The Physiology of a Neurodegenerative Disease: Huntington's Disease

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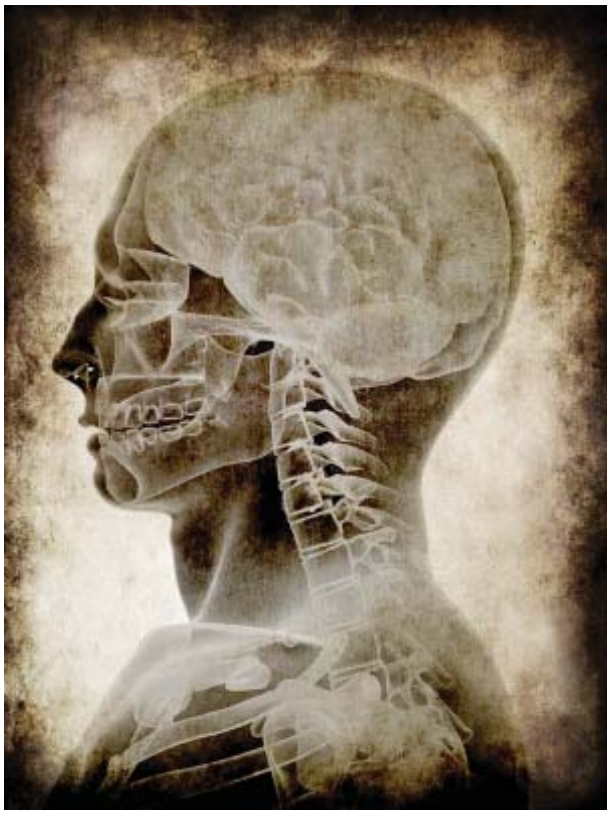
Case Introduction

Huntington's disease (HD) is an extremely rare, autosomal dominant disorder. It is a neurodegenerative condition, meaning that neuronal function is lost and neural cells die over time. Symptoms include chorea (jerky, uncontrolled movements), dementia, and depression. The condition is particularly devastating in that, while one can know one's fate quite early in life (through a genetic test), currently there is no cure.



Your Task

Prior to discussing this case in class, your task is to read one or more of the assigned resources listed at the end of this section and use that in combination with information in your textbook and notes to formulate answers to the focus questions listed below. You may also need to search for additional articles using such databases as PubMed, a searchable on-line database of articles from medical journals maintained by the National Library of Medicine (see Resources below for the web address). This information will help prepare you to address the scenario presented in the case study.

Focus Questions

- What are the causes of HD?
- What are the symptoms of HD, and how do they compare to other neurodegenerative diseases? (see Bossy-Wetzel et al. 2004)
- How does the disease progress (i.e., what happens as it gets worse) and how is it treated? (see Nance, 2007, and Shoulson and Fahn, 1979)
- What are striatal neurons and what is their role? How are gamma amino-butyric acid (GABA) levels related to striatal neurons? (see Picconi et al., 2006; Smith, Brundin and Li, 2005)
- What are the roles of the mitochondrial membrane potential and intracellular calcium levels in neuron function and in cell death? (see Cattaneo and Calabresi, 2002; Panov et al., 2002)

Resources

Basic Information

National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov/disorders/huntington/huntington.htm Last accessed: November 4, 2008

Huntington's Disease, On-line Index of Mendelian Inheritance in Man
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=143100 Last accessed: November 4, 2008

Huntington's Disease Society of America
http://www.hdsa.org/ Last accessed: November 4, 3008

Huntington's Outreach Project for Education at Stanford
http://www.stanford.edu/group/hopes Last accessed: November 4, 3008

Resources for Further Searches of the Scientific Literature

PubMed
http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed

See also specific databases available through institutional library websites (for example, Proquest, JSTOR, Web of Science, Biological Abstracts, etc.)

Resources for Researching Focus Topics

Genetics and Protein Dynamics:

Bossy-Wetzel, E., et al. 2004. Molecular pathways to neurodegeneration. *Nature Medicine* 10: S2–S9.

Neurobiology:

Picconi, B., et al. 2006. Plastic and behavioral abnormalities in experimental Huntington's disease: A crucial role for cholinergic interneurons. *Neurobiology of Disease* 22(1):143–152.

