PAINFUL SENSORY NEUROPATHY

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Distal painful sensory neuropathy represents one of the most enigmatic conditions facing neurologists in their everyday practice. It is an extraordinarily common condition with minimal clinical or electrophysiologic findings. Patients complain bitterly but there are few objective markers to document its existence.

For purposes of discussion it is useful to start out with a case presentation.

Case presentation: A 60-year-old woman presented with burning pain in the toes for one year. After the onset of pain she developed numbness and tingling in the same distribution. The pain gradually spread from the feet up to the knees. Burning was a predominant feature, although there were occasional sharp, shooting pains. The pain was accentuated at night. She experienced mild intermittent symptoms in the hands. There were no complaints of muscle weakness or muscle cramps in the extremities.

The patient had no sicca symptoms. There were no complaints of urinary retention, constipation or diarrhea. There was no history of smoking.

Past medical history indicated that the patient was treated with an ACE inhibitor for mild hypertension. She had no history of renal disease or diabetes. She had routine breast and pelvic exams which were normal. Mammograms were performed yearly which were also normal.

Her family history was negative for neuropathy.

Medications in the past which proved unsuccessful included carbamazepine, amitriptyline, gabapentin and local application of capscacin. She had some partial relief with tramadol hydrochloride (Ultram®)100 mg t.i.d.

On neurologic examination the blood pressure was 160/92. No orthostatic change was found. General physical examination included normal skin without eruptions. Gait was normal. Cranial nerve testing revealed no abnormalities. Muscle strength and muscle bulk were normal throughout. Muscle stretch reflexes were also normal. The sensory exam revealed increased touch threshold at the toes. Pin was decreased to the ankles. Vibratory and position sense were normal. There was no sensory loss over the trunk.

Approach to the patient with distal painful sensory neuropathy

Neuropathy vs. other cause for pain?
The first and most important question to address in the analysis of the patient with distal painful sensory neuropathy is whether peripheral nerve disease accounts for the patient's symptoms. It is impossible to develop a differential diagnosis or a treatment plan unless it is known whether or not the patient has a neuropathy. The battery of tests addressing this question include: electrodiagnostic studies, quantitative sensory testing, tests of autonomic nervous system reflexes, and tissue sampling (nerve and skin biopsies).

Electrodiagnostic Studies

Electrodiagnostic studies represent the initial approach in assessing the question of "neuropathy vs other cause for pain". If they are abnormal a diagnosis of neuropathy can be firmly established (obviously the findings must be put into the context of the clinical picture so as not to misinterpret unrelated findings such as focal signs of nerve compression). The electrodiagnostic studies can also address the anatomic distribution of the neuropathy (mononeuropathy, multiple mononeuropathy or symmetric polyneuropathy) and establish by noninvasive techniques the underlying pathophysiology as axonal degeneration or demyelination or a mixed pattern. Most axonal neuropathies represent length-dependent disorders reflected by reduced compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) beginning first in distal nerves as the peroneal and sural, respectively. Demyelinating neuropathies demonstrate significant reduction in conduction velocities, prolonged distal and F wave latencies, abnormal temporal dispersion and partial motor conduction block.

If a patient has abnormal electrodiagnostic studies, the first important question has been answered: "yes, the patient does have a peripheral neuropathy" accounting for the pain. However, in many cases of painful distal small fiber sensory neuropathies, the conduction studies are normal because there is preferential involvement of unmyelinated (C nociceptive) and small myelinated Aδ nerve fibers sparing large myelinated Aα and Aβ nerve fibers. In patients with a suspected painful sensory neuropathy and normal

electrodiagnostic studies other techniques must be used to address the "neuropathy vs. no neuropathy" question.

In the case presented above the patient had normal conduction studies and a normal needle EMG examination.

Quantitative Sensory Testing

Quantitative sensory testing (QST) using computer-assisted instrumentation to characterize and quantitate sensory thresholds has become an important tool to assess small fiber sensation. The most widely used instrument currently employed is the "computer assisted sensory examination IV" (CASE IV) which evaluates vibratory (VDT), warm (WDT), cool (CDT) and the heat-nociception or heat-pain (HNDT, HPDT) detection thresholds.

In distal painful sensory neuropathy, unmyelinated C and Aδ nerve fiber function is of particularly interest. The CDT is mediated by terminal branches of small myelinated, Aδ nerve fibers that penetrate the basal lamina and enter the epidermis devoid of a myelin sheath. The morphologic correlate of WDT is not as well-defined. The burning pain commonly described by patients is mediated by unmyelinated C fibers (HNDT).

Algorithms for QST Testing

The testing paradigm called "just noticeable difference" or JND is employed by the CASE IV and refers to the ability of the individual to discriminate between two levels of stimuli. Twenty-five standardized vibratory and thermal stimulation levels have been established for patient testing and analysis. In the CASE IV systems, the magnitudes of the twenty-five levels of stimulus intensity are distributed from smallest to largest. In the CASE IV system, the baseline for vibration begins at level 13 while thermal testing begins at the patient's skin temperature prior to the start of testing.

