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ORIGINAL RESEARCH

Genetic Counseling for Early-onset Familial Alzheimer Disease in Large Aboriginal Kindred from a Remote Community in British Columbia: Unique Challenges and Possible Solutions

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Abstract A novel, pathogenic presenilin 1 (PS1) mutation has recently been identified in a large Aboriginal kindred living in dispersed communities throughout British Columbia, Canada. Disseminating genetic information and ensuring that appropriate genetic counseling services are provided to all concerned relatives have posed several unique challenges. These challenges include knowledge exchange and continuity of care in a geographically remote and culturally distinct community. To our knowledge, this is the first time a specific genetic counseling approach has been needed for early-onset familial Alzheimer disease (EOFAD) in a North American Aboriginal community.

Keywords Genetic counseling · Rural · Aboriginal · Alzheimer disease

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Introduction

The University of British Columbia Hospital Clinic for Alzheimer Disease and Related Disorders (UBCH-CARD) is a multidisciplinary clinic located in Vancouver, Canada. Established in 1984, it provides diagnosis, management, and research opportunities for patients across British Columbia with a personal or family history of dementia and cognitive impairment. All new referrals meet with several team members including a genetic counselor who routinely documents a detailed family history.

Between 1998 and 2009, nine members of an Aboriginal kindred were referred to UBCH-CARD from different health districts of British Columbia for dementia assessments within the context of a strong family history of early-onset dementia. The relationships of the patients were established during their genetic assessments at UBCH-CARD and are documented in Butler et al. (2010). The kindred originates from a remote rural community which involves at least a 25-hour car trip or an eight-hour flight. Extended family members are dispersed throughout British Columbia. The kindred's band has a quarterly fixed budget for all medical expenses within the community, thus necessitating their local health team to triage all medical issues that arise with respect to the allocation of these limited resources.

Given the apparent autosomal dominant inheritance pattern of early-onset familial Alzheimer disease (EOFAD) in this family, genetic testing was offered to several affected family members, but it was only in 2006 that this option was pursued by one affected individual. There were several

reasons for the delay in pursuit of genetic testing including the family's understanding of the purpose of genetic testing (clinical versus research), miscommunication leading to many canceled or missed appointments, and lack of advanced appointment notice required for the genetic test to be successfully arranged through coordination of blood draw and shipment arrangement. A novel pathogenic G>T missense mutation at nucleotide position 998 in exon 7 of the Presenilin 1 (PS1) gene [causing leucine substitution by phenylalanine at codon 250 (L250F)] was subsequently identified (Butler et al. 2010).

The identification of an EOFAD mutation in this family required standard genetic counseling follow-up, including dissemination of genetic test results, identification of "at-risk" relatives, and coordination of diagnostic and pre-symptomatic genetic testing for affected and unaffected family members interested in pursuing these options. Although the established genetic counseling protocol for Huntington disease provides relevant and useful guidelines for the provision of genetic counseling for EOFAD (Craufurd and Tyler 1992), the unique cultural and geographic perspectives of this family raised several practical, logistical, and psychosocial considerations. These considerations led to our recognizing the need to identify genetic counseling challenges and potential solutions when providing services for heritable conditions prevalent in remote communities. Although this family's specific situation involves EOFAD in a geographically isolated Aboriginal population, it is anticipated that the proposed approach can be extrapolated for use in other communities facing similar challenges.

Methods

Standard Clinic Visits

Between 1998 and 2009, nine family members were individually referred for assessments at UBCH-CARD. These assessments involved neurological examinations, psychometric cognitive testings, diagnostic imaging, routine bloodwork and family history evaluation. Seven of these nine family members received clinical diagnoses of possible or probable Alzheimer disease (AD) according to the National Institue of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS ADRDA) criteria (McKhann et al. 1984). Pedigree assessment identified over 100 "at-risk" family members living in remote regions of the province. "At-risk" relatives are considered first degree relatives of affected individuals, as well as first, second and third degree relatives in the direct lineage of affected individuals. These assessment procedures were completed in accordance with genetic counseling principles of confidentiality, informed consent, and cultural sensitivity (NSGC 2010 http://www.nsgc.org/about/codeEthics.cfm).