Membrane Potential and Calcium Levels:

Panov, A.V., et al. 2002. Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. *Nature Neuroscience* 5(8):731–736.

Mitochondrial Function:

Cattaneo, E., and P. Calabresi. 2002. Mutant huntingtin goes straight to the heart. *Nature Neuroscience* 5(8):711–712.

Patient Care:

Nance, M.A. 2007. Comprehensive care in Huntington's disease: A physician's perspective. *Brain Research Bulletin* 72(2–3):175–178.

Shoulson, I., and F. Fahn. 1979. Huntington disease: Clinical care and evaluation. *Neurology* 29(1):1–3.

Research Techniques:

Smith, R., P. Brundin, and J.Y. Li. 2005. Synaptic dysfunction in Huntington's disease: A new perspective. *Cellular and Molecular Life Sciences* 62(17):1901–1912. [See especially animal model section.]

Supplemental Resources

YouTube
http://www.youtube.com/
Several videos are available that show the movement phenotype.

Part I—Symptoms of Huntington's Disease

Amanda is in her second year of graduate school. While working in the lab one afternoon, she receives a worrisome call from her parents. Her uncle Gerald has just been diagnosed with Huntington's disease (referred to as "HD") and Amanda's parents are trying to make sense of the diagnosis and figure out how to help.

There is only time for a brief conversation on the phone, but the diagnosis leaves Amanda very concerned. Her uncle lived nearby when Amanda was a child and often joined the family for dinners. He was an important part of the family and it was shocking to hear the diagnosis. What would it mean for her uncle, and what would she and her family be able to do to help him?

Amanda is the first in her family to pursue an advanced degree and the only scientist, so she knows that her parents will be looking to her to help them understand the diagnosis and consider a plan of action. As a genetics student, she knows that HD is inherited as a single-gene, autosomal dominant trait. In fact, it's a classic example of human genetic disease. Amanda remembers hearing that it usually strikes during middle age and causes neurodegeneration, but she can't recall much else about it. After attending the required research seminar for graduate students in biology departments at the university medical center, she catches up with a couple of fellow students, hoping they can help her better understand Uncle Gerald's diagnosis—Steven, a neurobiology student, and Michelle, an MD/PhD student. When Amanda tells them about Uncle Gerald's diagnosis, both friends express their sympathy.

"That's a pretty awful disease," Steven says. "Had anyone noticed any symptoms leading up to it?"

"Not really. Uncle Gerald works for a printing company. He's done pretty well with the business, but ever since he turned 40 a couple of years ago, some of the folks at the print shop said he was starting to be a bit of an eccentric—odd facial expressions, twitchy sometimes, a little harder to get along with. I guess he had a pretty bad fall last week—broke his leg. The doctor must have started putting the pieces together when he took the family history. But up until a few years ago, Uncle Gerald was always really easy to get along with, a pretty normal guy. I know the doctor suspects a neurodegenerative disease, and you can identify Huntington's with a genetic test, but how is this disease different from other cases of neurodegeneration, like Parkinson's or Alzheimer's?"

Question

1. What are the classic symptoms of HD, and how are these similar to and different from symptoms of Parkinson's or Alzheimer's?

Part II—Effects of Neuroanatomy and Neurotransmitters on HD

After Michelle explains the basic clinical symptoms of Parkinson's and Alzheimer's, she pauses and puts a hand on Amanda's shoulder. "I'm afraid that's not good news for your uncle. So far, no cure has been found for HD. As motor control deteriorates, most patients end up needing increasing amounts of care, sometimes beyond what a family is comfortable providing."[1]

Amanda thinks for a moment about all this, and then begins to wonder more about the biology of it. "So if HD results in the death of neurons, how does it end up causing the specific set of symptoms it does, as opposed to having other neurological effects?"

Steven chimes in: "We've just been talking about the nervous system in class. HD seems to especially target spiny neurons of the striatum. That affects production of the neurotransmitter GABA."[2]

Questions

2. What is the effect of GABA (gamma amino-butyric acid) on the nervous system? What does this do to membrane potential?
3. How would this change in membrane potential affect action potentials and muscle movement?
4. Would the loss of striatal neurons result in higher or lower GABA levels? Why might this lead to the symptoms observed with HD?

