New Medicine and Promising Research for Huntington’s Disease
Webcast
April 30, 2009
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Introduction

Andrew Schorr:
Andrew Schorr here on location at the American Academy of Neurology meeting for 2009 meeting in Seattle where neurologists around the country are discussing various neurologic conditions. One of the areas that is discussed here is Huntington’s disease, and of course that’s a genetic condition that can run in families and affects many people. Many people who are at risk don’t even know it that they have the gene, and it’s been a very serious condition of course as it develops for people and scary, and we had not had many things that can help for a long time, but that is changing.

Here to discuss it is Dr. Rajeev Kumar. He’s the medical director at the Colorado Neurological Institute right outside Denver in Inglewood, Colorado. Thank you for being with us doctor.

Dr. Kumar:
It’s a pleasure to be here. I hope I can provide some useful information.

Andrew Schorr:
Sure. Help us understand. First of all Huntington’s, so how many people do we think it affects, and how do we know that? Is it a genetic test? How do we know whether people are at risk for it or actually have it?

Dr. Kumar:
Huntington’s disease is an uncommon but not rare neurodegenerative disease that is caused by a mutation in a gene called Huntington, which exists on chromosome 4. Normally we have a certain number of repeats of a group of nucleotides, part of the DNA, called CAG. If one has too many repeats then one will come down with Huntington’s disease.

Huntington’s disease is characterized by progressive degeneration especially of an area of the brain called the basal ganglia. This results in progressive difficulties with involuntary movement, especially random flowing movements, which themselves can be impairing interfering with gait, movement of the hands, and can interfere with activities of daily living. It can result in progressive slowness as the disease progresses and involuntary posturing. Involuntary movement is one of the three cardinal manifestations. The second
The cardinal manifestation is cognitive dysfunction and eventually dementia, and lastly psychiatric disorders commonly accompany the other two disorders so specifically with depression and in time trouble with psychosis.

Andrew Schorr:
Yes.

Dr. Kumar:
So it’s an extremely disabling condition. It markedly shortens lifespan. The average time from symptom onset to death is roughly 10-20 years. The type of genetic mutation in an individual correlates with the type of symptoms and progression of disease.

Andrew Schorr:
So I’ve understood that the sort of number of repeats can give some clue as to the progression or even the severity of the disease?

Dr. Kumar:
Indeed. What we do know is that there is a rough correlation with the length of the mutation with age of onset and progression of disease. So if one has a longer mutation or a larger number of what’s called CAG repeats the disease will generally occur earlier and will progress more rapidly.

On average patients who have Huntington’s disease have a greater number of repeats than 37. Between 37 and 40 there’s a chance that one may have the mutation, but in a normal lifespan some individuals may not express the disease. However, with more than 40 repeats essentially with a normal lifespan eventually everyone will develop Huntington’s disease.

If one has typically between 40 and 50 repeats most people will have age of onset in their 40s or 50s. With fewer repeats it can be very late onset. With somebody who has repeats in the 50s it’s not uncommon to have individuals have onset of disease in their 20s. With high 50s and into the 60s it’s not uncommon to have juvenile onset Huntington’s disease with onset in adolescence or even earlier in childhood.

New Treatment Options for Huntington’s Disease

Andrew Schorr:
That’s where testing comes in. We’ll talk more about that in a minute, but it used to be you really didn’t have much that could help. What has changed in the last year, and then I want to talk to you about where we’re headed. So what’s changed now?

Dr. Kumar:
Sure, well there are a few different things. We have now some FDA-approved medications to treat symptoms of Huntington’s disease. We do not yet have any medications which have been proven to slow the progression of the disease, but there are many medications
now in clinical trials which are open to individuals who both are affected or are not affected but are gene-positive to participate in that we think show great promise in potentially having an effect in treating the underlying illness.

Now newly approved just last fall was a medication called tetrabenazine. It’s known by the trade name Xenazine in the United States. This medication was available in many countries in Europe and also in Canada for treatment of involuntary movements associated with Huntington’s disease as well as other movement disorder problems; however, this was not yet available in the United States. This fall it was approved by the FDA as the first medication specifically for the treatment of chorea; that’s the involuntary movements in Huntington’s disease.

