Cryptogenic Polyneuropathy
Clinical, Environmental, And Genetic Studies
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Linköping 2011
To Ulrika,
Andrea & Philip
List of Papers

The thesis is based on the following papers, which will be referred to in the text by their roman numerals.


IV. Lindh J, Söderkvist P, Fredriksson M, Hosseininia S, Tondel M, Persson B, Vrethem M. Polymorphism of GSTT1, GSTM1 and epoxide hydrolase in cryptogenic polyneuropathy. Accepted By Brain and Behavior.

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<tbody>
<tr>
<td>2,5-HD</td>
<td>2,5-Hexandione</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>CIAP</td>
<td>Chronic Idiopathic Axonal Polyneuropathy</td>
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<td>CIDP</td>
<td>Chronic Inflammatory Demyelinating Polyneuropathy</td>
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<td>CMAP</td>
<td>Compound Muscle Action Potential</td>
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<td>CMT</td>
<td>Charcot-Marie-Tooth disease</td>
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<td>COR</td>
<td>Crude Odds Ratio</td>
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<tr>
<td>CSPN</td>
<td>Cryptogenic Sensory and sensorimotor PolyNeuropathy</td>
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<td>CV</td>
<td>Conduction Velocity</td>
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<td>CYP2E1</td>
<td>Cytochrome P450 2E1</td>
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<td>DADS</td>
<td>Distal Acquired Demyelinating Symmetric Polyneuropathy</td>
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<td>DML</td>
<td>Distal Motor Latency</td>
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<td>EMG</td>
<td>ElectoMyoGraphy</td>
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<td>EPHX</td>
<td>Epoxide HydroXylase</td>
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<td>EQ-5D</td>
<td>EuroQol</td>
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<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
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<td>GST</td>
<td>Glutathione S-Transferase</td>
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<td>GSTM</td>
<td>Glutathione S-Transferase Mu (µ)</td>
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<td>GSTT</td>
<td>Glutathione S-Transferase Theta (ϑ)</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HR-QoL</td>
<td>Health Related Quality of Life</td>
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<td>ICD</td>
<td>International Classification Of Diseases</td>
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<td>IGT</td>
<td>Impaired Glucose Tolerance</td>
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<td>LOR</td>
<td>Logistic Odds Ratio</td>
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<td>MAG</td>
<td>Myelin Associated Glycoprotein</td>
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<td>Short Form</td>
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<td>MBK</td>
<td>Methyl n-Butyl Ketone</td>
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<td>mcs</td>
<td>Mental Component Summary</td>
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<tr>
<td>mEPHX</td>
<td>microsomal Epoxide HydroXylase</td>
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<td>MGUS</td>
<td>Monoclonal Gammopathy of Uncertain Significance</td>
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<td>OGTT</td>
<td>Oral Glucose Tolerance Test</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PAH</td>
<td>Polycyclic Aromatic Hydrocarbons</td>
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<td>pcs</td>
<td>Physical Component Summary</td>
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<td>QOL</td>
<td>Quality Of Life</td>
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<td>QST</td>
<td>Quantitative Sensory Testing</td>
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<td>Short Form 36</td>
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<td>SNAP</td>
<td>Sensory Nerve Action Potential</td>
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<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
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<td>VAS</td>
<td>Visual Analogue Scale</td>
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Introduction

Cryptogenic polyneuropathy is characterized by a dying-back neuropathy and patients present with symmetrical, distal loss of sensory and motor function in the lower extremities that extends proximally in a graded manner. The result is sensory loss in a stocking-like pattern, distal muscle weakness and atrophy, and loss of ankle reflexes.

Peripheral neuropathies are common neurological problems. They are caused by disordered function and structure of peripheral motor, sensory, and autonomic nerves. The overall prevalence in western communities, and also among Parsis in Bombay, is about 2,400 per 100,000 population (2.4%), but in individuals older than 55 years, the prevalence rises to about 8,000 per 100,000 (8%) [14, 17]. Other studies show a highly variable prevalence depending on the criteria for polyneuropathy and the population studied (e.g., general population, primary care, hospital, university hospital, neuropathy center). The prevalence in poor populations is not known, but leprous neuritis is still highly prevalent in Southeast Asia, India, Africa, and Central and South America [41] and it can be expected that polyneuropathy is at least as common in these areas as in wealthy populations.

There are many disparate known causes of polyneuropathy, such as diabetes mellitus, alcohol, heredity, inflammatory disorders, ischemia, paraneoplastic conditions, deficiency states, infections, toxins, and others. Leprosy (Hansen’s disease) is a major cause of neuropathy globally, especially in tropical and subtropical regions [41, 69], but is extremely rare in the Nordic countries. In an Italian primary care population, the prevalence of polyneuropathy was highest in patients with diabetes (18.3%), followed by alcoholism (12.5%), non-alcoholic liver disease (10.9%) and tumor (7.1%) [13]. The most common clinical
condition in the patients with cryptogenic polyneuropathy in the same study was hypertension.

Different terms for the condition are used in the literature. Chronic Idiopathic Axonal Polyneuropathy (CIAP) [45, 75, 82, 121, 138, 146, 170, 180, 183, 189] is used by several authors. Other names of the same or closely related conditions are: chronic polyneuropathy of undetermined cause [107], and Cryptogenic Sensory Polyneuropathy (which also includes sensory-motor neuropathies) [67, 98, 190], painful sensory neuropathy [133], sensory-predominant painful idiopathic neuropathy [91], burning feet syndrome [36, 161], and distal small fiber neuropathy [62, 77, 160]. The two latter conditions are, however, most likely a separate condition. In some cases the same author uses different terms for the same condition in separate articles [189-191].

It remains unclear how thorough the investigation of the patient’s polyneuropathy should be before calling it cryptogenic. Cryptogenic polyneuropathy should probably not be considered as a distinct disease, but rather a clinical syndrome with different mechanisms leading up to the same clinical picture. Nevertheless, the syndrome is clinically useful as the patients share the same clinical findings and prognosis [67].
Cryptogenic polyneuropathy

Definition

Figure: Schematic drawing of the spinal cord with a sensory nerve entering through the dorsal root and a motor nerve exiting through the ventral root into the plexus and finally forming a peripheral nerve.
By common definition, the peripheral nervous system includes the cranial nerves, the spinal nerves with their roots and rami, the peripheral nerves, and the peripheral components of the autonomic nervous system. The dorsal and the ventral roots are attached to the spinal cord by a series of filaments. After passing the subarachnoid space, each root enters a dural sac and the dural sheath. Immediately peripheral to the spinal ganglion of the dorsal root, corresponding dorsal and ventral roots join to form a spinal nerve. The dural sheaths become confluent at the ganglion, and then merge with the epineurium of the spinal nerve. Each spinal nerve quickly divides into a dorsal and a ventral ramus. The dorsal rami supply the back; the ventral rami supply the limbs and ventrolateral part of the body wall. In the cervical and lumbosacral regions, the ventral rami intermingle and form plexuses from which the major peripheral nerves emerge. As a general principle, each ramus entering a plexus contributes to several peripheral nerves, and each peripheral nerve contains fibers derived from several rami [38].
Peripheral nerve fibers are divided into two different groups, myelinated and unmyelinated nerve fibers. A nerve fiber is defined as an axon with its associated Schwann cell, which creates the myelin sheath. The nerve fibers are then arranged together in bundles or fascicles and then grouped into nerves. The nerve sheaths contain the intrinsic blood and lymphatic vessels as well as the nervi nervorum, which supply the connective tissue and vessels with sensory and autonomic fibers [38].

The terms "polyneuropathy," "peripheral neuropathy," and "neuropathy" are frequently used interchangeably, but are distinct. Polyneuropathy is a specific
term that refers to a generalized, relatively homogeneous process affecting many peripheral nerves, with the distal nerves usually affected most prominently. Peripheral neuropathy is a less precise term that is frequently used synonymously with polyneuropathy, but can also refer to any disorder of the peripheral nervous system including radiculopathies and mononeuropathies. Neuropathy, which again is frequently used synonymously with peripheral neuropathy and/or polyneuropathy, can refer even more generally to disorders of the central and peripheral nervous system. Symmetric distal sensory loss, burning, or weakness typically characterizes polyneuropathy. The polyneuropathies must be distinguished from other diseases of the peripheral nervous system, including the mononeuropathies and mononeuropathy multiplex (multifocal neuropathy), and from some disorders of the central nervous system [38].

Cryptogenic polyneuropathy is in essence a diagnosis of exclusion, established after a careful medical, family, and social history, neurologic examination, and directed laboratory testing. Patients must have a slowly progressive distal symmetric sensory or sensorimotor polyneuropathy on neurological clinical examination, and axonal degeneration on neurophysiological examination. Different authors have dealt with this in different ways. Richard Hughes defined CIAP as patients having a late onset symmetrical peripheral neuropathy of undetermined cause. The patients must have a had previous investigations including at least a clinical history and examination, urine analysis, blood count, erythrocyte sedimentation rate (ESR), renal, liver and thyroid profiles, random glucose, hemoglobin, vitamin B12 and folic acid concentrations, serum protein electrophoresis, antinuclear factor and chest radiograph [82]. Peter Erdmann made the diagnosis if the patients had a slowly progressive distal symmetric sensory or sensorimotor polyneuropathy on neurological clinical examination, and axonal degeneration on neurophysiological examination. Erdmann and
coworkers required normal values for hemoglobin, hematocrit, leukocytes, platelets, ESR, serum glucose, renal function and electrolytes, liver enzymes, serum calcium and phosphorous, creatinine kinase, serum protein, transketolase, vitamins B1, B6 and B12, thyroid function, immunoelectrophoresis, antinuclear antibodies, cryoglobulins, and rheumatoid factor. All their patients had undergone a routine chest X-ray [45]. Hoffman-Snyder used another definition of CIAP. Their inclusion criteria were (1) a documented history of positive sensory complaints more than 3 months in duration, with or without neuropathic pain; (2) a detailed neurological examination; (3) a fasting, non-gestational 2h-Oral Glucose Tolerance Test (OGTT) using a 75-g oral D-glucose (dextrose) load; (4) nerve conduction studies; and (5) a diagnosis of CIAP. Patients were excluded if they had documented evidence for a known cause of chronic axonal polyneuropathy, such as presence of a family history of neuropathy and “hammer” or “claw” toe deformities. Patients were also excluded if they had documentation of a toxic or pharmacological exposure or coexisting medical conditions associated with neuropathy such as chronic alcoholism; metabolic disturbances; diabetes mellitus; hypothyroidism; and autoimmune conditions such as connective tissue diseases, including sicca syndrome, malignancies, or human immunodeficiency virus (HIV) or other active infections (e.g., Lyme disease, Hansen disease, hepatitis C); general weakness except for distal leg muscle weakness; abnormal results on complete blood cell count, electrolyte levels, liver function studies, vitamin B12 levels, Thyroid Stimulating Hormone (TSH) levels, and serum protein electrophoresis with serum immunofixation. HIV testing was not routinely performed in this low-risk population, and nerve conduction studies excluded features of demyelination [75].

Gil Wolfe and Richard Barohn instead used the term Cryptogenic Sensory and Sensorimotor Polyneuropathy (CSPN). They defined CSPN on the basis of pain, numbness, and/or tingling in the distal extremities without symptoms of
weakness. Sensory symptoms had to occur in a roughly symmetrical pattern in the distal lower extremities or upper extremities or both and evolve over weeks to months. On examination, patients had to demonstrate distal sensory deficits not confined to an individual peripheral nerve. Slight weakness in foot or hand muscles were permitted [191]. In a second article Wolfe and colleagues added information about laboratory testing. Routine laboratory tests consisted of a complete chemistry panel and blood cell count, ESR, antinuclear antibodies, rheumatoid factor, vitamin B12 level, thyroid function tests, syphilis serologic screening, and serum protein electrophoresis with immunofixation electrophoresis. Patients with monoclonal proteins were included in the study population only if plasma cell dyscrasias were ruled out after evaluation by an oncologist and a diagnosis of monoclonal gammopathy of uncertain significance (MGUS) was made. Patients with identifiable causes of neuropathy such as diabetes, chronic alcohol use, metabolic disturbances, endocrine abnormalities, connective tissue diseases including sicca complex, malignant neoplasms, HIV or other infections, pertinent toxic or pharmacological exposures, hereditary neuropathy or amyloidosis, and primary amyloidosis were excluded by history and laboratory testing [190]. Their definition was criticized by Peter James Dyck for being too broad [33].

It is still unclear if idiopathic small fiber neuropathy is a specific entity or a subgroup of cryptogenic polyneuropathy [30, 67]. In our studies we decided to exclude patients with an isolated small fiber neuropathy.

A diagnostic problem is the “normal” neurological deterioration, both clinically and neurophysiologically, in older people. For example, in healthy people older than 60 years, sural responses may be absent [188]. Loss of proprioception has been reported to occur in 28% and hyporeflexia, in 12% of healthy men between
64 and 73 years of age [153]. One way to handle this in studies is to add an upper age limit for the diagnosis.

There is, as previously mentioned, no strict definition or even consensus about which disorders have to be ruled out to diagnose the patient with a cryptogenic polyneuropathy. It is very important to rule out diabetes, which has been reported to account for more than one-third of polyneuropathy cases [177]. Nevertheless, many cases of impaired glucose metabolism can be found in a patient series of cryptogenic polyneuropathy. A high prevalence of impaired glucose metabolism has been found in those with neuropathic pain [117]. However, the relationship between impaired glucose metabolism and polyneuropathy has been questioned [35].

Peripheral neuropathy is one of the most common reactions of the nervous system to toxic chemicals. Many industrial, environmental, and biological agents, heavy metals, and pharmaceutical agents are known to cause toxic neuropathies. Medications, most notably anticancer drugs, are the leading offenders in clinical practice today. All forms of neuropathies may be caused by toxic agents [69]; however, in most cases, it is difficult to assess the individual patient exposures and which substances are relevant.

Some studies have dealt with the contribution of “hereditary factors” in patients with cryptogenic polyneuropathy. Singleton et al. [152] showed that 5.6% of patients had first-degree relatives with foot sensory loss, weakness, or deformities. Hughes et al. [82] reported that 12% of patients had relatives with foot abnormalities. Hereditary neuropathies can present at all ages [177].

Other causes that need to be ruled out are inflammatory disease, chronic alcoholism, metabolic disturbances, endocrine abnormalities, vitamin B12/folic
acid deficiency, critical illness, and acute inflammatory demyelinating neuropathies, HIV, borreliosis or other infections, monoclonal gammopathy and malignancies (especially myeloma and small cell carcinoma of the lung).

