Huntington's Disease: Scientific Progress and Social Neglect

This year marks an important milestone for those affected with Huntington's Disease (HD), a devastating and fatal neurodegenerative condition caused by a single mutation in the Huntingtin (HTT) gene: for the first time, a genetic therapy is being tested clinically, started in June of 2015. The agent is an antisense oligonucleotide (ASO), a DNA-based therapeutic that decreases the levels of the Huntingtin protein, with the goal of halting disease progression. The advances in HD research that led to this watershed event benefitted greatly from several decades of field studies of Venezuelan populations especially afflicted by the disease, known as 'clusters'. In 1993, when the Huntingtin gene was cloned, sequencing of the human genome had not yet been accomplished. As a result, large and multi-generational families were needed to identify mutations associated with disease. This work by the Huntington's Disease Collaborative Research Group culminated in the discovery of the causative mutation in HD (MacDonald et al., 1993). This work comprised the collaborative efforts of 58 scientists representing a host of different institutions and countries, and was a landmark in the history of modern human molecular genetics. This work would not have been possible without the extensive participation of these Venezuelan HD patients, their families and their communities. Yet 2 decades out, the subjects of those studies have received little or no benefits from the research, lack access to genetic diagnosis and counseling, have scant legal protection, and suffer inadequate medical care. Their plight raises a question paradigmatic for such unique, and uniquely vulnerable, patient populations: Does the medical and scientific community have a moral responsibility to ensure some element of sustained support of such communities participating in and critical to their research?

Huntington's disease is a dominant genetic disorder; the children of affected individuals have a 50-50 chance of developing the disease. The mutation is an expansion in a DNA sequence repeat located within exon 1 of the Huntingtin gene. The longer the repeat, the earlier the onset. Once the disease starts, usually in the third or fourth decade of life (although about 5% of patients develop juvenile HD), its course is relentless: Severe degeneration of the basal ganglia and cortical structures leads to a host of devastating symptoms: inability to work, changes in personality, irritability, aggressiveness, depression, all while patients are conscious of their disease and the effects on their families. Ultimately, patients lose motor coordination, develop involuntary movements, lose the ability to walk, or ultimately to stand, speak or feed themselves; they typically die of pneumonia or acute aspiration once bed-ridden. Not only is it an especially demeaning way to die, but the terminal course is rendered much worse in the ravaged Venezuelan communities in which these HD patients reside, in which extreme poverty is as endemic as their disease.

As a scientist whose career is focused exclusively in developing therapeutics for treating HD, I struggle with the knowledge that the current quality of life of many affected by HD in poor regions of the world is deplorable, including some of the communities who have actively participated in research. I have seen people shunned and neglected by their relatives, sitting alone in darkened rooms, devoid of medical or social support. I have met the children of those affected, who are ashamed of their parent's condition and afraid of what will become of them. Tragically, suicide is common.

Throughout Latin America there are a number of clusters where the prevalence of HD is strikingly higher than in the average population (estimates suggest up to 100-500 times more prevalent in some communities, compared to the worldwide prevalence of 0.5-1 per 10,000; Pringsheim et al., 2012; Paradisi et al., 2008; Wexler, 2012; Cuba and Torres, 1989). These clusters probably arose from founder

populations, thought to be of European origin. Having visited many of these communities in Venezuela, Brazil and Colombia, I have been struck by their commonalities: they are extremely poor, largely uneducated and suffer high unemployment, and often lack access to basic necessities, such as fresh water, food, adequate housing, and basic care (see also Wexler, 2012; Perez et al. 2013; Giraldo, 2005). In most locations, at-risk people lack the basic knowledge of what causes HD, and have little or no access to primary medical care, let alone neurological or psychiatric medications.

One of the largest HD clusters in the world is nestled in the impoverished neighborhood of San Luis in the oil-producing town of Maracaibo, Venezuela, in which roughly a third of all families have a history of HD (Perez et al., 2013). When I last visited in 2013, of roughly 3000 residents, there were 106 symptomatic patients, but only one poorly equipped and understaffed outpatient clinic.. Pioneering scientist and HD advocate Dr. Nancy Wexler led the research in Maracaibo over 2 decades, and founded a privately run care center named Casa Hogar Amor y Fe, which houses roughly 40 patients with advanced HD, and provides access to food and medications (Wexler, 2012). However, spend any time wandering the streets of this shanty town, and you will find symptomatic patients on every street corner; to the uninitiated, their numbers are staggering.

