ambulation. Physical and occupation therapy ongoing will help to maintain function. Regular screening for scoliosis is important. Pulmonary function screening is also vital especially if there is scoliosis. There can be associated cardiac abnormalities including conduction abnormalities and filling defects. However, this is not in the majority of patients. Most patients with CMT have normal life expectancies. There is ongoing gene therapy research (NINDS 2011). High dose vitamin C was studied but was not found to be helpful in the majority of young patients (ages 12 to 25 years) with CMT1a. This same study also deemed that high dose vitamin C was found to be safe (Vehamme, 2009).

5. Case #4

History: A 16 year old left handed girl presents with a 6 month history of numbness in the left hand. She feels that her handwriting is mildly affected. There is no associated pain. She exercises on a regular basis but not more than an hour a day. Upon further questioning, the patient stated that during her 45 minute drives to and from school, she leans on her left elbow to text her friends.
Examination highlights: She has mild atrophy of the ADM and weakness in the interossei. There does not seem to be involvement of her Abductor Policis Brevis (APB). She has decreased sensation in the 4th and 5th digits. Only her left ulnar reflex was diminished.

Study	Findings
Right Median CMAP	Normal
Left Median CMAP	Normal
Right Ulnar CMAP	Normal
Left Ulnar CMAP	Normal at the wrist and segment from wrist to below elbow with a conduction velocity of 58 m/s. When stimulated above the elbow, conduction velocity diminishes to 33 m/s and drop in CMAP amplitude to 2.5 mV from 8.4 mV
Left Radial SNAP	Normal
Left Median SNAP	Normal
Left Ulnar SNAP	Normal

EMG/NCV

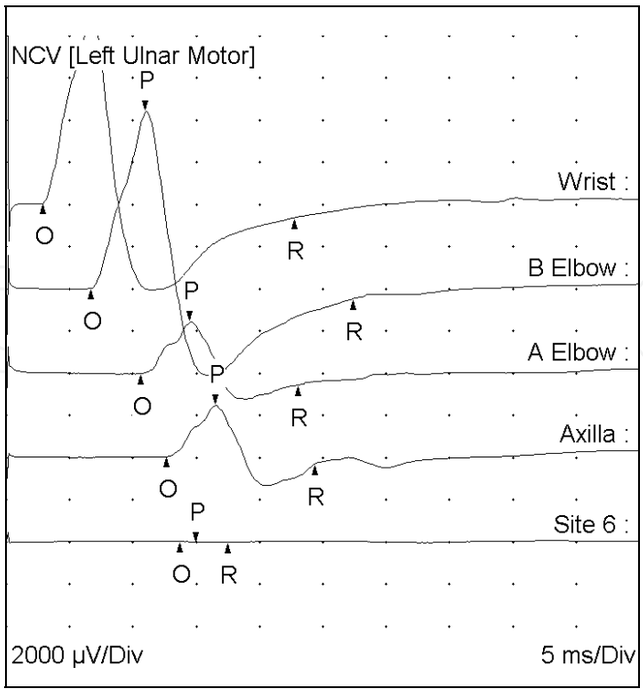


Fig. 3. Left ulnar CMAP

Diagnosis: left ulnar mononeuropathy in the segment across the elbow.

Discussion: A detailed discussion to separate a mononeuropathy, plexopahthy, and radiculopathy is beyond the scope of this chapter. These remain in the differential diagnosis in a child with numbness in the hand. Generally, in a lower brachial plexopathy (such as what is seen with thoracic outlet syndrome), there is involvement of the ABP (which is median nerve innervated). Pain is typically a prominent symptom. If a plexopathy is suspected, obtaining sensory nerve conductions of the medial and lateral antebrachial cutaneous nerves of the forearms bilaterally would be useful as these would be abnormal (typically of low amplitude) in lesions of the brachial plexus. If the patient had a radiculopathy of the C8 and T1 nerve roots, it would be expected that nerve conduction studies would be normal. Neck pain could also be present and as with a radiculopathy, there would be multiple nerve distribution involvement. In this patient, it is necessary to confirm that she has only a mononeuropathy and not a mononeuropathy multiplex or a more generalized neuropathic process. Differential diagnosis for a mononeuritis multiplex includes autoimmune disease (such as SLE), infections (such as Lyme disease), and diabetes mellitus.

