CURRENT NEUROLOGY®

STANLEY H. APPEL

VOLUME 11

CURRENT

NEUROLOGY®

VOLUME 11

Edited by

Stanley H. Appel, M.D.
Professor and Chairman
Department of Neurology
Baylor College of Medicine
Houston, Texas

Mosby Year Book

St. Louis Baltimore Boston Chicago London Philadelphia Sydney Toronto

Mosby
Year Book
Dedicated to Publishing Excellence

Sponsoring Editor: Amy L. Zekas
Associate Managing Editor, Manuscript Services: Denise Dungey
Assistant Director, Manuscript Services: Frances M. Perveiler
Production Coordinator: Max Perez
Proofroom Manager: Barbara M. Kelly

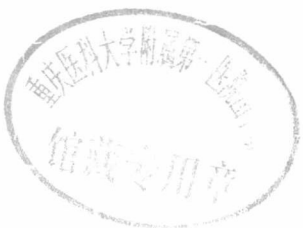
Mosby–Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146

Editorial Office:
Mosby–Year Book, Inc.
200 North LaSalle St.
Chicago, IL 60601

International Standard Serial Number: 0161-780X
International Standard Book Number: 0-8151-0234-8

Contributors

Mark J. Alberts, M.D.
Assistant Professor
Division of Neurology
Department of Medicine
Duke University School of Medicine
Duke University Medical Center
Durham, North Carolina



Stanley H. Appel, M.D.
Professor and Chairman
Department of Neurology
Baylor College of Medicine
Houston, Texas

Tetsuo Ashizawa, M.D.
Assistant Professor
Department of Neurology
Baylor College of Medicine
Houston, Texas

Sally J. Boyson, M.D.
Assistant Professor of Neurology and Pharmacology
Director, Movement Disorders Clinic
University of Colorado Health Sciences Center
Department of Neurology
Denver, Colorado

Salvatore DiMauro, M.D.
Department of Neurology
Columbia University College of Physicians and Surgeons
New York, New York

Carlos A. Garcia, M.D.
Professor
Department of Neurology
Department of Pathology
Louisiana State University School of Medicine in New Orleans
Louisiana State University Medical Center
New Orleans, Louisiana

J. Fielding Hejtmancik, M.D., Ph.D.
Laboratory of Mechanisms of Ocular Diseases
National Eye Institute
Bethesda, Maryland

Joseph Jankovic, M.D.
Professor
Department of Neurology
Director, Parkinson's Disease Center and Movement Disorders Clinic
Baylor College of Medicine
Houston, Texas

Maureen Leehey, M.D.
Fellow in Neuropharmacology and Movement Disorders
University of Colorado Health Sciences Center
Department of Neurology
Denver, Colorado

Jau-Shin Lou, M.D., Ph.D.
Resident
Department of Neurology
Baylor College of Medicine
Houston, Texas

Carlos T. Moraes, M.Sc.
Department of Genetics and Development
Columbia University College of Physicians and Surgeons
New York, New York

Gareth J. Parry, M.D.
Associate Professor
Department of Neurology
Louisiana State University School of Medicine in New Orleans
Louisiana State University Medical Center
New Orleans, Louisiana

Pragna I. Patel, Ph.D.
Assistant Professor
Institute for Molecular Genetics
Baylor College of Medicine
Houston, Texas

Donald W. Paty, M.D., F.R.C.P.C.
Professor and Head, Division of Neurology
The University of British Columbia
The Vancouver General Hospital
Vancouver, British Columbia, Canada

Vincent M. Riccardi, M.D.
Director
The Neurofibromatosis Institute, Inc.
Pasadena, California

Allen D. Roses, M.D.
Jefferson-Pilot Corporation Professor of Neurobiology and Neurology
Director, Joseph and Kathleen Bryan Alzheimer's Disease Research Center
Duke University School of Medicine
Duke University Medical Center
Durham, North Carolina

Eric A. Schon, Ph.D.
Departments of Genetics and Development and Neurology
Columbia University College of Physicians and Surgeons
New York, New York

Enrico Stefani, M.D., Ph.D.
Departments of Molecular Physiology and Biophysics
Baylor College of Medicine
Houston, Texas

Huda Zoghbi, M.D.
Assistant Professor
Department of Pediatrics
Baylor College of Medicine
Institute for Molecular Genetics and Neurology
Houston, Texas

Preface

Within the last year, tremendous progress has been made in defining the specific chromosomal assignments and the genetic abnormalities of selected neurologic diseases. These advances have been based upon the application of sophisticated molecular biological techniques and have provided significant insights into many previously unfathomable disorders.