Family Day

Once the novel P250F mutation was identified in the proband, the first step was to organize an on-site (UBCH-CARD) educational/information day ("Family Day") for all interested family members to disseminate this family's genetic test results and to determine the pathogenicity of L250F. With the consent of the proband, this event was advertised by telephone and by written invitations to family members who had attended UBCH-CARD, as well as to their physicians. Family letters and brochures were also created for patients to inform other family members of their possible genetic risk and UBCH-CARD services. These letters and brochures were developed using very simple language and diagrams, and they were reviewed by several UBCH-CARD team members before dispersing to the kindred. Approximately 20 family members attended this event, a small number considering the pedigree has approximately 400 members of which at least 40 are at 50% risk for EOFAD. Several UBCH-CARD health care professionals provided lectures on the genetics of AD, symptoms and natural history of AD, as well as current research and treatment options. Individual clinical assessments, genetic counseling appointments, and DNA banking were offered to all family members. With consent from the proband, the identification of L250F was discussed during this event, and the family was informed that although L250F was highly suspected to be the cause of EOFAD in their kindred, further analysis of affected and unaffected individuals would be necessary to clarify its pathogenicity. Five affected and two unaffected family members past the median age of onset in this kindred (age 56) volunteered to have their DNA collected for the purpose of confirming L250F pathogenicity. L250F was found to segregate with the disease in this kindred, thus supporting the pathogenicity (Butler et al. 2010). All research-related interactions with the family took place with appropriate UBC Clinical Research Board (CREB) approval and informed consent.

Outreach

The kindred's community nurse and Health Director contacted UBCH-CARD regarding the feasibility of UBCH-CARD staff attending their annual Health Fair. Their attendance was seen as an opportunity for members of UBCH-CARD to provide education regarding the novel PS1 mutation and offer clinical assessments and genetic counseling sessions to individuals who were unable to

attend the Family Day. Two staff members of UBCH-CARD (a geriatrician and a genetic counselor) worked closely with the community to develop a Brain Health theme for the Health Fair, and they created educational materials (e.g., posters, pamphlets, slideshows) and presented a lecture pertaining to the symptoms, pathology and inheritance of AD and the L250F PS1 mutation. In addition, individual genetic counseling appointments and clinical assessments were available upon request during the team's 3 day stay in the community. The UBCH-CARD team also met with physicians from neighboring communities to provide education about the genetic risk in the population and to discuss health resources.

Research Initiative

A joint clinical and research initiative was established between UBCH-CARD and the National Core for Neuroethics at UBC focusing on exploring perceptions of dementia and identifying other health resource issues within this Aboriginal community. This research has been initiated from within the community and follows the suggested approach to research within Aboriginal communities outlined in Arbour and Cook (2006). That is to say that advice was sought from strong community leaders (e.g. band leaders, health care workers, etc) to initiate the work and to relay information to the community members.

Results

Through the consistent follow-up of patients from this community at UBCH-CARD spanning several years, the organization of a Family Day in Vancouver, and UBCH-CARD's participation in the local community Health Fair, several goals were achieved:

Education

Education was provided to all interested community and family members (estimated to be close to 100 people) on the clinical and genetic aspects of AD. Despite UBCH-CARD's best efforts, individual members of the kindred often would still ask questions that illustrated they did not understand the genetics of AD. For example, after the lectures and pamphlets were presented at "Family Day," several individuals asked questions such as "Did this come from the White Man?", or I have a very healthy diet…is that why I did not get it [AD]." These misconceptions may be due to a combination of low education level, cultural beliefs, as well as some individuals displaying early signs of cognitive impairment. However, the combination of group education through lectures, as well as individual appointments, allowed most individuals the opportunity to clarify their questions or concerns. Ongoing education provided to local physicians allows for continuity of care and ensures consistency of the information provided to individual members of a single kindred from all health care providers. To date, most individuals that meet with members of the UBCH-CARD team seem to have a basic understanding of the inheritance of AD and EOFAD. However, further education and follow-up are still needed and different approaches to these services are currently being explored. These include joint counseling/follow up with local physicians and having family members in early stages of the disease work with us to help educate the community about the disease and inheritance.

Rapport

Through effort on the part of UBCH-CARD staff to visit the community, rapport was built with the community leaders and members. Initially at Family Day and at the Health Fair, there seemed to be some hesitation among several individuals to approach the UBCH-CARD team. By continuing to communicate with members of the kindred and the community leaders, a trust has been built and the intentions of UBCH-CARD have been understood. The community responded positively to UBCH-CARD's initiative to provide long-term involvement in their care.