In a 16 year old girl, connective tissue disease should be considered as a potential cause of peripheral neuropathy. A length-dependent predominantly axonal sensorimotor polyneuropathy or mononeuritis multiplex can be seen in pediatric patients with Systemic Lupus Erythmatosis (SLE). Vaso nevorum vasculitis, deposits of immune complexes, or damage to the neural tissue by antibodies against their components are proposed mechanisms. Because of the scarcity of published studies in the literature, treatment for the pediatric population is not well established. Limited published pediatric studies have reported response to steroids, azathioprine, and cyclophosphamide. Peripheral neuropathy associated with SLE tends to be concurrent with central nervous system

disease. Gabapentin and Carbamazepine can be used for symptomatic (pain control) treatment (Harel, 2002).

Hereditary Neuropathy with Pressure Palsies (HNPP) is in the differential diagnosis of a child who presents with multiple episodes of painless focal neuropathies in common sites of entrapment such as the ulnar nerve at the elbow and the peroneal nerve at the fibular head. Like CMT1a, the abnormality is in the PMP22 gene. However, rather than a duplication, PMP22 deletions lead to the HNPP phenotype.

In an otherwise healthy child with no history of trauma, especially with a family history of nontraumatic mononeuropathies, benign tumors such as osteochondromas compressing individual nerves should be considered. Although uncommon, case series' have been published on osteochondromas causing mononeuropathies and mononeuropathy multiplex. These are treatable causes of focal neuropathies. In some patients, this is hereditary. In these patients with autosomal dominant hereditary osteochondromata, sarcomatous transformation can occur and thus careful attention must be paid to these patients (Levin, 1991). Compressive mononeuropathies are not as common in children compared to adults. In one series, non-traumatic causes of ulnar mononeuropathies fared better than traumatic causes at one year follow-up (83% vs 56% improved) (Jones, 1986; Jones, 1996). In another small study, 4/5 focal compressive peroneal neuropathies had good recovery (Jones, 1986).

6. Case #5

History: An 11 year old girl with a history of acute lymphoblastic leukemia is admitted to the intensive care unit for hypotension and respiratory distress secondary to sepsis from her indwelling central line. She had received vincristine as one of her chemotherapeutic agents. She is intubated, paralyzed, and on pressors. Over the next three weeks, her condition slowly improves, she is weaned off of pressors, sedation and neuromuscular blockade are lifted. Despite apparent alertness and responsiveness, she does not hit parameters for extubation. Much more, after the intensive care physicians are concerned that 3 days after neuromuscular blockade is stopped, the ICU physicians and nurses note that she does not move any extremity.

Examination highlights: She is able to open her eyes spontaneously. She will fix and track. Pupils are equally reactive to light. She will grimace (although intubated) with noxious stimuli. She does not move her extremities spontaneously, to gentle, or to noxious stimuli. She is areflexic.

Studies: Her complete blood count is significant for pancytopenia (ANC <1.5, H&H 9.7 and 30, and platelets of 112). Her electrolytes were normal. Her LFTs normalized. Coagulation profile was corrected as well. CSF was with normal cell count, glucose, and protein level.

An exact cause is difficult to pinpoint in this patient's weakness. This case was used to springboard into a the following discussion of possible contributing factors.

An AIDP presentation has been described as both a paraneoplastic phenomenon as well as associated with complications of chemotherapy (Reddy, 2003).

There are multiple considerations of the underlying cause of this patient's weakness. Two likely contributors are an acquired neuropathy from vincristine and critical care neuropathy. Other possibilities are AIDP and critical care myopathy. Evaluation of the CSF may be

helpful in excluding AIDP as a potential cause. Regarding critical myopathy as a cause, it is not uncommon to have both a critical care neuropathy and myopathy in the same patient. The risk factors of critical care neuropathy do overlap with those of the myopathy. EMG findings may not be able to separate the two early in the course and the only definitive test is a muscle biopsy.

