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CASE PRESENTATION

Amyotrophic Lateral Sclerosis in a Patient with a Family History of Huntington Disease: Genetic Counseling Challenges

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Abstract Amyotrophic lateral sclerosis (ALS) and Huntington disease (HD) are generally considered to be distinct and easily differentiated neurologic conditions. However, there are case reports of the co-occurrence of ALS with HD. We present a 57-year-old male with a clinical diagnosis of sporadic ALS in the context of a family history of HD. This case adds to the limited literature regarding individuals with a family history of HD who present with features of ALS. There were several genetic counseling challenges in counseling this patient including the diagnostic consideration of two fatal conditions, complex risk information, the personal and familial implications, and the patient's inability to communicate verbally or through writing due to disease progression. DNA banking effectively preserved the right of our patient and his wife not to learn his HD genetic status during a stressful time of disease progression while providing the option for family members to learn this information in the future if desired. We present lessons learned and considerations for other clinical genetics professionals who are presented with similar challenging issues.

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Background

There have been case reports of individuals and families with features of both amyotrophic lateral sclerosis (ALS) and Huntington disease (HD), suggesting that there may be a rare presentation of ALS in individuals with HD (Rubio et al. 1996, Kanai et al. 2008, Papageorgiou et al. 2006, Phukan et al. 2010, Mandrioli et al. 2010, Sadeghian et al. 2011; Tada et al. 2012; Panse 1942; Gasbarrini 1964; Frank and Vuia 1973; Myers et al. 1985; Blin et al. 1992; Rubio et al. 1995; Chettri et al. 2013). These two conditions are typically considered to have little overlap in symptomology, though both conditions are fatal, typically adult-onset neurodegenerative conditions without effective treatment.

The type of neurodegeneration, associated clinical features, and genetic basis differ considerably between ALS and HD (Table 1). ALS causes degeneration of the upper and lower motor neurons, which leads to progressive muscle weakness, atrophy, dysarthria, and dysphagia, typically resulting in death due to respiratory failure within 3–5 years on average (Testa et al. 2004). Approximately 90 % of ALS cases are sporadic. The age of onset is highly variable but typically in the 6th or 7th decade for sporadic ALS (Testa et al. 2004) and the 5th or 6th decade for familial ALS (Juneja et al. 1997). Ten percent of ALS cases can be attributed to an autosomal dominant, autosomal recessive, or X-linked single gene cause and at least 10 genes have been associated with ALS (Table 1). The cause of ALS in individuals without a detectable single gene cause is largely unknown, though some environmental and genetic risk factors

Table 1 Clinical features and genetics of Amyotrophic lateral sclerosis (ALS) and Huntington disease (HD)

	Adult-Onset ALS	HD
Prevalence	4–8 per 100,000 (1)	0.1–15 per 100,000 (2)
Average age of onset	SALS[a] - 56 (1); FALS[b] - 46 (3)	35–44 (4)
Average disease duration	3–5 years (1)	15–18 years (5)
Clinical features	Motor neuron signs: Upper (hyperreflexia and increased muscle tone) and lower (muscle atrophy, hyporeflexia, and fasciculations); rarely significant cognitive impairments	Triad of motor (chorea), cognitive (decline to dementia) and psychiatric symptoms (depression, personality changes)
Inheritance	Sporadic (90–95 %); Autosomal Dominant (5–8 %); Autosomal Recessive (<1 %); X-linked (<1 %)	Autosomal Dominant (5)
Genetic basis	Point mutations in SOD1, TARDPB, FUS, ANG, OPTN, UBQLN2, other genes; GGGGCC expansion in C9orf72 gene (7–14)	CAG expansion in HTT gene (5)

References:

(1) Testa et al. 2004

(2) Pringsheim et al. 2012

(3) Juneja et al. 1997

(4) Bates et al. 2002

(5) Harper and Newcombe 1992

(6) The Huntington's Disease Collaborative Research Group 1993

(7) Shaw et al. 1998

(8) Sreedharan et al. 2008

(9) Kwiatkowski et al. 2009

(10) Greenway et al. 2006

(11) Maruyama et al. 2010

(12) Deng et al. 2011

(13) Renton et al. 2011

(14) DeJesus-Hernandez et al. 2011

[a] *SALS* Sporadic ALS

[b] *FALS* Familial ALS

have been implicated (Kondo and Tsubaki 1981; Armon et al. 1991; Savettieri et al. 1991).

