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Familial Creutzfeldt-Jakob Disease Cluster Among an African American Family

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Abstract

Familial Creutzfeldt-Jakob disease (fCJD) results from inheritance of mutations in the prion protein gene. Confirming fCJD diagnosis is essential for informing persons of their potential hereditary risk and for genetic counseling to support personal decisions for genetic testing and family planning. We describe a case of fCJD that was linked to a large cluster of African Americans with fCJD identified through a public health investigation, including 8 confirmed cases and 13 suspected cases involving 7 generations in 1 family. Genetic counseling is an important component of fCJD management for families coping with genetic prion diseases.

Keywords

familial Creutzfeldt-Jakob disease; genetic testing; pedigree; prion disease

Transmissible spongiform encephalopathies, commonly referred to as prion diseases, are a rare group of rapidly progressive neurodegenerative disorders among humans and animals caused by abnormal isoforms of the prion protein.[1] These invariably fatal disorders involve the progressive neuronal accumulation of abnormal prions in the brain, which are thought to interfere with the presumed neuroprotective effects of normal prion proteins.[2] CJD is the most common human prion disease, with a worldwide prevalence of approximately 1 case per 1 million persons annually.[3]

Variant CJD, discovered during the mid-1990s, has been causally associated with foodborne transmission of the infectious agent through consumption of cattle products affected by bovine spongiform encephalopathy (BSE), commonly known as mad cow disease.[2] Classic CJD occurs in sporadic, iatrogenic, and familial forms. Sporadic CJD is the most common

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type, accounting for approximately 85% of all cases of classic CJD.[4] Sporadic CJD is hypothesized to be caused by the spontaneous conversion of normal prion proteins to the pathologic form or random mutations of prion protein genes.[5,6] Iatrogenic CJD is the rarest type, involving the horizontal transmission of prion-contaminated biologic extract or tissue (eg, human growth hormone, dura mater grafts, or corneal tissue) through certain neurosurgical and medical procedures.[1] fCJD represents 10% to 15% of all cases of classic CJD and has been associated with approximately 14 different types of mutations in the prion protein gene.[3] The 2 most common mutations involve codon 200 (E200K) and codon 178 (D178N-129V), which depends on the presence of a valine at codon 129.[1] Inheritance is autosomal dominant, with offspring of affected parents having a 50% chance of inheriting the disorder.[1] Penetrance is essentially 100%; all persons with the mutation will almost certainly experience the disease, although onset age and clinical course are difficult to predict.[6,7]

Persons with suspected fCJD or a family history of CJD can be tested for mutations of the prion protein gene to confirm the diagnosis. Testing for CJD in the United States is performed at NPDPSC, which was established in 1997 as a surveillance center for prion disease after evidence emerged in Britain indicating cross-species transmission of BSE to humans during the 1990s.[3] Brain tissue, blood, and cerebrospinal fluid from suspected CJD cases can be sent to NPDPSC to help establish the diagnosis of prion disease and perform prion protein gene analysis.[3]

In February 2012, the Oklahoma State Department of Health (OSDH) was notified by NPDPSC of an African American man aged 56 years who had died and was identified with the D178N-129V mutation in the prion protein gene, consistent with the diagnosis of fCJD. A public health investigation ensued, which revealed that the index patient was in the same family as a previously investigated fCJD cluster in Oklahoma from 2003 that included at least 5 confirmed fCJD cases. Also, a review of the literature demonstrated a published report by Appleby et al[4] describing 9 cases of definite or probable fCJD among an African American family whose pedigree appeared very similar to our pedigree. After consultation with Dr Appleby and NPDPSC, we confirmed that our cases were indeed from the same family as described by Appleby et al.[4] Our subsequent investigation demonstrated an extensive pedigree including 8 confirmed fCJD cases and 13 suspected fCJD cases involving 7 generations in this family.