Study	Findings
Right Tibial CMAP	Normal distal latency Conduction velocity 38 m/s Amplitude <0.5 mV
Left Median CMAP	Normal distal latency Conduction velocity 45 m/s Amplitude <0.5 mV
Right Sural SNAP	Normal distal latency Conduction velocity 40 m/s Amplitude 2 uV
Left Radial SNAP	Normal distal latency Conduction velocity 48 m/s Amplitude 1.5 uV
Needle EMG Right Anterior Tibialis	fibrillation potentials and long duration, polymorphic MUAPs.

EMG/NCV findings

Chemotherapy induced neuropathy (CIN) generally are predominant sensory or sensorimotor in character, clinically and neurophysiologically. CIN can also affect the autonomic nervous system. Typically, CIN severity and permanence of symptoms depends on the agent, duration of treatment, and whether there is an underlying other cause of neuropathy (see below). Some agents (such as Taxol) have idiosyncratic neuropathy (there is no consistency of a threshold toxicity level) (Quasthoff, 2000).

Vincristine is one of the chemotherapeutic agents that can cause a peripheral neuropathy. The pattern is one of predominantly axonal. Typical presenting symptoms include paresthesias and diminished deep tendon reflexes. Although the neuropathy associated with vincristine is dose related, even at low therapeutic ranges, there is generally involvement of the peripheral nervous system. There is some ability for regeneration of damaged nerve fibers once the medication is stopped. In some patients who develop peripheral neuropathy as a side effect of chemotherapeutic agents, sometimes, their course can be completed with a lower dose of the agent (McLeod and Penny, 1969; Packer, 1994).

Another consideration in this patient would be quadriparesis as a result of vincristine given to a patient with an underlying hereditary neuropathy. Unusually rapidly developing severe vincristine associated neuropathy presenting with a flaccid quadriplegia resembling AIDP has been described in patients who also had an underlying hereditary neuropathy (Graf, 1996).

Cisplatin at a cumulative dose of 350mg/m^2 (although some report as little as 200 mg/m^2) has been demonstrated to be associated with a predominantly sensory neuropathy/neuronopathy that is characterized early as parasthesias, loss of vibratory sense and joint position sense, and absent ankle jerks. It tends to spare pain and temperature modalities (Reddy, 2003). Studies in adults have demonstrated accumulation of cisplatin in the dorsal root ganglia of patients undergoing this treatment (Thompson, 1984). Both Vincristine and Cisplatin (and other related platinum agents such as Carboplatin) may present after treatment has stopped (referred to as a coasting effect) (Quasthoff, 2000).

Thalidomide has been used to treat various inflammatory diseases in children and adolescents such as Crohn's and Bechet's Disease. Like some chemotherapeutic agents, the neuropathy course associated with Thalidomide is not predictable. Stopping this chemotherapeutic agent does not necessarily lead to resolution of CIN symptoms. In one study, after 4-6 years post cessation of Thalidomide, in those patients that had its associated neuropathy, only 25% had recovered completely (Strauss, 2000; Priolo, 2008).

There is no cure for CIN. Studies on prophylactic regimens to prevent its occurrence have not been fruitful so far. Alpha Lipoic Acid has been suggested as possibly helpful. Treatment of Chemotherapy induced neuropathy is symptomatic. Medications such as Gabapentin, Carbamazepine, and tricyclic anti-depressants have been used to treat CIN (Quastaff, 2000). However, there are some studies that contradict the helpfulness of tricyclic anti-depressants specifically for the neuropathic pain in CIN (Kautio, 2008; Wolf, 2008). Gabapentin and Carbamazepine have not been helpful either in more recent studies although Oxcarbazapine may (Wolf, 2008). Vitamin E may may be helpful in the prevention of Cisplatin associated CIN but further larger studies are needed to investigate its safety in chemotherapy patients (Wolf, 2008).