In contrast, HD causes selective degeneration of neurons in the central nervous system, resulting in cognitive decline, involuntary movements, and psychiatric symptoms (Roos 2010). The typical age of onset is mid-30s to early 40s (Bates et al. 2002) and death generally occurs within 15–18 years (Harper and Newcombe 1992). HD is an autosomal dominant disorder caused by a CAG repeat expansion in the *HTT* gene (The Huntington's Disease Collaborative Research Group 1993).

The prevalence of ALS, 4–8 per 100,000 and HD, 5–7 per 100,000 in the Western European population, give a predicted co-occurrence rate of 2–6 cases per billion in this population (Traynor et al. 1999, Walker 2007). However, 11 case reports of individuals presenting with features of ALS or motor neuron disease with genetically confirmed HD have been described (Table 2), along with eight case reports of individuals with concurrent ALS and with a clinical diagnosis of HD made prior to the availability of *HTT* genetic testing (Panse 1942; Gasbarrini 1964; Frank and Vuia 1973; Myers et al. 1985; Blin et al. 1992; Rubio et al. 1995). Tada et al. (2012) hypothesize that a *HTT* gene mutation predisposes a small subset of individuals with *HTT* mutations to develop clinical and pathological features consistent with ALS (Tada et al. 2012). Among these case reports, most, but not all, individuals developed concurrent HD symptoms, suggesting that ALS features could be the primary manifestation of HD in a small minority of individuals. The possibility that these individuals developed both HD and ALS by chance alone remains a consideration.

To add to this literature, we present a 57-year-old Caucasian male with a clinical diagnosis of sporadic ALS in the context of a maternal family history of HD. We describe the challenges that arose in this case, including providing genetic counseling to an individual with a fatal condition who is at risk for a second fatal condition, and the difficulties with communication given the patient's disease progression. We present lessons learned and considerations for other genetic counselors and clinical geneticists who are presented with similarly challenging cases.

Table 2 Case Reports of individuals presenting with features of amyotrophic lateral sclerosis (ALS) or motor neuron disease with genetically confirmed Huntington disease (HD)

Case	Presenting symptoms (age at presentation)/Gender	Family history	Subsequent symptoms (years of disease duration)	Genetic Test Results (number of CAG repeats in HTT gene)	Year, author
1	Cognitive changes (57)/Male	ALS (mother); neuropsychiatric disorder (maternal uncle)	Chorea, progressive weakness (23)	HD (45); SOD1 negative	Rubio et al. 1996
2	Chorea (72)/Female	Chorea (brother)	Muscle atrophy and weakness, fasciculations (unknown)	HD (40)	Papageorgiou et al. 2006
3	Muscle weakness (41)/Male	Chorea (father, siblings)	Mild chorea, mild cognitive disturbance (unknown)	HD (46)	Kanai et al. 2008
4	Muscle atrophy, weakness (56)/Male	HD (paternal first cousin)	Chorea, cognitive changes (unknown)	HD (≥40)	Phukan et al. 2010
5	Chorea (63)/Female	HD (mother, sister)	Dysarthria; dysphagia; muscle weakness, atrophy, and fasciculations (6)	HD (43); SOD1 negative	Mandrioli et al. 2010
6	Memory problems (67)/Male	Non-contributory	Fasciculations, muscle weakness, chorea (unknown)	HD (40)	Sadeghian et al. 2011
7	Chorea, cognitive and speech changes (~55)/Female	Chorea (paternal grandmother)	Muscle atrophy, weakness, fasciculations, hyperreflexia (~6)	HD (46)	Tada et al. 2012
8	Chorea, cognitive changes (~35)/Female	HD (father, paternal grandfather, sister, other relatives)	Rigidity followed by hypotonia, autopsy consistent with ALS (20–25)	HD (47)	Tada et al. 2012
9	Chorea (~55)/Female	HD (mother, maternal grandmother, siblings)	Muscle weakness (~12)	HD (42)	Tada et al. 2012
10	Dysarthria (56)/Female	HD (father)	Muscle weakness (2)	HD (39)	Tada et al. 2012
11	Irritability (48)/Male	HD (mother, brother)	Muscle atrophy, fasciculations, dysarthria, dysphagia, hyperreflexia (9)	HD (>39)	Chettri et al. 2013