The town of Barranquitas, 200 km away, is the largest known HD population in the world, with roughly 400 manifest patients in 2013 and another 2600 at-risk individuals (Solis-Añez et al., 2013). Although there is a small out-patient clinic, Barranquitas lacks a specialized care center. Aside from an insufficient if regular visits by physicians from Maracaibo (who travel 5-6 hours on rough roads to get there), these patients receive support only from community volunteers affiliated with patient associations (Avehun, *Asociacion Venezolana de Huntington's*). Yet it was the participation by several generations of these families that enabled the cloning of the *Huntingtin* gene, and the understanding of so many of the features of the disease. The situation in Venezuela is not unique. Other clusters exist in Colombia (in Juan de Acosta, Santa Marta, Barranquillas, Cordoba, el Choco), in Peru (in Cañete), and Brazil (in Feira Grande). These communities are similar to those of Maracaibo: at-risk individuals often marry blood-relatives, live in confined locations, and suffer wrenching poverty; HD families living in these clusters are financially devastated, as their affected members become unable to work during their most productive years, while their siblings and children are then forced to abandon school or work, to care for their affected family members. Frequently, multiple affected members live together.

For years, many have participated in numerous studies, donated samples of skin, blood and semen, agreed to donate organs of their deceased relatives, including those of their own children, so that advances could be made. But when I visited these communities that were the subjects of such intensive research, I often perceived a strong resentment and explicit distrust of the scientific community. I met individuals who expressed anger since they expected a return for their efforts and involvement (see Pineda 2010; Ceaser 2010; Burton 2013): at best, new treatments, but at base, help in the form of palliative medications and improved living conditions; and at the very least, feedback as to how their contributions helped. Yet what seemed to infuriate them the most was that, after so many years had past, that they still lacked readily available access to the genetic test results that could tell them whether they or their children will develop HD.

First, it was clear to me that most of the people to whom I spoke did not understand or realize that enrolling in a research study would not guarantee their access to results. Indeed, I spoke with many who were frustrated at the lack of information coming back to them – information that they wished to use

for family planning at the very least, as well as for planning their own futures (see Pineda, 2010). In addition, naturally if naively, they also thought that their participation in clinical studies would naturally afford them opportunities for treatment and therapy; this resulted in profound disappointments that often could have been simply avoided with more explanation of the research plans and process up-front. Second, a *diagnostic* genetic test must be administered with available genetic counseling and psychological support. Yet such expertise is limited or non-existent in most rural areas in South America. In Venezuela, for example, at-risk or sick individuals would need to travel the long distance to Caracas, where the test is available free or at a nominal cost - but most cannot afford to the trip. As a result, these vulnerable populations are largely ignored.

Historically, the scientific community has not taken on the responsibility to care for the vulnerable populations they have engaged in research. For many scientists, their way to contribute is by making advances in the laboratory. However, the reality is that those advances do not typically translate into an improved quality of life for those communities.

Research, and especially basic research, is fundamentally disconnected from the realities of vulnerable populations, which can experience a reality a world apart from that encountered by the researchers and clinicians who visit their communities, and who so benefit from those interactions. Would it not be reasonable to expect both investigators and their institutions to assume some responsibility for the care and treatment of these study populations, and hence for their quality of life?

What can be done?

First, we need to question entirely whether studies in vulnerable populations should be conducted at all unless a comprehensive, long-term plan is drafted in cooperation with local and national governments. In the case of the recent Colombian trial for Familial Alzheimer's disease sponsored by Genentech and Roche, patients participating in the study have been guaranteed access to the medication - if and when it indeed proves effective (http://www.gene.com/media/news-features/landmark-alzheimers-prevention-trial). But is this enough? Might it not be reasonable to expect that sponsors of drug trials support development efforts for those communities whose research participation enables corporate drug development? At a minimum, and as described in 2002 by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO), sponsors have a responsibility to ensure, when recruiting subjects from vulnerable populations, "*that research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research*". This clearly did not happen in the context of the Venezuelan and Colombian communities.