Public Health Investigation

CJD is a reportable disease in Oklahoma; all clinical information from the index patient was obtained according to Oklahoma's public health and safety code after confirmatory testing for fCJD was received in February 2012.[8] Medical records were faxed to OSDH and reviewed by epidemiologists to collect pertinent symptom, laboratory, and exposure data. Additional family history was obtained from an interview with the index patient's daughter. Notes were also reviewed from a 2003 fCJD investigation, which included interviews with the deceased patient's sister, his neurologist, and 2 nieces. NPDPSC records were reviewed to confirm genetic testing results.

Confirmed fCJD cases included family members with brain autopsy test results consistent with the diagnosis of fCJD, verified after discussion with NPDPSC officials. Suspected cases included family members with progressive neurologic disease, ranging from persons with the diagnosis of Alzheimer's disease to those described as having cognitive impairment, ataxia, and mutism, gathered from interviews with family members. A pedigree was constructed including all known confirmed or suspected fCJD cases using Microsoft Word 2010 software (Microsoft Corporation, Redmond, Washington).

The index patient was an African American man aged 56 years who initially presented to a hospital emergency department in August 2011 with mild tremors, dizziness, and memory disturbance. Results from an electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) performed during hospital admission were indicative of encephalitis, and treatment with acyclovir and steroids was initiated. He was discharged home with a home health aide for assistance. During the next 2 months, he experienced worsening tremors, dysphagia, and speech impairment. He was readmitted to the hospital in October 2011 for dehydration and deconditioning. Results from a repeat EEG and brain MRI were consistent with CJD. He was discharged to home hospice and died in November 2011. Brain autopsy specimens were then sent to NPDPSC, where genetic testing demonstrated the D178N-129V mutation in the prion protein gene, consistent with the diagnosis of fCJD, in February 2012.

An interview with the patient's daughter revealed she learned of a substantial family history of neurologic disease, including CJD, after conversing with distant family members at a different relative's funeral in 2011. Prior to that, she was unaware that there was a family history of neurologic disease in a branch of her extended family. As the public health investigation progressed, OSDH epidemiologists realized that this case was potentially linked to a previously identified fCJD cluster among African Americans in Oklahoma involving at least 5 confirmed fCJD cases. During the 2003 investigation of a confirmed case of fCJD, genetic counseling had been recommended for 2 at-risk family members who both tested positive for the genetic mutation associated with fCJD. After reviewing notes from the prior epidemiologic investigations, including interviews with the 2003 case patient's sister and 2 nieces, it was confirmed that both investigations involved the same pedigree.

In addition, a medical literature search for other fCJD clusters discovered a published report by Appleby et al[4] describing 9 cases of confirmed or probable fCJD among a large African American family that resembled our pedigree. We contacted Dr Appleby and confirmed that our pedigree described the same family as the published pedigree.

Collectively, from the findings of prior OSDH public health investigations of CJD beginning in 2003, the 2012 investigation, the report by Appleby et al,[4] and NPDPSC testing results, we identified a total of 8 confirmed cases (7 confirmed cases from NPDPSC, 1 confirmed case by brain biopsy performed at the University of Chicago) and 13 suspected cases spanning 7 generations in an African American family (Figure). As noted by Appleby et al,[4] African Americans had not been previously described to carry fCJD mutations, but the first-generation male of this family was reportedly of mixed-race ancestry, which could have introduced the mutation into the family. Genetic counseling was recommended to the index patient's daughter by OSDH.

Discussion

Our investigation expanded a previously reported large fCJD pedigree among an African American family. With this report, we aim to raise awareness about fCJD and outline genetic testing options for CJD provided by NPDPSC. In addition, we emphasize the importance of confirming fCJD diagnoses in suspected cases, which is essential for informing persons of their potential hereditary risk. For persons in families affected by fCJD, genetic counseling can help facilitate informed decision making about genetic testing and family planning options that avoid the risk of passing the variant gene to future generations (ie, nonchildbearing, adoption, sperm or egg donation, in vitro fertilization with preimplantation genetic testing).[9,10]

fCJD is unique because it is a hereditary disorder that is potentially transmissible iatrogenically by contaminated neurosurgical instruments or corneal or dura mater grafts, which is another important reason for individuals to be offered genetic counseling if family members have confirmed or suspected fCJD. Transmission through blood and solid organ donation is also possible. The American Red Cross excludes persons from donating blood who have received human pituitary growth hormone, a dura mater transplant, or those with blood relatives who had CJD because of concerns about secondary blood-borne transmission.[11] No formal CJD screening process exists for organ donation.

