Familial Creutzfeldt-Jakob Disease: Case report and role of genetic counseling in post mortem testing

Kristin Clift\textsuperscript{a}, Kimberly Guthrie\textsuperscript{a}, Eric W. Klee\textsuperscript{b,c}, Nicole Boczek\textsuperscript{c}, Margot Cousin\textsuperscript{c}, Patrick Blackburn\textsuperscript{d}, and Paldeep Atwal\textsuperscript{a,e}

\textsuperscript{a}Center for Individualized Medicine, Mayo Clinic, Jacksonville, FL, USA; \textsuperscript{b}Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA; \textsuperscript{c}Center for Individualized Medicine, Mayo Clinic, Rochester, MN, USA; \textsuperscript{d}Division of Health Sciences Research, Mayo Clinic, Jacksonville, FL, USA; \textsuperscript{e}Department of Clinical Genomics, Mayo Clinic, Jacksonville, FL, USA

ABSTRACT. Here we present a case of an asymptomatic 53-year-old woman who sought genetic testing for Familial Creutzfeldt-Jakob Disease (fCJD) after learning that her mother had fCJD. The patient’s mother had a sudden onset of memory problems and rapidly deteriorating mental faculties in her late 70s, which led to difficulties ambulating, progressive non-fluent aphasia, dysphagia and death within \textasciitilde 1 y of symptom onset. The cause of death was reported as “rapid onset dementia.” The patient’s family, unhappy with the vague diagnosis, researched prion disorders online and aggressively pursued causation and submitted frozen brain tissue from the mother to the National Prion Disease Surveillance Center, where testing revealed a previously described 5-octapeptide repeat insertion (5-OPRI) in the prion protein gene (\textit{PRNP}) that is known to cause fCJD. The family had additional questions about the implications of this result and thus independently sought out genetic counseling.

While rare, fCJD is likely underdiagnosed due to clinical heterogeneity, rapid onset, early non-specific symptomatology, and overlap in the differential diagnosis of Alzheimer disease and Lewy body dementias. When fCJD is identified, a multidisciplinary approach to return of results that includes the affected patient’s provider, genetics professionals, and mental health professionals is key to the care of the family. We present an example case which discusses the psychosocial issues encountered and the role of genetic counseling in presymptomatic testing for incurable neurodegenerative conditions. Ordering physicians should be aware of the basic issues surrounding presymptomatic genetic testing and identify local genetic counseling resources for their patients.

KEYWORDS. Familial Creutzfeldt-Jakob disease, genetic counseling, prion disease, \textit{PRPN}, return of results
INTRODUCTION

Prion diseases represent a range of spongiform encephalopathy conditions affecting the brain and nervous system. On an annual basis the prevalence of prion diseases is thought to be one person per million worldwide. Approximately 15% of prion diseases are inherited while the majority is sporadic and not acquired.

Familial Creutzfeldt-Jakob disease (fCJD) is an inherited form of prion disease. It is caused by highly penetrant pathogenic nonsense or missense variants, splice site variants, deletions, or insertions in the prion protein (PrP) gene (PRNP) [HGMD Professional 2015.4]. Pathogenic variants cause the prion proteins to misfold resulting in an abnormal insoluble form of the protein (PrPSc) that accumulates and results in destruction of neurons.1

Inherited Prion Diseases can have striking heterogeneity in presentation although the classic description is characterized by progressive cognitive impairment followed by development of ataxia and myoclonus. The clinical course from the initial onset of symptoms to death can range from a few months to several years. During the last phase of the disease, affected individuals typically have akinetic mutism with myoclonic jerks.2

fCJD is an autosomal dominant disorder meaning first-degree relatives of an affected individual have a 50% chance to have inherited the pathogenic variant and be at risk of developing the disease. At least 30 pathogenic variants that cause genetic prion disease have been identified. In many instances, genotype-phenotype correlations exist such that certain pathogenic variants are more likely to manifest a particular phenotype.3,4 Most variants demonstrate nearly complete penetrance such that nearly 100% of individuals will develop symptoms. However, even within the same family with the same pathogenic variant, there exists variable expressivity of the disorder in that age of onset and symptomatology differ between individuals.

Pre-symptomatic genetic testing is available for the PRNP mutation once a pathogenic variant has been identified in an affected relative. The age of onset can vary from the twenties to the eighties. Disease course can vary from a few months to several years (typically 5–7 years; in rare instances, >10 years). The exact age of onset cannot be predicted by genetic testing, although fCJD is invariably fatal. At this time there are no specific treatments for fCJD.