In the chapters of the present volume, we present the latest advances in Charcot-Marie-Tooth disease, myotonic dystrophy, neurofibromatosis, the spinocerebellar degenerations, and Alzheimer's disease. The volume reveals scientific discoveries that will form the basis of future therapeutic approaches to the genetic aspects of these disorders. The genetic approaches to mitochondrial disease are also discussed.

We review the important role of MRI not only in diagnosis of MS, but also in monitoring disease progression. The latest in biochemical studies of Parkinson's disease and in clinical approaches to tremor are also discussed. We conclude with a review of ALS. Our continuing goal is to provide the clinician with a better understanding of the basic aspects of neurologic disease and the potential these advances hold for improving the quality of patient care.

Stanley H. Appel, M.D.

Contents

CHAPTER 1

Charcot-Marie-Tooth Polyneuropathy Syndrome: Clinical, Electrophysiologic, and Genetic Aspects*

James R. Lupski, M.D., Ph.D.

Assistant Professor, Institute for Molecular Genetics, and Department of Pediatrics, Baylor College of Medicine, Houston, Texas

Carlos A. Garcia, M.D.

Professor, Department of Neurology, Department of Pathology, Louisiana State University School of Medicine in New Orleans, Louisiana State University Medical Center, New Orleans, Louisiana

Gareth J. Parry, M.D.

Associate Professor, Department of Neurology, Louisiana State University School of Medicine in New Orleans, Louisiana State University Medical Center, New Orleans, Louisiana

Pragna I. Patel, Ph.D.

Assistant Professor, Institute for Molecular Genetics, Baylor College of Medicine, Houston, Texas

*This work was supported by a Muscular Dystrophy Association Task Force on Genetics grant, a Baylor Mental Retardation Research Center grant, a Texas Higher Education Advanced Technology Program Grant, and National Institutes of Health (N.I.N.C.D.S.) grant R01 NS-27042-01 to J.R.L. and P.I.P.

The hereditary motor and sensory neuropathies (HMSN) are a heterogeneous group of genetic disorders of the peripheral nerves with both motor and sensory nerve involvement. Charcot-Marie-Tooth syndrome (CMT), the most common inherited peripheral neuropathy with a prevalence rate of 40/100,000,[1] is one type of HMSN. CMT is a clinically and genetically heterogeneous disorder of the peripheral nerves. It is characterized by progressive atrophy of the distal muscles, predominantly those innervated by the peroneal nerve. The syndrome produces variable progressive weakness and atrophy of intrinsic muscles of the feet and hands, leading to an associated pes cavus deformity and claw hand.[2, 3] Autosomal dominant, recessive, and X-linked forms of CMT have been reported, with the autosomal dominant form being the most prevalent.[4]

Classification of the hereditary peripheral neuropathies continues to be a subject of controversy. Differences in patterns of inheritance, variation in the progression of the syndrome, and variable neurophysiologic and pathologic features have been demonstrated between kinships with CMT. These differences have been used to classify the syndrome. The molecular genetic basis of the hereditary neuropathies is still unknown. Genetic linkage analysis can provide an objective method to separate the various subtypes of hereditary neuropathy and, by identifying the disease gene(s) involved, will greatly increase our understanding of the pathophysiology of these disorders. Availability of linked DNA markers should also permit accurate prenatal and presymptomatic diagnosis of CMT and, it is hoped, will open avenues for therapy.

In this chapter, we will review the clinical, pathologic, electrophysiologic, and genetic features of the autosomal dominant hypertrophic form of Charcot-Marie-Tooth disease, CMT1. We will address symptomatic treatment of the disease and discuss the genetic aspects with regard to Mendelian patterns of inheritance, penetrance, and genetic heterogeneity. Recent linkage studies will be described that demonstrate where the CMT gene(s) map within the human genome.

HISTORICAL PERSPECTIVE

In 1886, Charcot and Marie[2] described five cases of an unusual form of a progressive muscular atrophy. They summarized the patients' findings as: (1) slow progression of symptoms with an initial involvement of the feet and legs followed several years later by involvement of the hands; (2) relative sparing of proximal limb muscles and preservation of muscles of the trunk, scapulae, and face; (3) fibrillary contractions of affected muscles; (4) vasomotor abnormalities in the segment of affected limbs; (5) lack of joint contractures; (6) normal sensation in most cases; (7) frequent cramps; (8) reaction of degeneration within affected muscles; and (9) frequent onset in childhood and occurrence not only in siblings, but also in succeeding generations.