To summarize, different authors have used different terms for the same condition and authors using the same term are still using different definitions. There is no consensus document about how to define cryptogenic polyneuropathy or CIAP known to the author. If a document was available, it would have to be updated regularly as new information about the mechanisms of the genesis of polyneuropathy become available. Both in clinical practice and in research, however, a choice has to be made about how many investigations to perform, before calling the disorder idiopathic or cryptogenic.

We chose to use a broad definition based on clinical grounds. We defined polyneuropathy as one or more typical symptoms (numbness, pain, postural instability, paresthesias, distal weakness, burning sensation, muscle cramps, icing sensation, hypersensitivity to touch) with a distal distribution and at least two of three clinical findings (distal deficit of sensation, reduced distal muscle strength, and impaired or lost deep tendon reflexes). We regarded the diagnosis as probable if patients had one or more of the symptoms above and only one of three clinical findings as well as a chronic slowly progressive clinical course. Patients whose diagnosis was based on neurophysiological findings alone were not included.

A more detailed discussion about the diagnostic workup is presented in the chapter “Diagnostic approach to peripheral neuropathies”. In our studies the following laboratory investigations had to have been performed with normal results: hemoglobin, fasting blood glucose concentration, vitamin B12 (cobalamin), folic acid, and thyroid function.
Background

The cause of cryptogenic polyneuropathy is, as the term implies, not known. One suggestion has been that it is an inflammatory disorder. Clonal expansions of T cells were strikingly high in patients with CIAP, as compared with elderly normal controls, elderly controls with degenerative neurologic diseases, and elderly patients with idiopathic chronic inflammatory demyelinating polyneuropathy [54]. The relevance of T-cell clone expansion in relation to the pathogenesis of idiopathic sensory neuropathies is still not clear, but some cases can improve with treatment with steroids. In a recent study a significant increase in C reactive protein (CRP) was found in patients with CIAP compared to controls [142].

Another hypothesis is that the metabolic syndrome gives rise to chronic ischemia, which causes the polyneuropathy. The metabolic syndrome is a constellation of entities including impaired glucose tolerance, truncal obesity, hypertension, and dyslipidemia [142]. Different mechanisms for polyneuropathy secondary to the metabolic syndrome have been proposed. Patients with chronic idiopathic axonal neuropathy more often have manifest cardiovascular disease and cardiovascular risk factors than controls [80, 169]. In developed countries, type 2 diabetes is the most common defined cause of axonal neuropathy in middle and old age. Neuropathy is a common complication of chronic hyperglycemia: the overall prevalence in patients with diabetes is 45–60%, and in more than half of patients followed longitudinally, clinical symptoms of neuropathy developed within 25 years of diagnosis [152]. As a consequence, screening for diabetes is appropriate in evaluating patients with idiopathic neuropathy. It is still controversial whether impaired glucose tolerance or
impaired fasting glucose gives rise to polyneuropathy. Some reports have found an increased frequency of impaired glucose tolerance [75, 122, 152, 165], though others have found contradicting results [82, 117]. Other studies have found both impaired glucose tolerance and hypertriglyceridemia in increased frequencies [81, 138, 139, 154]. Hughes and co-workers found using a logistic regression analysis that environmental toxin exposure and hypertriglyceridemia, but not glucose intolerance or alcohol overuse, were significant risk factors that deserve further investigation as possible causes of cryptogenic polyneuropathy. These findings, on the other hand, did not support that mild/moderate hypertriglyceridemia was an independent risk factor for development of neuropathy.

Another hypothesis is that chronic pain, stress and depression are common in cryptogenic polyneuropathy patients and may predispose these patients to the metabolic syndrome and impaired glucose tolerance [142]. If impaired glucose tolerance is identified, the progression to diabetes is slow; frank diabetes develops in only 20-35% of patients with impaired glucose tolerance during 5-years of follow up [49]. However, the metabolic syndrome is an important factor to consider as it is possible to treat and successful treatment prevents other complications for the patient.

It is often believed that toxic substances in the environment cause many cases of cryptogenic polyneuropathy. Hughes found that this was one of the main causes in CIAP [82].
Pathology

In cryptogenic polyneuropathy nerve conduction and nerve biopsy studies are compatible with a length-dependent axonal neuropathy [66, 88, 107, 121, 190].

Axonal degeneration is the most common pathological reaction of the peripheral nerve. In most instances, axonal neuropathy is a chronic process, but changes may appear on nerve conduction studies as early as 3 to 5 days after the onset of
acute axonopathy caused by the rapid pace of Wallerian degeneration [61]. Systemic metabolic disorders, toxin exposure, and some inherited neuropathies are the usual causes of axonal degeneration [69]. The myelin sheath breaks down concomitantly with the axon in a process that starts at the most distal part of the nerve fiber and progresses toward the nerve cell body, hence the term dying-back or length-dependent neuropathy [69]. The selective length-dependent vulnerability of distal axons could result from the failure of the perikaryon to synthesize enzymes or structural proteins, from alterations in axonal transport, or from regional disturbances of energy metabolism [69].

After nerve transection, axons and their myelin sheaths regenerate. This process begins in the distal end of the proximal stump. Axons then form growth cones and begin regenerating, and at the same time Schwann cells divide rapidly [38].
The pathological features in sural nerve biopsy specimens consist of axonal de- and regenerative changes without evidence of inflammation. At the ultrastructural level an increased thickness of endoneurial vessel basal lamina can be observed indicating that ischemia plays a role in the development of the polyneuropathy, but this is a non-specific finding [19, 171]. Sural nerve biopsy shows an unspecific, axonal type neuropathy, mostly with secondary demyelination [66]. In skin biopsies a reduction in intraepidermal nerve fibers is observed [117].
The clinical picture in demyelinating polyneuropathies is quite different than in axonal injury. In demyelinating polyneuropathies, every part of the nerve can be affected and the typical neurophysiological finding is slowing of conduction velocity. If recovery occurs, it is more rapid and if there is no concomitant axonal injury, it will be more complete even though a loss of conduction velocity can often be measured.

Neurophysiology

The typical finding in cryptogenic polyneuropathy is mild nerve conduction abnormalities consistent with an axonal, predominantly sensory polyneuropathy [67]. In the typical distal, symmetric sensory, or sensorimotor neuropathy, there is an initial loss of sensory nerve amplitude in a length-dependent fashion followed by loss of motor amplitudes with gradual spread of these abnormalities
to the shorter nerve segments in the upper extremities [61]. This is largely because the more distal nerve segments are farther from their cell bodies. In some axonopathies, alterations in axon caliber, either axonal atrophy or axonal swelling, may precede distal axonal degeneration [69]. Later in the course of severe axonal disorders, conduction velocities may become abnormal because of secondary demyelination or loss of the fastest conducting fibers [61]. Because axonal regeneration proceeds at a maximal rate of 2 to 3 mm per day, recovery may be delayed and is often incomplete [69].

Axonopathies result in low-amplitude sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs), but they affect conduction velocities only slightly [69]. In cryptogenic polyneuropathy the findings are usually mild [107]. A problem with nerve conduction studies is, however, that nerve conduction velocity and amplitudes decrease with increasing age and are dependent on height and sex. The effect of height is greater than that of age [143]. Absent sural SNAPs combined with spontaneous muscle fiber activity in the anterior tibialis muscle support the diagnosis of neuropathy, since such abnormalities are rarely found in healthy, older individuals [180]. There is also evidence that finger circumference alters the amplitude of sensory recordings as does the patient’s Body Mass Index (BMI). The sensory and mixed nerve amplitudes are significantly lower in obese persons, but there are no differences in nerve conduction velocities [23]. An index based on 12 electrophysiological parameters has been suggested, which enables detection of slight impairments of nerve conduction. The relatively low variability between recordings of the index makes it suitable to follow the progression of a polyneuropathy with repeated measurements over time [157].

In patients with prominent symptoms, demyelinating features on nerve conduction studies are often found, giving rise to a combined axonal and
demyelinating polyneuropathy [107]. Sensory involvement is, in most cases, more profound than motor involvement [191]. Sensory and motor nerve conduction abnormalities typically consist of reduced amplitudes with normal or minimal distal latency and conduction velocity changes [191]. In many of the patients who presented with burning, painful paresthesias from resumed idiopathic distal small-fiber neuropathy, the nerve conduction studies are normal [62].

In a recent Dutch study of CIAP patients with pain, quantitative sensory threshold and autonomic tests showed more frequent abnormal test results compared to the healthy control group. The cold threshold and heat pain test in patients with CIAP were both affected. The RR interval variation of deep breathing tests and spectral analysis of RR intervals showed a significant decrease in the high-frequency power [30]. It remains unclear if all patients with cryptogenic polyneuropathy have small-fiber neuropathy or only those with pain.

An electromyography (EMG) of distal muscles shows acute, chronic, or both kinds of changes. Denervation activity such as fibrillation potentials or sharp waves are found in approximately two-thirds of patients [191]. Patients with cryptogenic polyneuropathy who have only sensory signs commonly have motor involvement on electrophysiological studies.

**Epidemiology**

The age of onset is predominantly in late middle age, with a median age of symptom onset between 50 and 60 years and a range of 12 years and up [62, 66, 67, 91, 107, 119, 190]. It can, however, be argued that in early presenting polyneuropathy a cause is likely to be found and that hereditary or metabolic
reasons are the most plausible. Men are overrepresented by as much as a 3:1 to 4:1 ratio [107, 119, 136].

Symptoms have usually been present for many years before the patient presents to the neurologist [67]. Most reports are from western countries, but some reports are available from developing countries indicating that it is a common condition there as well [17, 85].

Community studies have reported that symptomatic peripheral neuropathy may be seen in approximately 3% of the elderly [13, 14], but other studies have found a prevalence up to 8%, which is likely due to patient recruitment methods and wider age limits. The prevalence of idiopathic polyneuropathy in the Parsi community of Bombay (Mumbai) in India was 0.21%. They classified 20% of noncompressive neuropathies as idiopathic [17]. Diabetes is said to be the most common cause of peripheral neuropathy in the elderly [52, 80], and alcoholic and nutritional neuropathies are also common [52, 80]. In a study from London, all incident cases of neurological disorders were ascertained prospectively in an unselected urban population based in 13 general practices over an 18-month period. The age- and sex-adjusted incidence rates were calculated and they found 54 cases of diabetic polyneuropathy and 15 cases of peripheral neuropathies per 100,000 persons per annum [103].

In early studies the cryptogenic group was thought to comprise as much as 50-70% of polyneuropathy [47, 52, 80, 95, 106, 111, 145]. However, later studies have revised the frequency downward to 10-25% of patients despite a thorough medical investigation [13, 17, 107, 115, 119, 146]. In these cases the polyneuropathy is called cryptogenic. The reason for the lower percentage in more recent series is probably because of improved understanding of the causes of neuropathy and diagnostic advances. However, cryptogenic polyneuropathy
still remains a common clinical problem both for general practitioners and neurologists at secondary and tertiary centers.

**Sensory symptoms and findings**

Most patients with cryptogenic polyneuropathy have a predominantly sensory disease [67]. It is most commonly characterized by symmetrical, distal motor and sensory deficits that have a graded increase in severity distally and by distal attenuation of reflexes. The sensory deficits generally follow a length-dependent stocking-glove pattern. By the time sensory disturbances of the longest nerves in the body (lower limbs) have reached the level of the knees, paresthesias are noted in the distribution of the second longest nerves (i.e., those in the upper limbs) at the fingertips. When the sensory impairment reaches the mid-thigh, involvement of the third longest nerves, anterior intercostal and lumbar segmental nerves, gives rise to a tent-shaped area of hypoesthesia on the anterior chest and abdomen. The involvement of recurrent laryngeal nerves may occur at this stage with hoarseness [69]. The clinical picture is usually a mixed motor and sensory neuropathy; however, in some cases it is a prominently sensory neuropathy and in fewer cases, a predominantly motor neuropathy [107].

Discomfort or pain is a very common presenting symptom, reported in 65 to 80% of patients [62, 66, 119, 190]. The description of pain varies from patient to patient, but the most common description is a nagging pain [45]. Other common symptoms are numbness or tingling with or without pain, heavy feeling, or weakness in the distal limbs [119, 191]. These patients complain of tingling, prickling, numbness, or burning of the feet, and, often, stiffness of the toes. Worsening of sensory symptoms with heat or cold exposure, activity, or fatigue is commonly reported by patients [62].
On physical examination there is loss of pinprick sensation, together with loss of vibratory sensation in the feet, absent ankle reflexes, and mild toe-extensor weakness. Ability to sense vibration is the primary modality most likely to be abnormal in the feet. Vibration sensation was reduced in all patients in Notermans’ study, typically below the knees [119]. Pinprick and light touch is also reduced in most of the patients and position sense is least affected on sensory examination [119, 191]. These abnormal signs must be distinguished from normal manifestations of the aging in the peripheral nervous system. Loss of vibratory sense that is restricted to the toes can be a normal finding in healthy elderly controls (e.g., present in 28% of individuals age 65 years and older). Absent ankle reflexes are found in 38% of healthy controls older than 65 years. In an Australian population study of persons 75 years or older, 26% and 28% had impaired vibration sense and 20% and 21% absent ankle jerks on the right and left side, respectively. The study also had a subgroup free of neurological disease and in that group only, impaired vibration sense in the thumbs and gait instability significantly worsened with increasing age [184]. Gait instability and other symptoms of large fiber dysfunction are less commonly affected than those of small fibers [67]. Joint position sense is also only affected in a minority of patients [67].

**Motor symptoms and findings**

Approximately two-thirds of patients with sensorimotor polyneuropathy can be expected to have distal weakness and wasting [107, 119]. Motor weakness is greater in extensor muscles than in corresponding flexors. For example, walking on heels is affected earlier than toe walking in most polyneuropathies. It is helpful to determine the relative extent of sensory, motor, and autonomic neuron involvement, although most polyneuropathies produce mixed sensorimotor
deficits and some degree of autonomic dysfunction [69]. The typical finding on examination is distal muscle wasting and weakness in the lower limbs, in some cases quite pronounced with bilateral foot drop [107]. Muscle cramps occur, but they are seldom severe [67].

The average time for symptoms to spread from the lower to the upper extremities appears to be about 5 years [119]. It is rare for patients to report symptoms restricted to the upper extremities. Autonomic and cranial nerve findings are also rare in these patients [62].

