Human Physiology
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Lecture - 05

Hello everyone, welcome to another new class on human physiology. In this class, we will discuss nerve injury and repair. In the last few classes, we have been discussing neurons; we discussed topics like our nervous system, brain, and spinal cord. So, let us see how the nerve formation happens, followed by whether there is any injury to the nerve and if there is any repair mechanism for it. So, let us stick with it. So, what different concepts will be covered? Basically, we will discuss topics such as nerve injury, different types of nerve injury, and how it affects various areas of the nerve.

Then we will see the processes of nerve regeneration; we will discuss the Wallerian degeneration process followed by the nerve regeneration process. So, we are not going to have too much of an introduction, but as you remember, neurons are like the unit cells of the brain and the spinal cord, which are the most important cells in terms of this neuronal transmission process. And the bundle of neurons when they combine together is called a nerve. And then the nerve is basically bringing these sensory responses from the environment, and it sends the sensory responses via the spinal cord to the brain, and once those responses have been processed, the motor signals via the motor nerve go out to different types of skeletal muscles and the organs.

In this way, we kind of perform like neuromuscular functions, right? And in cases of different types of nerve injury, there can be crush injuries, cut injuries, or other forms of injury. And in the case of any nerve injury, what happens is that there can be loss or altered sensation. It can observe muscle weakness or paralysis, for example. There can be continuous pain, tingling, or numbness in various areas, maybe in the fingers or the toes. In severe cases, it can also impact organ function.

So, let us see, as we already discussed in our last class, how the nerve structure is, right? So, basically, if we have a spinal cord dissection, you can see that this is the posterior part and this is the anterior part, and from this posterior part, the dorsal root of the nerve came in, and from the anterior part, the ventral root of the nerve came in, right? So, you can see that when both this dorsal part and the ventral root combine together, it is called a spinal nerve. So, basically, combining the ventral root and the dorsal root together combines with the spinal nerve and the membrane of the spine, forming a combined spinal nerve called the epineurium. Now, from this, like the nerve, if you look closely, you will see there are a lot of bundles of vesicles. So, you can see there are a lot of bundles of fascicles which are called fascicles. So, if you remove one bundle of fascicles, you will see that there are again small and smaller fascicles, but this coil of nerve is also like a combination of a lot of neurons.

So, this membrane is called the perineurium, and I mentioned in the last class why this perineurium layer is important, especially in cases of significant nerve injury. So, in cases of nerve injury, As long as this perineurium layer is intact, then the doctor can basically pull one perineurium layer to another distant perineurium layer. So, basically, the doctor can combine this multiple perineurium layer of the injured area, and they can kind of stimulate nerve regeneration. So, at least we need to have an intact perineurium area in order to surgically mix the nerve for nerve regeneration purposes. If the perineurium area is also damaged, then the doctor may find it difficult to perform a surgical nerve regeneration procedure.

So, you can see from this coil of fascicles that there are small, small fascicles for that. So, if you pull out one more fascicle, you will see that there is a single neuron. In the single neuron layer, there is a membrane that is called endoneurium. So, there are three membranes in total: the whole spinal nerve, which is called the epineurium. From the epineurium layer, if we remove a bundle of vesicles, that particular membrane is called the perineurium, and we say that the perineurium layer is highly important because doctors can perform medical surgery to join or fuse these two perineurium areas.

In order for nerve regeneration to occur after a significant attack, gunshot, injury, or car accident. There might be a patient that needs to surgically fuse these two perineurium areas for a nerve regeneration process. And then from this area, if a single physical can be pulled out, you will see a single neuron, and the membrane of the single neuron is called endoneurium. And this neuron can perform like either sensory applications; basically, it can have a sensory application, or it can also participate in the motor application. So, both sensory and motor applications are there.

Now, let us see what type of different injuries can happen to the nerve. So, basically, nerves can experience a cut from any sharp object that severely cuts the nerve. It can experience crash-related injuries, right? It depends on a compression of the nerve specifically from an accident. It can also be like dislocation, which is basically similar to stretch injuries, right? There can be the formation of tumors which cause stress or compression on the nerve. There can be high blood sugar that can damage the nerves, which is called diabetic neuropathy.

There can be other types of infections, such as herpes zoster in cases of shingles disease; there can be viral infections that can affect the sensory nerve. There can be different types of accidents, such as herniated discs; even toxins or certain chemicals can also damage the nerve. So, there are different sorts of nerve damage or nerve-like injury processes. But let us see some of those nerve injury cases and see exactly what the damage is in the neuron. So, if you kind of categorize the nerve injury into three categories, it is mostly in three types.