The CASE IV uses two algorithms of sensory testing. In the "forced-choice" algorithm a trial includes two time periods in which a given level of intensity of stimulus is delivered. A stimulus is presented in only one of the time periods (never both) and the patient is asked to determine in which period the stimulus has occurred. For example, the cold stimulus at a certain level is presented during period one or period two of a trial and the patient is asked to depress a response key indicating that the stimulus is felt. If there is a failure to feel the stimulus, subsequent steps to larger or smaller events are given in predetermined increments. Turn-abouts occur at failures of perception and in the CASE IV system a threshold is based on median of the last six turn-around values.

A common criticism levied at the forced-choice testing mode is the time required for completion. For this reason a "one-time period 4-2-1 stepping algorithm is also used. In this test there is just one time period during which the stimulus may or may not be delivered. The response for each time period is "yes or no". The null stimuli allow for interpretation of false-positive or guessing results. The incremental or decremental steps change by 4, 2 and 1 JNDs with each turn-around established on the basis of a failed perception. The test ends after a total of twenty stimuli, five of which are null.

An important application for QST occurs in patients with painful sensory neuropathy when signs of neuropathy are minimal by neurologic examination and electrodiagnostic studies. In such patients, QST can provide an objective, noninvasive measure of peripheral neuropathy. Apart from the diagnostic capabilities of QST, the method also has a definite role in monitoring treatment (not the subject of this syllabus).

QST is not without its critics. If a patient is determined to demonstrate an abnormal result by QST it can be done. Thus, the results must be put into the context of the entire patient evaluation. QST can also be abused to document the presence or absence of such clinical entities as carpal tunnel syndrome. Take for example, persistent symptoms of carpal tunnel syndrome after surgical decompression. Both QST and electrodiagnostic studies remain abnormal for long periods after surgery making it difficult to recommend reoperation on the basis of an abnormality in these tests alone. QST as well as any laboratory test, must be used as only one component of patient evaluation.

The patient presented above demonstrated abnormal threshold for cold (CDT) and heat-nociception (HNDT).

Autonomic Nervous System Testing

Autonomic nervous system testing also represents an important tool in the evaluation of distal painful sensory neuropathy. In the patient with distal pain, not only can the general question of "neuropathy vs other cause for pain" be addressed, but also some insight into the differential diagnosis can be established. For example, painful sensory neuropathies with autonomic failure include disorders such as diabetes, amyloid polyneuropathy, paraneoplastic sensory neuropathy with autonomic failure, and hereditary sensory and autonomic neuropathies.

The components of autonomic nervous system testing include:

1) Examination of post-ganglionic sweating or sudomotor function [the quantitative sudomotor axon reflex test (QSART)]
2) Tests of adrenergic function measured by changes in blood pressure and heart rate to tilt and Valsalva

3) Tests of cardiovagal function measured by changes in heart rate to deep breathing, Valsalva, and tilt.

Post-ganglionic Sudomotor Function

In distal painful small fiber neuropathies with normal conduction studies, the assessment of distal sudomotor function by QSART is particularly valuable. Abnormalities in QSART provide objective evidence that a small fiber neuropathy is present. The reflex is mediated by the post-ganglionic sympathetic sudomotor axon. Within the dermis, the axon branches and innervates more than one sweat gland. Acetylcholine is iontophoresed into the skin, where it activates the axon terminal of the nearest eccrine sweat gland. The impulse is propagated antidromically, reaches a branch point and travels orthodromically to the axon terminal of a nearby sweat gland where acetylcholine is released. The acetylcholine binds to the muscarinic receptor of the sweat gland resulting in sweat output. Quantitation of sweat volume is determined using a multi-compartmental sweat capsule connected to a sudorometer and displayed on a computer. In normal individuals the sudomotor responses are highly reproducible and show little variation. In the assessment of peripheral neuropathies, four sites are tested to evaluate the distribution of sudomotor responses (medial forearm, lateral proximal leg, medial distal leg and proximal foot). In a small fiber neuropathy, support for the diagnosis would be a sweat volume-reduction at distal sites symptomatic of a length-dependent process. Of the painful sensory neuropathies, such a pattern would be especially indicative of hereditary sensory neuropathy type I (see discussion below).

Cardiovagal and Adrenergic Function

A battery of tests are used to screen for loss of cardiovagal and adrenergic function. In most discussions these functions are addressed separately, but in the testing paradigm they are investigated together. For these studies, the patient lies supine on a tilt table. Beat-to-beat blood pressure and heart rate recordings are measured using a photoplethysmographic methodology (Finapres®). This is a noninvasive technique which provides arterial wave forms from the finger.

Heart rate response to deep breathing: The testing begins with deep breathing as an assessment of cardiovagal function. Rhythmic variations in heart rate occur at the frequency of respiration and are detectable in most individuals. Rhythmic changes in heart rate are due almost entirely to changes in vagal activity. This produces a normal sinus arrhythmia. Loss of the normal sinus arrhythmia is one of the most sensitive measures of autonomic nervous system failure in peripheral nerve diseases.