Loss of reflexes is a common finding, most often found in the ankle and less often in the upper extremities [191]. Total areflexia is rare.

**Prognosis**

In an early study of cryptogenic polyneuropathy from the Neurological Unit at the Manchester Royal Infirmary, 31 patients were followed-up from 1940 to 1950, of whom 16 had a negative outcome, and 7 of the patients died of the disease [106]. Luckily, a great deal has improved since then. Today, both idiopathic sensorimotor and sensory polyneuropathies pursue a very slowly progressive course or reach a stable plateau [78, 107, 121]. The first more modern patient series was published in 1973, but it includes cases that today would be classified, even as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [78]. In McLeod’s series from the 1980s over 80% of patients were unchanged or improved at a mean follow up of 3 years, and only 13% experienced significant disability from their neuropathy [107]. In more recent studies, even after a course of more than 10 years, severe disability rarely occurs. In most cases patients remain ambulatory without severe disability or handicap [66, 88].
Spontaneous remissions have been reported at different rates. Grahmann reported a complete or significant remission in 4 of 29 cryptogenic cases on reevaluation and an even higher rate among cases that were initially classified as cryptogenic but were later solved [66]. One possible explanation might be that these were toxic neuropathies, which usually recover when the exposure ends, but it cannot be excluded that even non-toxic cases might improve spontaneously.

**Treatment**

There is no specific therapy for cryptogenic polyneuropathy. The management of these common neuropathies instead centers on the treatment of neuropathic pain, provision of braces in some cases, and patient education and reassurance about the favorable long-term outcome [191]. Options for the treatment of pain based on clinical experience and studies in other neuropathies include tricyclic antidepressants, gabapentin, carbamazepine, nonsteroidal anti-inflammatory drugs, opioids, capsaicin [67] and lidocaine medicated plaster [11]. Treatment response is often unsatisfactory.

*Effects of environmental toxins on the peripheral nervous system*

Exposure to neurotoxins may lead to dysfunction of any part of the central, peripheral, or autonomic nervous system and the neuromuscular apparatus. Neurotoxic disorders, especially those with an iatrogenic basis, are well described. Hence, in any neurological condition, such as a peripheral neuropathy, neurotoxins should be considered as possible cause. Peripheral neuropathy is, in fact, one of the most common reactions of the nervous system to toxic chemicals. Industrial, environmental, and biological agents; heavy metals, and pharmaceutical agents are known to cause toxic neuropathies.
Medications, most notably anticancer drugs, are the leading offenders in clinical practice today. Examples include cisplatin, taxanes, vincristine, metronidazole, hydralazine, nitrous oxide, thalidomide, and phenytoin [69].

Neurotoxic disorders are occurring increasingly as a result of occupational or environmental exposure to chemical agents and often go unrecognized. Neurotoxic disorders are recognized readily if a close temporal relationship exists between the clinical onset and prior exposure to a chemical agent, especially one known to be neurotoxic. However, it is much more difficult to identify neurotoxic agents when a group of persons are exposed to several agents over a long period of time and the effects do not appear until several years later [7]. This is common in industrial settings as well as in the home environment. Suicide attempts with chemical agents and recreational drugs are other possible causes of peripheral nerve damage.

For many agents only single case reports are available, but they may be unreliable, especially when the neurological symptoms are frequent in the general population. Epidemiological studies may be helpful in establishing a neurotoxic basis for symptoms. However, it is difficult to perform good studies. One major problem is finding adequate controls. A good study requires matching of exposed subjects and unexposed controls, not only for age, gender, and race, but also for social, and cultural background; and alcohol, recreational drugs, and medication use. Laboratory test results are often not helpful in confirming that the neurological syndrome is caused by a specific agent, either because the putative neurotoxin cannot be measured in body tissues or because the interval since exposure makes such measurements meaningless [7].

Most toxins produce symmetrical axonal degeneration in a dying-back (length-dependent) pattern, eventually spreading proximally with continued exposure. A
number of toxic axonopathies also affect the central nervous system, showing evidence of concurrent degeneration of dorsal column projections of sensory neurons and optic nerve axons. Central axon involvement has been linked to incomplete clinical recovery. Agents such as n-hexane cause simultaneous degeneration of peripheral nerves, dorsal column axons, and corticospinal pathways, often resulting in spasticity that may become apparent following recovery from the peripheral axonopathy. Electrophysiological investigations typically disclose an axonal pattern [69].

**Metabolism of hexacarbon solvents**

Solvents are examples of foreign and potentially toxic, generally lipophilic, substances absorbed into the body. They are therefore difficult to excrete as they will be reabsorbed in the kidney or from the gastrointestinal tract after biliary excretion and may remain in the body for long periods. The process of detoxifying and excreting a substance is called biotransformation, which is a complex process. The primary results of biotransformation are that the parent molecule is transformed into a more polar metabolite, molecular weight and size are often increased, excretion is facilitated, and elimination of the compound from the body is increased. However, biotransformation may also underlie the toxicity of a compound, of which n-hexane and methyl n-butyl ketone are both examples [173].

n-Hexane, present in many commonly used organic solvents, is known to cause primary axonal degeneration with secondary demyelination [24]. It is derived from cracking of petroleum and from natural gas liquids. It is typically present in motor fuels at 1 – 9 volume % and is currently employed in a variety of industrial and commercial processes, including rubber, adhesive, ink, and paint manufacturing, and in the extraction of vegetable oils for human consumption.
Inhalation is the primary route of entry for n-hexane as well as methyl n-butyl ketone (MBK). These solvents are also absorbed through the skin. Dermal absorption is affected by the duration of exposure, and the size and condition of any exposed area of skin [48]. Both n-hexane and MBK are lipophilic and easily cross the blood-brain-barrier and rapidly reach an equilibrium in the brain [48]. n-Hexane concentration also increases rapidly within peripheral nerve fibers after exposure. n-Hexane and its metabolites accumulate during chronic exposures and are released from the liver when the exposure ends [48]. The persisting effects of n-hexane and MBK are related to the ability of their mutual metabolite 2,5-hexanedione (2,5HD) to cross-link axonal neurofilaments chemically and to interrupt axonal transport mechanisms [48].

The clinical pictures of neuropathy as well as the histopathology of n-hexane and MBK are identical [48]. Results of a nerve biopsy in a severe case of n-hexane polyneuropathy showed giant axonal swelling due to accumulation of neurofilaments, myelin sheath attenuation, and widening of nodal gaps [24]. n-hexane induces hepatic cytochrome P-450 (CYP2E1, CYP2B6 and alcohol dehydrogenases) [84] and is metabolized to the neurotoxic agents MBK and 2,5-HD [158]. It is possible that individual differences in this specific metabolism may account for the difference in susceptibility. Nerve conduction studies reveal diminished amplitude of sensory nerve action potentials and slowed sensory and motor nerve conduction velocities in the distal extremities of n-hexane-exposed individuals [48]. Partial conduction block may also occur [128]. Acute inhalation exposure may produce feelings of euphoria associated with hallucinations, headache, unsteadiness, and mild narcosis. Thus, inhalation of certain glues for recreational purposes causes pleasurable feelings of euphoria in the short term but may lead to a progressive, predominantly motor neuropathy and symptoms of dysautonomia after high-dose exposure and a more insidious sensorimotor polyneuropathy following chronic use [6, 7, 63, 162]. Despite
cessation of exposure, progression of the neurological deficit may continue for several weeks or rarely months before the downhill course is arrested and recovery begins. Severe involvement is followed by incomplete recovery of the peripheral neuropathy. When the polyneuropathy does resolve, previously masked signs of central dysfunction, such as spasticity, may become evident [7].
2,5-HD is well known as the main neurotoxic metabolite of MBK and n-hexane, widely used as solvents in many industrial processes [131]. The neurotoxicity is potentiated by methyl ethyl ketone, which is used in paints, lacquers, printer’s
ink, and certain glues [7]. Several studies of the pathophysiology of neuropathies due to 2,5-HD and identification of the parts of the nervous system where 2,5-HD mostly exerts its toxic effect have been carried out [97, 159]. 2,5-HD is mainly a product of intermediate metabolism in the human body and only a minimal part could derive from n-hexane as a ubiquitous micropollutant [132].

**Genetic Factors**

Biotransformation of exogenous and endogenous compounds may play a role in individual susceptibility. The metabolism of biotransformation can be divided into two phases. In phase 1, the original foreign molecule is altered by adding a functional group, which can then be conjugated in phase 2. The conjugated molecule can then be excreted. Normally, these steps lead to a less toxic molecule, but in some cases, the opposite occurs. Glutathione is one of the most important molecules in the cellular defense against toxic compounds. This protective function is due in part to its involvement in conjugation reactions [173].

The glutathione S-transferases (GST) are a family of enzymes responsible for the metabolism of a broad range of xenobiotics and carcinogens [105]. The enzymes catalyze the conjugation of glutathione with a wide variety of organic compounds to form thioethers, a reaction that is sometimes a first step in a detoxification process leading to mercapturic acid formation, which is a classic excretion product of xenobiotics [105]. The GST enzymes have been shown to protect organisms from reactive oxygen compound damage through their abilities to bind with glutathione [72]. Two distinct superfamilies of GST isoenzymes exist. The larger superfamily comprises cytosolic, or soluble, dimeric enzymes that are principally, but not exclusively, involved in biotransformation of toxic xenobiotics. The other superfamily is composed of microsomal proteins primarily involved in arachidonic acid metabolism [72].
The GST family of soluble (cytosolic) enzymes is grouped into seven classes based on structure, substrate specificities, and immunologic properties: alpha, mu, kappa, pi, sigma, theta, and zeta. These classes are abbreviated in Roman capitals with class members distinguished by Arabic numerals. GST isozymes within a class share at least 40% homology of amino acid sequence, whereas between classes there is less than 30% common identity. Within the M class, five human isozymes were identified (M1 through M5), while two isozymes were categorized in the GST T class (T1 and T2) [56]. By contrast with other members of this superfamily, the class kappa GST is mitochondrial and, while soluble, it is probably not located in cytoplasm [72]. Although different transferases may exhibit overlapping substrate specificities, no common substrate exists that is metabolized by all isoenzymes [72]. All GST enzymes are dimers containing two subunits, with the identity of these subunits determining the GST present [56]. In recent years, a wide array of GST functions has received increasing attention, including the GST role in (1) conjugating endogenous electrophiles, (2) maintaining intracellular redox status, and (3) synthesizing and modifying leukotrienes and prostaglandins. Their ability to conjugate electrophiles makes these enzymes critical in the detoxification of a wide range of epoxides and certain other agents of environmental concern, including pesticides, therapeutic drugs such as chemotherapeutic agents, or dietary components [56]. Glutathione S-Transferase Mu-1 (GSTM1) and Glutathione S-Transferase Theta-1 (GSTT1) are both polymorphic in humans and deletions in the genes result in virtual absence of enzyme activity, particularly with deletions in both genes (null genotype) [3]. The genetic variations can change an individual's susceptibility to carcinogens and toxins as well as affect the toxicity and efficacy of certain drugs. GSTT1-mediated conjugation of halogenated solvents including bromobenzene, bromodichloromethane, methylene chloride, and trichloroethylene may lead to metabolic activation rather than detoxification [56].
The genes encoding the mu class of enzymes are organized in a gene cluster on chromosome 1p13.3 and are known to be highly polymorphic [193]. The mu class of enzymes functions in the detoxification of electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxins and products of oxidative stress, by conjugation with glutathione. GSTM1 isoenzymes are expressed predominantly in liver, followed by the testes, brain, and adrenal glands, with low levels in lung [55]. GSTM1 null occurs as a large deletion, which leads to complete loss of activity in homozygous variants [55]. It has been reported that individuals with GSTM1 null genotype and high exposure to solvents are at increased risk of developing solvent-induced chronic toxic encephalopathy [166] and Parkinson’s disease [32].

The GSTT1 gene is situated on chromosome 22q11.2 [192]. One variant involves deletion of the entire gene, GSTT1 null [130], and this variant lacks enzyme activity. GSTT1 levels are highest in liver and kidney with low levels in a variety of other organs [55]. The GSTT1 null genotype has, for example, been associated with an about four-fold increased risk of myelodysplastic syndrome [25]. In both the GSTM1 and GSTT1 genes, the null genotype has been associated with an increased risk of optic neuropathies [3], adverse events, including cognitive impairment after therapy, in patients with medulloblastoma [10], but not in patients with Leber’s Hereditary Optic Neuropathy [86] nor neuropathy in patients receiving oxiplatin-based chemotherapy [99].

Epoxide hydrolases play an important role in both the activation and detoxification of a wide range of exogenous chemicals such as polycyclic aromatic hydrocarbons (PAHs) [125]. Epoxides are three-membered oxirane rings containing an oxygen atom and may be metabolized by the enzyme epoxide hydrolase. This enzyme adds water to the epoxide to yield a dihydrodiol.
Epoxides are often intermediates produced by the oxidation of various substances. The enzyme exists in multiple forms with a broad range of substrate selectivity against a diverse group of epoxides [31]. It is found mainly in the endoplasmic reticulum in close proximity to cytochromes P450 [173].

Epoxides are metabolized via complex enzymatic mechanisms involving both activation and detoxification reactions. Reactive and toxic epoxides are frequently generated during PAH oxidative metabolism. Epoxides can be detoxified partly by microsomal epoxide hydroxylase (mEPHX), which catalyzes their hydrolysis, thereby yielding the corresponding dihydriodiols [124]. Although this hydrolysis is generally considered to represent a detoxification reaction because less toxic chemicals are produced, some dihydriodiols generated from PAHs are substrates for additional metabolic changes to highly toxic, mutagenic, and carcinogenic polycyclic hydrocarbon diol epoxides. Thus, epoxide hydrolase plays the same dual role in detoxification and activation of procarcinogens as found in some cytochromes P450 and, as a consequence, may also play an important role in neurotoxicity [68]. Epidemiological studies show that mEPHX activity in the liver, lung and peripheral blood leucocytes varies as much as 50-fold in white populations [125].

In humans, the gene is mapped to chromosome 1q42.1 [70], and is composed of eight introns and nine exons, of which exons 2-9 are coding [31]. Two amino acid polymorphisms have been identified in the coding region of exon three (EPHX1 exon 3), the tyrosine 113 histidine (Y113H) exchange, results in a low activity form of the enzyme [71], which may influence epoxide deactivation in the cell. A decreased risk for lung cancer among African-Americans with the low activity form of the enzyme has been found in Los Angeles, whereas the risk did not differ among Caucasians in the same population [102]. Patients with
Leber’s Hereditary Optic Neuropathy who were homozygous for histidine 113 developed the disease earlier than those without this genotype [86]. The polymorphism in exon four, histidine 139 arginine (H139R) has been suggested as a high activity isoform of mEPHX [15, 155].

