Neuroscience of Human Movement
Department of Multidisciplinary
Indian Institute of Technology, Madras

Lecture - 75
Parkinson's Disease – Current therapeutic approaches & the future

Welcome to this class on Neuroscience of Human Movement.

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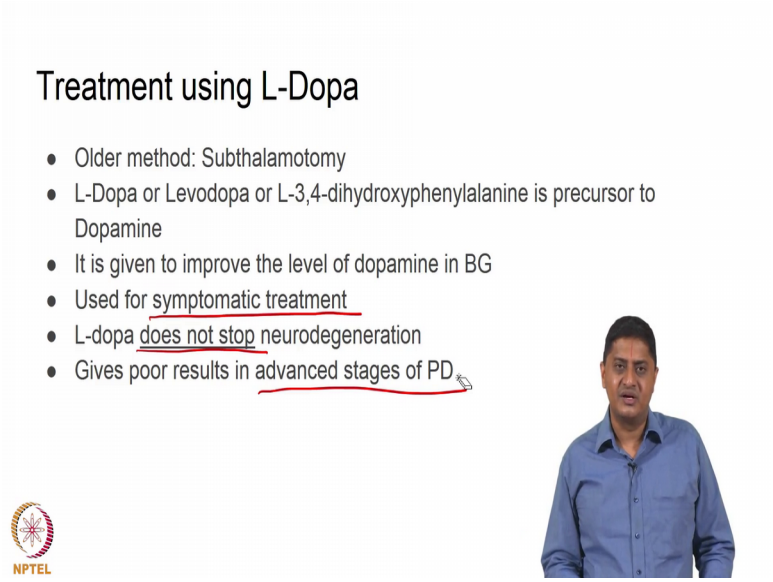

Subthalamotomy was the approach to treat Parkinson's disease. So, essentially what happens is that the subthalamic nucleus is removed right. This leads to reduction in inhibition thus leading to an improvement in the motor function right. So, L-Dopa or Levodopa is essentially L-3, 4-dihydroxyphenylalanine right. So, it is a precursor to dopamine right. So, removal of a carboxyl group from this actually leads to the amine; that is dopamine. So, what happens is that when this is taken this improves the amount of dopamine in the basal ganglia.

So, importantly here you are not treating the disease, you are not treating the pathology, you are treating the symptom. So, this is used for symptomatic treatment of Parkinson's disease. So, essentially you are managing the symptoms you are not treating the pathology. The pathology is degeneration of neurones in the substantia nigra pars compacta. It is not like taking levodopa if actually going to cause regeneration of these neurons in some sense right, that is one going to happen.

So, essentially also it does not even pause or stop neurodegeneration, L-Dopa does not pause neurodegeneration right. Unfortunately early on in the disease this gives very good results and very satisfied satisfactory results right, but later on in advanced stages the response of the patient to L-Dopa is less and less. So, as the patient's pathology progresses the ability of the patient to respond to L-Dopa reduces right. So, early on the patient response well, but as the pathology progresses the patient is no longer able to respond well ok.

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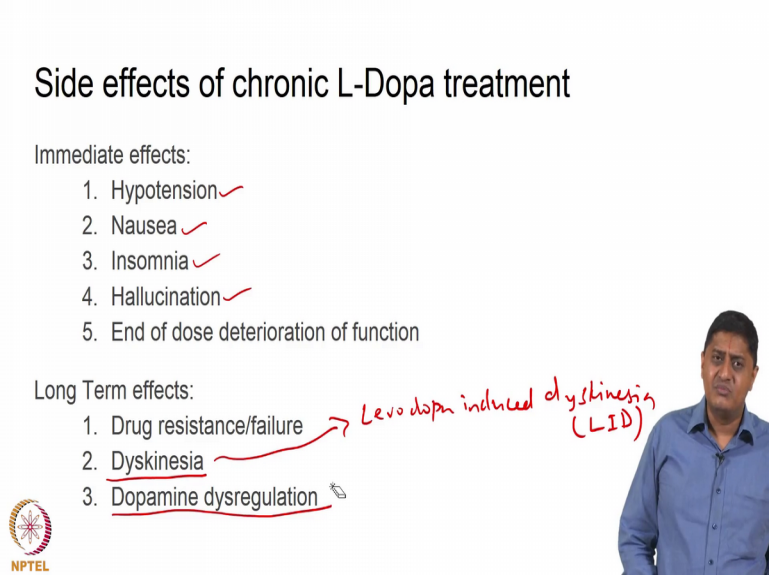