≥40 CAG repeats in HTT gene is consistent with Huntington disease. 39 CAG repeats is reduced penetrance allele

Case Report

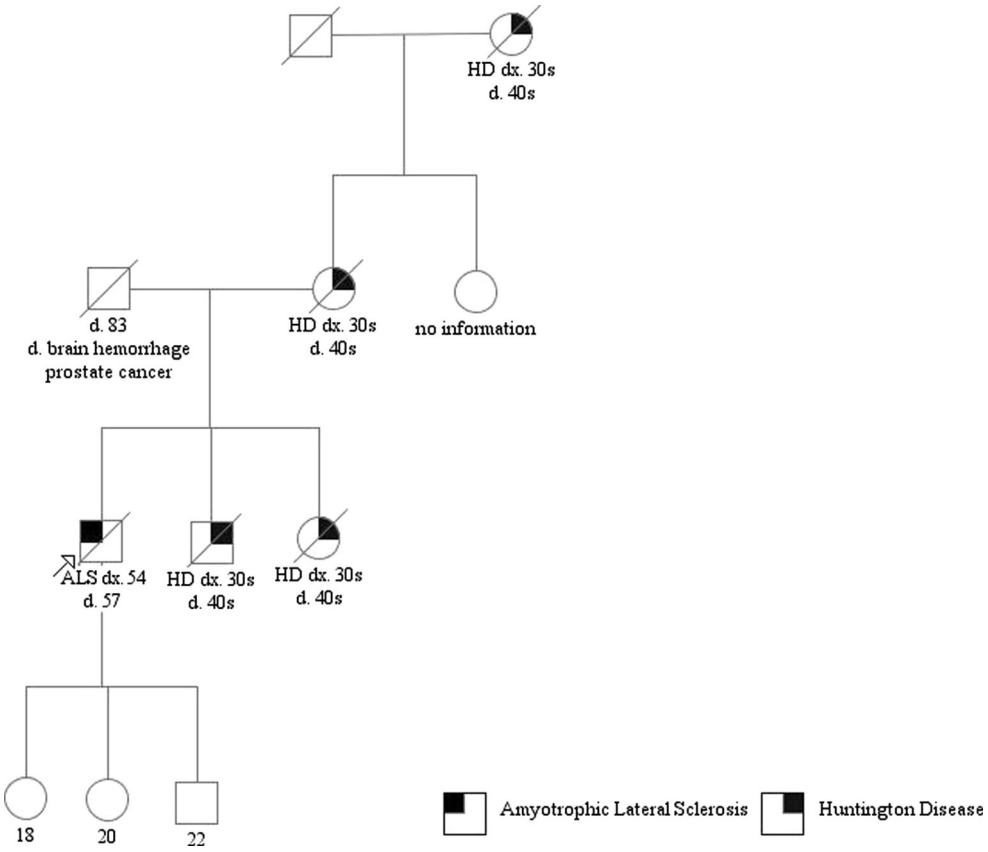
A 57-year old male patient presented at age 54 with a 6-month history of painless, progressive left upper extremity muscle weakness and a 10-month history of diffuse muscle fasciculations. The weakness started in his left hand and progressed to his proximal arm. He noticed that his muscles became smaller and that his arm was stiff. Neurologic examination revealed atrophy of his left upper arm, fasciculations in all four extremities, and hyperreflexia in the arms. Brain and cervical MRIs were ordered to rule out any structural cause for his progressive weakness, but were clinically unremarkable. An electromyogram showed active denervation and chronic reinnervation motor nerve injury in both arms. A repeat electromyogram 6 months later, at age 55, by our neurologist (JT) showed progression with involvement of his legs and muscles supporting his thoracic spine, which supported a diagnosis of probable lab-supported ALS by el Escorial criteria (Brooks 1994) .