Furthermore, epoxide hydrolase plays an important role in the detoxification of procarcinogens activated by some cytochrome P450s [15] and as a consequence, may also play an important role in adverse drug responses. It should be noted that some epoxides serve as important signaling molecules, regulating a large variety of physiological functions, ranging from the regulation of vascular tone, to inflammation, angiogenesis, and pain. Human soluble epoxide hydrolase, which is expressed throughout the body, is, at present, regarded as the primary enzyme in the metabolism of such endogenous epoxides [31].

The cytochrome P450 seems to be the most important phase 1 enzyme system by which most drugs and other oxidants are metabolized [127, 173] and one of these enzymes, cytochrome P450 2E1, is expressed in different tissues such as liver, and nerve tissue [101]. To date, three CYP2E1 polymorphisms have been identified in which the Rsa I has greater transcriptional and enzyme activity compared to the wild-type allele [186], and was associated with higher risk of developing alcoholic liver disease among Caucasians with alcohol abuse [135].

**Health Related Quality Of Life (HR-QoL)**

Traditionally, the physician’s evaluation of the patient’s symptoms and clinical findings has been a primary focus in the practice of medicine. Over time, outcomes such as survival, the ability to walk without aid, neurologic deficits, dysfunctions, neurophysiological findings and anatomical findings like number of nerve endings have been evaluated to help in medical decision making.
However, during the last ten years it has become increasingly important to evaluate the patient’s own subjective experience and to estimate the cost in relation to the improvement. This is particularly important in chronic conditions for which there is no cure and where therapeutic goals are to relieve symptoms and improve function and quality of life (QOL).

Quality of life is an often used but usually ill-defined term. It has been the subject of attention across a range of disciplines, including medicine, psychology, sociology, philosophy, economics, and geography leading to an array of definitions [22]. One way to define QOL is that there is an upper level with an overall assessment of well-being, which can include life satisfaction and general perceptions of well-being. Lower levels incorporate broad dimensions (i.e., physical, psychological, economic, social) and take account of the individual components of each domain and allow for variations in their content [22]. The World Health Organization in 1980 defined quality of life as an individual’s perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [187]. It includes the person’s physical health, psychological state, personal benefits, social relationships and other factors as well [1]. The range of dimensions is broad, and deciding which aspects to measure depends on what you want to study.

QOL is also becoming an important component in the discussion between health care providers and politicians, who, in part, will determine how limited resources are allocated. Measuring QOL helps describe the nature and extent of functional, psychological and psychosocial problems experienced by patients. Furthermore, and of much relevance in an era of cost containment, a thorough examination of an intervention’s effect on outcomes such as QOL and over-all well-being is a key component in the evaluation of both effectiveness and cost-
effectiveness [22]. It is also important for the treating physician to have a good understanding of the patient’s QOL before deciding how to treat the patient, especially if expensive or potentially life threatening treatments are being considered.

The state of being healthy is not only the absence of disease, but also a concept that incorporates notions of well-being or wellness in all areas of life (physical, mental, emotional, social, and spiritual) [1]. Health-related (HR)-QoL may be described as the patient’s perception of disease impact on well-being. The three dimensions of physical (impairment), mental (emotional status), and social well-being are usually the most important ones. The experience of health is also an important dimension, which can be divided into subgroups such as mental health, etc.

There are two types of HR-QoL measures, generic and condition-specific. An advantage of generic measures is that they can be used in people with a diverse range of illnesses or health problems, therefore enabling comparisons between groups. Generic measures are also useful when patients have several concurrent conditions. However, these measures are often unable to focus on the specific problems of a given condition [22]. Condition-specific scales are more sensitive to changes within and differences between individuals with the specific condition and are, therefore, suitable for treatment studies.

The severity of a patient’s polyneuropathy is the sum of a patient’s symptoms, neurological signs, test abnormalities, dysfunctions, and other adverse outcomes. An ideal scale or set of scales should provide a comprehensive and sensible evaluation of the activities of daily living, walking, running and climbing stairs, and measure motor, autonomic, or sensory functions as well as the psychological effects of the disease. The benefit of these scales is that they
provide additional characterizing information on the intervention of the disease in patients’ lives. In the case of treatment studies, the results indicate whether the treatment makes a real difference in the lives of the patients and from their own perspective. It is, therefore, an important and independent measure of the meaningfulness of the intervention and of the consequences of the disease. Several scales are available that quantitate neuropathic symptoms, impairments and outcomes [34].

Most studies on HR-QoL in polyneuropathy have been performed on patients with diabetic neuropathy. Increasing severity of polyneuropathy in diabetes is related to decreasing HR-QoL with patients without symptoms having an average 0.81 in EQ-5D$_{index}$ to 0.25 in diabetic patients with severe symptoms [29]. The QOL scores of diabetic patients, who had polyneuropathy with mixed pathogenesis and sensorimotor type, became worse with time, even if the patients did not have any clinical symptoms of polyneuropathy [126]. The presence and severity of neuropathic pain in different types of neuropathy has been found to be associated with a lower reported HR-QoL in the domains of physical and emotional functioning, sleep, role functioning and global QOL [89]. Two independent studies have shown conflicting data whether patients with neuropathic pain in CIAP have a poorer HR-QoL or not [45, 82].

**SF-36**

A Short Form 36 (SF-36) has been used to evaluate quality of life. The SF-36, which was developed by Ware and Sherbourne [185], assesses eight health concepts during the last 4 weeks: physical functioning (PF), role limitations because of physical problems (RP), social functioning (SF), role limitations due to emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP), and general health (GH) perception. Two norm-based (physical and
mental) scores can be calculated as summary scores. The score of the subgroups as well as the final global score of the SF-36 changes between 0 and 100, respectively, and higher scores better QOL. Different language versions of the SF-36 are available, including Swedish [163, 164]. SF-36 is designed for self-administration, telephone administration, or administration during a personal interview. Normal values depend on sex, age, and socioeconomic status [18].

SF-36 does not cover all important health concepts, like health distress, family functioning, sexual functioning, cognitive functioning, and sleep disorders. It describes a general health status and is not specifically designed for neuropathies or neurological disorders. SF-36 has, however, previously been shown to be applicable to inflammatory neuropathies. Merkies showed that the SF-36 scores of 113 stable patients with Guillain-Barré Syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), or paraproteinemic demyelinating neuropathies were lower than those of 1742 members of the Dutch population and that neurological disability was related to lower scores in PF and RE domains [108]. Abresch et al. measured QOL in people with Charcot-Marie-Tooth (CMT) disease. They found that these patients had significant bodily pain and that this was a much larger problem than had been reported in the literature, with physical role and energy/vitality considerably affected [2]. Ruhland and co-workers compared home exercise intervention with a non-exercise control group in patients with chronic polyneuropathy, using the SF-36 to assess impact on QOL. The exercise group improved on the role limitations scales [148]. The SF-36 was chosen in our study because of its brevity and its extensive use in clinical studies making it possible to compare peripheral neuropathy with other medical conditions.
Table: Interpretation of SF-36 Health Status Scales

<table>
<thead>
<tr>
<th>Concept</th>
<th>Abbrev-iation</th>
<th>No. Of Levels</th>
<th>Meaning of Low Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>PF</td>
<td>21</td>
<td>Limited a lot of performing all physical activities including bathing or dressing</td>
</tr>
<tr>
<td>Role limitations due to physical problems</td>
<td>RP</td>
<td>5</td>
<td>Problems with work or other daily activities as a result of physical health</td>
</tr>
<tr>
<td>Social functioning</td>
<td>SF</td>
<td>9</td>
<td>Extreme and frequent interference with normal social activities due to physical and emotional problems</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>BP</td>
<td>11</td>
<td>Very severe and extremely limiting pain</td>
</tr>
<tr>
<td>General mental health</td>
<td>GH</td>
<td>26</td>
<td>Feelings of nervousness and depression all of the time</td>
</tr>
<tr>
<td>Role limitations due to emotional problems</td>
<td>RE</td>
<td>4</td>
<td>Problems with work or other daily activities as a result of emotional problems</td>
</tr>
<tr>
<td>Vitality</td>
<td>VT</td>
<td>21</td>
<td>Feels tired and worn out all of the time</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>GH</td>
<td>21</td>
<td>Believes personal health is poor and likely to get worse</td>
</tr>
</tbody>
</table>

Based on Ware and Sherbourne 1992 [185]

**EQ-5D (EuroQol)**

EQ-5D is a generic measure of health status, which is also known as EuroQol. It is a patient completed questionnaire with a five-item scale that allows health status to be addressed across five dimensions: (1) mobility, (2) self care, (3) usual activities (work, study, household, family, or leisure), (4) pain or discomfort, and (5) anxiety or depression. Each dimension is subdivided into three categories, which indicate whether the respondent has no problem, a moderate problem, or an extreme problem. EQ-5D also includes a visual analogue scale (VAS; 0 denoting the worst imaginable health state and 100 the best imaginable health state). The three response categories combine for 243 possible health states. A weight can be assigned to each of the health states and be used as the final score. The final score is one number where 0 is death and 1 is the best health state. The resulting scores are used in economic
appraisals (such as cost utility analyses), in the construction of quality-adjusted life years for the calculation of cost per quality of life year gained [12]. EQ-5D has been widely used as a measure of QoL as well as in cost utility analyses. The validity and reliability are high [20]. The Swedish version of EQ-5D was used with permission from the EuroQol Group and the responses were analyzed according to the manual [46].

Although EQ-5D is one of the most frequently used HR-QoL scales in medicine, its use in polyneuropathy has been limited. It has, for instance, been used as a secondary measure in an open-label, non-randomized study comparing venflaxine and gabapentin as monotherapy or adjuvant therapy for neuropathic pain in peripheral neuropathy. There were no significant improvements in EQ-5D scores, EQ-5D domains of EQ-5D health status scores for any monotherapy or adjuvant therapy group, but other scales showed reduction in pain and anxiety [40]. In another drug therapy study using pregabalin, a modest reduction in pain was found as well as improvements in anxiety and sleep, but no difference was found in EQ-5D [112]. The effect of a home exercise program in persons with chronic peripheral neuropathies mainly consisting of CIDP was tested. The patients improved in the average muscle score and the RP, RE and SF scales of the SF-36, but there were no significant changes in EQ-5D [148]. On the other hand, a large study of pregabalin treatment of neuropathic pain containing more than 1,000 patients showed statistically significant improvements in all dimensions of EQ-5D except pain (p=0.059), which was markedly reduced in other scales [116]. A criticism of EQ-5D is that it is not sensitive to change in neuropathies as illustrated by these studies, but a strength is that it makes it possible to make comparisons between different patient groups and that it can be used to calculate cost-effectiveness.
From the patients’ perspective, most consider both SF-36 and EQ-5D as questionnaires equally suitable. Among those who were more satisfied with a short questionnaire (EQ-5D), several still preferred a longer and more comprehensive questionnaire (SF-36). Health outcome assessment seems to be acceptable, and even appreciated, by patients [118].

**Other dysfunction scores**

Since the planning of our studies, several polyneuropathy scores have been published [64, 65, 109]. They have the advantage of being more specific for problems in polyneuropathies, but they are more focused on motor functions and do not describe the whole clinical picture of the disease. They are also affected by concomitant disorders (which may be the cause of the neuropathy), poor volition, medicolegal gain, and psychological changes. There are also tools measuring neuropathic pain [50]. Ideally, in future trials, one or more generic QOL scales would be combined with at least one polyneuropathy scale depending of what kind of neuropathy is being studied and the design of the study. These scales should be supplemented with objective measures such as nerve conduction studies, summed scores of neurological signs, and test of muscle strength.
Cryptogenic polyneuropathy is in essence a diagnosis of exclusion. The following is a guideline to rule out other relevant polyneuropathies and medical conditions, especially treatable ones, and also to find possible exposures to toxic agents, orally or in the environment and to identify hereditary cases. The percentage of cases of neuropathies of undetermined cause has been steadily declining from a past prevalence of 50–70% [47, 52] to approximately 10% [37, 107, 146] more recently. This decline reflects the recognition of new disease entities as well as the availability of better diagnostic techniques, including genetic studies. Intensive evaluation of these neuropathies with unrecognized causes shows that most of these cases are either inflammatory–demyelinating or hereditary in origin. When patients are reevaluated a few years later, it is possible to find a cause in up to more than half of the cases [66, 146]. For the majority of these patients, this could have been known at the time of the diagnosis of CIAP, because firstly, not all the necessary tests according to the diagnostic guideline had been carried out, secondly, some test results had been misinterpreted, and thirdly, in some patients the neurological examination had been misinterpreted. In other patients there had been insufficient questioning on the medical history or family history or the diagnosis CIAP was established at an unusually young age. In the remaining patients it was the clinical course and the repeated neurological examinations that changed the diagnosis [146]. Two other studies found that in 29% and 36% of patients, respectively, a cause can be found at a follow up of 2 to 3 years. These studies identified cases of alcohol abuse, monoclonal gammopathy, malignancy, and vitamin B12 deficiency [66, 107]. In a more recent study a cause could only be identified in 4 of 75 patients after a 5-year follow-up (CMT, CIDP and alcohol abuse) [121]. It can be argued that a treatable cause of the polyneuropathy is not likely to be found and that
reevaluation is not cost effective. On the other hand, these studies were performed in centers with special interest in polyneuropathies and the yield for reevaluation is probably higher than in an everyday setting. At a minimum, patients who deteriorate should be reevaluated.
Careful history

As in all medical conditions, the medical history is of extreme importance. Information regarding onset, duration, and evolution of symptoms provides important clues. Knowledge of the temporal profile of disease (acute, subacute, or chronic), distribution of symptoms (symmetric or asymmetric, sensory or motor or both, distal or proximal) and the course (monophasic, relapsing, or progressive) points to different specific neuropathies. In the case of cryptogenic polyneuropathy it should be a progressive chronic, symmetric, sensory or sensorimotor polyneuropathy.

It is important to rule out toxic exposures at work or during leisure time. Many pharmaceutical agents have been reported to increase the risk of polyneuropathy, for example, chemotherapeutical agents (vincristine, taxanes, and cisplatin), antibiotics (isoniazid, nitrofurantoin, metronidazole), and phenytoin [81, 177].