Because inherited prion diseases have the same symptoms as other adult-onset neurodegenerative diseases, it may often go underdiagnosed. A recent study5 of a large population control cohort found that missense variants in PRNP previously reported to be pathogenic are at least 30 times more common in the population assuming complete penetrance.6,7 It is likely that many of these variants confer risk of developing sporadic disease (< 0.1–100% lifetime risk), while others appear to be benign (false attribution of pathogenicity), or remain undetected due to inadequate disease surveillance.5

CASE REPORT

The proband is a 53-year-old Caucasian female with a family history of familial Creutzfeldt-Jakob disease (CJD) due to a 5-OPRI mutation found in her mother. The patient’s mother was found to have familial CJD after posthumous frozen brain tissue was submitted to The National Prion Disease Pathology Surveillance Center. Western blot, histopathological, immunohistochemical and DNA testing were consistent with the diagnosis of familial CJD. DNA testing revealed a 5 octapeptide repeat insertion resulting in a predicted repeat domain of R1-R2-R2-R3-R2-R2-R2a-R2-R4 in the PRNP gene that is associated with disease.

The proband reported that her mother at age 77 had onset of memory problems and significantly worsened within a 3–6 month period. As her cognition rapidly deteriorated, she began to have difficulties ambulating. An MRI brain scan of her mother demonstrated cerebellar degeneration. The mother eventually lost the ability to swallow and had little to no speech at the end of her life approximately one year from initial symptoms.
The family history was negative for dementia or movement abnormalities. The mother had 10 siblings who were reportedly unaffected. Additionally, the mother’s parents were unaffected. The maternal grandfather lived to his 80s and died in a nursing home. His cause of death was not known. The maternal grandmother died at 51 y of age due to complications from diabetes.

The patient was the primary-care giver and medical decision maker for the mother and therefore would have been the one to give consent for the initial testing.

The patient researched her mother’s results further and sought out a genetic counselor. The initial visit included gathering medical and family history, reviewing the condition and genetic concepts, identifying and addressing informational misconceptions, discussing the patient’s motivations for testing, assessment of psychosocial issues for the patient and dynamics in the family, and reviewing insurance implications of pre-symptomatic testing.

Throughout the initial visit, the patient expressed a strong desire to undergo presymptomatic testing immediately. The patient’s motivations and current psychosocial stressors were assessed to help inform her readiness for testing and identify if it would be beneficial to address any issues prior to proceeding with testing. Consultation with a mental health professional prior to proceeding with testing was recommended both to assess for ability to cope with a potentially positive test result and to provide ongoing support in the event of a positive test result.

The patient expressed that her primary motivation to pursue testing was to determine if her adult children might be at risk. She stated that if not for her children, she would not want to know her genetic status. She disclosed that she had not yet shared her mother’s genetic test results with her daughters. She reported that her husband was against sharing the information with their children and did not want her to pursue testing. Barriers to having this discussion were further explored and this thought process was gently challenged during the session as the patient expressed that she wished she had known about the implications for results prior to her mother being tested. Ultimately, it was recommended that the patient discuss her decision to test with her daughters and explore their feeling and reactions to testing and strategies for the disclosure were discussed.

The patient returned a number of months later and pursued testing. She had reviewed the information with her daughters who were unsure if they would want to pursue testing but they were comfortable with their mother’s decision to test. At first the patient reported her husband was against the idea of seeking presymptomatic testing, but later supported her. She had not seen a mental health professional since the initial visit but cited her pastor and prayer group as a source of support and had discussed testing with the elders of her church.

The patient tested positive for the PRPN pathogenic variant identified in her mother. She was accompanied to the results visit by her husband, which was his first visit to the genetics clinic. The natural history and concepts of variable expressivity and incomplete penetrance were reiterated with respect to her test results. It was reviewed that genetic testing could not predict age of onset nor severity of symptoms. Patient support group information was offered (CJD Foundation). It was reviewed that currently there is no treatment available but avenues to monitor research were discussed and the offer to provide vetting of research protocols in the future was made. Additionally, discussion of the logistics and decision of whom to share this information with were explored. The patient’s initial emotional reaction was assessed and common emotional responses were discussed to validate and normalize the patient’s experience.

**DISCUSSION**

The manner in which this case presented to us is unique and may provide lessons for the future management of similar cases and help to inform standards of practice. After their mother’s rapid decline, the patient and family members were not satisfied with the general diagnosis of “rapid-onset dementia.” The family felt this diagnosis was too vague and after
doing their own research did not agree that this was the cause for the mother’s rapid decline. After reading about prion disorders online, the family aggressively pursued possible causation and requested the nursing home physician submit samples to the National Prion Disease Pathology Surveillance Center, who were successful in finding the correct diagnosis for the patient. The results were returned to the nursing home facility where the proband was called in to pick up the results from the front desk. She read her positive mother’s results in her car in the parking lot of the nursing home and was unsure of the implications of the test report and hence requested genetic counseling.