So, L-Dopa comes with it is own side effects, immediately after L-Dopa in take; there is hypotension, there is nausea, or lack of sleep, hallucination. Also when the dose ends or when the time of the dosage ends like it might be 12 hours in early cases, and it might be lesser in later stages of the disease; what happens is there is a deterioration of motor functions. So, essentially the motor function that was restored due to levodopa is now going back to it is original state so, which means that you have to take the next dose of the medication. So, this leads to a situation where the patient continue should depend on the medication for the motor function. But once again let us remember you are only managing the symptom, you are only treating the symptom not the disease, not the pathology right.

The long term effect is that you know resistance kind of situation where in the same dosage only produces lesser positive effect. So, early on the patient was able to manage

with the medication for about 12 hours, later on the patient can only manage for much lesser, so some sort of resistance like situation builds up. Then levodopa induce a Dyskinesia is developed; it is a very unusual and very difficult problem right what is called as Levodopa induced Dyskinesia right or in short LID and development. So, this is a situation in which the patient if he takes the levodopa; then he is going to have dyskinesia or unwanted movement. If he does not take the medication then he has no movements whatsoever.

Now, he has to choose between whether to have the medication and suffer its side effects or whether to not have the medication or suffer the pathology. So, it's there is no choice really one kind of suffering will continue. So, this is an unfortunate situation that happens in the long term with the intake of levodopa right. Also what happens is there is an amount of dysregulation of dopamine; so essentially a resistance kind of situation develops later on right. May be due to multiple factors, may be due to the role of receptors, or may be due to other factors right.

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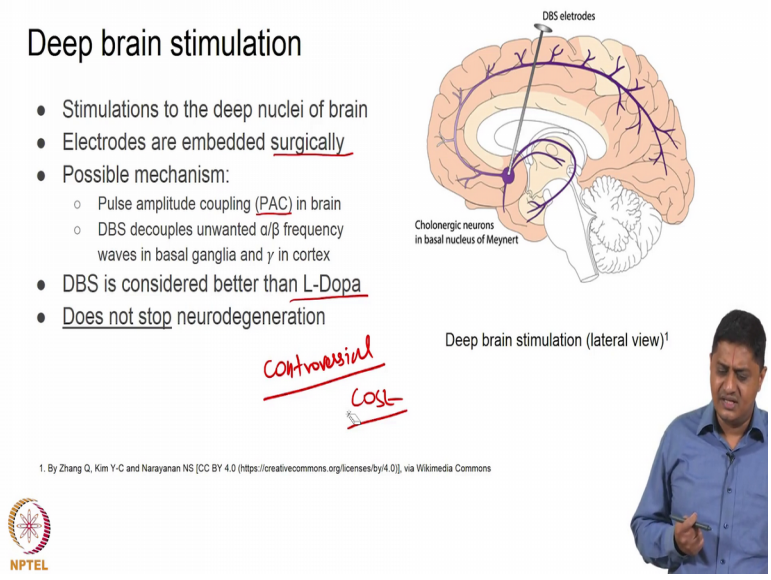

One alternative that has been suggested is deep brain stimulation, what this does is this implant pacemaker like devices deep inside the brain, specifically in the subthalamic nucleus for example. And so surgical implantations so these electrodes are embedded surgically deep inside the brain in the subthalamic nucleus and like you are activating a pacemaker, this system is activated using say a battery right. Now this is known to

improve motor function in patients right; actually how exactly does this work? Now that is not understood which is why this approach is in general considered a very controversial approach.

By the way not every patient can take this that is one the physician only can make the decision on whether a patient is suitable candidate for this. Not just that since we do not understand; how this works, or why this works, right. Because, of that reason because we do not understand how or why deep brain stimulation works. It is not clear which particular cases will result in what kind of improvements. So, that is continuing to be a case of trial and error type of improvement. A lot of information is now available still there is not a clear understanding of how or why the brain stimulation works right.

Several mechanisms have been proposed and speculated and one is that there is PAC or Pulse amplitude coupling in the brain between different regions. Now deep brain stimulation essentially decouples this alpha and beta frequency waves in basal ganglia inhibiting the gamma activity in the cortex. Thus, reducing the abnormal activity in the cortex and improving the possibility that the cortex can actually work in a more normal fashion. Now, that is probably the reason why deep brain stimulation is effective; these are just hypothesis we actually do not know how or why deep brain stimulation works. And why some patients are respond better to deep brain stimulation than others right.