In many cases the history reveals that the neuropathy is hereditary without the need for genetic testing [146]. It is also important to ask specific questions about current and previous medical history, as the neuropathy can be secondary to other medical conditions. Alcohol intake must be evaluated in a systematic way.

Other causes that should be ruled out are metabolic disturbances, endocrine abnormalities, connective tissue diseases, amyloidosis, critical illness, and acute inflammatory demyelinating neuropathies, HIV, borreliosis, or other infections, monoclonal gammopathy and malignancies (especially myeloma and small cell carcinoma of the lung).
Detailed physical and neurological examination

During the physical examination, the investigator should look for signs of other medical conditions and especially signs of a malignancy. The skin should be examined looking for signs of inflammatory diseases like sarcoidosis, Sjögren’s syndrome or vasculitis. The extent of neuropathy should be evaluated including sensory abnormalities (touch, vibration, heat, cold, pain, stereognosis and proprioception), strength (proximal and distal), reflexes, and ataxia [21]. If motor symptoms and findings dominate, then the diagnosis of hereditary motor and sensory neuropathy type 2 should be considered, especially in younger patients [170]. In patients with axonal neuropathy with MGUS, the arms were more frequently affected and the disability was worse [120].

Electrophysiological studies

Nerve conduction studies should, in principal, be performed on all patients with clinical symptoms or signs of polyneuropathy [43, 181], with the possible exception of patients with mild symptoms or very elderly patients. Cryptogenic polyneuropathy is an exclusively axonal or combined axonal and demyelinating polyneuropathy in which the axonal involvement is dominating. If the demyelination is dominating, another cause should be sought. The electrophysiological studies also characterize the distribution of involvement: sensory only, motor only or both, and provide an objective picture of the parts of the body that are involved.

Needle EMG plays a limited role in the evaluation of axonal neuropathy, but remains important during initial diagnostic evaluation to exclude potential clinical mimics (e.g., anterior horn cell disease, radiculopathy, myopathy). Vrancken and colleagues investigated patients and controls older than 65 years of age. They found that absence of the sural nerve sensory action potentials or
presence of spontaneous muscle fiber activity in the anterior tibial muscle was common in patients, but exceptional in controls [180].

Important factors in patients that might influence the conduction velocities and amplitudes are patient age and height [143], limb temperature, variants of peripheral nervous system [61], and body mass index [23].

If nerve conduction studies and EMG are normal, quantitative sensory testing (QST) for vibration and temperature detection thresholds should be considered. An advantage of QST is that it assesses small fiber function. QST has been reported to be a subjective test dependent on patients attention and cooperation [191], while other authors argue that it has a high sensitivity at least for thermal testing [67].

**Laboratory studies**

Several articles have been published recently discussing the laboratory work-up of peripheral neuropathies [41, 42, 114]. Approaches vary from very limited testing to the shotgun approach in which a large number of tests are performed to rule out as many causes as possible. Saperstein has, for instance, recommended that the initial laboratory testing should only include fasting blood glucose, vitamin B12, thyroid function tests, and serum protein electrophoresis including immunofixation electrophoresis [150]. The costs of the test procedure, sensitivity, and specificity have to be considered. The cause of most polyneuropathies is evident when the information obtained from the medical history, neurological examination, and electrophysiological studies are combined with simple screening laboratory tests. Laboratory test results must be interpreted in the context of other clinical information since the etiologic yield
of laboratory testing alone is limited by the low specificity of many of the tests [42].

If the history does not reveal the cause of the neuropathy, the following blood tests are suggested: blood glucose (consider oral glucose tolerance testing), complete blood count, ESR, renal function, liver function, vitamin B12, folic acid, serum protein immunofixation electrophoresis, and TSH [41, 42, 114]. Whether or not OGTT should be performed is still under debate [138]. One major issue is that the reproducibility of IGT (Impaired Glucose Tolerance) has been found to be only fair to poor and the only study that used multiple OGTTs was negative [138]. Vitamin B12 deficiency is relatively frequent in patients with polyneuropathy, and the yield is greater when the metabolites of cobalamin (methylmalonic acid and homocysteine) are tested. Serum methylmalonic acid and homocysteine have been reported to be elevated in 5–10% of patients whose serum B12 levels were in the low normal range of 200–500 pg/dL [42]. Homocysteine may also be elevated in pyridoxine deficiency and heterozygous homocystinemia. Both homocysteine and methylmalonic acid may be elevated in hypothyroidism, renal insufficiency, and hypovolemia [42].

IgM monoclonal gammopathies may be associated with autoantibody activity, type I or II cryoglobulinemia, macroglobulinemia, or chronic lymphocytic leukemia. IgG or IgA monoclonal gammopathies may be associated with myeloma, POEMS (Polyneuropathy, organomegaly, endocrinopathy, M-band and skin changes) syndrome, primary amyloidosis, or chronic inflammatory conditions [42].

Lumbar puncture is only necessary if an inflammatory neuropathy is suspected or in cases of asymmetric axonal polyneuropathy in which borreliosis can be expected [114].
In cases of a chronic sensory polyneuropathy or a rapidly progressing motor polyneuropathy, an asymptomatic cancer has to be suspected. An X-ray of the chest is the first option and the result is normal, a computer tomography of the chest and abdomen should be considered [114].

Genetic testing shall not be performed in routine cases. The majority of genetically determined polyneuropathies are variants of Charcot–Marie–Tooth (CMT) disease, and genetic testing is available for an increasing number of these neuropathies [140]. The clinical phenotype of CMT is extremely variable [42]. Muscle cramping in the legs and feet and the absence of paresthesias favor a hereditary neuropathy over other etiologies [37]. For patients with a cryptogenic polyneuropathy who exhibit a classic hereditary neuropathy phenotype (autosomal dominant, primary demyelinating), routine genetic screening may be useful for CMT1A duplication/deletion and Cx32 (causing an X-linked neuropathy, CMTX) mutations in the appropriate phenotype. Further genetic testing may be considered in selected cases guided by the clinical question [42].

Tests for antibodies are normally not indicated. Antibodies against Myelin Associated Glycoprotein (MAG) should be tested for in cases of a demyelinating polyneuropathy with distal sensory loss as in DADS (distal acquired demyelinating symmetric polyneuropathy) [113]. High levels of antibodies against gangliosides (GM1) are positive in 20-80% of patients with multifocal motor neuropathy and support the diagnosis [60], but are, like other antibodies against nerve structures, of low value in unselected cases of polyneuropathy [60, 190]. In patients with sicca syndrome, tests for Sjögren’s syndrome should be performed. However, polyneuropathy is a rare manifestation of primary Sjögren’s syndrome, although the most common
manifestation is sensory- or sensorimotor-neuropathy. Anti-nuclear antigen (ANA), rheumatoid factor (RF) or Anti-neutrophil cytoplasmic antibodies (ANCA) tests are only indicated when patients exhibit vasculitis or rheumatic symptoms [114]. Tests for sarcoidosis should only be performed if the patient is symptomatic. Celiac disease should be evaluated with antibody testing in cases with diarrhea, malabsorption, or cerebellar ataxia [114]. Infectious diseases should also to be considered. HIV infection has been reported to have a prevalence up to 16% of cases of symmetrical neuropathy, but the risk depends on the population studied [81]. In the area where our studies were performed, the risk of borreliosis is high [73, 92].

When heavy metal toxicity is suspected, blood, urine, hair, and nail samples can be analyzed [41]. To decide which tests to perform, the following need to be considered: the area the patient is living in, the patient’s occupation, family history, and symptoms. Thus, to choose the appropriate test panel, a careful history and examination must be performed.

Nerve biopsy is only indicated if vasculitis is suspected, i.e., in axonal polyneuropathy with subacute onset [114]. Sural nerve biopsy is of limited value as findings in sural nerves are similar in CIDP and CIAP [19, 191] and the procedure may result in sensory loss and neuropathic pain. Skin biopsy can confirm the presence of small fiber neuropathy, but should be done by clinicians with expertise in the technique [41].

Several reports have described patients with a progressive and disabling idiopathic axonal neuropathy responsive to treatment (prednisone, intravenous immunoglobulin), and it has been suggested that these patients could be affected by an immune-mediated neuropathy with the axon as the primary immunological target. In the normal case of cryptogenic polyneuropathy,
treatment is not efficacious and not recommended. A progressive or intermittent disease course, asymmetric or proximal deficits, neuropathic pain, moderate to severe disability, and abnormal laboratory findings were prominent in patients with progressive idiopathic axonal neuropathy and in patients with vasculitic neuropathy. A wide range of other possible clinical features has been observed including cranial neuropathy, sensory ataxia, and small fiber neuropathy. Such diversity of clinical manifestations has also been described in vasculitic neuropathy [182], but not in CIAP. There is, however, no need for nerve biopsies in CIAP as Vrancken and co-workers found that there is a small chance of finding sural nerve vasculitis upon scrutinizing biopsy examination in progressive idiopathic axonal neuropathy [182].

<table>
<thead>
<tr>
<th>TABLE: Routine Work Up</th>
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<tr>
<td>Blood glucose</td>
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<td>Complete blood count</td>
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<td>Serum electrophoresis</td>
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<td>Renal function</td>
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<td>Liver function</td>
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<td>Vitamin B12/folic acid</td>
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<td>TSH</td>
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<td>Chest X-ray</td>
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<tr>
<td>Neurophysiology</td>
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</table>
Hypothesis & Aims

The previously published patient series on the clinical picture of cryptogenic polyneuropathy are from the early 1990s or earlier. However, since then, the diagnostic possibilities have improved considerably, especially for hereditary and inflammatory neuropathies, and new causes of neuropathies have been found. Despite the progress in determining an etiological cause for polyneuropathy in many patients, there are still a considerable number of cases with unknown etiology, thus regarded as cryptogenic. Even data published in the late 1990s show that there are up to 10% of patients have MGUS in such material [191]. This means that there is a need for descriptive studies on cryptogenic polyneuropathy, both concerning symptoms, clinical and neurophysiological findings, and QOL.

It is well known that many chemical compounds are toxic to peripheral nerves and thereby can cause polyneuropathy. However, other new substances have been found to cause neuropathy and we wanted to elucidate this field further. Our hypothesis is that individuals with particular genotypes may have difficulties in metabolizing certain environmental toxins and that this poor metabolizer status make them susceptible to develop polyneuropathy following exposure to such toxins.
Patients and Methods

Patients

Totally included
n=255

Study I
n=168

Alive
n=232

Study II
n=164

Alive
n=158

Alive, 50-74 years
n=87

Study III
n=62

Study IV
n=79
We collected data from three departments of neurology (University Hospital of Linköping, Motala Hospital, and Ryhov County Hospital in Jönköping). The hospital databases were searched for all outpatients between the ages of 40 and 79 years with a diagnosis of cryptogenic polyneuropathy from January 1, 1993 to December 31, 2000. Patients under the age of 40 years were excluded to avoid including hereditary forms of polyneuropathy that had not yet been diagnosed [121]. Older patients were not included in the study to exclude lesions caused by the normal aging process in the nervous system and to avoid other confounding diseases or medications. All patients were referred to the departments of neurology from other physicians; usually a general practitioner, and the neurologist continued the work up to exclude cases of known origin.

Patients with an ICD-9CM (International Classification of Diseases, 9th Swedish edition) diagnosis of 356E, 356X, or 357X or an ICD-10 diagnosis of G60.9, G61.9, or G62.9 (cryptogenic polyneuropathy) were included. The initial inclusion was based on each neurologist’s judgment of the diagnosis because there was no strict definition of cryptogenic polyneuropathy. In total, 255 patients fulfilled these criteria.

Population data obtained from the National Central Bureau of Statistics in Sweden showed that the mean population aged 40–79 years in the study area during that period was about 296,000. It is not possible to calculate incidence during this period as most cases were probably diagnosed by general practitioners and not evaluated by a neurologist.

In the study “Occupational determinants of cryptogenic polyneuropathy” (Study II), all 232 patients who were still alive were included and were sent a
A total of 164 patients replied and were included in this study. The reason for not excluding any patients was that we wanted the sample size to be as large as possible so that power could be as high as possible.

In the other studies, we reevaluated the medical records, as we wanted to ascertain that the polyneuropathy was cryptogenic/idiopathic. The following laboratory investigations had to have been performed with normal results: hemoglobin, fasting blood glucose concentration, vitamin B12 (cobalamin), folic acid, and thyroid function. We defined polyneuropathy as one or more typical symptoms (numbness, pain, postural instability, paresthesias, distal weakness, burning sensation, muscle cramps, icing sensation, hypersensitivity to touch) with a distal distribution and at least two of three clinical findings (distal deficit of sensation, reduced distal muscle strength, and impaired or lost deep tendon reflexes). We regarded the diagnosis as probable if there were one or more of the symptoms above and one of three clinical findings. Patients whose diagnosis was based on neurophysiological findings alone were excluded. We also excluded patients when neurography showed a demyelinating neuropathy to exclude inflammatory and hereditary neuropathies. These criteria were used to reflect the clinical picture at a secondary center.

A total of 255 patients were retrieved from the databases, and of these, 168 fulfilled the criteria of cryptogenic polyneuropathy. A total of 136 patients (81%) fulfilled the criteria of polyneuropathy and 32 (19%) had probable polyneuropathy. The reasons for exclusion of 87 patients are listed in the table below. Patients were not screened routinely for HIV because the prevalence in the study area is low.
<table>
<thead>
<tr>
<th>Reason for exclusion</th>
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<tr>
<td>Alcohol + diabetes</td>
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<tr>
<td>Alcohol abuse</td>
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<tr>
<td>Alcohol + heredity</td>
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<td>Basedow's Disease</td>
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<tr>
<td>Diabetes</td>
<td>9</td>
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<tr>
<td>Dominantly demyelinating</td>
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<td>Jejuno-ileal by-pass surgery</td>
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<tr>
<td>PMR + testicular cancer</td>
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<tr>
<td>Rheumatoid Arthritis</td>
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<tr>
<td>Renal Failure</td>
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<tr>
<td>Simvastatin treatment</td>
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<td>Sjögren's Syndrome</td>
<td>1</td>
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<tr>
<td>SLE</td>
<td>1</td>
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<tr>
<td>Tumors</td>
<td>8</td>
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<tr>
<td>Vitamin B12 deficiency</td>
<td>18</td>
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<td>Vitamin B12 deficiency + phenytoin</td>
<td>1</td>
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<tr>
<td>Non-symptomatic polyneuropathy</td>
<td>4</td>
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</table>

When the genetic study (Study IV) was performed, 158 of the initial 168 patients were still alive, and they were asked to participate. Blood samples were collected and analyzed from 79 of the patients (response rate 50%). The QOL study (Study III) was performed during the same time period, but only those patients aged 50 to 74 years were included. The upper age limit was selected to match the reference material and the lower age limit was used, as there were only two patients, who had not reached 50 years of age.