Critical Care neuropathy has been recognized more frequently in recent years. Much of the description has been in adult patients. However there are case reports and case series in the pediatric population. The presentation in children is similar to that in adults. The risk factors are also similar including sepsis (critical care neuropathy is typically seen 2-3 weeks after the onset of sepsis) and multiorgan failure. There are likely several mechanisms of injury resulting in critical care neuropathy. These include hypoperfusion of the peripheral nerves, ischemic injury leading to impairment of axonal transport, hyperglycemic injury to the peripheral nervous system, malnutrition leading to vitamin deficiency and consequently vitamin deficiency neuropathy, possible injury from antimicrobials (such as aminoglycosides and metronidazole which can also be associated with axonal polyneuropathies), and low albumin levels resulting in endoneural edema. Clinically, patients present with difficulty with extubation. Patients are reported to be either paraplegic or tetraplegic with hyporeflexia or areflexia (Petersen, 1999).

Neurophysiological studies are abnormal in 70% of patients and demonstrate a predominantly axonal polyneuropathy of the motor nerves. Sensory nerves are not spared. Both CMAPs an SNAPs have decreased amplitudes with significant slowing of conduction (Gutman, 1999). There is no direct treatment for critical illness neuropathy. Treatment is treating the underlying disease and supportive care. Unfortunately, recovery is prolonged and not as favorable compared to adults. A favorable outcome (complete recovery) is seen in approximately 50% of patients with critical care neuropathy (Petersen, 1999). Folate deficiency has been associated with peripheral neuropathy. Especially in children with brain tumors who also have seizures, consider older generation AEDs as a

potential course/contributor to peripheral neuropathy symptoms if they are using these (Figueroa, 1990).

7. Case # 6

History: A 17 year old boy was referred to the EMG lab with a 3 month history of progressive weakness of his bilateral lower extremities with involvement of the right greater than the left. The specific question asked by the referring physician was whether the patient needed surgery. He complained of shooting pains down the right leg. His mother reports that he started having enuresis at this time. His pediatrician had ordered an MRI of his lumbosacral spine and this was "positive" for a small disc bulge at L5. At this time, his mother asked if this had anything to do with the medication that was given to him a week and a half prior to his presentation. His PMD was contacted. Faxed records revealed he had a hemoglobin A1c of 16.6%. He had been started on Metformin 1 1/2 weeks prior to his appointment in EMG lab.
Examination highlights: Significant weakness (3-4/5 strength) of the hip flexors, quadriceps, hip adductors, hip extensors, plantarflexion, and dorsiflexion. He was using 2 canes to walk that he borrowed from his grandmother. Although he did not complain of upper extremity weakness, he had 4+/5 strength in the interossei with the remainder of his upper extremity muscles having good strength. He had a positive Gower's sign.
Studies: Review of his outside films demonstrated a small central disc bulge at L5 but there was no compression of the roots and there were no abnormal cord signals.

Study	Findings
Left Peroneal CMAP	Distal Latency 6.30 ms CMAP Amplitude 2.2 mV Conduction Velocity 32.5 m/s
Right Peronal CMAP	Distal Latency 7.9 ms CMAP Amplitude 8.1 mV Conduction Velocity 36 m/s
Left Peroneal F-Wave	Prolonged
Right Peroneal F-wave	Prolonged
Needle EMG right anterior tibialis	Fibrillation potentials 2+ polyphasic MUAPS with increased duration
Needle EMG right gastrocnemius (medial)	Fibrillation potentials 2+ polyphasic MUAPS with increased duration
Needle EMG right lumbar paraspinal muscle	Fibrillation potentials 2+ polyphasic MUAPS with increased duration