Accurate Information Gathering

Whenever possible, medical records were obtained to document dementia reported in family members. However, many reportedly affected family members had never been formally assessed, making accuracy of information questionable. Through outreach, an enormous amount of information was made available to extend the family pedigree for many generations. Elderly individuals who could not travel to Vancouver were able to provide family history details regarding previous generations. This was very helpful in establishing the "at-risk" branches of the family, as well as clarifying relationships.

Furthermore, information about the clinical findings associated with L250F were identified. For the six individuals with a confirmed PS1 mutation, the mean age of onset is 55.7 years (range 47 to 59 years of age). Education ranged from no formal education to an upper level of grade 10. Alcoholism is a major confounder in this kindred and head injury may also be a potential confounder. The main presenting symptom for these 6 individuals is memory loss and the clinical phenotype appears to be most consistent with typical AD. There are no atypical neurological findings in any member of this kindred as

compared to other EOFAD kindreds (Butler et al. 2010). To date, no members of this family have had neuropathological examinations.

Research Collaboration

The research focusing on the community's perspectives on dementia and AD has allowed the Clinic team to tailor genetic counseling appointments and clinical assessments to better meet the needs of this unique population. These services have benefited the community as well as the research and Clinic team. For example, through this research UBCH-CARD has learned that there are legends within the community regarding the origin of AD, which are discussed below. This has lead to a stigma associated with a diagnosis of AD. As UBCH-CARD learns about such information, these issues can be addressed.

Discussion

During the development of an approach for genetic counseling services in this community, several genetic counseling challenges were faced including (i) developing an accurate pedigree, (ii) maintaining and organizing standard in-person contact despite financial restrictions that limit travel, (iii) understanding cultural attitudes towards health, dementia, and genetics (iv) communication, and (v) ensuring patient confidentiality in a small community.

i. Identification of "at-risk" family members in complex family pedigree

Interpreting the family history in this kindred was challenging for several reasons. The exact biological relationships among family members are complicated by half- and step-siblings, informal adoptions, non-paternity, consanguinity and the recurring use of names in different generations or branches of the family. Many family members were never formally assessed for reported cognitive impairment, and the pedigree interpretation was further confounded by the high rate of health conditions with signs and symptoms that can mimic EOFAD including alcohol and drug abuse, head injuries and psychiatric illness. For individuals that received formal neurological examinations at UBCH-CARD, these confounders could often be separated from AD. However, in this pedigree of approximately 400, dementia is reported to affect many who have not attended UBCH-CARD and therefore their disease status is unknown. Diagnostic genetic testing will greatly aid in separating symptoms of AD from confounders in the future. Finally, the accuracy of the family history relies upon information provided by the Clinic patients and their caregivers. This information was often limited due to cognitive impairment and decreased familiarity with relatives living in different geographic regions.

Taken together, these factors make interpretation of the history difficult with regards to determining which family members are at risk to develop EOFAD. Yet, UBCH-CARD's outreach visit to the community greatly facilitated obtaining more accurate and thorough information to clarify "at-risk" individuals in the pedigree.

ii. Geographical and financial considerations

Rural communities have limited access to health services in Canada, as distance to urban settings to seek medical assistance is a major logistical and financial barrier. More than two-thirds of residents in northern and remote regions in Canada live more than 100 km from a physician (Ministerial Advisory Council 2002; Romanow 2002; Statistics Canada 2003). Although the neuromedical and genetic counseling services offered by UBCH-CARD are easily accessible to individuals living in metropolitan Vancouver and its neighboring communities, they are not equally accessible to British Columbia residents living in remote rural communities. Members of our kindred reside in rural communities that have no local genetic counseling or geriatric services. In addition to the usual stress that accompanies any medical appointment, out-of-town patients and family members attending UBCH-CARD must contend with the added stress of psychosocial effects of being removed from their supportive and familiar home environment, and financial expenses (travel, accommodations, lost time at work, etc). For example, the flight from UBCH-CARD to the kindred's community costs $1200. Traveling can be especially challenging in harsh winter conditions.