This is a real breakthrough and can be very helpful in improving individuals’ quality of life. This medication has less psychiatric side effects than other medications we’ve used in the past such as medications for schizophrenia like haloperidol, Haldol, Risperdal. Those medications although they can sometimes improve chorea have a variety of different adverse effects and are only modestly efficacious. Tetrabenazine has a different spectrum of adverse effects. It is generally felt pretty well tolerated in patients who have Huntington’s disease and is very effective in treating chorea. So when chorea is mild it may not need to be treated, but when it begins to interfere with day-to-day activities and throws individuals off balance then tetrabenazine is a very good option in selected individuals.

Andrew Schorr:
How often do people take it?

Dr. Kumar:
Tetrabenazine is usually dosed three times a day. Usually we begin at once a day and gradually titrate the dose up to twice a day and then three times a day and then slowly increase the dose over several weeks. Patients should be monitored when taking this medication for adverse effects. The most common side effects are causing lightheadedness because it can reduce blood pressure, causing depression, so individuals should be monitored for the advent of depression, and causing difficulties with sedation or insomnia. There are other side effects, these are a little less common, but because the medication needs to be slowly increased and because side effects can occur individuals should be followed very frequently when the medication is being increased until the dose is stabilized.

Andrew Schorr:
All right, so we have now an approved medicine to help with this symptom of Huntington’s but we still don’t have anything to stop the progression of the disease, and of course we look for other symptom management drugs too. Where are we now with the science? If this was maybe the vanguard where are we headed?
Dr. Kumar:
There are a number of medications which are being tested both for symptom management in Huntington’s disease as well as to potentially slow progression of disease, and this is because our understanding of what’s going on in the brain and in individual cells in Huntington’s disease has advanced significantly. We expect substantially more advances over the next couple of years, and this was discussed in part today at the American Academy of Neurology meeting.

So let’s review briefly what medications are in clinical trials. Most of the major clinical trials are being conducted by a large consortium of academic investigators known as the Huntington’s Study Group, and we at the Colorado Neurological Institute are part of that. Let’s first of all talk about medications to treat symptoms of Huntington’s disease that are in clinical trials. There’s a medication called ACR16, which is being studied as part of what’s called the HART study, which is being looked at to reduce slowness, trouble with balance, as well as speech amongst other motor symptoms of Huntington’s disease but not chorea.

This is important because accompanying chorea these symptoms can significantly interfere with quality of life and ability to perform simple activities of daily living such as even dressing or walking safely. So that’s an exciting new drug, and this is what we call a dopamine modulator. So in Huntington’s disease blocking or reducing dopamine functioning can improve chorea; that’s one of the things that tetrabenazine and some neuroleptic medications do, but that’s not the only problem in that at the same time patients become too slow, so we need to improve that function too, so that’s complicated. This medication punitively may reduce overactivity and improve underactivity in selected brain regions as needed in a more physiologic fashion.

There is going to be a study of a new medication for cognitive impairment in Huntington’s disease which will be beginning this summer. This is a medication called Dimebon. Now Dimebon is an interesting medication in that it has recently been shown to have positive effects for cognition in Alzheimer’s disease, and in a phase II study in Huntington’s disease it also showed a great deal of promise, and this was a positive study. A large phase III study will begin this summer looking at patients with early-to-mid stage Huntington’s disease with cognitive impairment to see if this will improve cognition.