The first one is neuropraxia, which is the mildest and lowest form of nerve injury. Specifically in this case, no structural damage occurs to the axon. We will discuss them one by one. So, we will draw the picture and see exactly where the damage happens. The next one is axonotmesis, which is more severe compared to neuropraxia, and there is damage specifically in the myelin sheath of the axon.

The most severe form of nerve damage is called neurotmesis, where there is also damage to the axonal membrane, which is called the endoneurium. So, let us see one by one the different types of nerve damage and how they affect us. So, the first one is neuropraxia. So, this is like one neuron; you can see this is the cell body. So, this is one neuron; you can see this is the cell body, this is like the action area, right? This is the action area, this is the myelin sheath, this is the myelin sheath, right? This is the myelin sheath.

So, basically, what happens in cases of neuropraxia is that it is the mildest, or lowest, form of peripheral nerve injury, and it can be caused by compression or mild stretch, right? And what is the basic symptom that has been observed is that you will have temporary muscle weakness.

So, for example, if we put our hand below our head and sleep for a few hours, after we wake up, we will observe that there is a little time of muscle weakness or numbness in our hand muscles. So, this is basically a situation called neuropraxia, where you will see that the endoneurium layer is intact. So, it is important that there is no injury in the endoneurium area. Even though there is no injury in the axon area.

So, there is no injury in the endoneurium area; there is no injury in the axon area. What is mostly observed is that there is a little bit of demyelination that occurs in the myelin sheath. So, what happens? There is mild damage or demyelination that can be observed in cases of this mild form of nerve injury, which is called neuropraxia. And what it affects is basically, as you know, the myelin sheath, which increases the conduction speed. So, if there is demyelination, what will happen is that it will reduce the conduction.

So, basically, the conduction speed will be reduced. A good thing is that neuropraxia is a short-term phenomenon; within a very quick time, this condition reverts back and is completely healed. So, the next condition, which is called axonotmesis, is that in cases of axonotmesis, the endoneurium layer is intact. So, basically, the endoneurium layer is intact, but there is damage in the axon area; along with the axon area damage, there is also demyelination. So, basically, there is also moderate demyelination.

So, basically, there is also moderate demyelination along with the fact that the action is damaged; the action is not intact. And how and why can this happen? This type of injury can happen due to severe crash injuries or prolonged compression or stretching. As you can see, there is some damage in the axonal conduction; the block is a little more severe compared to the neuropraxia. But the good thing is that this injury can be healed. So, basically, this injury can be healed.

So, this type of nerve injury can be repaired via the process of Wallerian degeneration and regeneration. We will discuss after one or two slides. So, the good thing is that this can be healed or repaired, although the process of healing is very slow, depending on the injury, which may take anywhere from about 5 days to sometimes even 6 months; but still, the nerve injury can be completely repaired, and it can regain the conduction speed. The final and most severe form of injury that can occur from a severe accident or a significant cut is called neurotmesis. So, you will remember that in the last two cases, we said that in the case of neuropraxia, there is only a little bit of demyelination, but the action is intact.

So, let us compare them one by one. So, in cases of neuropraxia, you remember what we said: the myelin sheath is damaged, the axon is intact, and the endoneurium is intact. But in cases like axonotmesis, what we said is that there is myelin damage, there is axonal damage, but the endoneurium is intact. In both cases, there is a low to severe conduction block, but depending on the injury, it can be recovered through the process of Wallerian degeneration followed by nerve regeneration. But this is the most significant form of injury, which is the neurotmesis, where you can see there is not only damage in the axon.

So, basically, there is damage in the axon; there is demyelination, and along with that, there is damage in the endoneurium also. So, basically, damage to the myelin sheath, demyelination of the myelin sheath, damage to the axon, along with damage to the endoneurium. So, this is a significant form of injury called neurotmesis. So, in cases of neurotmesis, remember the myelin sheath is damaged, the axon is damaged, and the endoneurium is also damaged. Now, let us see in these cases what happens if the endoneurium is damaged; then the chance of nerve repair is almost nonexistent, and in this case, because the endoneurium is damaged, the doctor cannot, naturally, repair it.

So, basically, it cannot repair naturally. So, the doctor has to go for a surgical repair process. So, what I said in the last slide, if you remember, a few slides before that, is that the doctor can eventually connect the perineurium area. So, the important thing is that if the endoneurium is damaged, natural repair would not occur, but the doctor can still find those coils of the perineurium layer and fuse them together for a surgical regeneration process. So, although natural repair is not possible, surgical regeneration and repair are still possible.