Response to Valsalva Maneuver: This phase of testing which records heart rate and blood pressure responses during the Valsalva maneuver and incorporates both adrenergic and vagal autonomic reflexes. The patient is asked to blow into a bugle for 15 seconds with expiratory pressure reaching 40 mm Hg. There are *four phases* of response during the Valsalva maneuver:

Phase I: transient *increase of blood pressure* due to mechanical compression of the aorta accompanying the increase of intra-abdominal and intra-thoracic pressure.

Phase II divided into early (II_e) and late II_L):

II_e: a progressive *fall of blood pressure* occurs resulting from a reduction of venous return with concomitant reduction in stroke volume and cardiac output.

During this phase a *compensatory tachycardia* takes place.

II_L: total peripheral resistance increases in response to reduction in blood pressure by means of increased sympathetic outflow and increased plasma norepinephrine. This halts the fall in blood pressure and *restores blood pressure to the mean resting levels* of arterial pressure.

Phase III: during this phase there is an increase in intrathoracic pressure from the mechanical influences of deep inspiration and *blood pressure falls*

Phase IV: the *blood pressure overshoots above baseline* values because venous return and cardiac output have returned to normal but there is persistent vasoconstriction of the arteriolar vascular bed. *Bradycardia is present* during this phase.

Valsalva ratio: During the Valsalva maneuver changes in heart rate between phase II (tachycardia) and phase IV (bradycardia) provide the basis for calculating a ratio which is also an index of cardiovagal function.

Typical abnormalities in the Valsalva maneuver are summarized in the Table 1. Vagal failure as the only finding in a patient with distal painful sensory neuropathy is typical of diabetes. Sympathetic or combined sympathetic and vagal failure occurring in the evaluation of distal painful sensory neuropathy ischaracteristic of amyloid polyneuropathy and may also be seen in paraneoplastic sensory neuropathy. Sympathetic overactivity (adrenergic hypersensitivity) is seen in conditions such as the postural tachycardia syndrome (POTS).

TABLE 1. Results of Components of Valsalva Maneuver

Response	Phase I*	Phase II_E*	Phase II_L*	Phase III*	Phase IV*	VR**
Vagal Failure	N	↓	N	N	N	↓
Sympathetic Overactivity	N	↑	↓	N	Excessive	N
Moderate Symp. Failure	N	↑↑	Absent	N	Variable	↓
Symp and Vagal Failure	N	↑↑↑	Absent	N	↓	↓

** **Blood pressure responses**
* **VR: Valsalva ratio**

Response to Tilt-up Testing

The final component of the autonomic battery is the *response to tilt-up testing*. Orthostatic blood pressure recordings are made with the patient supine and following tilt to 80 degrees. The duration of the tilt is usually five minutes with cuff recordings obtained at one-minute intervals. A grading system for orthostatic intolerance has been recommended by Philip Low [Table 2(9)]

TABLE 2. Orthostatic Intolerance to tilt-up

Grade 0: Normal

Grade 1: Any of the following changes:

Excessive blood pressure oscillations	$> \pm$ 15 mm Hg
Pulse pressure reduction	$\geq$ 50%
Heart rate increment	$\geq$ 30 beats/minute

Grade 2: Transient orthostatic hypotension with recovery

Grade 3: Sustained asymptomatic orthostatic hypotension with drop in blood pressure:

Systolic blood pressure	>30 mmHg
Diastolic blood pressure	>15 mmHg
Mean blood pressure	>20 mmHg

Grade 4: Sustained symptomatic orthostatic hypotension

The patient presented above had normal autonomic reflex testing.

Tissue Diagnosis

Role of the Nerve biopsy

Patients should be carefully selected for nerve biopsy. In the evaluation of painful sensory neuropathy, the nerve biopsy should not be the diagnostic tool addressing the question of "neuropathy vs other cause for pain". Rather this is done by the battery of tests already outlined (electrodiagnostic studies, QST and autonomic testing) and/or by skin biopsy(discussed below). If a nerve biopsy is done it should address a specific etiologic question. Patients expect an answer from an invasive procedure such as a nerve biopsy, especially one that causes some degree of discomfort. Merely telling a patient that the nerve biopsy is diagnostic of neuropathy without a cause is not good enough for most patients!! This is a lesson unfortunately learned by experience!!!

In the work up of painful sensory neuropathy the nerve biopsy is indicated in three situations:
1) If the electrodiagnostic studies demonstrate nonuniform conduction studies indicative of a multiple mononeuropathy, a vasculitis may be the cause for the painful sensory neuropathy even in the absence of systemic manifestations (i.e., isolated peripheral nerve vasculitis). In this circumstance the nerve biopsy is the best method to establish a tissue diagnosis.

2) In situations where autonomic nervous system tests are abnormal, amyloid polyneuropathy (familial or primary) emerges as a major consideration and a nerve biopsy is appropriate.
3) If there is a monoclonal gammopathy or if the urine shows Bence-Jones protein (light chains), amyloid polyneuropathy again must be considered a diagnostic consideration.

The patient under consideration exhibited none of these features. A nerve biopsy was not recommended.