The distance and limited health care resources of remote rural communities adds significant challenges to the predictive genetic testing service and to neuropathology. Privacy, confidentiality and the threat of genetic discrimination are all ethical issues that arise with predictive genetic testing (D'Agincourt-Canning 2004). At UBCH-CARD and most other genetic institutes in North America, a predictive testing protocol for EOFAD has been established using Huntington disease as a role model (Craufurd and Tyler 1992). This protocol stipulates that genetic counseling for EOFAD predictive testing is carried out over several appointments and involves more than one health care provider. Adhering to this protocol in remote locations with limited health care resources is logistically impractical. Conducting genetic counseling prior to predictive testing solely via telephone is difficult and arranging genetic counseling sessions at UBCH-CARD has been challenging for many of the individuals potentially interested in pursuing this option. With no local physician specifically involved and no telehealth services, local predictive testing

is currently neither feasible nor ethically sound. UBCH-CARD also explored reasons behind the lack of individuals pursuing neuropathology consent at the time of death. The community has expressed that they do not have any spiritual beliefs or values that are against autopsy. However, in the past autopsy arrangement has been unsuccessful due to the logistics of geography and lack of specialists in the remote community who are able to do brain removal. To date, two living patients have consented to autopsy. By providing standard outreach visits to the community, UBCH-CARD hopes to make their clinic services more accessible to community members.

iii. Unique Culture

Cultural sensitivity is one of the fundamental tenets of genetic counseling (NSGC 2010 http://www.nsgc.org/about/codeEthics.cfm). Meeting the genetic counseling needs of this kindred requires an awareness of their methods of learning and communication, and an understanding of their perceptions of health, dementia, and inheritance.

An increased awareness of cultural and health issues specific to this Aboriginal population is facilitated by open communication between health care providers and community members, as well as the research team's work exploring perceptions of dementia.

The Neuroethics team led three focus groups on the themes of concepts of dementia, values and coping mechanisms, and resources for health and research (Lombera et al. 2009). Four distinct themes emerged: awareness of EOFAD, causes of EOFAD, responsibility of care, and lack of resources. Focus group members were aware of EOFAD in their community and associated forgetfulness, wandering, and restlessness with EOFAD. Participants attributed the rise in EOFAD to a number of factors including the environment, the effect of eating non-traditional foods, industrial activities on their territory, and alcohol and drug misuse, in addition to genetic factors. These non-genetic factors are consistent with how Elders of an Interior BC First Nation (Secwepemc) explain the causes of dementia (Hulko et al. 2010) and suggest that members of both Nations relate the symptoms to disconnection from the land and traditions. Due to the extraordinary care required as EOFAD advances in an individual, it is necessary to transfer affected individuals to long-term care facilities outside the traditional territory. The individual, the family, and the community all suffer when an individual with EOFAD must leave the traditional territory. Focus group participants reported that the person with EOFAD becomes disoriented when transferred, the family feels it has abrogated its duty of care to their loved one, and the community experiences the transfer as a death. The participants further described an acute lack of relevant informational resources for care partners on EOFAD symptom recognition, care, and disease progression. They mentioned support groups, forums and workshops as ways to help educate the community about EOFAD, care for affected community members, and mitigate stigma. Six months after the focus groups were held in the community, members were more comfortable speaking about EOFAD [Community Nurse, personal communication].

Aside from EOFAD, this community has many other urgent health care issues including a high prevalence of mental health disorders, alcoholism, head injuries, and domestic violence. It must be recognized that these health concerns might take priority over dementia-related medical and genetic counseling issues.

iv. Communication

Effective dissemination of information and explanation of genetic concepts can be impacted by both education level and cognitive impairment. As many individuals in the affected generation of this kindred have low education level (completion of less than primary school) and given that they are affected by a degenerative brain condition, the provision of Clinic services and the development of learning tools must take these factors into account. For example, when family members attended UBCH-CARD or when team members did outreach, many individuals from the kindred expressed that they wanted to have the genetic test to find out if they were going to get AD. Some of these individuals expressed that they thought this was helping UBCH-CARD research to find a cure for the disease. The genetic counselor and geriatrician constantly explained that genetic testing was a clinical service that the efforts of UBCH-CARD were not research based. It was explained that any individual pursuing genetic testing should do so for personal reasons and not to help research. It was clearly outlined that UBCH-CARD was not using their family to find a cure for AD. These individuals were made aware they must attend many counseling sessions to address the complex issues that must be considered before testing can be pursued. Once this message was successfully relayed, most individuals to date have not pursued predictive genetic testing. There are also many individuals who have never attended UBCH-CARD or visited team members during outreach to their community. Reasons behind this are currently being explored.