While there was no family history of ALS, our patient's family history was significant for HD in his mother, two siblings, and his maternal grandmother. Each of these relatives had onset of HD symptoms in the fourth decade and death in the fifth decade. The family's medical records were not available for review, but the patient and his wife did not believe that any affected family member had genetic testing to confirm the diagnoses of HD. Our patient had three healthy teenage children (Fig. 1). There were no motor, cognitive, or psychiatric symptoms in our patient concerning for an underlying or concomitant diagnosis of HD. Given that his symptoms were not consistent with HD and the many issues that surrounded his new diagnosis of ALS, his HD risk was not initially addressed.

The patient was followed in our multidisciplinary ALS clinic. His weakness progressed over the next 3 years to affect other muscle groups causing immobility, dysarthria, and dysphagia. Approximately 1 year after diagnosis, at age 56, he began to utilize a power wheelchair for long distances. A few months later, he experienced speech and swallowing difficulties and started using a speech generation device for communication. He began to experience dyspnea with minimal exertion and his respiratory function continued to decline. Cognition, however, remained grossly intact and no formal neuropsychiatric testing was initiated.

In regards to his family history of HD, our neurologist (JT) re-evaluated the patient at age 56 and found no features

Fig. 1 Pedigree



consistent with HD. He had normal eye movements with normal saccades and no dystonia, tremor, choreaform movements, or known cognitive or psychiatric disturbances. However, it was noted that his significant muscle weakness likely would have precluded the exhibition of some of the characteristic symptoms of HD. The finding of normal eye movements was of particular importance since HD typically causes marked abnormalities of ocular motility, while ocular motility remains grossly normal until the latest stages of ALS (Mizutani et al. 1990, Roos 2010).

At this time, our genetic counselor (AS) joined the multidisciplinary ALS clinic and became involved in this case. The patient was reminded of his 50 % a priori risk for HD given his family history. Based on this risk, as well as case reports indicating that a rare subset of individuals with HD may present with features of ALS (Table 2), the clinic's genetic counselor (AS) presented the option to have genetic testing for HD and discussed the personal and familial implications of HD with the patient and his wife. The patient's wife facilitated communication, as the patient's dysarthria had made his verbal communication unintelligible and hand immobility rendered him unable to write. He was also no longer able to use his speech generation device because progressive limitations in his head range-of-motion made the device's head-controlled mouse ineffectual. Direct communication with our patient was limited to yes/no questions to which he responded with eye and head movements.

The patient and his wife were overwhelmed by this HD risk, as it differed from their former understanding of his risk. The recent loss of the patient's ability to speak and swallow also added significant stress to the situation. The couple requested that the genetic counselor (AS) return for further discussion about HD genetic testing at the time of an upcoming hospitalization for a feeding tube placement. During this discussion, the patient's wife revealed that the patient had genetic counseling as a young man and that the couple had planned to use a sperm donor to avoid the possibility of passing HD to their children. However, they felt that he was "in the clear" when he passed the familial age of onset and the couple elected not to pursue testing or to utilize a sperm donor. They went on to have three healthy children who they presumed were not at risk to develop HD.

