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Alzheimer's Disease: What Does the Future Hold For Treatment?

Alzheimer's disease is a devastating condition that will cause an incredible burden on our society. What does the future hold in terms of promise for treatment. Welcome to The Clinician's Roundtable on ReachMD XM 160, The Channel For Medical Professionals. I am Dr. Lee Freedman, your host and with me today is Dr. Samuel Gandy, Professor and Director of the Farber Institute For Neurosciences at Thomas Jefferson University and Chair of the Medical and Scientific Advisory Council of The Alzheimer's Association.

DR. LEE FREEDMAN:

Thank you so much for being with us Dr. Gandy.

DR. SAMUEL GANDY:

Thank you.

DR. LEE FREEDMAN:

Alzheimer's is on the rise as our population ages. What type of numbers are we looking at as we look to the future in terms of the burden of this illness?

DR. SAMUEL GANDY:

Well illness effect that that has of the over 85 population, so that threat is incredible. The cost of Alzheimer's alone will exceed the entire budget of Medicare by the year 2050. The numbers now of the affected people in the United States are in the 4 million range and that is going to quadruple really in the next 5 years.

DR. LEE FREEDMAN:

So the cost in dollars as well as the human cost is staggering?

DR. SAMUEL GANDY:

It will overwhelm many parts of the society, both the economic and the social structure of the society.

DR. LEE FREEDMAN:

Given that ominous forecast is there progress being made in terms of prevention or treatment of this illness?

DR. SAMUEL GANDY:

Well the way we look at Alzheimer's disease has really been revolutionized, I guess, since the 1970s. By that point, it was first recognized that senility was not an inevitable part of aging. Remember people living past 100 that were totally cognitively intact and ultimately it became clear that the main cause of this was a disease called Alzheimer's that had originally been attributed only as a rare disease of middle-aged people. The first patient described by Professor Alzheimer was 55 years' old and was thought to be this rare disease of midlife from really 1907 until the mid 70s, and then it became clear that senility that many of the older population were developing and being put away in nursing homes, looked just like this, thought to be a rare disease. So in the 80s then as biochemistry began to sort of mature and chemists and biochemists took on the problem, the proteins that build up in the brain began to be identified as well as how the proteins that were or the substances that were deficient. So the deficiency of acetylcholine was discovered and that was then immediately compared to what we already knew about dopamine deficiency in Parkinson's. So we thought well this will just be

a simple transmitter deficiency disorder and we will replace it and everything will be fine. That turned out not to be the case. There are proteins that build up both between these nerve cells and inside the nerve cells and the ones that build up outside form miliary spheres called amyloid plaques. They are amyloids of all different tissues that renal amyloid, cardiac amyloid. They are different in their amino acid sequence, but the structure of the deposits, the structures are all similar. So they all bind standardized diflavin incongruent. These are proteins that are produced normally and exist in at least 2 different confirmations, ones that are shaped, that is soluble, but another that precipitates and forms these plaques.

DR. LEE FREEDMAN:

So we have this abnormal accumulation of beta amyloid plaque in the brain?

DR. SAMUEL GANDY:

That's right. Despite that, this substance, a soluble form for it has been deposited is made all throughout the body, all throughout life by every cell all throughout the brain and one of the great mysteries is why deposits only in certain regions of the brain and only in the brain, but we still don't understand. The first clue to the genetics was the recognition that people with trisomy-21 all develop Alzheimer's by their mid 40s and that then was followed a few years later in the mid 80s by the sequencing of amyloid and the discovery that amyloid was on chromosome 21. So that then immediately suggested that the reason people with Down syndrome were getting Alzheimer's was because they have a genetic overdose of amyloid. About 5 years later, the first mutations in amyloid were discovered that cause rare forms of familial Alzheimer's and since then other genes have been identified that all converge on the amyloid pathway. So we believe that Alzheimer's begins with the formation of amyloid. The other sort of not so rare, but not very common dementia, the frontotemporal dementia may be responsible for 15% of all dementia. This is also due to mutations, but that is due to mutations in the protein that builds up inside nerve cells. Protein called Tau that forms the skeleton of the cells. If you mutations in the Tau gene, you get frontotemporal dementia with just tangles in their plaques. If you have mutations in the amyloid, you get Alzheimer's disease with both plaques and tangles.

DR. LEE FREEDMAN:

So it would seem to me that if we were starting to understand the genetic basis for this, there certainly is possibility for intervention and to change some of these genes and perhaps prevent.

DR. SAMUEL GANDY:

The genetics has really been the turning point, because it enabled us to only to have rational therapy because before you always thought pathology, whereas it was the burned out neurons destroyed, accumulation of amyloids in tangles and no way of knowing what came first and what came second. So the genetics told us that amyloid came first. The genetics also gave us tools to model the disease in laboratory animals, usually mice. Turns out that the mouse amyloid gene is slightly different from ours, so mice never get Alzheimer's. Mice no matter how long they live, their amyloid doesn't clump the way ours does. So we only began to be able to model Alzheimer's in mice when we put in the human gene or transgenic mouse. We take the human Alzheimer genes, the mutated human amyloid genes, put them into a mouse ovocyte as the egg is being fertilized, we just put in this human gene that gets incorporated into the mouse's DNA genetic material and that mouse then expresses the human gene and now we have a mouse that has amyloid plaques. So is it really what happened from there was that biochemists and cell biologists began to study amyloid metabolism and cell culture in dishes and then these mice and notions began to come along that would cure the mice. Approaches that we could intervene and either usually most effectively prevent the mice that had the human genes, prevent them from getting the Alzheimer pathology.

