



Charcot-Marie-Tooth
Association

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Excerpt from Charcot-Marie-Tooth Hereditary Neuropathy Overview

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EVALUATION STRATEGY

Establishing the specific cause of CMT hereditary neuropathy for a given patient involves a medical history, physical examination, neurologic examination, and nerve conduction velocity (NCV) and EMG testing, as well as a detailed family history and the use of DNA-based testing, when available.

CLINICAL EVALUATION

In individuals who have no family history of neuropathy, the first step is to exclude potential acquired causes of neuropathy by standard neurologic evaluation. In CMT1, the most common variety, NCVs are very slow and peripheral nerves may be palpably enlarged. This is not true of CMT2 or CMTX.

FAMILY HISTORY

A three-generation family history with attention to other relatives with neurologic signs and symptoms should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or review of their medical records, including the results of molecular genetic testing and EMG and NCV studies. Patients with CMT may have a negative family history for many genetic reasons, including mild subclinical expression in other family members, autosomal recessive inheritance, and a new mutation for a dominant gene. About one third of patients with identifiable mutations causing the CMT1 hereditary neuropathy phenotype have new (*de novo*) mutations, and thus present as “sporadic” cases.

MOLECULAR GENETIC TESTING

Molecular genetic testing is clinically available for CMT1A, CMT1B, CMT1D, CMT2E, CMT4E and CMT4F, and CMTX. Because molecular genetic testing is available for mutations in several different genes associated with remarkable phenotypic overlap, the following strategy may provide the most efficient and cost-effective approach to testing. However, it should be noted that in many clinical laboratories, the testing for mutations involving hereditary neuropathy

genes is done as a grouped panel, which may be less expensive than sequential testing of each individual gene (if more than two or three genes are analyzed).

TESTING STRATEGIES FOR PATIENTS WITH CMT

Positive family history.

In families with at least two-generation involvement, known male-to-male transmission, and slow NCVs, the CMT1A (*PMP22* dup) test should be obtained first, and then, if normal, followed by the CMT1B (*MPZ*) test.

In families with at least two-generation involvement and slow NCVs, but without male-to-male transmission, CMT1A, CMT1B, and CMTX DNA tests should be done sequentially.

In families with probable X-linked inheritance of the CMT phenotype, molecular genetic testing of the *GJB1* gene (encoding the protein connexin 32) for CMTX is appropriate in order to confirm the diagnosis.

In patients with the CMT2 phenotype, molecular genetic testing of *MPZ* and *GJB1* is appropriate, given that the CMT2 phenotype can be seen in patients with these mutations.

Negative family history.

CMT1A, CMT1B, and CMTX DNA tests should all be performed on males and females who have no family history of neuropathy, because new duplications of the 17p11 region often occur, giving rise to CMT1A, and because female carriers of a *GJB1* mutation causing CMTX may be asymptomatic.

Testing for rare causes of CMT.

Mutations in *EGR2* (CMT1D, CMT4E), *NFL* (CMT2E), and *PDX* (CMT4F), and point mutations in *PMP-22* are rare causes of the CMT phenotype. DNA-based tests are available to identify mutations in these genes. When tests for the more common forms of CMT are negative, the physician must decide if searching for the other, much more rare types of CMT justifies the cost. Prognosis and genetic counseling are frequently mentioned reasons for such extensive testing.

(continued)

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NEGATIVE MOLECULAR GENETIC TESTING RESULTS

Negative DNA testing results do not rule out a diagnosis of CMT since those normal test results are compatible with undetected mutations in other genes causing hereditary neuropathy.

GENETIC COUNSELING ISSUES

Considerations in families with an apparent *de novo* (new) mutation. When the parents of a child with an autosomal or X-linked dominant condition are unaffected, possible non-medical explanations include alternate paternity or undisclosed adoption.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy. One study found that many patients with CMT give themselves high disability ratings and 36% would choose not to have children.

Testing of asymptomatic adult relatives who are at risk of developing CMT is possible after direct DNA testing has identified the specific gene mutation in an affected relative. Such testing should be performed in the context of formal genetic counseling.

Testing of asymptomatic at-risk children is discouraged. (See also the National Society of Genetic Counselors resolution on genetic testing of children).

DNA banking. DNA banking is the storage of DNA that has been extracted from white blood cells for possible future use. Because it is likely that testing methodologies and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA. DNA banking is particularly important in situations in which molecular genetic testing is available on a research basis only or the sensitivity of currently available testing is less than 100%.

PRENATAL TESTING

Prenatal diagnosis for pregnancies at increased risk for CMT1A, CMT1B, CMT2E, or CMTX is possible. DNA extracted from cells obtained by chorionic villus sampling (CVS) at about 10 to 12 weeks' gestation* or amniocentesis at 16 to 18 weeks' gestation is analyzed. The disease-causing allele of an affected family member

must be identified before prenatal testing can be performed.

Requests for prenatal diagnosis of (typically) adult-onset diseases are uncommon. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

MANAGEMENT

No treatment for CMT that reverses or slows the natural disease process exists. Treatment is symptomatic and patients are often evaluated and managed by a multi-disciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Daily heel cord stretching exercises to prevent Achilles' tendon shortening are desirable. Special shoes, including those with good ankle support, may be needed. Patients often require ankle/foot orthoses (AFOs) to correct foot drop and aid walking. Orthopedic surgery may be required to correct severe pes cavus deformity. Some patients require forearm crutches or canes for gait stability, but fewer than 5% of patients need wheelchairs. Obesity is to be avoided because it makes walking more difficult. Exercise is encouraged within the patient's capability and many individuals remain physically active. Important career and employment implications exist because of the persistent weakness of hands and/or feet.

Drugs and medications such as vincristine, paclitaxel, cisplatin, isoniazid, and nitrofurantoin that are known to cause nerve damage should be avoided.

The cause of any pain should be identified as accurately as possible. Musculoskeletal pain may respond to acetaminophen or nonsteroidal anti-inflammatory agents. Neuropathic pain may respond to tricyclic antidepressants or drugs such as carbamazepine or gabapentin. Initial, but not long-term improvement has been shown in a few patients with CMT1 and sudden deterioration who were treated with steroids (prednisone). ★

* Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.