Another area of communication that has proved challenging is appointment bookings. Many patients do not have answering machines. Often individuals go on hunting excursions or trips visiting other communities for extended periods of time and will not be available via telephone. Lastly, often other community members may answer the patient's telephone and UBCH-CARD staff will not leave a message due to patient confidentiality. These factors combined have

led to many missed or canceled appointments. For example, in arranging Family Day, when UBCH-CARD staff first let people know about the event, the majority of patients and family expressed that they would attend the event. However, as the event date got closer, the vast majority of these individuals either stated they were no longer coming, or they did not give a definite response. Two days before the event took place, again most people expressed that they would come, or they simply showed up to the event. It seems that this type of communication is common among the Aboriginal culture, but makes it very difficult to plan such an event in a clinical setting.

v. Confidentiality

Maintaining confidentiality is a common dilemma in close-knit rural communities which, by their nature, have a greater overlap between health care providers, residents, family members and business people in their social networks (D'Agincourt-Canning 2004). For example, when collecting family history information, extra caution must be taken to ensure that information provided from other family members is not breached. This can be particularly challenging when determining paternity and adoptions as well as in assessing confounders for EOFAD such as head injuries, alcohol and/or drug abuse. For example, there were several siblings whose exact relationship was different depending on which individual gave the family history. This made it difficult to determine genetically "at-risk branches." Furthermore, family members often wanted to view the family pedigree. The genetic counselor had to ensure that this was kept confidential as exact relationships among certain family members could not be breached.

Genetic test results can easily jeopardize health insurance eligibility as residents of rural communities often have limited insurer options available and may personally know the employees with whom they have to interact. When visiting the community, the health clinic is in the centre of town and everyone can see individuals as they enter the clinic, thereby decreasing confidentiality of appointments. Furthermore, family members of the kindred are staff at the clinic, which again compromises confidentiality. The complicated nature of maintaining confidentiality in this particular kindred is poignantly illustrated by the concerns of one family member who wished to disclose her carrier status to her children who are at 50% risk to inherit EOFAD. She hesitated to do so based on her fear that her children could not be relied on to maintain her privacy within the community, given their tendency to alcoholism and binge-drinking episodes. Such instances serve to remind health care professionals of the distinguishing characteristics inherent in isolated populations necessitating adjusting the usual approach to genetic services and testing within similar communities.

Future Directions

To continue to build bridges with the community, UBCH-CARD has ongoing collaboration with local health care providers and is currently working with these individuals to find alternate sources for travel funding and outreach services. UBCH-CARD has also been investigating the use of telehealth in this community. This is a service that is becoming more readily available in remote communities across Canada, which would allow counseling sessions to take place via television at a local community clinic. Promoting the need for telehealth service in this community would facilitate predictive genetic counseling sessions and decrease the need for travel. Clinical and research collaboration will continue to facilitate a broader and more comprehensive approach to the needs of the community.

Limitations

Further research is needed to assess whether or not this approach successfully meets the needs of the community and individuals. In addition, further research focusing on cultural concepts of dementia at the interface of genetic testing and the healthcare needs of this community are necessary to enable appropriate health services and other outreach activities. Meeting these challenges requires cooperation among clinical service providers, government and granting agencies as well as local Aboriginal leaders and community members.

Conclusions

The experience of UBCH-CARD has allowed the Clinic team to develop a genetic counseling approach that strives to meet many of the needs of the community. This approach includes education (through standard clinic visits, family meetings, lectures, involvement in Health Fairs, workshops, conferences, brochures, family and physician letters), rapport building (with community members, learning from other's experiences and providing services with cultural awareness and competency), and research (assessing community needs, gauging perceptions of risk in community, learning about local resources). The challenges identified while developing this approach (e.g., access to medical services, cultural sensitivity, liaisons between research and clinical practice) are not unique to this family or situation and are not limited to genetic counseling scenarios. We

hope that this approach can therefore be used more broadly in situations involving health care in rural communities.

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