This medication interestingly has a rather complex mechanism of action. Initially it was thought to be an antihistamine, and it was first used in Russia. We know that beyond that it also has some beneficial effects on mitochondria. Mitochondria are the individual powerhouses within individual cells. We know that in Huntington’s disease energy production is defective in mitochondria, and as a result of this mitochondrial dysfunction there is an undersupply of energy to specific cells that degenerate and subsequently die. If we could boost mitochondrial function that might help in Huntington’s disease.
Now Dimebon seems to have a very widespread mechanism of action. It may significantly improve cognition through its effects on multiple types of receptors. It’s even possible, we don’t know, that Dimebon might have even a disease modifying effect, and there’s some indication it might do so in Alzheimer’s disease. We don’t know if it will do so in Huntington’s disease, and the primary reason to do this next study with Dimebon is first to look at just improvement in cognition, but it may have an effect on the actual disease.

New Studies and Clinical Trials

Dr. Kumar:
Let’s move on to specific therapies that are being studied to slow progression of the actual underlying disease, Huntington’s disease. As I’ve mentioned mitochondrial function seems to be defective in Huntington’s disease as a result of a downstream manifestation of the abnormal gene and gene product. If we could boost mitochondrial function, that might slow the degeneration in Huntington’s disease. So there are two interesting supplements actually being studied in Huntington’s disease on a wide-scale basis. The first is coenzyme Q.

Andrew Schorr:
Really?

Dr. Kumar:
Yes. So coenzyme Q is used as a supplement. You can buy it in the health food store. Unfortunately when you buy a supplement in the health food store you don’t really know what you’re getting because these are not regulated in any significant way by the FDA.

Andrew Schorr:
Right.

Dr. Kumar:
So you could be getting what’s on the bottle. You could be getting a lot of other stuff you don’t necessarily want. You may be getting not the amount that is actually on the bottle, again, because supplements are not significantly regulated in a very tight way by the FDA.

Now we know that pharmacological-grade coenzyme Q might have beneficial effects in Huntington’s disease, and in its preliminary studies there was some signal that coenzyme Q might slow progression of Huntington’s disease. Coenzyme Q seems to boost mitochondrial function as part of a specific complex within the mitochondria that is important in the generation of the energy-storing compound called ATP. So if you can boost ATP function, boost mitochondrial function, that might prevent cell death.

So a large-scale study called the 2CARE Study is being conducted over six years by the Huntington’s Study Group involving approximately 600 patients. This is a large, double-
blind, placebo-controlled study. Patients are randomized to either high doses of coenzyme Q or a placebo. Coenzyme Q seems to be extremely well tolerated even in high doses in pharmacological grade.

**Andrew Schorr:**
Just one comment though. Again the idea of that study would be participate in the study not just run out and get CoQ yourself.

**Dr. Kumar:**
Correct. What we need to know is we really need to know whether or not coenzyme Q will work. We don't know. It may even be harmful, and in fact in other studies we've done of other nerve degenerative diseases such as for example let's take Parkinson's disease; we recently looked at a new compound called CEP developed by Cephalon initially, and we thought in animal models that it looked very promising. Unfortunately when we studied this in the largest study in the world for disease modification in Parkinson's disease involving about 800 patients called the PRECEPT study we found it was ineffective. In fact patients who got the drug progressed more quickly than patients who got placebo.

**Andrew Schorr:**
Oh my.

**Dr. Kumar:**
So that's why we have to maintain ethical equipoise when we don't know and encourage patients to participate in the study. Also in getting coenzyme Q one has to be aware of we don't know exactly what the effective dose is. In the 2CARE study we're studying a high dose, 2400 mg per day. Getting pharmacological-grade CoQ is not easy. You can't purchase it in the routine health food store. What you get is unregulated. You can purchase that online, but it's very expensive to get pharmacological-grade CoQ. That amount of CoQ would probably cost between $500.00 and $1000.00 per month.

**Andrew Schorr:**
But if you're in the study it's provided?

**Dr. Kumar:**
Correct.

**Andrew Schorr:**
Now was there one other supplement you're studying as well?

**Dr. Kumar:**
The second supplement is creatine. Creatine is widely used as a supplement by body builders to improve muscle building. We're looking at high-dose creatine to see if we'll again boost mitochondrial function and slow cell death and slow progression of symptoms in Huntington's disease. The 2CARE study is looking at very early patients with symptoms of Huntington's disease. What's called the CREST-E study for creatine is looking at both
early and mid-stage patients with Huntington’s disease so patients who have a little bit more advanced disease are being accepted into that study. That study has not yet begun. It’s slated to begin this summer. Creatine requires significantly more monitoring when using the high doses that we’re going to be using in this study, up to 40 grams per day.