EMG/NCV FIndings

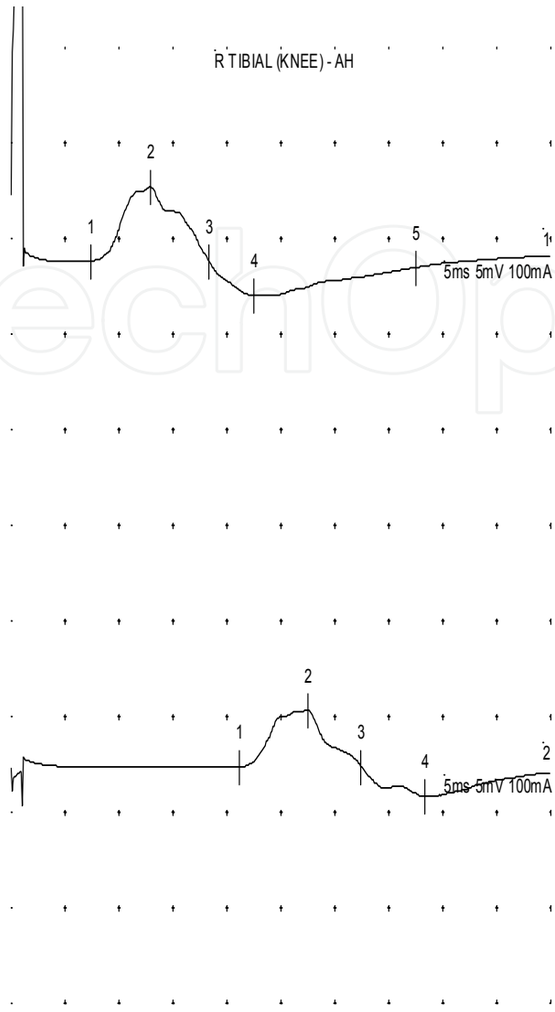


Fig. 4.

Diagnosis: diabetic peripheral neuropathy, diabetic amyotrophy.
Clinical Course: The patient was admitted from the EMG lab to the hospital. He was seen by an endocrine consult who determined that the patient had insulin dependent diabetes mellitus. LP performed demonstrated mildly elevated protein of 55 mg/dL. His CSF glucose was also elevated at 100 mg/dL. There were no abnormalities in the cell counts. He completed a course of IVIG (2 grams per kg divided over 5 days). He remained on the inpatient rehabilitation service for 2 weeks, By the time of his discharge, he was walking independently and his sugars were under control on a regimen that included the use of Lantus insulin. Although at follow-up 3 months later, he still had weakness in the hip flexors, quadriceps, hip abductors, hip adductors, hip extensors, anterior tibialis, and gastrocnemius muscles, there was an improvement to 4-4+/5 strength. He was then lost to follow-up when he turned 18 years of age.
Discussion: Diabetic neuropathy is present in approximately half of patients who have had the diagnosis for more than 5 years. Like adults, impaired glucose metabolism prior to the diagnosis of diabetes mellitus can affect nerve function. Hemoglobin A1c and glucose

tolerance tests can be helpful in diagnosing impaired glucose metabolism in patients that have normal random glucose levels (Nelson, 2006).

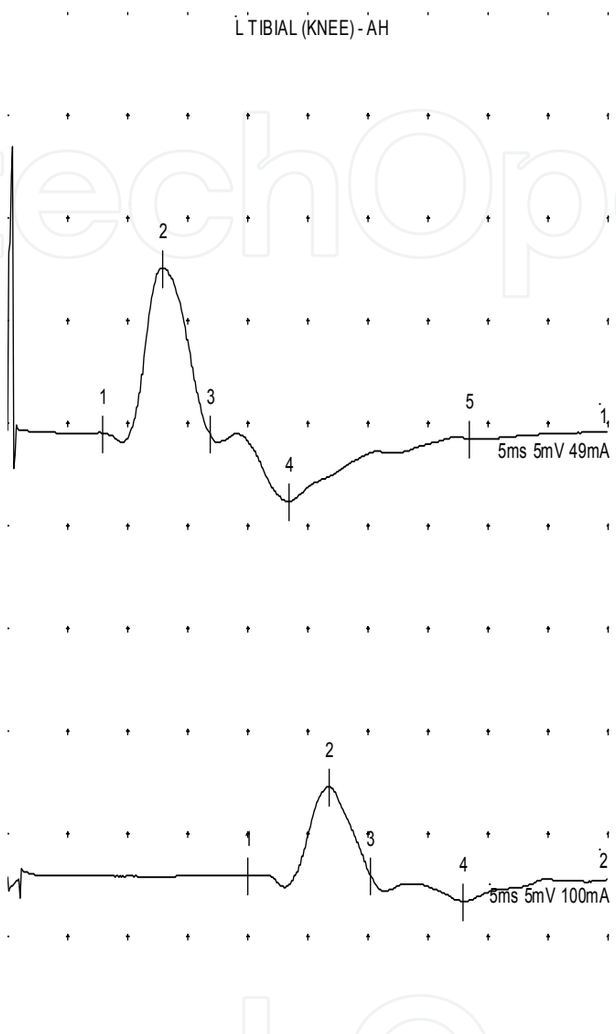


Fig. 5.