Skin Biopsies

Skin biopsies for analysis of intraepidermal nerve fibers represents a recently introduced technique for establishing a diagnosis of peripheral neuropathies . Skin biopsies are very valuable in addressing the question of "neuropathy vs other cause for pain". This is especially true in circumstances where small fiber neuropathy is suspected but SNAPs (even surals) are preserved. A typical indication is reflected by the patient presented above with painful feet and relatively normal neurologic examination (except for diminution of pinprick, temperature and light touch over the toes and feet), normal nerve conduction studies and autonomic testing. In this setting a tissue diagnosis to confirm the presence of neuropathy is best established by skin biopsy.

Intraepidermal nerve fibers were described by Langerhans in 1868 and his findings were confirmed by others. In 1959, Arthur and Shelley provided a detailed description of intraepidermal nerve fibers using methylene blue-stained sections. Despite the careful work of these early observers, the methods

were capricious and not easily applied to clinical practice. This all changed with the discovery of neuropeptides which selectively stain nerve fibers in the skin. The neuropeptide, protein gene product (PGP) 9.5, has proved particularly useful because it selectively stains the intraepidermal nerve fibers (12-14). The report by Kennedy and Wendelschafer-Crabb was the first to illustrate the existence of a full network of nerve endings extending to the surface of the skin using PGP 9.5. Subsequent studies have demonstrated nerve fiber loss in a variety of conditions including painful sensory neuropathies and diabetes.

Punch biopsies, 3 millimeters in diameter, are removed from the skin at various sites following infiltration with lidocaine and epinephrine. The biopsy is simple, non-painful and heals readily. Skin biopsies can be done repeatedly and may be valuable for monitoring potential therapeutic agents. The selection of the skin to be biopsied will depend on questions understudy. Nonglabrous skin of the distal extremity (calf) or proximal regions (thigh or trunk) are most often sampled. Nonglabrous skin contains unmyelinated nerves in the epidermis, and demonstrates both sudomotor axons to sweat glands and vasomotor axons to blood vessels. The glabrous skin of the toe or the finger pads is usually not sampled, although myelinated nerve fibers to Miessner's and pacinian corpuscles may be of interest in some conditions. Within the epidermis, unmyelinated axons can be directly viewed and quantitated, especially by employing confocal microscopy. These distal nerve fibers of the neuroaxis remain unaddressed by most means of study. Conventional nerve biopsies and clinical electrodiagnostic studies do not assess the status of these distal nerve fibers. In addition, innervation to the sweat glands, hair follicles and arterioles of the dermis can be directly examined. Furthermore, the skin biopsy can also be used to address the question of amyloid infiltration which can be observed in the blood vessel walls of the dermis.

The patient presented above had a severely abnormal skin biopsy with a marked loss of intraepidermal nerve fibers.

Laboratory Studies

In the evaluation of >200 patients attending the Painful Sensory Neuropathy Clinic at The Ohio State University a battery of blood tests has emerged based on a prospective evaluation of patients with painful sensory neuropathies of diverse etiology. This laboratory work up is highly focused and covers the most important hereditary and acquired neuropathies encountered in the differential diagnosis of painful sensory neuropathy. The laboratory evaluation consists of selective assessment of autoantibodies to nerve and other blood and urine tests.

Nerve antibodies: In general the role of autoantibodies has been greatly overemphasized in the evaluation of painful sensory neuropathies. With regard to specific autoantibodies the following comments should be emphasized:

1) GM1 and ganglioside antibodies: It is surprising how many patients referred to our sensory neuropathy clinic have had testing for GM1 and other ganglioside antibodies. While such antibodies

may be potentially important in the evaluation of motor neuropathies, ganglioside antibodies have no role in the evaluation of sensory neuropathies. They should not be ordered in the evaluation of distal painful sensory neuropathies.

2) Sulfatide antibody: This autoantibody has been overemphasized as a marker for sensory neuropathy but our studies have shown that sulfatide antibodies fail to define any specific syndrome. There is no justification for its current use in the evaluation of distal painful sensory neuropathy.

3) Anti-Hu antibody: This autoantibody can be very valuable in the evaluation of painful sensory neuropathies. A positive anti-Hu antibody is a highly sensitive marker for the sensory ganglionitis associated with small cell lung cancer (and rarely other neoplasms including prostate, small-cell adrenal cancer, adenocarcinoma of the lung, neuroblastoma, and chondrosarcoma). It is entirely appropriate to obtain this blood test in the setting of painful sensory neuropathy, although the anti-Hu syndrome is rare. It is worth remembering, however, that most patients with paraneoplastic sensory neuropathy will distinguish themselves by objective findings on physical examination (loss of muscle stretch reflexes and many will exhibit loss of large fiber sensory function), abnormal electrodiagnostic studies (reduced or absent SNAPs) and some will have abnormal autonomic tests.

4) Anti-myelin associated glycoprotein(anti-MAG): This autoantibody is usually associated with a slowly progressive distal sensorimotor neuropathy with gait ataxia. Objective features of neuropathy should be present on neurologic examination and by electrodiagnostic studies before obtaining this blood test.

Blood and Urine studies: The following battery of blood and urine studies (Table 3) is appropriate for all patients with painful sensory neuropathy. The tests listed below will be sufficient to diagnose virtually all the pertinent conditions in the differential diagnosis (see Table 3 and 4).