Andrew Schorr:  
Will these be typically available such as at your institution and at the Huntington’s Disease Center’s of Excellence?

Dr. Kumar:  
Yes. These studies should be available to individuals who are interested in about 50 sites throughout the world, about 30 or 40 of which are scattered throughout the United States. If one goes to the Huntington’s Study Group website you can find your closest center throughout the nation.

Advantages of Knowing Your Gene Status Early

Andrew Schorr:  
Let me pull this together. So where we are now is we have as of last fall in 2008 an approved medicine for one of the symptoms of Huntington’s and now you have all this research coming forward, so it would seem that individuals affected by it and families concerned about it want to be in a relationship with a center such as yours or one of the others to see whether existing medicine or others coming as far as participating in the trial could be of benefit.

Dr. Kumar:  
Indeed. I think that’s the case. It should also be emphasized that knowing one’s gene status can be very helpful in determining life planning, such as family planning, as well as thinking about careers, thinking about a number of other important life events.

Andrew Schorr:  
But you know how terrifying that can be for people saying I know it’s in my family but do I want to know about me?

Dr. Kumar:  
Exactly. So I think it’s important to learn about the risks and benefits of gene testing and when we offer presymptomatic gene testing all individuals go through significant counseling so they can understand that both in terms of financial ramifications, insurance ramifications, and personal psychological ramifications.

One nice thing that has occurred in the past year has been the passage by Congress of GINA, which is the Genetic Information Nondiscrimination Act, and that is helpful in potentially preventing discrimination based on a presymptomatic or even a symptomatic status of individuals who could have Huntington’s disease. So that’s a very important thing one should be aware of but only by learning what the pros and cons are of testing
that one can make an appropriate decision, so it’s important to not be ignorant, to learn the risks, and learn what testing is all about, and how that could be helpful or not helpful to you to make an informed decision.

One should also be aware that there are a number of studies now being offered for individuals at risk of Huntington’s disease or individuals who have been tested and tested gene-positive. So that’s an additional advantage.

So there’s a study called the COHORT study in which we are collecting individuals who are relatives of people who have symptoms of Huntington’s disease, patients who are presymptomatic who have Huntington’s disease, or patients who are at risk and have not been tested to study a number of symptoms and correlations between the genetics of Huntington’s disease and the biology of Huntington’s disease. That data will allow us to better advance the science and develop hopefully a cure for this disease.

Closing Comments

Andrew Schorr:
Amen. So Dr. Kumar, you’ve been at this a while, and hopefully you’ll be in this field a long time to where we can see huge breakthroughs. Do you feel we’re at the beginning of a new day? I don’t want to overpromise, but it seems like there’s activity, there’s an approved medicine, others that are in various stages of research. How do you feel about the tempo of things, and are you encouraged?

Dr. Kumar:
I’m extremely encouraged. I would say five years ago we had no drug therapies that were approved, and we had no significant drug therapies that had a great deal of promise, and when the final phases of development potentially for either disease modification or for treatment of symptoms, so this is extremely encouraging.

I anticipate based on the basic science that we will have several other new medications for both symptom management as well as for disease modification being studied in the next year.

Andrew Schorr:
All right. Well it’s all about a dialogue with families affected by this, getting the testing information as the disease might be developing to have an active dialogue with neurologists such as yourself who are involved in the science and the treatment. Thank you so much for being with us Dr. Rajeev Kumar from the Colorado Neurological Institute. Thanks for being with us on Patient Power.

Dr. Kumar:
It’s been a pleasure.
Andrew Schorr:
This is Andrew Schorr reporting from the American Academy of Neurology 2009 meeting in Seattle, and as I always like to say, knowledge can be the best medicine of all. Thanks for joining us.

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