The studies used different control materials, however all control subjects lived in the same area as the patients and were in the same age range.
Data collection

Medical records

The following features were recorded: age, sex, hospital, year of first symptom and year of diagnosis, ICD-9 or ICD-10 code, symptoms and clinical signs at first visit, and neurophysiological findings. The severity of the condition was based on Prineas’ classification [136]: 0 = normal; 1 = minor motor and/or sensory symptoms without functional deficit; 2 = minor to moderate symptoms with functional deficit, including slight ataxia; 3 = severe symptoms with functional deficit and at least some need for assistance; 4 = required assistance in eating; 5 = not ambulant.
Neurophysiology

Of the 168 patients, 139 were examined with neurography and 117 with EMG. Nerve conduction studies were performed with surface electrodes using standard techniques. Skin temperature was maintained at 33°C. The following nerves were studied: median and/or ulnar motor and sensory nerves, peroneal motor, and sural sensory nerves. Distal motor latency (DML), motor and sensory conduction velocity (CV), the compound muscle action potential (CMAP) amplitude, and the sensory nerve action potential (SNAP) amplitude were recorded. A conduction block was defined as reduction of more than 30% of the proximal: distal amplitude ratio. Axonal polyneuropathy was diagnosed if neurography showed decreased or absent amplitudes of CMAP or SNAP and relatively preserved CV (>70% of the lower limit of normal) and absence of conduction block in at least two nerves. Denervation activity on EMG was also regarded as a sign of axonal degeneration. Demyelinating polyneuropathy was diagnosed if CV was <70% of the lower limit of normal (<35 m/s in the arms and <30 m/s in the legs), or prolonged DML >150% of the upper limit of normal in at least two nerves. Conduction block was also regarded as a sign of demyelinating polyneuropathy. All others were classified as mixed axonal and demyelinating. Normal reference values from each laboratory were used as cut-off values. EMG recordings from the anterior tibial muscle were regarded as either normal or chronic neurogenic (decreased interference pattern or motor unit potentials with increased amplitude and duration). Denervation activity (sharp waves or fibrillation potentials) was also recorded. The neurophysiological findings were graded as follows: 0 = normal findings; 1 = slight decrease of CMAP, SNAP, or CV in at least two nerves; 2 = all findings between 1 and 3; or 3 = loss of sensory or motor responses in at least two nerves.
Questionnaires

At two different time points, questionnaires were mailed to cases and referents. The first questionnaire included questions about previous medical history, symptoms and information on occupational and leisure time exposure to metal dust, gases/smoke, solvents, engine exhausts, impregnating agents, plastic/rubber, other chemicals, pesticides and vibrations. The subcategories used in the questionnaire were chosen from substances suggested in the literature to be neurotoxic.

In the second questionnaire the questions about symptoms were repeated and the QOL instruments SF-36 and EQ-5D (EuroQol) were added. Up to 4 reminders were sent to non-responders until they answered or refused participation. For incomplete questionnaires, a telephone interview was conducted with the subject.

Blood samples

Blood samples were collected from 79 of the patients fulfilling the criteria for cryptogenic polyneuropathy (response rate 50%). The samples were analyzed for the different genotypes of EPHX1 exon 3, GSTM1 and GSTT1. Whole blood was collected and leukocyte DNA was isolated with Wizard Genome DNA purification kit (Promega Inc., Madison, Wisconsin, U.S.A.). The GSTM1 and GSTT1 null genotypes were assessed in a multiplex polymerase chain reaction (PCR) with β-globin as an internal control gene for a successful PCR-amplification [9]. The amino acid polymorphisms in the mEPHX gene (EPHX1 exon 3) were determined by a PCR-RFLP (restriction fragment length polymorphism) assay [96, 155]. For exon 3, there are 3 possible genotypes: YY, YH and HH. The wild type normal activity allele is YY and the low activity genotype is HH.
Results

Study I: Clinical and neurophysiological findings

Approximately twice as many men as women were affected with cryptogenic polyneuropathy. The incidence of polyneuropathy increased with age. With regard to clinical severity, 90 patients (54%) had slight symptoms and findings, 68 (40%) had moderately severe, and 10 patients (6%) had severe polyneuropathy.

The mean age at first symptom was 61 years and at diagnosis, 64 years. Regarding time from first symptom to diagnosis, 82% of the patients had a delay from first symptom to diagnosis of less than 5 years, 14% had a delay of 6 to 10 years and 4% had a delay of more than 10 years. Patients with the longest delay had more severe disease (clinical score 2.0 for >10 years compared with 1.5 for <5 years), but there were no significant differences between the clinical or neurophysiological scores in the groups.

The most common symptom was distal numbness, which was recorded in 115 case notes (65%). The patients with distal weakness or impairment of balance had higher mean clinical severity scores. They also had significantly higher neurophysiological severity scores. Patients who complained of burning sensations had significantly lower neurophysiological severity scores. No other differences were significant. Most patients (65%) had two or three symptoms, with a mean of 2.3. There was no significant correlation between the number of symptoms and age, clinical severity score, or neurophysiological severity score. The shortest delay from first symptom to diagnosis was 1.8 years for burning sensation and 2.8 years for hypersensitivity to touch, whereas the longest was
4.1 years for pain. The mean number of abnormal clinical findings (decreased or lost responses or hypersensitivity) was 3.6.

Of the 168 patients, 139 had neurographic examinations. Those who were not examined were older and had a lower mean clinical severity score although not significant. The median or ulnar nerves and the peroneal and sural nerves on both sides were examined in 132 patients. In 127 of these patients, at least 2 of 6 nerves showed abnormal values. Twelve patients had abnormal findings in only one nerve or had normal findings, and these patients had significantly lower mean clinical severity scores. Most patients had a combination of sensory and motor nerve involvement with a mean clinical severity score of 1.7. The 6 patients with motor nerve involvement alone had the same clinical severity score (1.7). The 29 patients with sensory nerve involvement alone had a lower mean clinical severity score (1.3), which was significantly lower than the score of those with sensorimotor involvement.

In 131 patients it was possible to state whether the nerve involvement was demyelinating, axonal, or combined. Axonal polyneuropathy was the most common (n=85) and these patients had a mean clinical severity score of 1.5. The 46 patients with the axonal and demyelinating form had a significantly higher clinical severity score (1.8). The most common neurographic finding was that of a mixed sensory-motor nerve involvement with axonal degeneration (n=62).

EMG examinations had been performed in 117 of the 168 patients. In 24 patients EMG in the anterior tibial muscle was normal. These patients had significantly lower clinical severity scores than patients with abnormal EMG (p<0.001). The 22 patients with chronic neurogenic findings and denervation activity had significantly higher clinical severity scores (2.0) than the 70 patients
with chronic neurogenic findings alone (1.6) (p<0.05). One patient had denervation activity alone.

Of the 139 patients who underwent neurography, 4 had neurophysiological severity grade 0, 46 patients grade 1, 48 patients grade 2, and 41 patients grade 3. There was no difference in neurophysiological severity between men and women. The patients in the most severe group were significantly older than those in group 1 and 2 (p<0.01); and had significantly higher clinical severity scores. Patients in the moderate group (grade 2) also had a higher clinical severity score than those in the mild group (grade 1) (p<0.001). However, there was no significant correlation.

**Study II: Occupational determinants**

Male sex increased the risk for cryptogenic polyneuropathy, COR (Crude Odds Ratio) 2.33 (95% CI 1.61-3.38), and increasing age was a determinant for both men and women showing significantly statistical trends. Fewer women reported chemical or vibration exposure; 19% of female referents were exposed compared to 64% of male referents. Exposure in men to Stoddard solvent, petrol exhausts, herbicides, and hand and foot vibrations were significantly associated with increased COR, respectively.

As individuals tended to have multiple exposures, logistic regression was performed. In men the logistic regression showed particularly increased risks (LOR, Logistic Odds Ratio>3.50) for occupational exposure to sulphur dioxide, xylene, methyl ethyl ketone, and herbicides. Risks remained increased (LOR>1.50) for occupational exposure to lead, hydrogen sulphide, Stoddard solvent, petrol exhausts, fungicides, and vibration exposure to the feet, respectively. For leisure time only exposure to gases/smoke and solvents
showed increased risks in the logistic regression, but only solvents was significant, LOR 8.84 (95% CI 2.43-32.04). In women half of the CORs above 1.50 remained that high in LOR i.e., lead, mercury, nitrous oxide, and insecticides. Comparing LORs in men and women, only the exposure to lead showed increased risk in both sexes. However, our results do not contradict risks in both sexes as the confidence intervals are overlapping, except for mercury exposure.

In the second logistic model including exposure categories and without an unexposed reference group, the results were identical with the former results both for men and women.

Interaction between occupational and leisure time exposure could only be analyzed in detail for men. Occupational pesticide exposure was the only statistically significant determinant without a concomitant leisure time exposure, COR 3.13 (95% CI 1.20-7.91). Comparing the results, interaction was particularly strong for leisure time exposure to solvents especially in combination, with occupational exposure to metal dust, gases/smoke, solvents, engine exhausts and vibrations, respectively. However, even if the interactive effect seems strong, the largest contribution to the risk estimates is from the occupational exposures as sole leisure time exposure is rare.

**Study III: Health related quality of life**

This study comprised 62 patients with an average age of 64.9 years. The mean time from diagnosis was 6.9 years (range 2-21 years). As reference, 1,429 women and 1,292 men from the general population were used, with a mean age of 60.6 years, which was significantly lower than in the patients.
When comparing the group of patients with cryptogenic polyneuropathy as a whole with the general population, patients had lower QOL in all scales except for MH (Mental Health) and mcs (Mental Component Summary). In the general population, women had lower QOL than men for all scales. Women with polyneuropathy tended to have lower QOL than men in all scales but the differences did not reach significance. When patients and referents were grouped according to age and sex, the physical scales PF (Physical Functioning), RP (Role Physical), BP (Bodily Pain) and GH (General Health); and mental scales VT (Vitality) and RE (Role Emotional) were decreased in most groups of patients except for older women where only GH and VT were significantly affected. On the other hand, no significant differences were observed in any group in MH and mcs.

In the general population, the scores in PF, RP, GH, RE and both sum scales decreased with increasing age. In polyneuropathy patients, the only statistically significant difference was that 50- to 64-year old women had lower BP scores than those who were 65 to 74 years old.
SF-36 versus age in men

SF-36 versus age in women

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<thead>
<tr>
<th>Age Group</th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
<th>Pcs</th>
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<td>76.2</td>
<td>83.4</td>
<td>34.5</td>
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</table>
To analyze patients with polyneuropathy by duration of the disease, patients were grouped into three categories, based on the disease duration: 0 to 5, 6 to 10 and more than 10 years. None of the scales in SF-36 showed any significant difference between these groups.

**SF-36 vs duration (years from first symptom) of polyneuropathy**

![Bar chart showing SF-36 scores for duration of polyneuropathy]
Because of the small number of patients in each group, all patients reporting any problem have been analyzed together. Patients with cryptogenic neuropathy reported significantly more problems in walking (mobility) (42%) than reference subjects (14%). Problems with usual activities were reported by 31% of patients, which was significantly more common than in the general population (8%). Six percent of the patients reported problems with self-care (washing and dressing) compared to 2% of the reference subjects. Pain was common in both patients (85%) and the general population (56%). Anxiety or depression was reported by 35% of patients and 29% of reference subjects, which was the only not significant difference. No significant differences were seen between men and women. The results were not affected by disease duration for any of the five questions.

**EQ barometer**

Health state measured by the Visual Analogue Scale (VAS) was significantly lower in male polyneuropathy patients older than 60 years and in women younger than 70 years compared to the general population. The VAS scores tended to decrease with increasing age, but there were no significant differences between groups except between 50- to 59-year-old males and 60- to 69-year-old males. Women with polyneuropathy tended to have lower VAS scores than men in all age groups, but the difference was only significant for 50- to 59-year-old patients. No relationship was seen between the QOL measured by the EQ barometer and disease duration. However, patients reporting many symptoms had lower EQ barometer values.
**Study IV: Genetic polymorphisms**

In total, 79 cases with cryptogenic polyneuropathy and 398 controls were tested for genetic polymorphisms in the GSTM1, GSTT1, and mEPHX genes. The OR for the null genotype of GSTM1 and GSTT1 was 0.99 (0.61-1.61) and 1.86 (0.82-4.24), respectively and for EPHX*3 YY versus YH/HH the OR was 1.06 (0.65-1.71). Among the controls there were significantly more women with GSTT1 null than in men, (p=0.04), and the homozygous HH variant in mEPHX was more common in men (p<0.01). The other variants did not differ between men and women. There were no statistically significant differences between cases and controls in any group.

Regarding clinical findings, 24 patients were considered to have mild findings and 39 patients had severe findings. No significant differences were found between the groups in clinical or neurophysiological severity at diagnosis except a tendency for GSTM1 null to have more severe clinical findings than GSTM1 positive cases (mean 1.55 vs. 1.31, p=0.064). Axonal neuropathy was observed in 41 patients and combined axonal and demyelinating neuropathy in 19 patients. Regarding neurophysiological findings, 2 patients had pure motor neuropathy, 13, pure sensory neuropathy, and 64, a mixed sensorimotor neuropathy. Genetic polymorphisms were not significantly related to these neurographic findings.

We also investigated the effects of different exposures. The frequencies are presented in the table below.
The odds ratios for cryptogenic polyneuropathy among exposed individuals were calculated. GSTT1 null among smokers reached the highest odds ratio (3.72, \(p=0.08\)), and EPHX*3 HH vs. YY among solvent exposed had the lowest odds ratio (0.30, \(p=0.14\)). A logistic regression analysis for the different polymorphisms, sex, age, and exposures did not show any confounding effects except that increasing age and male sex increased the risk of cryptogenic polyneuropathy. Interactions between genes were analyzed and showed an increased odds ratio for GSTT1, which was strongest if the patients had the HH form of EPHX*3 (OR 2.37, \(p=0.234\)).