In summary, in cases of rapidly progressive dementias, causation should be considered. In this case, fCJD would not have been discovered if not for the family’s aggressive pursuit of causation. Formal pre-test counseling is not practically feasible in many instances as this diagnosis is often made post-mortem and during an extremely difficult time for the family. However, physicians should acknowledge some of the barriers for informed consent in these situations and make every effort to engage the decision maker in the informed consent process for testing. It can be helpful for the ordering physician to meet with the next of kin in person, if possible, to review genetic test results on a deceased individual and facilitate appropriate referrals. Physicians involved in ordering testing have an opportunity to lay the groundwork by addressing potential test implications at a high-level in the pre-test setting, providing families with anticipatory guidance for the process of genetic counseling and identifying local genetics professionals. A directory of genetic counselors is available online via the National Society of Genetic Counselors (www.nsgc.org). As diagnostic accuracy improves and more cases are identified, it will be increasingly important for clinicians to be aware of the resources available for patients and their families.

**ABBREVIATIONS**

| Abbreviation | Definition |
|--------------|------------|
| fCJD         | Familial Creutzfeldt-Jakob Disease |
| 5-OPRI       | Five-octapeptide repeat insertion |
| PrP          | Prion protein |
| GSS          | Gerstmann-Sträussler-Scheinker syndrome |
| FFI          | Fatal familial insomnia |
| GINA         | Genetic Information Nondiscrimination Act |

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

No potential conflicts of interest were disclosed.

**ACKNOWLEDGMENTS**

The authors would like to thank The Mayo Clinic Center for Individualized Medicine for supporting this research.

**REFERENCES**

[1] National Library of Medicine (US). Genetics home reference [Internet]. Cystic fibrosis; [reviewed 2012 Aug; cited 2013 Sep 19]. Bethesda, MD: The Library; 2013 Sep 16. Available from: https://ghr.nlm.nih.gov/gene/PRNP

[2] Mastrianni JA. Genetic prion diseases. In GeneReviews®, edited by Roberta A. Pagon, Margaret P. Adam, Holly H. Ardinger, Stephanie E. Wallace, Anne Amemiya, Lora JH Bean, Thomas D. Bird, et al. Seattle (WA): University of Washington, Seattle, 2014. http://www.ncbi.nlm.nih.gov/books/NBK1229/.

[3] Mead S, Webb TEF, Campbell TA, Beck J, Linehan JM, Rutherford S, Joiner S, Wadsworth JD, Heckmann J, Wroe S, et al. Inherited prion disease with 5-OPRI: Phenotype modification by repeat length and codon 129. Neurology 2007; 69(8): 730-738; PMID:17709704; http://dx.doi.org/10.1212/01.wnl.0000267642.41594.9d

[4] NHGRI “Genetic Information Nondiscrimination Act of 2008.” Reviewed March 16, 2012 http://www.genome.gov/24519851. http://www.genome.gov/24519851

[5] Minikel EV, Vallabh SM, Lek M, Estrada K, Samocha KE, Sathirapongsasuti JF, McLean CY, Tung JY, Yu LP, Gambetti P, et al. Quantifying prion disease penetration using large population control cohorts. Sci Transl Med 2016; 8(322):322ra9; PMID:26791950; http://dx.doi.org/10.1126/scitranslmed.aad5169

[6] Rossi G, Giaccone G, Giampaolo L, Iussich S, Puoti G, Frigo M, Cavaletti G, Frattola L, Bugiani O, Tagliavini F. Creutzfeldt–Jakob disease with a novel
four extra-repeat insertional mutation in the PrP gene. Neurology 2000; 55(3): 405-10; http://dx.doi.org/10.1212/WNL.55.3.405

[7] Windl O., Giese A, Schulz-Schaeffer W, Zerr I, Skworc K, Arendt S, Oberdieck C, Bodemer M, Poser S, Kretzschmar HA. Molecular genetics of human prion diseases in Germany. Hum Genet 1999; 105(3):244-52; http://dx.doi.org/10.1007/s004390051096

[8] Roberts JS, Uhlmann WR. Genetic susceptibility testing for neurodegenerative diseases: Ethical and practice issues. Prog Neurobiol 2013; 110:89-101; http://dx.doi.org/10.1016/j.pneurobio.2013.02.005