When Sporadic Disease Is Not Sporadic

The Potential for Genetic Etiology

Jill S. Goldman, MS, MPhil, CGC; Bruce L. Miller, MD; Jiri Safar, MD; Sunita de Tourreil, MSc; Jennifer L. Martindale, BS, BA; Stanley B. Prusiner, MD; Michael D. Geschwind, MD, PhD

Background: Approximately 2% of Alzheimer disease cases and 10% to 15% of prion disease cases are due to mutations in autosomal dominant genes. Mutations have been found in patients without family histories of neurological disease.

Objectives: To emphasize the need for consideration of a genetic etiology of prion disease and early-onset Alzheimer disease, regardless of the absence of a significant family history, as well as the need for pretest genetic counseling of all patients or their families.

Design: Three case reports.

Patients and Results: Patient 1, a 53-year-old man with possible Creutzfeldt-Jakob disease, was enrolled in a research study that included sequencing of the prion protein gene. Although there was no family history of neurological disease, an E200K mutation was found. This unexpected result caused the family significant distress.

Patient 2, a 55-year-old woman with biopsy-proven Creutzfeldt-Jakob disease, participated in a prion disease research study. Her family was counseled about the possibility of hereditary Creutzfeldt-Jakob disease, despite the lack of family history. After assessing the ramifications, the family decided not to learn about the patient's genetic test results. Patient 3 was a 54-year-old man with a 6-year history of memory loss. A diagnosis of probable Alzheimer disease was given, and the patient and his family were counseled on the availability of presenilin 1 testing, although there was no known family history of dementia. The family agreed to testing, and a presenilin 1 mutation was identified.

Conclusions: Certain neurodegenerative diseases may have a genetic etiology, despite the lack of a positive family history. Revealing a newly discovered hereditary cause of Creutzfeldt-Jakob disease or Alzheimer disease can have a profound effect on families. Pretest counseling on genetic issues is essential to better prepare families and to allow them to make an informed choice about learning genetic test results.

Arch Neurol. 2004;61:213-216

MOST ADULT-ONSET neurodegenerative disorders, such as Creutzfeldt-Jakob disease (CJD) and Alzheimer disease (AD), occur sporadically. However, 10% to 15% of CJD cases comprise autosomal dominant disorders associated with mutations in the prion protein gene, PRNP. More than 22 PRNP mutations have been identified, most of which are fully penetrant. Approximately 2% of AD cases are inherited as autosomal dominant diseases due to mutations in the presenilin 1 (PS1), PS2, or amyloid precursor protein genes. Although most patients with hereditary AD have known family histories of dementia and many patients with hereditary CJD have significant pedigrees, mutations in PS1 and PRNP have been found in the absence of a positive family history. The European and Allied Countries Collaborative Study Group of CJD reported that approximately 15% of patients with CJD had PRNP mutations, yet only 40% of these patients had positive family histories for prion disease. Explanations for such findings include prior misdiagnoses, incomplete or lost family history, false paternity, incomplete or delayed penetrance, and de novo mutations.

Although a genetic etiology for AD or CJD is unlikely without a family history of a neurological disorder, a physician may wish to order DNA testing to rule out this possibility or, conversely, to confirm a diagnosis, or to help the patient's family understand the cause of disease and assess potential inheritance risks. Because genetic prion disease involves a single gene, a negative PRNP sequencing result would eliminate a genetic etiology. Because several genes have been implicated in early-
onset familial AD, genetic testing for AD is less definitive, as the only clinically available test in the United States for autosomal dominant forms of AD is PS1, accounting for about 50% of cases. However, even when only a slight chance of finding a mutation exists, genetic testing should not be initiated without thorough education and counseling for the patient or the patient’s family. The following 3 case histories demonstrate the importance of genetic testing in CJD and AD, as well as the necessity of pretest counseling for the patient or his or her family.

REPORT OF CASES

CASE 1

Patient 1, age 53 years, was referred to a CJD research study at our institution because of suspected sporadic CJD. Consent for participation in the study, which included drawing blood for PRNP sequencing, was obtained from the patient’s durable power of attorney for health care decision making, his 23-year-old daughter. The informed consent for this project explained that, if the family wanted to learn genetic test results, they could choose to do so, but that these were research, not clinical results. They were told that if they wished to have definitive results, the DNA could be sent to a Clinical Laboratories Improvement Act–approved laboratory. Soon afterward, the patient died, and subsequently an E200K mutation was identified in the PRNP gene. His daughter returned to review her father’s neuropathologic findings and receive genetic test results. Because of the lack of positive family history of any neurological condition, she was stunned to learn that her father’s disease was genetic and that she was at 50% risk for carrying the mutation. The genetics of the disease and her presymptomatic testing were discussed. She was told that if she wished to be tested for the same PRNP mutation, a Huntington disease (HD) protocol would be followed.8 The HD protocol includes 2 or more counseling sessions and psychological and baseline neurological evaluation. Several weeks later, she decided to initiate the testing protocol.