[1] Nance, M.A. 2007. Comprehensive care in Huntington's disease: A physician's perspective. *Brain Research Bulletin* 72(2–3):175–178.

[2] Cattaneo, E., and P. Calabresi. 2002. Mutant huntingtin goes straight to the heart. *Nature Neuroscience* 5(8):711–712.

Part III—Role of Calcium and Membrane Potential in Neural Function

Amanda thinks back to what she knows of the basic genetics of HD. "OK. I remember that the disease is caused by a mutant form of the Huntingtin gene, which produces a protein containing too many copies of the amino acid glutamine. But how could that lead to death of the striatal neurons?"

"That's something no one's completely sure about yet, I think," Steven replies. "But it is clear that mitochondria are involved.[2,3] We just read a paper about this. The mutant form of the protein shows up in the mitochondrial membranes of some neurons. This seems to result in changes to the membrane's permeability as well as changes to levels of calcium ions in the cell. Remember all that apoptosis stuff we talked about in our cell seminar? Well, mitochondria are important for the intrinsic apoptosis pathway, one of the main ways that cells commit "suicide." In this pathway, the mitochondrial membrane permeability transmission pore (PTP) opens, and this sets off a series of events leading to cell death. While it seems that not all the cell death in HD is caused by apoptosis, HD's affect on the mitochondrial membrane may be part of the story. Excitotoxicity from altered glutamate neurotransmitter levels also seems to be important."[4]

Questions

5. What happens to the mitochondrial membrane potential in HD patients? Why might that lead to a change in the membrane's ability to release calcium into the cytoplasm?
6. What kinds of effects might the altered intracellular calcium level have on the cell itself?
7. What is excitotoxicity, and how is it related to calcium levels? What role might this play in neurodegeneration?

[2] Cattaneo, E., and P. Calabresi. 2002. Mutant huntingtin goes straight to the heart. *Nature Neuroscience* 5(8):711–712.

[3] Panov, A.V., et al. 2002. Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. *Nature Neuroscience* 5(8):731–736.

[4] Elmore, S. 2007. Apoptosis: A review of programmed cell death. *Toxicologic Pathology* 35:495–516.

Part IV—HD Research and Treatment

As Amanda takes in this new information, she thinks about the basic research techniques that would have been necessary to discover how HD works. "I guess all those techniques we talked about in Dr. Patel's class really are useful for clinical applications, too, not just basic science."

Question

8. What are some of the basic physiological techniques or types of experiments used to understand the mechanism of HD? Consider the generation of animal models of the disease as well as techniques for measuring membrane potential, ion concentration, and cell- or tissue-level changes.

"I think I'm starting to get a much better understanding of the disease now," Amanda says. "But I'm still not sure what this means for Uncle Gerald. If there's no cure, what can we do for him?"

"We've talked a little in some of my classes about basic palliative care," Michelle offers. "There are some relatively predictable stages of the disease that you can expect to see. At first, things probably won't be so bad, and your uncle can continue with his usual life and work. For some patients, the psychological strain—knowing what's coming and not being able to change it—may be the hardest part. It may help your family to talk to a patient advocacy organization or a support group for caregivers to get a sense of what kinds of choices other families have made."[1,5]

Questions

9. What are the basic stages of disease progression in HD? What types of symptoms are likely to require Uncle Gerald to need some degree of professional care?
10. What are some specific organizations or resources (websites, etc.) that might be helpful to Amanda's family in caring for Uncle Gerald?

"Thanks, guys. I'm planning to visit home as soon as I can leave the lab on Friday, and now I have a better sense of what to discuss with my family. In the meantime, I'll do some searching on PubMed and see what else I can learn. Who knows—maybe one of us will help to find a cure for HD someday."

[1] Nance, M.A. 2007. Comprehensive care in Huntington's disease: A physician's perspective. *Brain Research Bulletin* 72(2–3):175–178.

[5] Shoulson, I., and F. Fahn. 1979. Huntington disease: Clinical care and evaluation. *Neurology* 29(1):1–3.