The inclusion of HD in legislation covering rare disorders is a critical first step: this guarantees specific rights and protection (access to social and financial benefits, avoid discriminatory practices), and access to the very expensive medications that are needed to manage HD symptoms. This will become extremely important as new therapeutic avenues are being explored. Given the expected high cost of gene therapy-based treatments, enabling access to these novel therapeutics, when available, is a topic of unquestionable importance for these impoverished communities.

Recent legislation has been passed in Colombia (2010 Law 1392 for orphan disorders), Chile (Ley Ricarte Soto of 2015), and Argentina (2011 national law 26.689 for rare disorders). In Brazil, a Rare Diseases National Attention Policy was enacted in 2014 (Arnold et al., 2015). In other countries, there is no

specific legislation covering Huntington's disease as a rare disorder (such as in Chile or Venezuela), under whose umbrella patients and families can appeal for specific protections and assistance in the form of financial aid. These governments are taking steps to support affected individuals, and are engaged in a dialogue with the patient associations, although the lack of a legislative framework complicates access to care at the required level, including providing support for families dealing with chronically afflicted patients, most of whom reside at home with their families. Beyond merely providing antipsychotics, anxiolytics and antidepressants (which are not readily available and many times not prescribed by specialists), the unique features of HD require additional measures: Patients suffer numerous psychiatric issues, ranging from early dementia to frank psychosis; they lack adequate nutrition and can have exceedingly poor dental health (a common source of death in HD is asphyxiation due to swallowing their own teeth). They need access to wheelchairs, feeding utensils, diapers and other supportive material to enable adequate care. Transportation and access to medical centers must be provided. During the final stages of the disease, hospital beds and provision for skilled nursing care should be made accessible. I believe that it is the collective responsibility of the scientific and medical community to pressure these national governments to enact and enforce these policies. Yet as welcome as such legislation would be, it covers only individual access to care, and does not address the systemic and crushing disease-associated poverty of these communities. Generally, society has not acted to help these clusters from a community-development perspective; yet such an approach could improve the communities as a whole, providing more and better care for the afflicted, and hence greater freedom and opportunity to their unafflicted kin (similar to what has been done in societies dealing with HIV; Piat et al., 2015, and to nascent efforts in the West for the family-centered care of patients with Alzheimer's and other terminal neurodegenerative and demyelinative diseases).

Governments need to guarantee access to genetic tests free of cost for everyone at risk, and to provide adequate psychological support, even in remote communities. In order to do this efficiently, a proper census of communities with suspected cases of HD is necessary, as many of these communities are unknown to government institutions. Without support, the cases of HD in these communities will increase and create a serious public health issue. Governments can develop effective family planning and gene carrier identification programs to curtail the prevalence of HD in these communities. This type of effort has been successful at the governmental level, for instance in the efforts of Sardinia to diminish the incidence of beta-thalassemia (Cao et al., 1996), or by non-governmental organizations, such as the efforts in the Ashekenazi Jewish community to abrogate genetic leukodystrophies and lysosomal storage disorders so prevalent in that population. Provided appropriate resources, analogous programs could be readily established to manage the incidence of HD in the Latin American clusters.

There is a real opportunity to make a significant impact, since HD only affects a few thousand people in each country. With targeted programs and an adequate legislative framework, we can change the reality of these communities for the better. With the newly initiated gene therapy trials, and other therapeutic strategies in the drug development pipeline, there is now the real hope of developing effective treatments. If we tackle the scientific and social aspects of the disease concurrently, we may hope for synergistic benefits that fundamentally alter the course of HD, greatly improving the lots of afflicted patients and their communities.

Acknowledgements

I would like to thank the following people for helpful suggestions: Adrian Burton, Drs. Trudie Lang, Vahri Beaumont, Ernesto Solis, Roger Cachope, Thomas F. Vogt, Leon Rosenfeld, Steven Goldman, Elena Cattaneo and Roberto Weiser. Special thanks to James Hawkins.

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