Main Submission

Huntington's Disease: Advances, controversies, and challenges

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Huntington's disease (HD) is a progressive neurodegenerative disorder with a worldwide prevalence of about 4-7 per 100,000.[1] In 2011, there were approximately 639 people diagnosed with HD in Canadian long-term care facilities alone.[2] HD is characterized by progressive motor dysfunction, cognitive impairment, and psychiatric disturbances.[1] Motor abnormalities can manifest with chorea, bradykinesia, and apraxia, and later progress to dystonia.[3] Cognitive impairment involves difficulties with executive functioning, as well as visual and attention deficits, while psychiatric symptoms can lead to aggression and depression.[3] HD normally appears between the ages of 30 and 45 with variability in onset and severity of symptoms.[3] It is caused by a CAG triplet repeat expansion in the *huntingtin* (HTT) gene located on the short arm of chromosome,[4] producing a mutant protein responsible for CNS degeneration.[4,5] More than 40 repeats of CAG is associated with occurrence of the disease by age 65, with longer CAG repeats predicting earlier onset.[5] A juvenile form of HD also exists that can occur as early as five years of age.[1]

There are many standard pharmacological medications available for the treatment of psychiatric symptoms, and motor dysfunction can be alleviated with tetrabenazine and antipsychotic drugs.[3,4] However, no well known treatments have been found to greatly improve cognitive impairment.[3] To date, psychotherapy, speech therapy, and physical and occupational therapy are the most effective treatment methods available.[6] Advances are being made through stem cell research to replace lost neurons as a form of late-stage intervention, making it possible to regain some loss of function.[5] Evidence also suggests that coenzyme Q10 and daily doses of creatine may improve the functional decline in HD patients; Phase III studies are under way to assess these effects.[3] Neuroprotective strategies are being examined to help delay the progression of HD while the use of disease modification biomarkers can recognize HD development before disease onset.[7] In the future, scientists are looking towards enhancing clearance of mutant HTT, improving transcriptional deregulation, preventing production of the toxic N-terminal of mutant HTT, and switching off expression of the gene itself.[4]

Although we continue to make advances in HD, certain controversies still exist. HD is an autosomal-dominant disease; therefore, bearing children becomes a difficult choice for known carriers. Parents may opt for prenatal screening, however pretest counselling is needed to acknowledge the possibility of pregnancy termination.[4] Direct prenatal screening will reveal the HD gene carrier's status, so linkage analysis may be preferred to maintain status anonymity while using the grandparent's DNA to determine HD risk in the child.[8] Controversy exists around pregnancy termination, not only because many perceive it as the taking of a human life, but the child may not manifest the disease for decades with a possibility of no disease development.[8] Conversely, non-engagement in screening can be interpreted as immoral and irresponsible.[9] Undergoing genetic testing can cause unnecessary stress and significant reduction of "healthy time" with no cure for the disease. Those with HD can also be discriminated against by employers and insurance companies. Although The Canadian Charter of Rights and Freedoms and The Canadian Human Rights Act attempt to prohibit discriminatory practices under enumerated grounds, it continues to be a highly sensitive topic that gives rise to ethical issues of eugenics and genetic discrimination.[10]

Challenges also arise when searching for a cure. For example, making the HD gene inoperative may be a complicated procedure as the gene involved also serves other vital brain functions.[7] The research required to find remedies for HD are impeded by the fact that they require a massive acceleration of a biological process that takes ▶

many decades to develop in humans. It is difficult to find animal models that mimic the progression of the disease in humans. Being a carrier of HD also introduces personal challenges: patients must find new ways to cope with the disorder, both mentally and physically. Their quality of life decreases in conjunction with an increased dependency on others, and there is a negative stigma related to HD that not only affects the patient but also places a burden on those who are closely related. Most importantly, the decisions in life that once seemed fulfilling and simple are now a cause for great concern.

HD sparks the scientific minds of today and emphasizes the ethical issues surrounding life and death. There is a fine balance between what is considered right and wrong while the options available to those with HD are not as straight forward as one may think. It is a debilitating illness that affects all aspects of the individual's life and their decisions moving forward. Many challenges and controversies exist, however experimental research and medical advances are continually being discovered to manage and treat HD. The future seems especially optimistic for a pharmacological breakthrough within this field. Although HD is a difficult illness to endure, in time it may be conquered. ■

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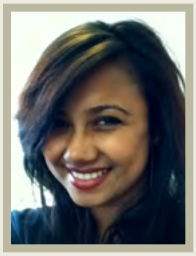

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