DR. LEE FREEDMAN:

If you have just tuned in, you are listening to The Clinician's Roundtable on ReachMD XM160, The Channel For Medical Professionals. I am your host, Dr. Lee Freedman, and with me is Dr. Samuel Gandy, Chair of the Medical and Scientific Advisory Council of the Alzheimer's Association and we are talking about future directions for treatment of Alzheimer's disease.

Dr. Gandy with these understandings are there specific products now that have been looked at that may soon come into practice?

DR. SAMUEL GANDY:

The strategies aimed at amyloid really fall into 3 different categories. There are immunotherapies and there are those in clinical trials, those vaccines in which the amyloid is used like a flu shot or if infusion by chemotherapy that have the antibody already made synthetically. That's in phase 2 and phase 3 clinical trials now. There are medicines, there is one called PBT2 that helps to keep amyloids dispersed, to keep them from clumping, so the brain can deal with it. That's also in phase 2 clinical trials. There are some medicines that are also aimed at the tangles. Now we know the tangles may be important in how the nerve cell responds to amyloid

poisoning or amyloid toxicity. There are some people who believe that if you stabilize the tangle, the Tau protein that the nerve cell might actually be able to resist the amyloid poisoning. So a medicine called Rember also, its actually a derivative of methylene blue in a preparation that used to be used for urinary tract infections seems to help to stabilize the skeleton of the nerve cell and help it cope with these in animal models and in phase 1 and phase 2 trials looks somewhat promising. We only in the past 6 months heard of the first medicines that like this that are aimed at tangles. We have had some amyloid therapies for almost 10 years now, but these medicines for tangles are new. Another one which is also very promising that's called demabond has a very, very strange history. It's not clear exactly how it fits into the plaque and tangles story. This is a medicine, its in phase 3 trials now, there is a lot of safety data behind it and the FDA has been very encouraging about how its going to go. You may have watched the series finale of Boston Legal, the William Shatner character was suing for access to demabond, but it was an antihistamine in Russia used for initially for hay fever. The Russian scientist was screening drugs to try and find a medicine that would combine the actions of cholinesterase inhibitors and Namenda. This is what he pulled out. He then gave it to aging rats and their memories improved and ultimately a small biotech company in California saw the data, was convinced there was something there and did a clinical trial in Russia, but with scientists that were overseen by clinical trialists from the United States who are among the best in the world and that report came out in Lancet by the summer and is clearly better than anything we have. There is improve of cognitive function over the first 4 to 6 months and stabilization for up to 18 months thereafter and that's better than anything we again assuming that's repeated and that's confirmed, that looks better than anything we currently have.

DR. LEE FREEDMAN:

And as an antihistamine I imagine well tolerated and as you say lot of safety data behind it.

DR. SAMUEL GANDY:

That's right, yeah, I assume it looks very safe and the cognitive benefits, you know, again as it was reported, really very striking.

DR. LEE FREEDMAN:

I have seen some reports about insulin or hypoglycemic drugs?

DR. SAMUEL GANDY:

So it seems that, I mean I am sure you are aware that people with diabetes have increased risk of vascular disease including cerebrovascular disease and there is some link between that, between cerebrovascular disease and Alzheimer's. It is no longer thought of there is this clear distinction between degenerative dementia on one hand and vascular on the other. There is a big overlap and vascular seems to increase the risk for the Alzheimer's. Diabetes seems to play into this in someway, it is not clear whether its because the diabetes is aggravating the vasculopathy, the vascular pathology or whether insulin cells is playing a role. There is exploration of that disease, they are just trying to really try to understand what the link is between diabetes and Alzheimer's and of course if we can understand better, perhaps we can aim novel therapies, especially as people who have diabetes are at increased risk for Alzheimer's.

DR. LEE FREEDMAN:

Very interesting and as you look to the future, are there any treatment paradigms or there can be combinations of the immunotherapies with the other therapies, any feel for that.

DR. SAMUEL GANDY:

There are 2 sort of visions for the future. The first is that where we think we really need to get is prevention because we really don't know how to repair the damaged brain, damaged adult brain very well. The best thing we can do I think is to get to the point where we have either a blood test, a genetic test, or brain scan that predicts who is at the highest risk so they can start on medicines for plaques and tangles very early. By the idea of combination therapy the other thing that you mentioned is definitely on the horizon and we think that, it would take a page from the play book of cancer where we would use medicines that attack several different steps in the pathway and that way by hitting several different steps have a greater chance of shutting their pathway down altogether.

DR. LEE FREEDMAN:

I want to thank Dr. Samuel Gandy, the Chair of the Medical and Scientific Advisory Council of the Alzheimer's Association for discussing with us the future outlook for Alzheimer's, the incredible potential burden that it may be for our society, but then balanced by some promising new therapies and hopefully with more support for research, we will be able to meet this challenge.

This has been The Clinician's Roundtable on ReachMD XM160, The Channel For Medical Professionals. Thank you very much for listening.