In general this is considered better than L-Dopa and in general patients for whom L-Dopa fails to function right or probable candidates for DBS of course, there are multiple reasons there are multiple factors that are considered before making a decision on that. Of course, cost is a consideration it is a very expensive procedure, it is a surgical procedure. So, the moment you say surgery the cost associated with the surgery come into the picture. So, it is a more expensive procedure and it is a controversial procedure because we do not understand what is causing this positive effect right.

And also it turns out that a particular frequency right if it does not work right. Then the patient will have to go back to the doctor and the doctor will reset the frequency of the stimulation; to something else that will actually work. Now at that point it is not clear why the previous frequency did not work and the current frequency is now working. It is also not clear why the current frequency did not work earlier in the first attempt and why is it working now. A lot of confusion so which is why this procedure remains

controversial people are trying to understand the physiology behind this, the exact pathophysiology and the improvement due to this continues to be elusive for us.

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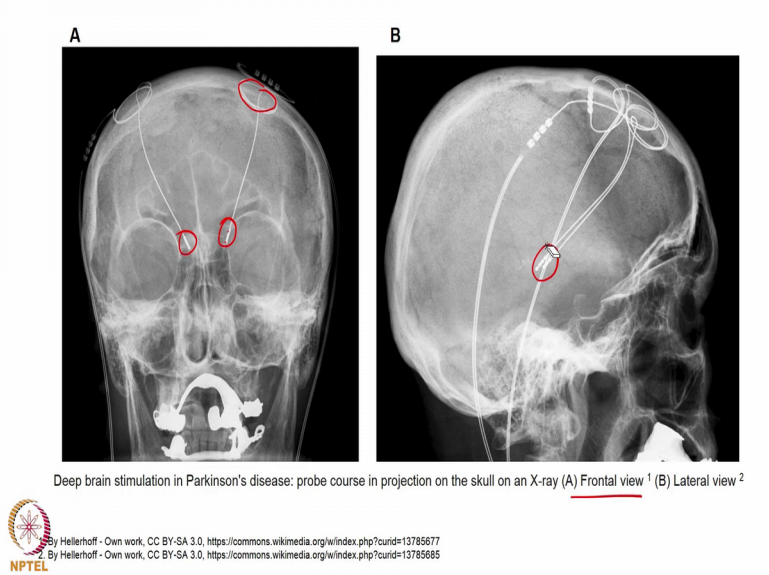

So, here is X-ray picture showing the electrodes the probe course in projection on an X-ray; this is the frontal view so there you see the implant so that there. So, that is the electrode that is where you see in the lateral views also that is where you see right, by laterally on both subthalamic nuclei right.

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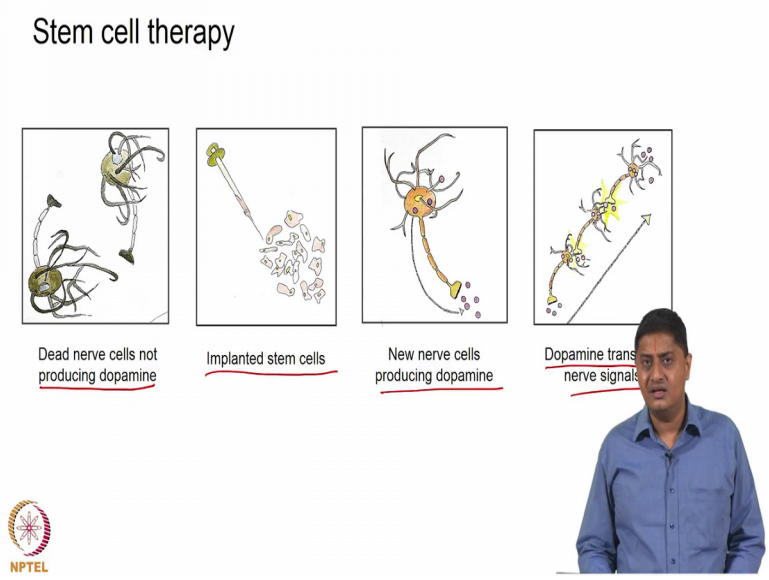

Well the other approach is also controversial we know that the neurones in the substantia nigra pars compacta degenerate or die and so they cannot produce dopamine right. Suppose you can implant these stem cells in the particular region and they can now produce a dopamine. Then this dopamine or this dopaminergic neuron, then communicate information then it transmits signals. Then you essentially have a situation that is very similar to the natural system. Of course, many of these steps have to be crossed to reach that point.