During these conversations, the patient's wife revealed a culture of secrecy in the family, including deaths from HD that had not been revealed as such and relatives' fear that revealing this information would affect family members' marriageability. Though the couple's own children were aware of HD in the family, the patient's wife did not wish her children to be informed of the recent discussions regarding his HD risk; she felt it would be an additional psychological burden on the children to have to consider the possibility of their own future

with HD while coping with their father's rapid deterioration in health. Therefore, she requested that the genetic counselor not discuss the topic if the children were to enter the room.

Though our patient retained legal guardianship over medical decision-making, it became clear through yes/no questioning that our patient gave the decision-making right and responsibility for his own genetic testing to his wife. She revealed that she felt internal pressure to make the responsible decision in regards to his testing for their children's sake and that she did not feel that she was ready to deal with potentially positive HD results. Coping with her husband's terminal illness compounded the difficulty of facing the possibility that her children may be at risk for an equally devastating condition. Nevertheless, some hope was provided when discussing the children's risk of HD given their young ages and the potential for medical advances. She expressed hope that more medical treatments may be available to her children if they were to develop HD than were available to her husband and his family members.

Further conversations made it evident that they were not ready to make a decision about HD genetic testing. The option of DNA banking was presented as an alternative. DNA banking would preserve and ensure a sample from our patient was available for future genetic testing should the patient or his family members decide that they would like to know whether or not he had a gene mutation for HD, but would remove the pressure to make a decision or proceed with genetic testing during a stressful time. A follow up phone call by the genetic counselor (AS) to the patient's wife confirmed their decision to pursue DNA banking. Blood was drawn by a home healthcare professional and sent to a laboratory offering clinical DNA banking.

Home hospice care was initiated for our patient within weeks of banking his DNA. He passed away 6 months later at the age of 57 in his home due to respiratory failure. A brain and cervical spine autopsy was performed on our patient as part of an ongoing research protocol. The brain autopsy revealed atrophy of the ventral nerve roots and astrogliosis of the cortical spinal tracts, consistent with a diagnosis of ALS. The brain weight was within normal limits and there was no observed atrophy of the striatum, as would be expected in a patient with HD. The patient's wife was informed of the autopsy results.

Discussion

This case adds to the limited number of cases which have been reported of individuals with ALS in the context of a family history of HD. In addition, this case presented several genetic counseling challenges given the diagnostic consideration of two fatal conditions, complex risk information, the personal and familial implications, and the patient's inability to communicate verbally or through writing due to disease progression. This case offers several learning points for the genetic counseling community at large, and especially for those genetic counselors and clinical geneticists working with patients with fatal, neurodegenerative diseases.

Risk Assessment

Though our patient's a priori risk for HD was 50 % given his family history of HD, his risk at age 57 was more difficult to assess. Bayesian analysis based on age-related HD penetrance estimates could be utilized to calculate an estimated current risk for HD of approximately 22 % (Harper and Newcombe 1992). The rare possibility that our patient's ALS symptoms could have resulted from an underlying *HTT* mutation complicate these calculations. Our patient's age of ALS symptom onset is similar to these case reports and like cases 3, 4, and 9, our patient presented with symptoms of motor neuron degeneration in the context of a 50 % a priori risk to develop HD. Like case 9, our patient had not developed any known features of HD in the years since his initial ALS symptom onset (Table 2).

Determining the appropriate risk information to convey to the patient and his wife given this complex risk assessment was also a challenge in this case. Genetic counseling had to effectively convey each of the following possibilities: 1. that our patient had sporadic ALS coincidentally in the context of a family history of HD and he did not inherit the HD allele, 2. that he had sporadic ALS coincidentally in the context of a family history of HD and he had inherited an HD allele and was not yet symptomatic, or 3. that his ALS symptoms were actually an unusual phenotype of HD. For the latter two possibilities, each of his children would have a 50 % risk for HD. The likelihood of each of these possibilities was unknown, given the limited understanding of how often *HTT* expansions cause a clinical picture of motor neuron disease.