That same year, Tooth[3] independently described the peroneal type of progres-

sive muscular atrophy, with almost identical clinical features as those described by Charcot and Marie, but placed a greater emphasis on the inheritance factor, the early age of onset, and the predominant peroneal muscle involvement. Tooth postulated correctly that the disorder was due to a peripheral nerve lesion, contrary to a myelopathy as postulated by Charcot and Marie. Since that time, other less consistent clinical features have been added, different modes of inheritance have been described, and new technologies have become available and used to study this disorder. The latter include electrophysiologic methods to measure the conduction of nerves, histometry to quantitate nerve fibers in biopsy material, electron microscopy to examine the ultrastructure of involved nerves, and linkage analysis to map the genes involved. While nerve conduction velocity (NCV) studies have enabled more accurate diagnosis and linkage analysis is facilitating localization of the genes involved, an understanding of the basic pathophysiology in this group of disorders is still lacking.

Important historical events will be highlighted, but the reader is referred to exhaustive reviews previously described on the subject.[5–7] Gombault and Mallet[8] were the first to recognize a hypertrophic form of neuropathy in a patient with tabes. Dejerine and Sottas,[9] and later Hoffman,[10] described cases of peroneal muscular atrophy associated with hypertrophic nerves. This finding, as we now know, is a nonspecific feature due to segmental demyelination and remyelination seen in a variety of acquired and inherited disorders. Roussy and Levy[11] described pes cavus, loss of tendon reflexes, ataxia of gait and tremor in the hands, features suggestive of forme fruste of Friedreich ataxia or a clinical intermediate state between Friedreich ataxia and peroneal muscular atrophy.

The electrophysiologic studies applied in this disorder by Henriksen[12] and Gilliat and Thomas[13] segregated two groups of patients, one with severe slowing of motor NCV and the other with normal nerve conduction. Dyck and Lambert,[14, 15] in a prospective study, correlated the electrophysiologic features with the nerve biopsy findings and inheritance patterns and further subdivided these two groups. One group with slow nerve conduction velocities was subdivided into those with a dominantly inherited and those with a recessively inherited hypertrophic neuropathy. The second group, with normal or borderline nerve conduction velocities and without hypertrophy of the nerves, called neuronal type, was subdivided into five different subgroups showing different modes of inheritance, some of them associated with spastic paraplegia or spinocerebellar degenerations. Later, Brust et al.[16] and Davis et al.,[17] based on clinical features, genetic patterns, and nerve biopsy findings, but mainly using electrophysiologic studies, described an intermediate group of patients (NCV, 25 to 45 m/sec) without hypertrophy of the nerves and with more rapid progression. Brust et al.[16] concluded that peroneal muscular atrophy probably includes a substantial number of different diseases sharing clinical and electrodiagnostic features.

The classification of this syndrome has been confusing because of the variety of criteria used by different reviewers on the subject.[18] Most of the classifications are based on inheritance patterns, nerve conduction velocity, histopathologic charac-

teristics of nerves, and populations of neurons affected. However, Dyck's classification[14, 15, 19] of hereditary motor and sensory neuropathies into HMSN type I, or hypertrophic form, and HMSN type II, or neuronal form, are the most frequently used terms to designate Charcot-Marie-Tooth disease, a traditional term too strongly established in the neurology literature to be abandoned. Genetic linkage analysis requires clinically homogeneous groups of patients for analysis and large pedigrees to obtain more informative results. CMT1 is the most common form of hereditary neuropathy and is quite frequent in the French-Acadian population in Louisiana. Our review will concentrate on this type of peroneal muscular atrophy.

CLINICAL FEATURES OF CMT1

The disease has an insidious onset over several years and a slowly progressive course to the point that some patients are unaware of their disease. The symptoms of CMT may appear at the end of the first decade or early in the second decade and may be preceded by slightly delayed motor milestones. Patients with the disease diagnosed in the second or third decade may relate to the physician that they were clumsy and never participated in sports at school. The penetrance of the phenotype may be low in the first decade but increases with age. The chance of a patient showing first symptoms after the third decade decreases markedly with increasing age. Patients consult a physician because of abnormalities of gait, foot deformities, or loss of balance. Children with CMT often walk on their toes. Older patients may complain of difficulty finding shoes because of the small high arched feet (pes cavus). Some older patients may have had surgical procedures to correct foot deformities in childhood, preceding the diagnosis of the disease.