Most pediatric patients who have the peripheral neuropathy associated with diabetes mellitus are not detectable clinically. Both vibratory and tactile perception thresholds are not reliable. Most patients with diabetes are asymptomatic. Approximately 40% can be detected with a careful clinical examination. A larger percentage, approximately 60% can be detected with neurophysiological tests. It is important to identify which patients have diabetic neuropathy because they are at higher risk for retinopathy and nephropathy (Nelson, 2006).
Presentations of diabetic neuropathy in clinidren to childern include Carpal Tunnel Syndrome (CTS) (seen in 1/5 of type I diabetics and 1/3 of type 2 diabetics), 3rd nerve with sparing of the pupil, intercostals neuropathy (severe abdominal and chest pain that can mimic cardiac disease), chronic inflammatory demyelinating polyradiculopathy, small fiber neuropathy, autonomic neuropathy (seen in 16% of type I diabetics and 22% of type

II diabetics), and in the case of our patient, amyotrophy. Diabetic amyotrophy is a consequence of uncontrolled diabetes mellitus. It usually presents as progressive proximal greater than distal lower extremity weakness, muscle wasting, and significant weight loss. It is a rare complication of pediatric patients and often occurs with significant peripheral neuropathy (Trotta, 2004).

Symptoms of autonomic neuropathy can be seen in 15-20% of adolescent patients with long-standing diabetes. Autonomic neuropathy impairs the epinephrine response to hypoglycemia and thus places patients at risk for severe complications. Multiple systems can be involved with diabetic autonomic Neuropathy including the cardiovascular and gastrointestinal systems (Trotta, 2004). Please refer to the excellent review written by Trotta et al, 2004 for a discussion of the symptoms of autonomic neuropathy associated with Diabetes Mellitus in children.

Although some degree of neuropathy cannot be avoided in even the best controlled patients, controlling sugars is the best way to slow down progression and complications.

8. Case #7

History: A 2 year old girl is referred to the neurophysiology laboratory for absent reflexes. Per her mother, she had been developmentally normal for the first 8 months of her life. At this point, her development became stagnant. She developed increased tone, never attained the abilities to crawl, stand, or walk. She was able to sit but lost this ability several months before the test. Her mother stated that she had an abnormal MRI. Review of the report indicates that she has a leukodystrophy.

Physical examination highlights: The patient was awake with eyes open. She did not track consistently. Despite increased tone in her trunk and extremities, she had absent reflexes. During her appointment in the neurophysiology laboratory for nerve conduction studies, the patient had several 10-15 second seizures with a semiology of head and eye deviation to the right and lip smacking.

Studies: NCV demonstrates a generalized demyelinating neuropathy. Further bloodwork revealed a very low level of arylsulfatase.

Diagnosis: Metachromatic Leukodystrophy (MLD).

Inborn errors of metabolism are rare but important causes of neuropathy in childhood. Causes of inborn errors of metabolism that are associated with peripheral neuropathy include metachromatic leukodystrophy. Metachromatic leukodystrophy has multiple forms based on the mutation as well as the age of onset. Our patient has the most severe form (infantile) which is generally fatal in one to two decades. MLD can also present in childhood, adolescence, and young adulthood. These forms are less progressive and the neuropathic component can be more prominent. No cure exists for this disease but bone marrow transplant can be helpful. In some studies, it was able to significantly slow down the progression or halt the disease for short period of time from a cognitive standpoint. However, the peripheral neuropathy component continued. Patients with the later onset forms of metachromatic leukodystrophy have presented with peripheral neuropathy without clinical evidence of CNS involvement (de Silva, 1993). Very rarely, a patient can have peripheral nervous system involvement without apparent central nervous system involvement (Coulter-Mackie, 2001).



