

HD - genetic choices across the life-cycle

by Professor Patrick Morrison - An excerpt from a journal article first published in *Clinical Genetics* 2014; 85: 76-77.

Choices for patients and families with Huntington disease (HD) have multiplied considerably in the last decade. My own interest in this difficult disease started in the 1980s when I met a patient with HD as part of a neurological attachment. I was struck then and on meeting subsequent families, with the lack of information about both the condition and its

management, and the lack of choice for clinicians - the only tool appeared to be a diagnostic label which often was an indirect death sentence. Despite that, the resolve and determination and kindness of families and carers of patients with HD has never wavered. The condition then had considerable stigma, not so much so nowadays when HD is often used in film and television drama as a story to draw in the viewer, so the general population now has a wider exposure to what used to be an infrequently discussed or recognised disorder.

Diagnosis and management of HD has come a long way since the 1980s when the neurologist whose clinic I was sitting in with, broke the news of the diagnosis to the patient with the not uncommon phrase 'I'm sorry, it's Huntington disease - there's nothing more I can do'.

We now have accurate figures on how common HD is - the prevalence being roughly 10-15/100,000 in recent studies (2013). A disease that was thought to have an onset mostly in 'early middle life' (between 35 and 50 years of age), is known to affect a range of onset ages from early childhood through to the ninth decade.

Awareness of HD in paediatric neurology and elderly care medicine has vastly improved, and the implications for care of patients and their families also extend to early pregnancy - a true example of a disease that covers the entire human life cycle.

Characteristically early onset HD with a longer triplet repeat length is more severe than later onset milder phenotypes. Current management is also much better with a range of treatments available for neurological and psychiatric dysfunction. Clinician awareness if an

HD patient has pneumonia, allows health professionals in primary care to recognize that they are experts in treating the pneumonia or other common complications, rather than referring almost as a reflex for specialist opinion into tertiary care as 'they know nothing about HD' thinking that pneumonia treatment is more complicated just because the patient has a strange name to their underlying disorder. Lifespan of affected patients has accordingly increased, with patients having a longer and better quality of life because of simple awareness of the issues affecting families, and applying management and support to the entire family situation, both medically and socially, and considering the role of the unaffected carer and other at-risk family members.

All this is now possible despite a lack of a specific treatment to halt the progression or reverse symptoms of HD.

Pre-symptomatic testing protocols are well advanced and are part of routine practice. These have acted as a model for other late onset and incurable diseases.

We now know that around 14% of at-risk relatives approach genetic centres for testing - a small number understandable given the lack of treatment available but none the less giving certainty for those who do not carry the gene on testing, and the potential for disease modification in those who are shown to be gene carriers. Even being a gene carrier now means that around a third of the age at onset is not due to the actual triplet repeat size and therefore careful diet, stimulation of the brain, exercise and other lifestyle factors may help ameliorate the onset of symptoms.

So the journey towards the end of the life cycle is perhaps now a little easier. What about the start of life? Prenatal diagnostic options have considerably improved over the last decade.

Patients now have a menu of choices from direct testing of the foetus, through exclusion testing, to pre-implantation genetic diagnosis (PGD). The number of patients terminating a high risk HD pregnancy has reduced in comparison with the number of couples now continuing with a pregnancy that most likely will result in a carrier foetus, possibly being told their carrier status earlier than they may have wished to find out for themselves from a genetic clinic.

This may reflect maturity of the assimilation of the knowledge of HD by parents, and better treatment and life expectancy experienced by families, in the context of society where whole exome and genome screening is revealing all sorts of potential mutations and increasing the complexity of genetic counselling.

Pre-pregnancy diagnosis through PGD is now possible, with an uptake of PGD in the Netherlands steadily increasing year on year to a level seen in other European countries such as Belgium and France, making it almost routine. This reflects improved genetic counselling and the fact that more HD families are taking control of their disease and influencing its management. Some countries have very low uptake of PGD reflecting a series of factors, not least in Germany where prenatal diagnosis for HD is still prohibited by law, but the choices are becoming available worldwide, and leading to a better understanding not only in HD, but in other diseases where less scrutiny has been available over the decades.

Hopefully continued advances in the epidemiology, natural history, genetics and reproductive choices for HD patients and their families will make living with HD through the entire life cycle much easier than it was, and remove any remaining stigma from the disorder.

Families with HD and the general public now realise that better management of the disease is possible and that there is much more choice than some families (and often also their clinicians) realise.