CASE 2

Patient 2, age 55 years, had a 4-month course of rapidly progressive dementia and was diagnosed as having CJD by pathological confirmation of prion protein in a brain biopsy specimen. Because the patient had an unremarkable family history, the local physician sent blood for PRNP sequencing without genetic counseling with the patient or family. The patient was then referred to our institution for a CJD research study, which includes PRNP sequencing. The family met with a genetic counselor to discuss whether they wished to be informed of the genetic test results. At that time, the patient’s son and daughter-in-law were expecting their first child. The family thought that there would be tremendous guilt if they learned that the condition was genetic. Despite the small probability of a positive test result, the patient and family decided that they did not want to know the genetic test results. They were advised to inform their local physician of this decision so that the results of the prior genetic test would not be revealed to them.

CASE 3

Patient 3, age 54 years, was brought to our institution by his wife, daughter (age 30), and son (age 29). He had a 6-year history of slowly progressive cognitive decline. A clinical evaluation, including neurological examination, neuropsychological testing, routine laboratory tests, and magnetic resonance imaging scanning, led to a diagnosis of probable AD. Despite an unremarkable family history, but because of his early age at onset, PS1 testing was considered. The benefits, limitations, risks of testing, and the implications of disclosing these results to family members were discussed. The daughter decided that she would not want to know if she had the mutation, but did not object to her father being tested. The son wanted to know his personal gene status if a PS1 mutation was found. The family decided to proceed with the patient’s testing.

The patient tested positive for a known causal PS1 mutation. The family returned for the results. The patient and his wife were upset by the possibility of their children inheriting the mutation and remarked that they would prefer that their children not be tested. When meeting individually for genetic counseling, the daughter again stated that, because she had already started a family, she did not want to know her own gene status, nor did she want to know her brother’s. However, the son reiterated his desire for presymptomatic testing. Although he had begun the HD protocol for PS1 presymptomatic testing, he terminated the process before actual testing because of family dynamics.

COMMENT

Because 2% of AD cases and 10% to 15% of human prion disease cases are due to autosomal dominant mutations, it is important for physicians to consider genetic etiologies for these neurodegenerative conditions. As demonstrated by the case histories described herein, to learn that an incurable genetic disorder exists in one’s family can have a damaging effect on the individual’s psychological status and on family dynamics. When other family members have had similar symptoms, families usually, but not always, consider and are somewhat prepared for the possibility of a hereditary condition. However, when previous family history is absent, a positive diagnostic DNA test result can create additional distress and family strife.

A comparison of cases 1 and 2 illustrates how pretest genetic counseling allows families to prepare for and make informed decisions about the results of their genetic testing. The family in case 2, on realizing the potential psychological consequences of obtaining a positive genetic test result, chose not to be informed of the results. If the patient’s daughter in case 1 had better understood the possibility of a positive PRNP test result and the ramifications for herself, she might have postponed learning the results until after she had dealt with her father’s death. Case 3 demonstrates how a positive genetic test result can disrupt a family, even with genetic
counseling and preparation. Nevertheless, genetic counseling and the HD protocol provide a framework that allows for informed decision making. The HD protocol has been extensively studied and has been shown to reduce the risk of adverse effects of genetic testing.9,10 Physicians may choose to modify this protocol because of lack of resources or cost to patients.

Genetic testing can be helpful in diagnosis when several diseases are in the differential and can eliminate the need for more extensive evaluation and testing. The results of the European and Allied Countries Collaborative Study Group of CJD1 on the frequency of PRNP mutations, particularly the high percentage of cases (60%) without a family history, should raise concerns for all physicians considering DNA testing for their patients with dementia and potential CJD.1 Certain forms of familial CJD may present like sporadic CJD. However, genetic forms of human prion disease, including Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, and certain forms of familial CJD, can present as more slowly progressive dementing illnesses that may be mistaken for other non–autosomal dominant syndromes, such as parkinsonian dementias.3 On occasion, PRNP testing may be a valuable tool to help distinguish between CJD and other neurodegenerative diseases, particularly when neuropsychiatric symptoms present with early onset.2 Likewise, PS1 testing can be valuable, in some cases, for diagnosing patients and giving information to families. As seen with CJD, cases of AD believed to be of a sporadic etiology may be genetic; therefore, counseling should precede genetic testing. Some families may choose not to have a clinical genetic test because neither the diagnosis nor the treatment of the disease would be altered by the result. Autonomous decisions of patients and families regarding DNA testing and whether individual family members wish to receive DNA results need to be respected. However, whether or not they wish to learn results, in the case of CJD, families should be informed not to be blood or tissue donors, because of concern for potential transmissibility of the disease.