Predictive or Diagnostic HD Testing?

Another challenge that arose was whether our patient's HD genetic testing should be treated as predictive because he had no clear findings of HD or diagnostic given the aforementioned case reports (Table 2). Our patient's physical limitations and the time, travel, and effort involved in the additional appointments stipulated in the HD predictive genetic testing guidelines (International Huntington Association 1994, MacLeod et al. 2013) would have been a barrier to proceeding with predictive genetic testing. In addition, the utility of following the predictive testing protocol for our patient, who was already suffering from a fatal, neurodegenerative condition with a shortened lifespan, was likely limited compared to a truly presymptomatic patient.

This case made us consider the distinctions between diagnostic and predictive testing and when it is appropriate to modify the existing predictive HD testing protocol. For our patient, modifications would have been necessary given his physical limitations and fatal condition. In particular, modifications to the specified number of visits and timing between visits would have been required. Flexibility in carrying out protocols for predictive testing for late-onset neurodegenerative diseases was supported by a recent qualitative study of individuals undergoing predictive testing (Guimaraes et al. 2013), as well as in guidelines published in 2013 for predictive genetic testing for adult-onset monogenic conditions (Skirton et al. 2013).

Family Culture and "in the Clear" Thinking

Beyond the difficulty with risk assessment, genetic counseling for this patient and his wife was further complicated by the broader family dynamics and the nuclear family's risk beliefs. The family culture of secrecy surrounding HD was a possible inhibiting factor in identifying at-risk and affected relatives, decision-making about testing, and potentially disclosing information. In addition, our patient's wife's decision not to discuss the conversations regarding their father's HD risk was consistent with the culture of secrecy surrounding this diagnosis. This decision is consistent with several studies which have reported that a family history of HD is not always disclosed within a family (Forrest et al. 2003; Forrest Keenan et al. 2009; Holt 2006; Klitzman et al. 2007; Nagaraja et al. 2006; Quaid et al. 2010). Our case report highlights that a culture of secrecy may be created and maintained with altruistic, if not paternalistic, intentions to protect family members. The patient's wife cited protecting her children from unnecessary psychological stress as the reason for not disclosing his HD risk immediately.

Additionally, the patient and his wife felt that he was "in the clear" for HD since he was older than the familial age of onset. This historically held belief appeared to affect their ability to process and cope with new conflicting information regarding his HD risk. It appeared that the dissonance created by the possibility that he had inherited HD was intensified by their "in the clear" thinking and the predictive testing and reproductive decisions that they had made based on this assumption. As our case illustrates, it is important to assess risk beliefs and family dynamics in communication of medical information.

Counseling Communication-Impaired Patients

Communication was a significant genetic counseling challenge in this case because of our patient's inability to effectively communicate verbally or through writing. Assessment of our patient's nonverbal communication was also limited given his disease progression, which significantly limited his physical movements. Genetic counseling typically relies on verbal communication for interviewing and psychosocial assessment, as well as nonverbal cues (Uhlmann et al. 2009). Therefore, alternative approaches had to be used in order to establish a working relationship with the patient and understand his needs and desires. Our approach was to limit the information conveyed to what was most necessary to communicate and to utilize yes/no questioning to facilitate our patient's involvement. Additional counseling time was also provided to accommodate the patient's limitations. More typical genetic counseling communication methods were employed with the patient's wife, who served as a representative for her husband.

No genetic counseling guidelines currently exist for providing counseling to individuals who require speech generation devices or other forms of communication assistance. However, approximately 95 % of individuals with ALS will lose their ability to communicate verbally (Ball et al. 2004) and lack or loss of intelligible speech is also present in other genetic conditions. Therefore, genetic counselors, especially those working in neurogenetics, need to be prepared to counsel nonverbal or communication-impaired patients. Based on our experience with this patient and others, use of yes/no questioning and limiting presented information can facilitate participation of nonverbal patients in genetic counseling.

