Hereditary Neuropathy With Liability to Pressure Palsies Is Not a Major Cause of Idiopathic Carpal Tunnel Syndrome

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Background: Carpal tunnel syndrome is a debilitating neuropathy affecting millions of individuals. Although there are published reports of familial associations of carpal tunnel syndrome, the molecular mechanisms are unknown.

Objective: To determine the prevalence and potential role of the chromosome 17 microdeletion associated with hereditary neuropathy with liability to pressure palsies in patients diagnosed as having carpal tunnel syndrome.

Design: Prospective study.

Patients and Methods: Since hereditary neuropathy with liability to pressure palsies may present as carpal tunnel syndrome, we evaluated 50 patients with idiopathic carpal tunnel syndrome for hereditary neuropathy with liability to pressure palsies.

Results: No hereditary neuropathy with liability to pressure palsies deletions were detected.

Conclusion: Molecular genetic testing for hereditary neuropathy with liability to pressure palsies in patients with idiopathic carpal tunnel syndrome is of limited value.

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Recent genetic and molecular studies have suggested conditions that could either mimic the symptoms of carpal tunnel syndrome (CTS) or predispose one to develop CTS. A peripheral neuropathy known as hereditary neuropathy with liability to pressure palsies (HNPP) is one such condition. Hereditary neuropathy with liability to pressure palsies most frequently manifests initially as a peripheral nerve entrapment, including median nerve compression at the carpal canal with delayed nerve conduction velocities. Potocki et al described a family with dominantly inherited CTS that was associated with the chromosome deletion in 17p12 that causes HNPP. Hereditary neuropathy with liability to pressure palsies is believed to be underdiagnosed because it typically has episodic and transient clinical manifestations. The association between idiopathic CTS and undiagnosed HNPP has been hypothesized but untested.

We performed a prospective study to estimate the prevalence of HNPP in the population of patients with CTS presenting for surgery. Our specific hypothesis addressed the prevalence and potential role of the chromosome 17 microdeletion associated with HNPP in patients diagnosed as having CTS.

RESULTS

Thirty female and 20 male patients diagnosed as having idiopathic CTS were enrolled in this study. Of these patients, 20 had CTS diagnosed in a first-degree relative and 2 patients reported a first-degree relative with other peripheral neuropathy symptoms. The patients’ ages ranged from 18 to 76 years (mean age, 50.5 years). No PMP22 deletions were detected. This predicts that the upper limit of the 95% confidence interval for the prevalence of PMP22 deletions as a cause of idiopathic CTS is around 6%.

COMMENT

Predictive or susceptibility testing for CTS has the potential to save millions of individuals the pain and suffering of this common debilitating mononeuropathy. It also has the potential for discriminatory use by insurance agencies and employers. To our knowledge, to date, there are no published data to establish the validity of susceptibility testing for CTS.

Carpal tunnel syndrome has a reported population incidence of less than
PATIENTS, MATERIALS, AND METHODS

Fifty unrelated patients scheduled for carpal tunnel release were studied. Diagnosis of CTS was made by both clinical evaluation and electrodiagnostic study. Only individuals with idiopathic CTS sufficiently evaluated and severe enough to need surgical release were included. Exclusion criteria consisted of those with anatomical changes decreasing the available volume within the carpal tunnel (eg, fractures or congenital anomalies), diagnoses that may result in the increased size of the carpal canal contents (including amyloidosis, rheumatoid arthritis, or edema), those diagnoses associated with soft tissue impingement (ie, lipomas, hematomas, or urate crystal deposition), and other causes of peripheral mononeuropathies such as diabetes mellitus. There were no enrollment restrictions based on race, age, or sex. After informed consent was obtained, a blood sample was transported in a heparin sodium–containing vacuum container (Vacutainer) for fluorescence in situ hybridization testing on interphase cells with a set of cosmids containing the PMP22 gene to detect the deletion associated with HNPP.5