**Additional results**

**Evaluation of symptoms**

In 2000 and again in 2002, a questionnaire was sent to the patients, and 105 patients (77 men and 32 women) replied to both of the questionnaires. Of those who responded, 87 fulfilled the criteria for cryptogenic polyneuropathy (61 men,
26 women). They were asked if they were experiencing any of 9 different listed symptoms in either hands or feet. At the time of the first questionnaire 1.4 (0.88-1.9; mean and 95% confidence intervals) symptoms from the hands, and 3.3 (2.7-3.9) symptoms from the feet were reported. At the time of the second questionnaire 1.7 (1.2-2.2) and 3.8 (3.3-4.4) symptoms were reported respectively. The total number of symptoms increased from 4.7 (3.8-5.6) to 5.5 (4.7-6.4). The differences were not statistically significant. In hands 18 patients reported fewer symptoms and 29 reporting more symptoms (n.s). In feet the difference was statistically significant (Wilcoxon p=0.016), with 21 patients reporting fewer symptoms and 39 reporting more symptoms. A total of 43 patients experienced an increase in the total number of symptoms, and 19 had a lower total number of symptoms (p=0.007).

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Number of reported symptoms in 2000 and 2002.

The number of the respective symptoms was also analyzed. Numbness, impaired sensation, pain, paresthesias, and distal weakness in the feet were the most common symptoms reported. Pain in hands and feet, distal weakness in hands, numbness and muscle cramps in feet were increasing most in frequency.
Burning sensation in hands and impaired sensation in hands and feet were decreasing in frequency.

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Frequency of different symptoms of polyneuropathy with a 2-year interval.
SF-36 in all patients that responded (n=104), in the published material aged 50-74 (n=62) and in the general population.

To evaluate the impact of cryptogenic polyneuropathy on QOL, 158 patients fulfilling the criteria of cryptogenic polyneuropathy were sent validated instruments (SF-36 and EQ-5D). Responses were received from 104 patients (70 men, 34 women [66% response rate]). Their average age was 70.3 years (range 43-88 years), and the mean time from diagnosis was 7.2 years (range 2-23 years). No significant differences were observed between responders and non-responders in age at diagnosis, age at questionnaire, number of symptoms at diagnosis, clinical or neurophysiological severity. However, the patients who were no longer alive any longer would have been significantly older at the time.
the questionnaire was sent out and were older at first symptom and diagnosis, but did not differ in number of symptoms or clinical or neurophysiological severity. As the control population had an upper age limit at 74 years and as only two of the patients were younger than 50 years, the age limit in the final study was changed to 50-74 years. The data of both the complete and published materials are shown above. The older excluded patients had a lower HR-QoL in most of the scales.

Diabetes risk evaluation

According to the information in the medical records as described in Study I, 168 patients were considered as cryptogenic. All of these patients were sent the questionnaire described in Study II. This questionnaire also included questions about the medical history. A total of 110 patients replied (76 men, 34 women), 58 did not reply (37 men, 21 women) and 604 controls replied (274 men, 330 women).

It has been described in the literature that patients with cryptogenic polyneuropathy have an increased frequency of impaired glucose tolerance [75, 122, 152, 165] and probably are at risk of developing diabetes, though others have found contradicting results [82, 117]. As the patients’ data were collected during a 7-year period, one important question was if they still were cryptogenic. We, therefore, asked specifically about diabetes. The patients had a mean age of 68.2 years (66.2-70.1; 95% confidence interval) and the controls were 62.2 (61.3-63.1) years old (p<0.001) at the time of the questionnaire. Three patients, who initially were not diagnosed with diabetes, reported that they had developed diabetes (2.7%) and 30 controls (5.0%) reported that they had diabetes. The incidence of diabetes type 1 and 2 in Sweden for 60- to 69-years-olds is 732 cases per 100,000 and year [172], therefore, the incidence in our material is at the same level.
Discussions and Conclusions

Clinical picture

Polyneuropathy is one of the most common neurological disorders and patients are seen by physicians with many different specialties. The clinical diagnosis is based on the finding of a distal, fairly symmetrical impairment of sensation, muscle strength, or muscular atrophy, and progression over a period of months or years. Reflexes are decreased or lost in the affected parts, but particularly in the ankles. Symptoms usually occur in the feet before the hands [179]. Neurophysiological investigations with nerve conduction studies and EMG can support the diagnosis.

The 182 cases of polyneuropathy in our first study were diagnosed as cryptogenic by the treating neurologist. To make certain that there was no known cause of neuropathy, the medical records were reviewed according to our protocol. In many cases the patients had been followed up after the initial visit. The questionnaire that was sent to the patients also included questions about disorders known to cause polyneuropathy. As the patients were diagnosed up to 7 years before the first questionnaire, it is likely that tumors presenting with polyneuropathy, as the first symptom would have been diagnosed. 8 patients actually were excluded due to tumors. The risk of developing diabetes was also low, confirming that the cases were correctly diagnosed. The major problem with the diagnosis is that it is always possible to do a more thorough investigation. Unfortunately, neurophysiological examinations were performed in only 139 of the patients. It is, however, unlikely that any of these patients would have an inflammatory neuropathy such as CIDP, as patients who were deteriorating would have been followed up or referred back to our clinics. There are no other clinics in the study area treating progressive neuropathies. In fact,
the patients who were not examined neurophysiologically had a lower clinical severity at diagnosis supporting that they were cryptogenic. The most common reasons for not performing neurophysiological tests were old age and low clinical severity. Our definition of cryptogenic polyneuropathy is relatively broad, but has the advantage of reflecting the clinical picture that is seen by a neurologist at a secondary or tertiary center, which was the aim of our study. The study has the drawback of being retrospective.

Polyneuropathy was more common in elderly patients and about twice as many men as women were affected. This difference is in agreement with most previous studies [37, 66, 107, 119] except one [190]. A male predominance may support our hypothesis that polyneuropathy could be caused by a chronic toxic effect of occupational or environmental factors.

In our series two thirds of the patients complained of numbness and about one third complained of paresthesias, pain, impairment of balance, or distal weakness. In a smaller study of 29 cases of unclassified polyneuropathy, 28 patients had hypoesthesia or hyperalgesia, 26 paresthesias, and 10 pain [66]. Vrancken reported higher prevalences of symptoms in CIAP, this is, however, probably due to study design [180]. In a study of chronic cryptogenic sensory polyneuropathy, distal numbness was reported in 86% and pain in 72% of the patients [190]. In our series impairment of balance and muscle weakness was as common as pain, probably reflecting the fact that we also included patients with motor or sensorimotor polyneuropathy.

Two symptoms brought patients more rapidly to the neurologist: a burning sensation and hypersensitivity to touch. These symptoms are very disturbing to patients and make them seek medical attention early. In contrast, patients with pain and muscle cramps had the longest delay from first symptom to diagnosis.
Wolfe also found that patients with pain had their symptoms significantly longer than those without pain, for which they had no clear explanation [190]. Wolfe and colleagues also found that only 10% of their patients complained of pain alone [190].

When patients were asked about symptoms with a 2-year interval, the number of symptoms increased. All symptoms except burning sensation and impaired sensation in hands or feet became more common. Unfortunately, we do not have any data about the development of severity of the symptoms.

The most sensitive signs of polyneuropathy are decreased or lost distal proprioception or sense of vibration, and ankle jerks, both with a sensitivity of 75-80%.

Our scale for clinical severity focused on functional deficits (particularly ataxia and need for assistance), so it was not surprising to find that the symptoms impairment of balance and distal weakness had the highest clinical severity scores. However, other symptoms such as pain and burning or icing sensations probably affect the QOL as much. We classified 93% of the patients in this series as having mild or moderate disease; but they probably had a more severe disease than patients in other studies. Some of the previous epidemiological studies were based on people in primary care [14, 103] and there might be important differences between those studies and ours. Because of the large number of patients in primary care with mild symptoms, some patients might be diagnosed as having cryptogenic polyneuropathy, but later turn out to have other diseases or simply normal aging of the peripheral nerves.

Of the 84% of patients who had neurographic examinations performed, more than half had a mixed motor and sensory nerve involvement and only 4% had
motor nerve involvement alone, which is in accordance with the results of Notermans et al. [119], who found only 3% with motor involvement alone. Several of their patients who initially had sensory neuropathy later developed sensorimotor involvement [121].

The EMG studies showed chronic neurogenic signs with denervation in 23 of 123 patients, compatible with a mainly axonal polyneuropathy, which is in agreement with others [119]. The EMG findings also suggest that even if most cryptogenic polyneuropathies are mainly sensory or sensorimotor, there is also an involvement of motor nerves, which is important when judging the relevance of neurophysiological findings and their correlation with somatic neurological findings [66, 119, 190].

We found a weak correlation between clinical and neurophysiological severity. A larger prospective study with a better classification of neurophysiological severity would probably find a stronger correlation. In some cases the neurophysiological severity is greater than expected from the neurological examination. Another reason for neurophysiological examination is that axonal and demyelinating polyneuropathies can be distinguished. The latter includes hereditary neuropathies and the treatable chronic inflammatory demyelinating polyneuropathy (CIDP) [144].

**Health related quality of life**

Cryptogenic polyneuropathy has usually been regarded as a relatively mild neurological condition, which commonly does not severely affect the patient’s ability to walk or perform activities of daily living (ADL). However, we found that 42% of patients reported problems with walking and 31% had problems with usual activities such as work, study, household work, family or leisure activities. These problems were not affected by age. In another study focusing
on QOL in patients with CIAP, fatigue and walking disability were found to interfere markedly with patients’ functioning in daily life [44].

Disease duration did not affect SF-36 or EQ-5D barometer scores in our study. That finding might, in part, be explained by the study design as patients were recruited over a 7-year period and some patients had short time of follow-up from diagnosis to participation in our study. However, the results of a prospective follow-up study of 40 patients with chronic polyneuropathy of undetermined cause support that the disease is a stable or only slowly progressive disorder in most cases [88].

Teunissen and co-workers showed that patients with CIAP have lower scores than expected in all areas of the SF-36 except for ‘role limitations due to emotional problems’. The differences in ‘social functioning’, ‘pain’, and ‘physical functioning’ were most marked [168]. Their patients and the reference population were not sex and age matched. These results are in line with our results, although we did not find any difference in ‘mental health’. Hughes reports that QOL in CIAP was worse than norms from Australian Bureau of Statistics in all SF-36 scales except ‘role emotional’. In the scale ‘mental health’, they only found a difference among patients with pain [83]. The patients reported by Hughes had lower scores in almost all scales most likely because these patients were older or due to selection of the patient material. All three studies support that chronic idiopathic or cryptogenic polyneuropathy impairs physical functions and that the disease limits the ability to perform usual activities in daily life.

In our study, 85% of the patients reported pain in EQ-5D. However, EQ-5D is a very sensitive instrument for assessment of pain, which was reported by 56% of females in the general population older than 50 years of age and at a slightly
lower frequency in men. In a study of Italian patients with chronic polyneuropathy, the QOL was affected not only by the presence of neuropathy, but also by the presence and intensity of pain. Moreover, the mental domains of the SF-36 were only correlated with pain. Pain per se worsens the QOL of neuropathic patients, regardless of disease severity [27]. Abresch and co-workers have investigated the QOL in patients with different slowly progressive neuromuscular diseases (myotonic muscular dystrophies, limb-girdle syndromes, CMT disease, fascioscapulohumeral dystrophy, spinal muscular atrophy and post-polio syndrome). Their results indicated that, except for adult spinal muscular atrophy, the prevalence and severity of pain reported in slowly progressive neuromuscular diseases were significantly greater than levels of pain reported by the general US population. There was a significant correlation between increased pain and lower levels of general health, vitality, social function, and physical role, which confirms that pain is an essential symptom affecting QOL in patients with diseases in the peripheral nervous system and muscles [2]. They found the same results in patients with diabetic neuropathy, which indicates that patients who have moderate or severe levels of pain may benefit from a pain management program, rather than focusing on only physical impairment [1]. These results were confirmed in patients with different kinds of polyneuropathy by Liedberg and Vrethem [100].

In a study focusing on pain in CIAP it was found that non-neuropathic pain was as common as neuropathic pain and that pain was strongly associated with the physical functioning domain of the SF-36 in patients with mixed neuropathic and non-neuropathic pain [45].

HR-QoL has been described in several studies of diabetic neuropathy showing lower HR-QoL in patients with diabetes than in our group of patients with cryptogenic polyneuropathy [8, 28, 74].
**Exposures in work and leisure time**

Considering the magnitude of risk, the confidence intervals and the confounding effect from other exposures, in our study, the independent determinants for polyneuropathy in men seemed to be occupational exposure to lead, sulphur dioxide, hydrogen sulphide, xylene, methyl ethyl ketone, herbicides, fungicides and foot vibrations. Among leisure time exposures only solvents could be regarded as a strong independent determinant. All other leisure time exposures, except perhaps gases/smoke, seemed to be of minor importance for polyneuropathy since the increased risk could be explained by concomitant occupational exposures. In women the corresponding occupational determinants were lead, mercury, nitrous oxide and insecticides, however no leisure time determinant could be identified. Our study was limited by small numbers of cases and by low frequency of exposure, especially in women, which was reflected in broad confidence intervals, not always including unity.

Some individuals, especially in the older ages, might have found it difficult to remember their lifetime exposures, but as cases were older than referents, memory bias should work in the direction of lowering the risk estimates. None of the referents answered that they had polyneuropathy. Evaluation of the validity of information from subjects in case-referent studies has also failed to find any recall bias of importance [90, 134]. In a study of 188 metal-exposed subjects, exposure assessment performed by an industrial hygienist was compared with self-reported exposures, showing an agreement in the assessments from 83 to 94% for different metals. Interestingly, the hygienist classified more workers to be exposed than the workers themselves [149].
Our study was too small to allow any further analyses of the exposure i.e., length or intensity, thus including only ever exposed. As a majority of the male cases and referents were exposed to several potential determinants, a reference category free of such exposures was used. Although Swedish women have a relatively high employment rate, only a minority were exposed to occupational chemicals or vibrations. This is the reason why the study was analyzed with men and women separated.

Out of the initial list of well-established, but often rarely occurring, substances that cause polyneuropathy, only lead, n-hexane and nitrous oxide showed an increased risk in our study [158]. We also showed some synergistic effects with increased risk estimates in various occupational and leisure time exposures combined.