TABLE 3. Blood and Studies to be Obtained in Evaluation of Painful Sensory Neuropathies

Blood or Urine Test	Disorders
CBC, Liver function studies, creatinine	Cancer, amyloid, Fabry, Tangier
Hemoglobin A1c	Diabetes
Cholesterol, triglycerides, HDL	Fabry disease
ANA, ENA, RF, serum & urine immunofixation	Sjögren's, vasculitis, monoclonal protein
Heavy metals (arsenic)	Arsenic toxicity
HIV, FTA	AIDS, Tabes
Autoantibodies: anti-Hu	Paraneoplastic

Differential Diagnosis of Painful Sensory Neuropathy

Both acquired and inherited neuropathies can present as predominantly painful conditions.
In the analysis of >200 patients referred to the Ohio State University with painful sensory neuropathies one entity, ***distal painful axonal idiopathic neuropathy (distal PAIN*** to be a specific nosologic entity with distinctive*)* is seen far more frquently than any other. We believe distal PAIN has distintive features (Table 4). It can be differentiated from other acquired painful sensory neuropathies (Table 4).

TABLE 4. Features of Distal Painful Axonal Idiopathic Neuropathy (Distal PAIN)

- Age of onset greater than 50 years
- Woman 1.5:1 Men
- Distal loss of pinprick, touch (vibration variable)
- Muscle stretch reflexes preserved in 2/3
- MNCVs normal; SNAPs normal to slightly reduced
- Elevated pain and temperature thresholds (CASE IV)
- Pathologic diagnosis based on loss of intraepidermal nerve fibers

ACQUIRED PAINFUL SENSORY NEUROPATHIES

A comparison of the most important conditions observed in the differential diagnosis of acquired painful sensory neuropathies is presented in Table 5.

TABLE 5. Differential features of Acquired Painful Sensory Neuropathies

Disease	ElectoDX	Autonomic	Lab Tests	Tissue Dx
Distal PAIN	nl to slightly ↓ Sural SNAP	(under study)	Normal	Abn skin bx
Paraneoplastic	↓/absent SNAPs	↓ sudomotor ↓ or nl orthostatic	Anti-Hu antibodies	Ax neuropathy
Sjögren's	↓/absent SNAPs	↓ tears	+ ANA, SS-A/SS-B	Ax neuropathy
Vasculitis	↓/absent SNAPs	-	? +ESR, ANA	+ Vasculits
Amyloidosis	↓/absent SNAPs	↓ sudomotor	Monoclonal protein	+ fat,skin,nerve
AIDS	↓/absent SNAPs	normal	HIV +	_
Toxic (arsenic)	↓/absent SNAPs	-	+ Arsenic	Ax neuropathy
MGUS	↓/absent SNAPs	-	Monoclonal protein	Ax or Demyel
Diabetes	↓/absent SNAPs	↓ sudomotor	+ HbA1c	Ax neuropathy
Infiltrative tumor*	↓/absent SNAPs	-	-	+ cells in nerve

* Occult neoplasm may be difficult to diagnose and require high index of suspicion; CSF may be necessary.

INHERITED PAINFUL SENSORY NEUROPATHIES

In addition to the acquired neuropathies, four inherited conditions must be considered in the differential diagnosis of the distal painful sensory neuropathy. These include: hereditary sensory and autonomic neuropathy type I (HSAN I), familial amyloid polyneuropathies, Fabry disease and Tangier disease. The other variants of HSAN II-V all present in early childhood and are not part of the differential diagnosis of this adult group of patients.

Hereditary Sensory Autonomic Neuropathy Type I (HSAN I)

This disorder can have features which are difficult to distinguish from distal PAIN. It is inherited as an autosomal dominant disease. A family history allows for a clear distinction from distal PAIN. However, some cases may be sporadic. The clinical features are as follows: In general most patients with HSAN I are younger than those with Distal PAIN. The first symptoms develop in the second to fourth decade of life . One of two features usually bring patients to clinical attention: foot ulcers or spontaneous pain. If foot ulcers or foot deformities are present from recurrent infections and stress fractures the condition can be easily differentiated from distal PAIN. However, another group of HSAN I patients present because of severe burning or lancinating pain in the feet which may recur in bouts of variable frequency and intensity. Shooting pains may also be experienced in various parts of the body including the hands, shoulders, back and legs.

On physical examination, the sensory deficits are symmetrical, affect the feet more than hands and spare the proximal limbs, trunk, and head and neck. The sensory loss for pain and temperature predominates but all modalities can be involved in some patients. Loss of sweating over the feet is typical. Other autonomic features such as bladder control, impotence and postural hypotension are not features of HSAN I. Muscle stretch reflexes at the ankles are usually depressed or absent and preserved at other joints. In the typical case, distal muscle weakness is not a prominent symptom; foot abnormalities such as pes cavus, if present, help distinguish HSAN I from distal PAIN.

Motor conduction velocity is usually normal or only mildly affected. The SNAPs are reduced in amplitude or absent. In some cases, sensory potentials may be less affected in the arms. Signs of chronic denervation may be present in distal lower limb muscles.
Loss of distal sudomotor function is typical of HSANI.