We recommend extensive pretest counseling as shown in the Table. In certain cases, physicians may wish to refer their patients to genetic counselors in their areas. Available genetic counselors and clinics can be found on the Internet.11,12 Continued research on the frequency of de novo mutations in neurodegenerative disease and the penetrance of these mutations will allow us to provide more complete information to families.

Accepted for publication October 15, 2003.

Author contributions: Study concept and design (Ms Goldman and Drs Safar and Geschwind); acquisition of data (Mss Goldman, de Tourreil, and Martindale and Drs Miller, Safar, Prusiner, and Geschwind); analysis and interpretation of data (Mss Goldman and de Tourreil and Dr Geschwind); drafting of the manuscript (Ms Goldman and Dr Geschwind); critical revision of the manuscript for important intellectual content (Mss Goldman, de Tourreil, and Martindale and Drs Miller, Safar, Prusiner, and Geschwind); obtained funding (Ms Goldman and Drs Safar and Prusiner); administrative, technical, and material support (Ms Goldman, de Tourreil, and Martindale and Drs Safar and Prusiner); study supervision (Drs Miller and Geschwind and Ms de Tourreil).

These studies were carried out in part at the General Clinical Research Center, Moffitt Hospital, University of California, San Francisco, with funds provided by grant M01 RR00079 from the National Center for Research Resources, National Institutes of Health, Bethesda, Md. Dr Geschwind was supported in part by the John Douglas French Foundation for Alzheimer’s Research, Los Angeles, Calif, McBean Family Foundation, San Mateo, Calif, and Betty Ferguson Fellowship, San Francisco.

Corresponding author and reprints: Jill S. Goldman, MS, MPhil, CGC, University of California, San Francisco, Memory and Aging Center, 350 Parnassus Ave, Suite 706, Campus Box 1207, San Francisco, CA 94143-1207 (e-mail: jgoldman@memory.ucsf.edu).

3. Gambetti P, Petersen RB, Parchi P, Chen SG, Capellini S. Inherited prion dis-

Table

<table>
<thead>
<tr>
<th>Issues to Be Addressed in Counseling of Patients or Their Families Before Diagnostic Genetic Testing for an Untreatable Neurodegenerative Genetic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detailed exploration of family history, including nondementing and dementing neurological illnesses (eg, movement disorders, psychiatric illness, and other conditions)</td>
</tr>
<tr>
<td>Explanation of the potential etiologies (ie, sporadic or genetic) of the probable diagnosis or diagnoses</td>
</tr>
<tr>
<td>Possibility of a hereditary condition</td>
</tr>
<tr>
<td>Benefits, risks, and limitations of available genetic tests (eg, will the result change the diagnosis or treatment?)</td>
</tr>
<tr>
<td>Implications to the patient and family of positive and negative test results</td>
</tr>
<tr>
<td>Presentation of “what if” scenarios, in which family members reflect on how they would handle positive and negative test results, which other family members might be informed, and, if so, how to inform them</td>
</tr>
<tr>
<td>Availability of presymptomatic testing and the protocol (ie, the Huntington disease protocol) used in such testing</td>
</tr>
<tr>
<td>Discussion of whether testing should be done and, if so, whether the family wishes to receive results</td>
</tr>
<tr>
<td>Alternatives such as DNA banking or testing without receiving results</td>
</tr>
<tr>
<td>Requirement for results to be given in person by the physician or genetic counselor who can continue, or refer for, individual support and counseling as needed</td>
</tr>
<tr>
<td>Referral to mental health professionals when needed</td>
</tr>
</tbody>
</table>

Call for Papers

ARCHIVES Express

The ARCHIVES launched a new ARCHIVES Express section in the September 2000 issue. This section will enable the editors to publish highly selected papers within approximately 2 months of acceptance. We will consider only the most significant research, the top 1% of accepted papers, on important insights into the pathogenesis of disease, brain function, and therapy. We encourage authors to send their most exceptional clinical or basic research, designating in the cover letter a request for expedited ARCHIVES Express review. We look forward to publishing your important new research in this accelerated manner.

Roger N. Rosenberg, MD
Editor