Fig. 7. T1 FLAIR image of patient with MLD

Krabbe's disease is an autosomal recessive disorder of galactocerebrosidase metabolism abnormality resulting in galactocerbrosidase beta galactosidase deficiency. Neurophysiological features include a demyelinating motor neuropathy on NCV and denervation on EMG. Like Metachromatic Leukodystrophy, there are different forms of the disease characterized by the time of their onset. The early infantile form can result in death after quick progression, sometimes by the second birthday. Other forms include the late infantile form (presents between 1.5 and 3 years), juvenile form (presents from 3-10 years) and the late onset form (presents later than 10 years of age) that makes up 10-15% of the patients. Late onset Krabbe's disease has been reported to present initially only as a peripheral neuropathy before the clinical onset of CNS manifestations. However, typically, the peripheral neuropathy associated with Late Onset Krabbe's disease is one of many other symptoms including limb weakness, termor, ataxia, nystagmus, blindness, psychomotor regression, and bulbar symptoms (Marks, 1997).

Other disorders associated with neuropathy include, Refsum, Mucopolysaccharidoses (which can present with bilateral Carpal tunnel syndrome) (Gschwind, 1992), Lowe's, and mitochondrial disorders (Wierzbicki, 2002; Charnas, 1998; Moosa, 1970). Other leukoencephalopathies associated with peripheral neuropathy include Fabry's Disease, Adrenoleukodystrophy/Adrenomyeloleukodystrophy, hypomyelination with congenital cataract, and Cockayne Syndrome (Kohlschutter, 2010).

POLG-1 mutations have been described in patients who present with a CMT- like appearance but tested negative for PMP-22 and related abnormalities. Profound sensory ataxia is seen in this phenotype. SANDO (sensory ataxic neuropathy with dysphagia and ophthalmoplegia) is another mitochondrial cytopathy that is associated with peripheral neuropathy (Harrowe, 2008).

9. Conclusion

Pediatric neuropathy presentations are quite varied. Evaluation of these disorders can be challenging in this population. Careful history and review of the available diagnostic work-up is essential. EMG/NCV studies continue to be an important tool in the evaluation of a child with neuropathy. Genetic classification and testing has been improving our diagnostic abilities. It is important to decipher as quickly as possible which ones warrant prompt treatment.

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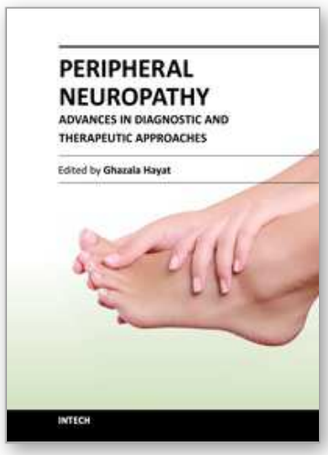
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Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches

Edited by Dr. Ghazala Hayat

ISBN 978-953-51-0066-9
Hard cover, 206 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

Over the last two decades we have seen extensive progress within the practice of neurology. We have refined our understanding of the etiology and pathogenesis for both peripheral and central nervous system diseases, and developed new therapeutic approaches towards these diseases. Peripheral neuropathy is a common disorder seen by many specialists and can pose a diagnostic dilemma. Many etiologies, including drugs that are used to treat other diseases, can cause peripheral neuropathy. However, the most common cause is Diabetes Mellitus, a disease all physicians encounter. Disability due to peripheral neuropathy can be severe, as the patients suffer from symptoms daily. This book addresses the advances in the diagnosis and therapies of peripheral neuropathy over the last decade. The basics of different peripheral neuropathies is briefly discussed, however, the book focuses on topics that address new approaches to peripheral neuropathies.

How to reference
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Leigh Maria Ramos-Platt (2012). Clinical Cases in Pediatric Peripheral Neuropathy, Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches, Dr. Ghazala Hayat (Ed.), ISBN: 978-953-51-0066-9, InTech, Available from: http://www.intechopen.com/books/peripheral-neuropathy-advances-in-diagnostic-and-therapeutic-approaches/clinical-cases-in-pediatric-peripheral-neuropathy

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