1% to 3.8%.7-9 These cases require an estimated 400000 to 500000 carpal tunnel releases in the United States at an annual cost of more than $2 billion.10 This recognized public health problem constitutes 3% of all Workmen’s Compensation Insurance claims and has prompted consideration of legislative limitations on tasks of repetitive motion or vibration exposure in the workplace. These limitations would potentially be applied to workers uniformly because of a lack of recognized criteria for identification of individuals at increased risk.11-13

Carpal tunnel syndrome is routinely thought to be idiopathic and sporadic. However, there are clearly susceptibility differences as evidenced by 2 individuals doing identical tasks where one develops CTS and the other does not. Often, when it is considered to be inherited, it is the manifestation of a systemic illness.14 In the past, epidemiological studies generally overlooked the possibility of familial occurrence.15 There are, however, multiple literature reports of familial CTS displaying a dominant pattern of inheritance.16-21 One group reported idiopathic median nerve entrapment “inheritance” as familial CTS and suggested it to be a genetically distinct disorder.17 Multiple claims of pedigrees of affected first-degree relatives in numerous generations of families have been reported.22-25

With current advances in genetic medicine, a much better understanding of the molecular and cytogenetic causes of many disorders is known. Recent cytogenetic and molecular studies have directly linked abnormalities of the proximal short arm of chromosome 17 to the dominantly inherited peripheral neuropathies HNPP and Charcot-Marie-Tooth disease type 1A (CMT1A).26,27 Charcot-Marie-Tooth disease is the most common inherited peripheral neuropathy, estimated to occur at an incidence of 1 per 2500 persons.28 The disease-causing mechanism in most patients with CMT1A and HNPP has been identified as a 1.5-megabase DNA duplication and its reciprocal 1.5-megabase deletion, respectively.29,31 Although the true incidence of HNPP is unknown, the frequency of new mutations in HNPP is expected to be similar to CMT1A given the shared mutational mechanism.27 The submicroscopic duplications or deletions can be assayed by several techniques5,30,32-35; 2-color fluorescence in situ hybridization analysis of interphase nuclei, however, is very specific, sensitive, relatively inexpensive, and simple to interpret.

Hereditary neuropathy with liability to pressure palsies is also known as “tomaculous neuropathy." It manifests transient episodes of numbness, muscular weakness, and atrophy after minor compression or trauma to peripheral nerves in addition to symptoms normally associated with entrapment neuropathies. Affected patients and asymptomatic carriers have mildly slowed nerve conduction velocities with conduction block. Segmental demyelination and remyelination with tomacula or sausage-like focal thickening of the myelin sheaths are observed on peripheral nerve biopsy specimens.20 Carpal tunnel syndrome may be the first or only manifestation of HNPP.4,50 Potocki et al4 described a patient who had a duplication of a region of 17p11.2 and a deletion of 17p12 encompassing PMP22 on the homologous chromosome. Further molecular analyses revealed the duplication to be a de novo event, but the deletion containing PMP22 deletion was familial. Three generations of family members with PMP22 deletions had dominant CTS, documented by electrodiagnostic testing prior to molecular analysis.9 The identification of the chromosome 17p12 deletion in this family was incidental to the evaluation of developmental delay in a family member.

The prevalence of HNPP in idiopathic CTS is unknown. With the estimated incidences of CTS (1%-3.8%)7-9 and HNPP (0.04%),20 HNPP could be responsible for 1% to 4% of CTS. The results of this clinical survey of 50 patients, however, found that no patients with idiopathic CTS had the 1.5-megabase HNPP-associated deletion.

Making the diagnosis of HNPP as the cause of the CTS in these patients could have significant health consequences for individuals and their family members by avoiding unnecessary surgical release of the carpal canal and promoting preventive measures to avoid nerve pressure or trauma in areas such as the fibular neck in the legs, the elbows, and at the wrists. Hereditary neuropathy with liability to pressure palsies should be suspected and testing considered in all patients with a history of multiple transient mononeuropathies or any family showing dominantly inherited pressure palsies as well as those in which multiple members are affected with CTS or other entrapment neuropathies. The contribution of HNPP to isolated CTS is likely to be relatively small, thus continued screening for PMP22 deletion in patients with idiopathic CTS in the absence of any other clinical signs of HNPP is of limited clinical value.
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