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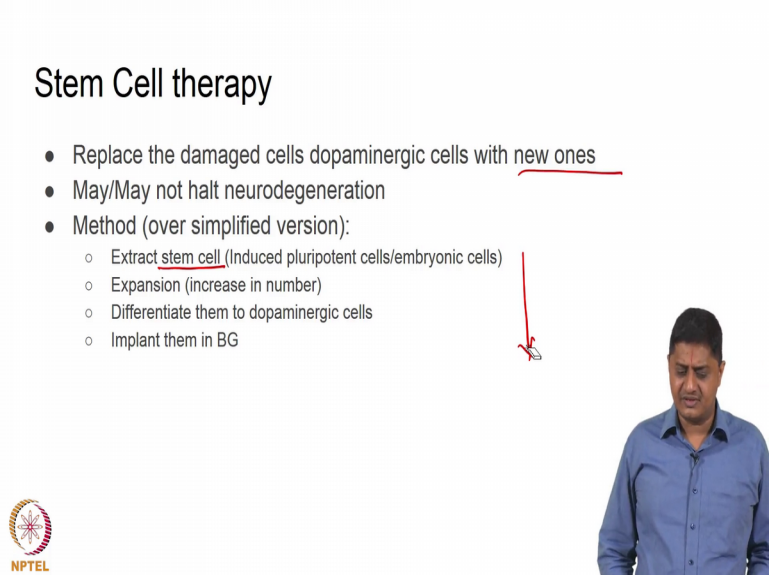

What are the steps? Essentially replace the damaged cell in the dopaminergic area with new cells. Let us remember that it may or may not halt neurodegeneration most likely it will it is not going to halt neurodegeneration. An over simplified version of the method is you have to extract the stem cell right and allow it to expand in number and differentiate them into particular type into the dopamineric type, and then implant, then in the BG. Looks super simple right, but very difficult to cross all these steps and this particular this technology is not yet ready for use in humans.

Where, it again also other problems come with this like other than the fact that in DBS we do not understand the pathophysiology. And why the pathophysiology in what sense there is improvement that is not understood. In this case there are also ethical concerns and other concerns that come with this. In general whenever you say stem cell therapy that is some concern that happens it is still and open and hard area of research.

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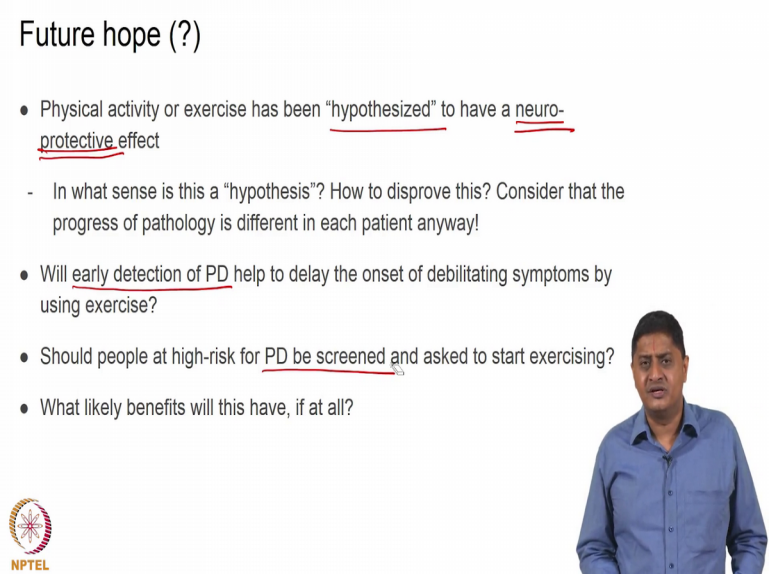

Then the question is; what is our future hope? So; that means, there is no hope. So, L-Dopa is going to work only for some time and DBS is a controversial approach; we do not know why or how it works. And stem cell therapy is again a controversial approach. What is our hope? Well physical activity or exercise has been hypothesized to have a neuro protective effect, very important to underline that. Essentially neither L-Dopa nor DBS nor stem cell therapy have a neuro protective effect, it does not save the dying neurones right.