Public health officials and health care providers should continue to encourage brain autopsies for all suspected CJD patients to confirm diagnosis and classify CJD type. NPDPSC provides free autopsy services and facilitates access to pathologists who are willing to perform brain autopsies. Upon fCJD confirmation, the next step is to address questions and concerns of relatives through genetic counseling. This report illustrates that members within an affected family can remain unaware of their potentially devastating genetic history. Awareness among public health officials and health care providers about the availability of genetic counseling and other family planning options can empower those with a family history of CJD to learn more about their genetic predisposition and options available to prevent transmission.

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Implications for Policy & Practice

- Familial Creutzfeldt-Jakob disease (fCJD) is associated with a variety of mutations in the prion protein gene and represents 10% to 15% of all cases of classic Creutzfeldt-Jakob disease (CJD).
- Public health officials and health care providers should encourage brain autopsies for all suspected CJD patients to confirm the diagnosis and to classify CJD type, which is essential for informing persons of their potential hereditary risk.
- Those with suspected fCJD or a family history of CJD can be tested for mutations of the prion protein gene to confirm the diagnosis at the National Prion Disease Pathology Surveillance Center (NPDPSC).
- Upon fCJD confirmation, the next step is to address questions and concerns of relatives through genetic counseling, which can help facilitate informed decision making about genetic testing and family planning options to avoid the risk of transmission to future generations.

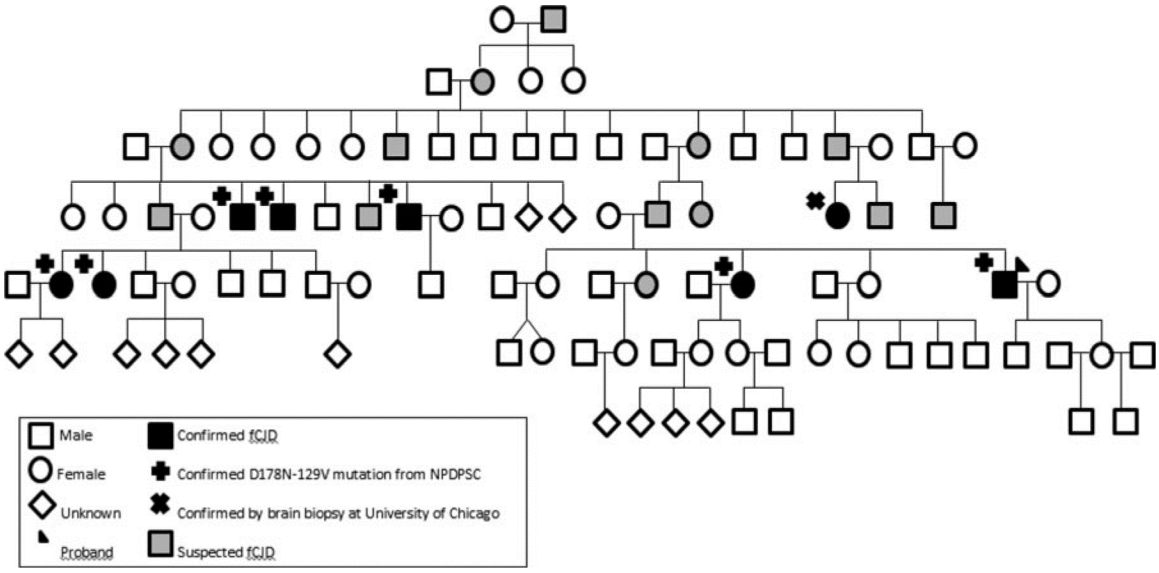

FIGURE. Genealogy of an African American Family With Familial Creutzfeldt-Jakob Disease
Abbreviations: fCJD, familial Creutzfeldt-Jakob disease; NPDPSC, National Prion Disease Pathology Surveillance Center.