Occupational mercury exposure occurs in workers associated with glass cutting and in the manufacture of scientific instruments, in dental personnel, and following release of mercury vapor from amalgam tooth fillings. Methyl mercury is used in the manufacture of paper, in the chloralkali industry, and in other chemical production. General human exposure usually results from ingestion of fish obtained from water contaminated with industrial effluents [178]. Mercury was a determinant for cryptogenic polyneuropathy in women according to our study. Organic mercury is clearly associated with polyneuropathy [178]. However, there are case reports that elemental mercury can also cause polyneuropathy in humans [4, 5, 26, 76, 79, 87, 151, 178]. Only one study of workers exposed to mercury has failed to find any relationship with polyneuropathy [176]. Unfortunately, our questionnaire did not distinguish between organic and inorganic mercury.
Sulphur dioxide and hydrogen sulphide appeared to be strong determinants for cryptogenic polyneuropathy in our study, and these associations have not been previously published. A well-known mechanism of hydrogen sulphide is respiratory paralysis and subsequent hypoxia to the central nervous system, but there could also be a direct toxic effect on the brain [110]. Several enzymes in the brain are inhibited by hydrogen sulphide i.e., carbonic anhydrase, an enzyme involved in the neuronal lipid synthesis and/or re-organization of myelin membranes [147]. Whether these mechanisms also are applicable to the peripheral nervous system is less clear.

In our study toluene did not show an increased risk in the logistic regression analysis although polyneuropathy has been described after abuse of toluene-containing products [162]. Polyneuropathy has also occurred in different occupational settings where toluene has been present [57, 104]. In contrast to toluene, xylene was a relatively strong determinant in our study; a finding supported by case reports on intoxication with products containing 5-10% xylene [57]. Xylene (dimethylbenzene) is also chemically closely related to toluene (methylbenzene) and can, therefore, be suggested as a potential agent to cause polyneuropathy despite less documentation.

Methyl ethyl ketone was a relatively strong determinant in our study. In the literature only case reports have been found, but the neurotoxic potential of methyl ethyl ketone is difficult to evaluate as these cases have been exposed to a mixture of solvents [6, 39, 63]. It has also been reported that methyl ethyl ketone can act indirectly as an inducer of n-hexane-metabolizing enzymes [84].

7 male cases and 4 referents added exposure to jet fuel and jet engine exhausts in the questionnaire, COR 6.73 (95% CI 1.54-33.21). There are only two previous reports on this relationship in the literature [93, 94]. As both civilian
and military airports as well as an aircraft industry are located in southeast Sweden, where our investigation was performed, this result seems reasonable.

In our study herbicide, and to some extent also fungicide, exposure in men and insecticide exposure in women were determinants. Herbicides are not commonly reported to cause peripheral polyneuropathy in the literature. In fact, only three case reports describe polyneuropathy after occupational exposure to the herbicide 2,4-D with predominant dermal uptake [16, 59, 174]. A case report describes intoxication with weed killers containing phenoxyacetic acid that resulted in a delayed peripheral neuropathy [123]. On the other hand, an evaluation of soldiers exposed to Agent Orange (50:50 mixture of 2,4-D and 2,4,5-T) has concluded that there is inadequate or insufficient evidence for an association with peripheral neuropathy [58]. Therefore, our results contribute to the evidence that herbicides might cause polyneuropathy.

In contrast, exposure to organophosphates is a recognized cause of polyneuropathy [7], but these compounds are no longer extensively used in Sweden. Organophosphates are used mainly as pesticides and herbicides but are also used as petroleum additives, lubricants, antioxidants, flame-retardants, and plastic modifiers. Certain organophosphates cause a delayed polyneuropathy that occurs approximately 2 to 3 weeks after acute exposure even in the absence of the otherwise typical acute cholinergic toxicity [7]. Another insecticide, dichlorodiphenyltrichloroethylene (DDT), was widely used in Sweden until the ban in 1970. DDT belongs to the organochlorine pesticides known to cause symptoms of the central nervous system at high doses, but the effects of chronic low-level exposure are uncertain [7]. Lindane, another widely used insecticide, has also been reported to cause polyneuropathy [175]. However, there were too few exposed in our study to obtain a risk estimate. Pyrethroids are synthetic insecticides that affect voltage-sensitive sodium channels and possibly also
voltage-sensitive calcium and chloride channels. Occupational exposure has led to paresthesias that have been attributed to repetitive activity in sensory fibers as a result of abnormal prolongation of the sodium current during membrane excitation [156]. Convulsions may occur if substantial amounts are ingested [137]. Fungicide exposure has not been suggested to be a determinant for polyneuropathy, but in our study, the risk was a doubled in men.

Exposure to vibrating tools may cause a variety of symptoms depicted as the hand–arm vibration syndrome. The symptoms may be of vascular, neural, and muscular origin and may appear as digital vasospasm (vibration white fingers; VWF), sensorineural disturbances, and/or as muscular weakness and fatigue [53]. A negative relationship has been observed between nerve conduction velocities in motor and sensory nerves in the arms, on the one hand, and age at the time of the study or total number of working years with vibrating tools, on the other [53]. Until now, there have been no reports that vibration of the feet can cause a more generalized polyneuropathy, and therefore, in that respect our finding should be interpreted with caution.

**Genetic polymorphisms and risk of cryptogenic polyneuropathy**

The frequency of GSTM1 null is 42-60% in Caucasians [51]. The frequency of homozygous null GSTT1 varies greatly with ethnicity and is 10-20% in Caucasians [141]. The EPHX*3 gene can be found in three different forms, the wild type/normal activity variant (YY), heterozygous (YH), or homozygous/low activity (HH) genotypes. In a Caucasian population, approximately about 40% of subjects are heterozygous and 12% are homozygous for the HH genotype [51]. The frequency of these polymorphisms in our study population was similar. No differences in allele frequencies by age or sex were seen in large studies [51]. Unfortunately, we had an imbalance in our control group with 19%
of the women and 12% of the men having the GSTT1 null polymorphism and 9% of the women and 18% of the men having the EPHX*3 HH polymorphism. Thus, it is not possible to draw any conclusions about differences in risks of cryptogenic polyneuropathy among men and women separately.

In Study IV of patients with cryptogenic polyneuropathy, we examined the association of GSTM1 and GSTT1 null polymorphisms and EPHX1 exon 3 HH polymorphism in relation to several environmental and chemical exposures. Although we did not find any statistically significant increased risk, the GSTT1 null genotype was associated with an almost two-fold increased risk of polyneuropathy. Our hypothesis is that the GSTT1 null polymorphism may be related to an impaired metabolism of toxic substances and reactive oxygen that could lead to nerve damage, involving multiple sites along motor and sensory axons in the peripheral nervous system. This may result in axonal atrophy or axonal swelling, leading to progressive distal axonal degeneration. The myelin sheath may break down concomitantly with the axon. This could contribute to, or directly result in, an axonal or combined axonal-demyelinating neuropathy.

Components of cigarette smoke are examples of exogenous substrates that are toxic and, furthermore, are subject to bioactivation and may both directly and indirectly be neurotoxic. We found a nearly four-fold increased risk of polyneuropathy in GSTT1 null smokers that almost achieved statistical significance. Teunissen and co-authors reported an odds ratio of 2.1 for current smoking in patients with CIAP [169], and it has also been found that tobacco use may predispose to earlier development and more severe symptoms of diabetic neuropathy [167]. Our data indicate that this risk might be explained by smokers carrying certain genetic polymorphisms leading to impaired detoxification of the toxic compounds in cigarette smoke. The mechanism for the toxicity of cigarette smoke on nerves is not known, but it has been
speculated that chemicals in the smoke mediate it, where PAHs are regarded as the most important component. Impaired breakdown of PAHs in persons with the null genotype of GSTs may lead to an increased exposure on nerves and thereby increased loss of nerves. n-Hexane is another toxic substance that is present in cigarette smoke and is a well-known cause of polyneuropathy [194].

We did not find a significant correlation between clinical or neurophysiological severity and genotype except a small increase in the severity of clinical findings in GSTM1 null patients that almost reached statistical significance. It is possible that a correlation will be found if a more sensitive scale for clinical or neurophysiological severity was used in a larger material.

There are several possible reasons why we did not find any significant differences. The main reason is probably the small number of patients in our study. However, in a Chinese study of 22 cases of polyneuropathy working in a printing factory and 163 controls, an association was found with CYP2E1 Dra, but not GSTM1 and GSTT1, indicating that either a more pronounced exposure to a toxic agent is necessary or that other genes may have greater importance for the development of polyneuropathy [194]. It is also possible that the referring general practitioner or the diagnosing neurologist identified most cases of toxic neuropathies.

**Conclusions**

Cryptogenic polyneuropathy is a slowly progressive sensorimotor nerve lesion with minor or moderate severity. Men are affected almost twice as often as women. The typical patient is at least 60 years old and complains of numbness in the feet. Neurological investigation reveals impaired proprioception and/or sense of vibration and decreased or lost ankle tendon reflexes.
Neurophysiological examination shows sensorimotor polyneuropathy with mainly axonal involvement.

We have found that patients with cryptogenic polyneuropathy have poorer HR-QOL, except for mental health scores, than the general population. Pain seems to be one of the main contributors to the poor HR-QoL. More than 3 out of 10 patients reported problems performing activities of daily living, and it was even more common to have problems walking, which was more common than expected. Age and disease duration did not seem to affect QOL, but this is contradicted by the fact that patients reported more symptoms when the questionnaires were repeated 2 years later. However, our data support that cryptogenic polyneuropathy is a slowly progressive disorder.

Our study is the first case-referent study focusing on occupational and environmental determinants for cryptogenic polyneuropathy. The study has limitations in size and exposure assessment as we had to rely on self-reported exposure. Our results suggested that not only known determinants could be confirmed, but also some new ones appeared i.e., sulphur dioxide, hydrogen sulphide, fungicides, and vibrations in the feet. Moreover, our results point to a synergistic effect of various exposures. Men were more often exposed to neurotoxic chemicals and vibrations than women, probably explaining most of the increased risk for polyneuropathy in men.

No significant correlation was found between GSTM1, GSTT1, and EPHX1 polymorphisms in patients with cryptogenic polyneuropathy compared with controls. A strong tendency, however, was seen for the GSTT1 null phenotype, which was enhanced among smokers compared to controls (OR 3.7). The GSTT1 null polymorphism may be related to an impaired metabolism of toxic substances and reactive oxygen that could lead to nerve damage in the peripheral
nervous system. This could contribute to, or directly result in an axonal or combined axonal-demyelinating neuropathy. A larger study of unselected polyneuropathy cases and controls is warranted to confirm these data.

Future work should also include a larger community-based prospective study of slowly progressive symmetric polyneuropathy in which all patients have a thorough neurological examination, and laboratory tests including blood glucose, complete blood count, ESR, serum electrophoresis, renal and liver function, vitamin B12/folic acid, TSH, and chest X-ray. In addition, nerve conduction velocities and amplitudes should be performed before diagnosis. It would also be of value to assess QOL using both generic and neuropathy-specific QOL scales and perform clinical evaluation of patients with repeated functional assessment and neurophysiological evaluations to describe the implications in patients with cryptogenic polyneuropathy and the prognosis over a longer period.
Acknowledgements

This work was carried out as a collaboration project between the Departments of Neurology, Neurophysiology and Occupational and Environmental Medicine at the University Hospital in Linköping; the Department of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg; Division of Cellular Biology, Department of Biomedicine and Surgery, Linköping University; the Department of Internal Medicine, Division of Neurology, Motala Hospital, and The Department of Internal Medicine at Ryhov County Hospital, Jönköping.

I wish to express my sincere gratitude to:
Assistant Professor Magnus Vrethem, main supervisor, co-author
for his immense knowledge of neurology and neurophysiology in general and of polyneuropathies in particular,
for his never-ending enthusiasm and encouraging support during the long project and for constructive criticism during the preparation of manuscripts and most of all for being a very good friend

Professor Eva Svanborg, co-supervisor
for her extensive knowledge about neurophysiology,
for her guidance in the scientific world and bureaucracy.

Med dr Martin Tondel, co-author
for deep knowledge in environmental medicine and public health,
for always asking questions and raising new possible hypotheses.

Med dr Bodil Persson, co-author
for her knowledge about the metabolism of toxic substances.

Professor Peter Söderkvist, co-author
for introducing me into the world of genetic polymorphisms and their importance in the metabolism of solvents and other toxic substances.

Assistant Professor Mats Fredriksson, co-author
for his expertise in statistical methods,
for sorting everything out

Med dr Anders Österberg, co-author
for recruitment of patients

Dr Shahrzad Hosseininia, co-author
for laboratory work

Pia Jönsson, co-author
for epidemiological expertise

Research nurses Miriam Carlsson and Gun Johansson
for their outstanding assistance in collecting blood samples and questionnaires,
for bringing joy and laughter into the work.

Professor Jan-Edvin Olsson
for advice and help

Associate Professor Raymond Press
for advice and encouragement
Professor Anna-Christina Ek
for advice and for sharing her expertise in quality of life study methodology

Professor Bo-Erik Malmwall
for supporting me to take the step to work as a researcher

Dr Margareta Hultgren
for her endurance in clinical neurology and cooperative support during these years

Co-workers at the Section of Neurology at the Department of Internal Medicine at Ryhov County Hospital: Med Dr Anna Budzianowska, Dr Anna Eklund, Dr Helena Bruhn, Dr Greta Gustafsson, Dr Owe Lannemyr, Dr Robert Bielis, Med Dr Sven Pålhagen, nurses Gudrun Carlsson, Ingvor Lindh and Ulla Andersson
for cooperative support during years of studies.

The heads of Internal Medicine at Ryhov County Hospital: Dr Leif Ockander, Dr Staffan Schöön and Dr Agneta Ståhl

The staff at the medical library at Ryhov Hospital
for always being nice and helpful in the search for literature

And finally to my wife Ulrika and our children Andrea and Philip
for supporting me during these years of too much work.
References


with glutathione transferase theta 1 (GSTT1) gene defect. Lancet 347:295-297


(EPHX1) to human chromosome 1q42.1 by in situ hybridization. Cytogenet Cell Genet 83:44-45


124. Oesch F (1973) Mammalian epoxide hydrases: inducible enzymes catalysing the inactivation of carcinogenic and cytotoxic metabolites derived from aromatic and olefinic compounds. Xenobiotica 3:305-340


159. Spencer PS, Schaumburg HH (1975) Experimental neuropathy produced by 2,5-hexanedione—a major metabolite of the neurotoxic industrial solvent methyl n-butyl ketone. Journal of neurology, neurosurgery, and psychiatry 38:771-775


sensory polyneuropathy: clinical and laboratory characteristics.[see comment]. Archives of Neurology 56:540-547