It is believed that physical activity or exercise can have a neuro protective effect. The question is; in what sense is this hypothesis? Because, a hypothesis is a particular statement that can be disproved; how can you even disprove this? In that sense it is very difficult to even consider this to be a hypothesis. Consider that the pathology is progressing at different rates in different patients. So, essentially it is not like I can take two groups of people and ask one of them to exercise and leave the other without exercising right.

If you know that both of these people have both of these groups have Parkinson's disease why would you not ask the other group to exercise or why would you ask the other group to not exercise right that is controversial. It is not just that you can also identify groups of individuals who are predispose to developing the pathology. Suppose I know this particular person is highly likely to develop Parkinson's disease; let us say

based on family history, let us say based on genetics, let us say based on a whole bunch of analysis I am able to predict. For example, that this person is highly likely to develop Parkinson's disease. Well then again you do not know if the person will surely develop Parkinson's disease.

Then your advice is ok; go and exercise and the chance that you will develop Parkinson's disease is going to reduce. Let us say that the person does not get Parkinson's disease, is it because the person did not develop other symptoms other situations that actually lead to the pathology or is it because of exercise. In that sense you actually cannot control that experiment that is the problem. So, in what sense early detection of Parkinson's disease; let us say that we are having a device a magical device that is going to help you detect the onset of Parkinson's disease much before the patient actually presents right. I earlier said that about 80 percent of the pathway is already compromised right.

By the time the patient presents to the clinic 80 percent of the dopaminergic pathway has been compromised. Suppose I could detect this early somehow right; what can you do? Is not like you know you can start levodopa early. Because levodopa shelf life is limited it is going to work only for so many years after that it is not going to work. So, you start levodopa on this people earlier lot of confusions right. So, will early detection of Parkinson's disease is it going to help; to postpone the debilitating symptoms by some more years if the person starts exercising. Is it going to help or is it that this persons is having a slow progress anyway.

Let us different patients have different rates of progress right, not every patient is the same. So, because of this reason you do not know to what extent a particular patient is getting helped by that pathology right. So, should people at high risk for Parkinson's disease be screened and should they be asked to start exercising. Well everybody should start exercising, but is this going to actually work; again we do not know. What are the likely benefits if at all, if at all there is going to be some benefit what are those benefits; again that is not clear. So, essentially a exercise and stem cell therapy and a deeper understanding of DBS offer some hope in therapeutic approaches towards stating Parkinson's disease right.

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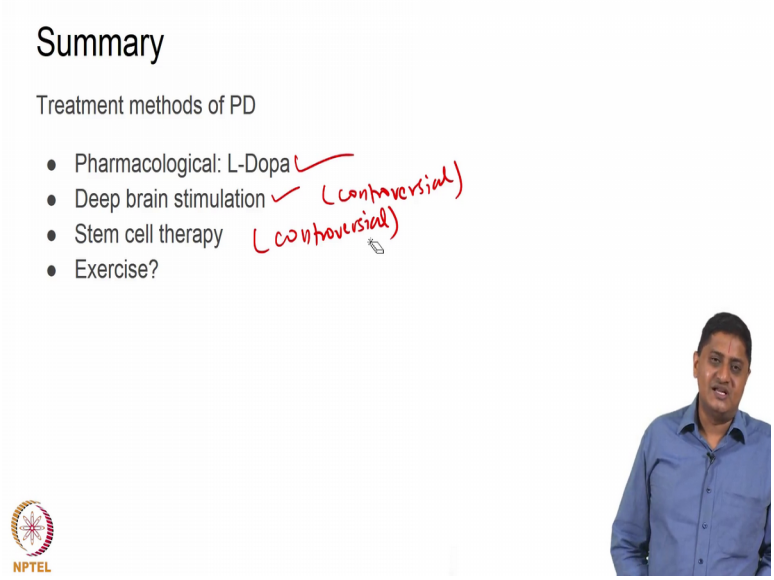

What we have seen in today's class is the therapeutic approaches towards stating Parkinson's disease. One is levodopa or L-Dopa which is a pharmacological approach, and the other is a surgical approach deep brain simulation it is a controversial approach, and other is the stem cell therapy again a controversial approach. Lot more research is needed before it can actually be used and the other is of course, exercise but exercise can help everybody not just people with Parkinson's disease.

It can help everybody, is it going to help people with high likelihood of development of Parkinson's disease to postpone the possible onset of symptoms; we do not know the answer to that question. So, I am offering more questions than answers at the end of this lecture. So, with this we come to the end of this lecture.

Thank you, very much for your attention.