Facilitating Decision-Making for Patients with Life-Limiting Conditions

Facilitating decision-making in an individual with a life-limiting condition brought a new set of challenges and complexities to this case as well. The timing of counseling during a period of medical crisis and after severe progression of the condition also affected the family's level of stress and anxiety surrounding the decision-making process.

Doing it for the Children

For our patient and his wife, the strongest motivating factor in decision-making about HD genetic testing was their children, as this information did not hold promise of changing our patient's prognosis or medical treatment. Our patient's wife's decision-making was motivated by the responsibility to do the right thing for her children's sake. However, she had an internal conflict as to what the "right thing" for her children was. The feeling of obligation to children that our patient's wife expressed is commonly cited by individuals at-risk for HD as a factor affecting their decision to undergo predictive testing (Bloch et al. 1989; Craufurd et al. 1989; Dufrasne et al. 2011; Evers-Kiebooms et al. 1989; Evers-Kiebooms et al. 2002; Quaid and Morris 1993; Smith et al. 2013). Providing children with relevant information for their reproductive

decision-making can also influence parental decisions to test or not test (Smith et al. 2013).

The conflict that our patient's wife felt about whether this obligation to children promoted or inhibited a decision to test has also been acknowledged in the HD literature. For example, Craufurd et al. (1989) found that an important motivating factor for individuals undergoing predictive HD testing was to clarify the risk for their existing children, while Quaid and Morris (1993) found the biggest factor in at-risk individuals' choice *not* to undergo predictive testing was "if my risk goes up so does that of my children." Therefore, a feeling of obligation to children can either promote or prevent someone from undergoing genetic testing. Our patient's wife showed that decision-making can be especially distressing when conflicting internal notions exist as to whether or not genetic testing would benefit or harm the children.

Deferring Decision Making to Others

As noted above, our patient deferred decision-making regarding HD genetic testing to his wife because the results were most relevant to their children. Implicit in his decision to transfer decision-making authority to his wife was the knowledge that she would soon become the sole parent to their children. The use of a family member as the decision-maker regarding genetic testing, as we observed with our patient's wife, may provide some genetic counselors with an internal uneasiness given the profession's commitment to preserving patient autonomy and preventing undue coercion from family members (National Society of Genetic Counselors 2013). However, genetic counselors need to recognize and take into account how the patient's diagnosis and prognosis affect decision-making and explore the patient's wishes to defer genetic testing decisions to family members, who likely will be more affected by results than the patient him/herself. In some cases, allowing the patient to defer decision-making to another family member should be viewed as respecting, instead of violating, the autonomy of a patient with a life-limiting condition.

DNA Banking

DNA banking allows for long-term storage of DNA and is particularly useful for patients with life-limiting conditions (Uhlmann et al. 2009; National Society of Genetic Counselors 2013). Determining our patient's carrier status for HD would have clarified his children's risk for developing this condition. However, the patient and his wife were not ready to learn this information. Their decision was understandable given the limited life span of our patient and the expressed desire to protect the family from more immediate painful news. DNA banking was a beneficial option to consider because it preserved the right of our patient and his family *not* to know his HD genetic status, while providing the option for this information to be learned in the future, if desired.

Summary

This case adds to the literature regarding individuals with a family history of HD who present with features of ALS. Genetic counseling to patients for whom more than one condition is being considered will become more common, as the availability of genomic testing increases and our understanding of the phenotypic spectrum of single gene disorders expands. In addition, this case presented challenges and potential solutions for facilitating effective communication with non-verbal, cognitively intact patients, as well as with patients with fatal conditions. Lastly, this case reinforced the utility of DNA banking in the practice of genetic counseling.

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Conflict of Interest Andrea L. Smith, James W. Teener, Brian C. Callaghan, Jack Harrington, and Wendy R. Uhlmann declare that they have no conflicts of interest.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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