Sural nerve biopsies demonstrate a loss of nerve fibers of all sizes. The unmyelinated nerve fibers are severely reduced in number and show a shift toward smaller diameter fibers. There is also a loss of myelinated fibers, the smaller diameter fibers being most affected. Autopsy studies show preferential loss of neuronal cells from the DRG of the lumbosacral region with sparing of the ventral roots. There is degeneration of the posterior columns of the spinal cord and degenerative changes extending to the peripheral nerves.

Familial Amyloid Polyneuropathies

There are three plasma proteins that cause inherited or familial amyloid polyneuropathies:

transthyretin, apolipoprotein A-I and gelsolin. All are inherited as autosomal dominant disorders. Painful neuropathies occur with either transthyretin or apolipoprotein A-I making these conditions important in the differential diagnosis of distal PAIN. The neuropathic syndrome seen with gelsolin is distinctly different from distal PAIN (see below).

Transthyretin Amyloidosis. This aberrant plasma protein accounts for the majority of familial amyloid polyneuropathies. Transthyretin is a normal plasma protein which binds both thyroxine and retinol binding protein. In earlier reports the term prealbumin (named because it migrates ahead of albumin in standard protein electrophoresis) was used in preference to transthyretin.

In the old classification of amyloid polyneuropathy, two types of familial amyloidosis were included in this group, FAP I and II. The cardinal features suggesting transthyretin-related amyloid polyneuropathy include a sensorimotor polyneuropathy with autonomic nervous system impairment, carpal tunnel syndrome, vitreous opacities, cardiomyopathy and nephropathy. The degree of expression of these characteristic clinical features varies according to ethnic origin.

The onset of the transthyretin amyloidosis varies from the third to the sixth decade or even later in some patients. Cranial nerves are not affected except for occasional patients with a scalloped pupil from ciliary nerve involvement. Vision may be reduced by vitreous opacities which may be seen as granular, dark deposits using the direct ophthalmoscope. Some patients exhibit a dissociated sensory loss, i.e., preferential loss of pain and temperature with relative preservation of position and vibratory sensation. Other patients have a panmodality loss.

Two features, if present will differentiate transthyretin-related amyloid polyneuropathy from distal PAIN: distal weakness and autonomic nervous system involvement. Distal weakness with foot drop and milder degrees of wrist and intrinsic hand muscle weakness is present in most patients. Autonomic manifestations are also common and include postural hypotension, gastric atony, constipation, diarrhea, urinary retention, impotence and hypohidrosis. Autonomic features are absent in patients with certain transthryretin mutations, especially those originally classified as Indiana / Swiss and Maryland / German variants.

A carpal tunnel syndrome may precede the polyneuropathy or manifest later in the course.

In most forms of transthyretin-related polyneuropathies, death is caused by congestive heart failure due to cardiomyopathy. Rarely, patients may have a fatal cardiac arrhythmia.

Electrophysiologic studies demonstrate findings characteristic of an axonal neuropathy. Sensory nerve action potentials are reduced or absent. Motor nerve conduction studies show reduced evoked amplitudes, usually in a length-dependent manner. Many patients will have features of a median neuropathy at the wrist.

The sural nerve biopsy shows diffuse or nodular amyloid deposits in the connective tissue and blood

vessels of the endoneurium and epineurium, and less often, in the perineurium . There is an accompanying nerve fiber loss; preferential involvement of unmyelinated and small myelinated fibers may be seen, especially in the early stages. Biopsies of rectum and skin may also be useful for diagnosis.

Abnormalities in the tests of autonomic nervous system function will be of particular value in identifying the transthyretin-related amyloid polyneuropathies.

Other organ system involvement may manifest with elevated BUN and creatinine, elevated bilirubin and alkaline phosphatase. Serum liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST) or γ-glutamyl transferase (GGT)] may be mildly increased. Cardiac conduction defects may be detected in the electrocardiogram of some patients.

At least 50 different mutations of the transthyretin gene have been described (66). This large number of mutations is to be kept in mind when ordering laboratory tests. One of the commercial laboratories offers testing for only a single amyloid mutation, a substitution of methionine for valine at position 30 of the transthyretin (so-called "met 30 mutation"). While this may be the most common mutation of the transthyretin-related amyloidoses, it is not an adequate screen for amyloid polyneuropathy.

Apolipoprotein A-I Amyloidosis. The apolipoprotein A-I variant of amyloid polyneuropathy, originally referred to as FAP III, was described in 1969 by Van Allen in an Iowa kindred of English, Irish, and Scottish descent. The disorder is rare; a second kindred of Italian origin has been identified. The condition is inherited as an autosomal dominant trait. The usual age of onset is in the thirties but the range varies from twenties to seventies. Shooting pains and dysesthesias in the lower extremities herald the onset of the peripheral neuropathy. Upper extremity involvement becomes apparent with evolution of disease. Preferential involvement of small fibers is restricted to the early stages; most patients demonstrate a panmodality sensory loss. Many patients have ataxia and this may be secondary to amyloid deposition in the dorsal root ganglion. Motor involvement is variable but can proceed to significant muscle atrophy in both arms and legs. Loss of muscle stretch reflexes will follow. Carpal tunnel syndrome is not a prominent feature. Hearing loss will be present in a significant number of affected individuals.