Another frequent complaint is tripping over objects on the floor, secondary to a dropped foot that is caught by the object on the swing-through phase of the gait. Ankle sprains are also frequent and are due to weakness of dorsiflexion of the foot produced by weakness and atrophy of the peroneal and anterior tibial muscles. Pes cavus is frequently variable, is usually not seen early in the disease, and seems to progress with age. However, it may be seen early in the first decade or may not be a feature seen in elderly patients. Corns over the dorsal surface of the toes and calluses over the lateral surface of the feet are frequently painful and may develop with a pes cavus deformity. Hammer toes are seen in advanced cases but rarely need surgical correction. Foot ulcers are rare. Atrophy of the legs, giving the appearance of stork legs or champagne glass deformity, may be a prominent feature in some patients, but a thicker layer of subcutaneous fat, especially in women, may mask the leg muscle atrophy. Cramps are a frequent complaint and are worse after long walks.

Weakness of the intrinsic hand muscles usually occurs late in the course of the disease, but may not be related to the degree of leg weakness or atrophy and is not

related to the age of the patients. The most frequent complaint concerning hand involvement is difficulty using zippers, buttoning, unbuttoning, and manipulating small objects when using fine finger movements. Opening screw cap tops on jars and turning doorknobs can also be difficult. The thumb frequently rotates due to weakness of the muscle of the thenar eminence, producing the simian or ape-like hand. The fingers are semiflexed at all joints and there is interdigital wasting, giving a guttering appearance on the dorsal surface of the hand due to atrophy of the interossei. All these previously described features give the appearance of claw hands. Hand weakness progresses with the duration of the symptoms.

Stretch reflexes disappear early in the gastrocnemius and soleus muscles (absent Achilles) and later on affect the patellar and the upper limb reflexes. The plantar reflex is frequently flexor or absent but may occasionally be extensor. Enlargement of the greater auricular nerve can be seen and palpated in the neck in some patients. This is easier to detect in slender individuals and is more frequently found in men. A thickened ulnar nerve may be palpated above the elbow, superficial radial nerve at the wrist, the peroneal nerve behind the head of the fibula and over the dorsum of the foot. Sensory involvement is rare in CMT1, but decreased pain to pinpricking in a stocking distribution may be seen in some patients. Vibratory sense in the feet is the most frequently affected modality. Poor tolerance to cold weather is a frequent complaint, as is excessive coolness in the legs, which is often associated with trophic changes in the legs such as loss of hair, edema, and discoloration of the skin of the legs. A decrease of skin and muscle temperature of 5° C to 10° C has been recorded. Loss of muscle mass may explain the decreased temperature. Scoliosis can occur, but kyphosis is rare.

CLINICAL SPECTRUM FOR ALL FORMS OF CMT

In an effort to further address the clinical spectrum observed in CMT, we have attempted to analyze a very large patient cohort with a retrospective analysis of questionnaires completed by patients with CMT. The patients were ascertained through two organizational support groups for patients with CMT: CMT International based in Canada, and CMT Association based in the United States. Slightly greater than 30% (n = 356) of the CMT International patients responded while less than 10% (n = 110) of those registered with CMT Association responded. The completed questionnaires were entered into a computer data base (dBase III Plus). This type of study has several limitations, such as ascertainment bias, heterogeneity of the patient population, and lack of uniformity in individual observers. Nevertheless, the large size of the sample and congruity between group responses, CMT International vs. CMT Association, can be informative for the clinician in that it represents a clinical spectrum of the disease phenotype for all forms of CMT.

We tabulated the patient responses to questions concerning the first sign or

symptom that brought the patients with CMT to the physician, and signs and symptoms since time of diagnosis (Fig 1). As can be seen in Figure 1, loss of balance, gait disturbance, muscle weakness, and foot deformity were the most common presenting complaints. As a function of time in disease progression, there were an increased number of symptoms experienced by patients with CMT. There is remarkable congruity between the two groups of patients ascertained through two different support groups.