Impotence is a common manifestation of this neuropathy but it is not the result of autonomic involvement. Rather, it is secondary to amyloid deposition causing testicular atrophy. Other endocrine manifestations are the result of hypothalamic-pituitary amyloid deposits and include hypothyroidism and stress-related adrenal insufficiency.

A striking, yet unexplained incidence of peptic ulcer disease occurs in patients with apolipoprotein A-I amyloidosis. Amyloid deposition is minimal in the bed of the ulcers. Other gastrointestinal features are unusual and few symptoms arise from amyloid infiltration to the liver.

Cardiac involvement is also minimal with amyloid deposition restricted to the endoneurium sparing the myocardium.

Renal failure is the most common cause of death in this form of inherited amyloidosis, usually within 12-15 years after onset. Only mild degrees of glomerular or interstitial amyloidosis occur. Renal vascular amyloid deposits are believed to cause ischemia and subsequent renal atrophy.

Measurable laboratory abnormalities relate mostly to renal function, especially blood urea nitrogen and creatinine. Proteinuria is not abundant. Thyroid stimulating hormone will provide a sensitive measure of hypothalamic-pituitary dysfunction. Spinal fluid protein is elevated reflecting amyloid deposits in the nerve roots.

Electrodiagnostic studies demonstrate an axonal neuropathy with decreased or absent SNAPs. Needle EMG changes typically show denervation.

A sural nerve biopsy is appropriate for diagnostic purposes, but as in all forms of amyloid neuropathy tissue deposits are multifocal and often occur in proximal segments of the nerve. A negative nerve biopsy does not exclude the diagnosis of amyloid polyneuropathy. Autopsy material from several of the cases reported by Van Allen showed extensive deposits of amyloid in the spinal roots, dorsal root ganglia, and the sciatic nerve trunk. Even the autonomic nerve trunks demonstrated amyloid despite relatively few symptoms of autonomic neuropathy.

Gelsolin Amyloidosis. This disorder as already mentioned is not in the differential diagnosis of distal PAIN. This form of amyloid polyneuropathy is characterized by four predominant features: cranial neuropathies (severe facial weakness), corneal lattice dystrophy, mild peripheral neuropathy and skin abnormalities. The disease shows a marked clustering in the southeast of Finland (Kymenlaakso district) and in a smaller area in Southern Finland (South Häme district). This form of amyloid polyneuropathy occurs in other countries including the United States, the Netherlands, Denmark, and Japan.

Fabry Disease

Fabry disease represents a rare, inborn error of glycosphyngolipid catabolism, inherited as an X-linked recessive disorder. Deficient activity of the lysosomal hydrolase, α-galactosidase A, causes a symptom complex of acroparesthesias, angiokeratoma, corneal and lenticular opacities and anhydrosis. The major disease manifestations are caused by deposits of the ceramide trihexoside, globotriaosylceramide, in vascular endothelial and smooth muscle cells, heart, kidney, cornea, and dorsal root ganglia. Galabiosylceramide, another glycosphyngolipid, accumulates to a lesser extent.

Because the neuropathy typically presents before 20 years of age it is usually not in the differential diagnosis of distal PAIN. However, the symptoms can be quite similar. Episodic burning pain in the extremities is characteristic. The pain lasts from a few hours up to weeks, aggravated by exercise or changes in environmental temperature and humidity. Pain is usually felt in the palms and soles but

may radiate to the proximal extremities and other parts of the body. Abdominal or flank pain may simulate appendicitis or renal stones. In addition to the intermittent pain, there may be a more persistent dysesthetic discomfort in the hands and feet.

On neurologic examination clinical signs of neuropathy are strikingly absent in most Fabry patients much like they are in distal PAIN. Rarely, diminished muscle stretch reflexes may be present at the ankles. Sweating is often decreased over the feet, most likely the result of direct glycosphyngolipid deposits in sweat glands. There are no other features of autonomic nervous system.

Other features can help distinguish Fabry disease from distal PAIN. The most important are the cutaneous vascular angiokerotomas which are the hallmark of Fabry disease which develop slowly from childhood and increase with age. The lesions appear in clusters of individual punctate, dark red to blue-black angiectases in the superficial layer of the skin. The skin lesions may be flat or raised but do not blanch. Clusters are most dense in a "bathing-trunk" distribution over the hips, thighs, buttocks, penis, and scrotum. In some cases skin changes may not be prominent, seen only upon careful examination of the scrotum and umbilicus. The oral mucosa, conjunctiva and nails may be involved. In addition, patients have corneal deposits of glycosphyngolipid seen by slitlamp examination. One type of lens opacity, the"Fabry" cataract is pathognomonic, appearing whitish, almost translucent, with spoke-like deposits of fine granular material on or near the posterior lens capsule.

Patients with Fabry disease develop significant kidney disease, having a fixed azotemia by the third to fifth decade. Death will ensue without dialysis or renal transplantation usually before age 50.. Vascular deposits of glycosphyngolipid also cause small vessel disease of the brain.

The heart is also affected resulting in cardiac arrhythmias angina pectoris and/or infarction, and congestive heart failure.