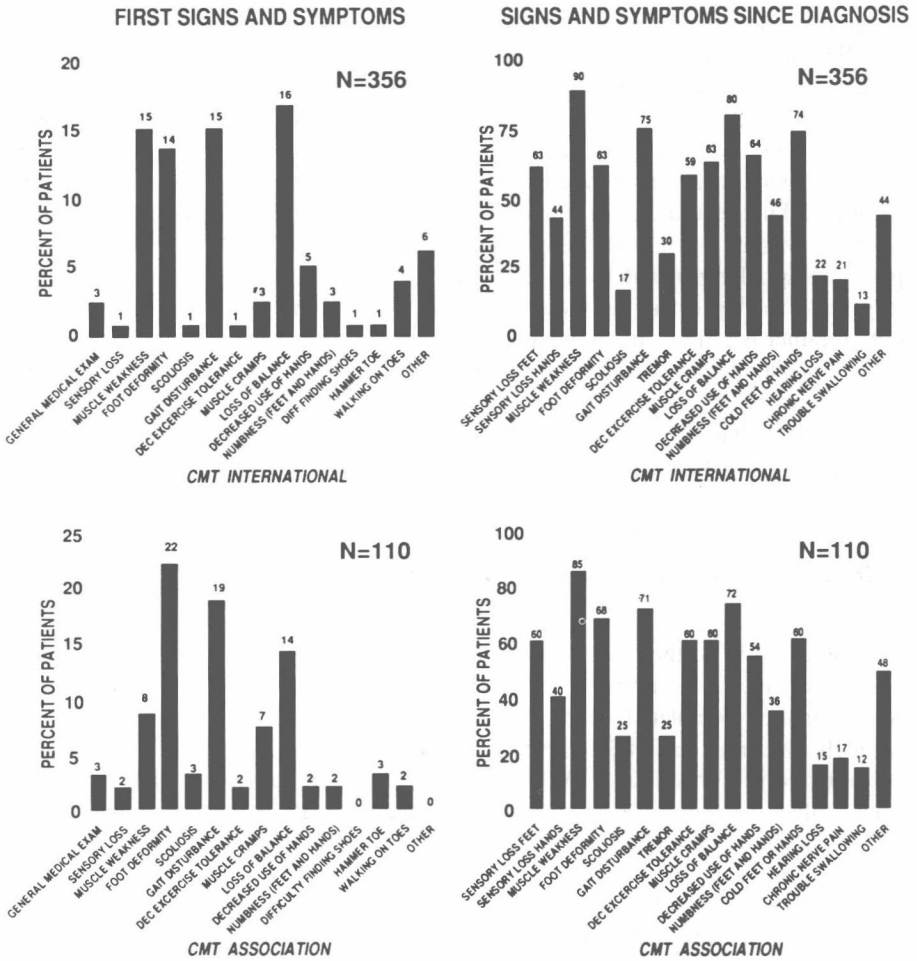


FIG 1.

Clinical spectrum for all forms of CMT. The data in this figure represent the compilation of information from questionnaires of 466 patients with CMT ascertained through two CMT support groups: CMT International and CMT Association. It represents a compilation of all forms of CMT.

PATHOLOGY OF CMT1

In the few autopsies that have been performed, the findings are confined to the peripheral nerves and the spinal cord. Gliosis and demyelination of the posterior columns, greater in the fasciculus gracilis of the cervical cord, are prominent. In biopsy specimens of the peripheral nerves, there is a moderate increase in epineurium and perineurium, and there is a variable decrease in the number of myelinated fibers depending on the severity of the disease. Onion bulb formation occurs around myelinated and demyelinated internodes and consists of circumferentially directed spindle cells and their processes. There is a decrease in myelinated fiber density with only a small amount of non-myelinated fiber loss. Teased fiber preparations have shown segmental demyelination and bleb formation in myelin.[19] Ultrastructural studies have shown that onion bulbs consist of circumferentially directed Schwann cells and their processes, separated by collagen fibers.

ELECTROPHYSIOLOGY OF CMT

CMT1 has considerable variability of its phenotypic expression with conventional clinical criteria. However, all patients have severely slowed motor nerve conduction velocity (MCV) and, as a result, the MCV is almost universally used to define CMT1. Asymptomatic patients with CMT1 also have slowed MCV of similar degree, although it is rare that there are no other signs of the disease on careful neurologic examination. Once the diagnosis is established or suspected in a patient, family members at risk need to have a neurologic evaluation and have NCV tests to confirm or discard the diagnosis. This is particularly important for genetic counseling of risk recurrence in subsequent progeny. In some individuals, NCV studies may detect inheritance of the CMT gene decades before clinical manifestations.

Patients with the neuronal form of Charcot-Marie-Tooth syndrome (CMT2) may also have mild slowing of conduction velocity, proportional to the degree of axonal loss. In the study of CMT1 by Dyck and Lambert,[14, 15] the mean median MCV was less than 25 m/sec, but in a few patients it was as high as 42 m/sec. This led them to suggest an upper limit of 45 m/sec for median MCV for patients with CMT1. Davis et al.[17] studied 116 individuals with CMT inherited as an autosomal dominant disease and divided them into two groups based on median MCV. Their first group, in whom MCV was less than 25 m/sec, clearly correspond to CMT1. However, the second group, in whom the median MCV was 25 to 45 m/sec, is heterogeneous and probably includes patients with CMT2. Harding and Thomas[20] studied 180 patients with CMT and also found that they could be divided into two groups based on a median MCV of 38 m/sec. Individuals with median MCV less than 38 m/sec correspond to CMT1. With this dividing line, only three individuals were incorrectly classified; that is, they belonged to pedi-