The nerve conduction studies are normal in most reported. Sural nerve biopsies show a decreased number of myelinated nerve fibers with preferential loss of small myelinated nerve fibers. In addition there is significant loss of unmyelinated nerve fibers. Dorsal root ganglia show a preferential decrease of the small cell bodies corresponding to the pattern of fiber loss in the sural nerve (84). Electron dense inclusions are found in the cytoplasm of perineurial cells, endothelial and perithelial cells, as well as the cell bodies of the dorsal root ganglia. The inclusions are usually not seen in Schwann cells. Ultrastructural examination of these inclusions reveals concentric lamellae with varying degrees of compaction.

The diagnosis of Fabry disease is confirmed by the demonstration of deficient α-galactosidase A activity which can be measured in plasma or serum, leukocytes, tears, or cultured skin fibroblasts..

Tangier Disease. Tangier disease is a rare autosomal recessive disorder characterized by severe

deficiency or absence of normal high-density lipoproteins (HDL) in plasma. The total number of cases reported worldwide is fewer that sixty, about half of whom have a peripheral neuropathy. The condition is named for the location of the original two siblings described on Tangier Island, Virginia in the Chesapeake Bay Cases have now been reported from all parts of the world including other parts of the United States.

The major clinical manifestations of Tangier disease include yellowish tonsils, splenomegaly and peripheral neuropathy. In about one-third of cases, the symptoms of peripheral neuropathy may be the presenting manifestation. The age of onset ranges from as early as the first decade to as late as the seventh decade. Three neuropathic patterns are characteristic: mononeuropathies and multiple mononeuropathies, usually seen in younger patients, a syringomyelia-like condition and a sensorimotor polyneuropathy; the latter two are more commonly seen in older patients. A prominent motor component is seen in most of the cases differentiating Tangier from distal PAIN. Further, multifocal neuropathy of Tangier disease is usually not painful. However, the syringomyelia-like syndrome may have a prominent pain component although other features will distinguish the picture. Typically the syringomyelia-like syndrome is a slowly progressive condition with features that include facial diplegia, bilateral wasting of the hand muscles and loss of pain and temperature over the trunk and limbs especially the upper extremities with sparing of the distal lower extremities. Patients often complain of spontaneous pain predominantly in the upper extremities.

Cholesteryl ester deposition in histiocytes of the reticuloendothelial system account for many of the symptoms of Tangier disease. Involvement of the tonsils, spleen, liver and rectal mucosa are common manifestations. The unique appearance of the tonsils makes it possible to diagnose Tangier disease by the examination of the oropharynx. The tonsils appear large and lobulated and have a distinctive orange or yellowish-gray color. Recurrent tonsillitis may necessitate early tonsillectomy. Splenomegaly is accompanied by mild thrombocytopenia and reticulocytosis in many patients. Splenectomy may be necessary because of progressive anemia and thrombocytopenia. Liver enlargement occurs in approximately one-third of patients but may be a transient finding. The rectal mucosa is abnormal in a significant proportion of cases and may be the most reliable physical finding when tonsils have been removed. Proctoscopy demonstrates a mucosa studded with 1-2 mm discrete orange-brown spots. Rectal biopsy demonstrates foamy histiocytes throughout the mucosa and submucosa.

The electrodiagnostic studies will help differentiate Tangier disease from distal PAIN. The EMG shows a reduction in the number of motor unit potentials and denervation. Nerve conduction studies reveal abnormal SNAPs in both the upper and lower extremities.

In Tangier disease lipid accumulates in Schwann cells of myelinated and unmyelinated in the form of non-membrane-bound vacuoles. These vacuoles are not disease-specific. This may reflect a diminished ability to transfer lipid by-products to macrophages because of the reduced amounts of HDL. Sural nerve biopsies show reduced numbers of both myelinated and unmyelinated nerve fibers with a shift toward smaller fiber size diameters.

The diagnosis of Tangier disease is established by a characteristic plasma profile demonstrating severe deficiency or absent HDL and decreased total plasma cholesterol with normal or elevated triglycerides. The low plasma cholesterol concentration in Tangier disease is similar to patients with abetalipoproteinemia but the presence of normal to elevated triglyceride levels and absent HDL in Tangier disease readily differentiates these two dyslipoproteinemias. Thus, the parallel findings of very low plasma cholesterol and elevated triglycerides are unique and provides a diagnostic lipoprotein profile for homozygotes with Tangier disease.

In Tangier disease the plasma apoA-I concentration is reduced to less than 3 percent of controls. ApoA-II concentration is also low, in the range of 5 to 10 percent of normal. Despite these rather dramatic laboratory features, neither of these proteins represents the primary molecular defect in Tangier disease.

CONCLUSIONS

Painful sensory neuropathy is a common malady seen by neurologist. Collectively it is a heterogeneous condition, but through a combination of approaches outlined in this syllabus a diagnosis can be established. The most frequently seen variety of painful sensory neuropathy is distal PAIN. A skin biopsy provides a pathologic diagnosis based on loss of intraepidermal nerve fibers. Presently, little is understood about the pathogenesis or the natural history of this condition. Treatment can also be quite challenging.

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