Now, let us see how the process of nerve regeneration happens in cases of both neuropraxia and axonotmesis. So, let us see the process; the first process we will discuss is Wallerian degeneration. So, this is one of the only very cells where degeneration happens before regeneration. So, the repair mechanism—basically, you have to remember that the repair mechanism is combined first with degeneration, followed by regeneration. So, first the cell gets degenerated, then it is followed by its regeneration.

So, what are the different steps? Let us see. So, this is a neuronal cell; let us consider that there is myelin demyelination. So, there is a demyelination that happened; along with that, there is an injury in the axon, and there is also an axonal injury. So, let us see a condition called axonotmesis due to a severe crush injury. Then first, what will happen is that you can see this process, which is called chromatolysis.

So, this step of chromatolysis will happen, where you see the cell body; the size of this cell body is large. You see from the initial size of the cell body that the cell body size becomes bigger. And this nucleus, which was initially located almost in the middle of the cell body, migrates to one end of the cell membrane. So, basically, the nucleus moves close to the membrane. And all these small nasal bodies are like small Golgi bodies or nasal bodies along with ribosomes.

All these ribosomes and Golgi bodies basically concentrate and surround the nucleus. So, what we said is that in cases of chromatolysis, the first step is that the cell body will grow. So, the cell body will become larger. So, the cell body will become larger. And once the cell body becomes larger, the next step is that the nucleus will basically move to this membrane area.

So, the nuclear nucleus will shift towards the membrane area. After that, all the ribosomes, Golgi bodies, and nasal bodies will come and surround this; they will get concentrated near the nucleus. And what will happen basically after the injury is that this nucleus will get a signal, and it will form a lot of growth factors; it will form a lot of proteins that are needed for healing. So it will form a lot of growth factor proteins and even some anti-inflammatory factors.

Protein, okay. So, that may kind of contribute in terms of reduction of stress; mainly growth factors and different types of healing proteins will help to regenerate the damaged area of the neuron. So, this process, the whole process, is called chromatolysis, okay. So, in the next process, you can see that, let us consider the damage that happens. So, let us go to the next slide.

Let us see if we have this. Action if we have this action right, if we have this action and the damage happens in between this action. So, there is in between damage happens. So, there are like two areas, right? One is the proximal area. So, basically, this is the proximal area, and this is like this terminal area, which is called the distal area. So, basically, two steps will happen in both cases of the proximal segment and in cases of a distal segment.

So, let us see, one by one, what changes will happen in the cases of both the proximal segment and the distal segment. So, what we said in the last slide, if you remember, is that chromatolysis will happen right after that. Let us go to the next slide. So, in this injured area, for example, there are a lot of myelin sheaths, right? So, a lot of myelin sheath is there in this injured area. What the cell will basically do is, it will eventually chop off the adjacent node that is near the injury.

So, what we just said is that after the chromatolysis process in the proximal segment area, the cell will basically degrade or chop off the near myelin sheath area adjacent to this injured site, and you can see this is happening in this proximal segment area. So, this is happening near the proximal segment area. And let us see what happens in the distal segment area. So, what we just said in the case of the proximal segment area is that it will chop off the adjacent myelin sheath. So, this is one form of degeneration that is happening, and then in the distal segment area, also initially if there is this myelin sheath.

So, there will also be a myelin sheath in the distal area. So, it will also degenerate. So, basically, it will also get degenerated, and once it degenerates, you can see that slowly it will also degenerate the axonal area, leaving this type of axonal fragment residue. So, basically, it will also start to degenerate the axon, leaving axonal fragments. What else will you leave? All the myelin sheaths in these distal areas are degenerated, right? The axons are degenerated; slowly, they left like different types of axons, like a kind of residue.

And what else is left? There are these Schwann cells, basically, these glial cells which are also called Schwann cells. These cells are eventually left, not in high numbers, but maybe in few numbers. Now, what happens is that this endoneurium layer, right, you can see this endoneurium membrane layer of the axon, starts to secrete different types of molecules, for example, serotonin and histamine. So, these molecules, once this endoneurium layer secretes, attract macrophages. So, what does it attract? It attracts macrophage cells, and you know that these macrophage cells are immune cells, right? So, basically, what we just said in the distal segment area is that initially, it is degenerating like the myelin sheath, then it starts to degenerate the axon area, leaving some small axonal kind of membrane residue.

After that, there are also a lot of degenerate Schwann cells, but few Schwann cells may still be left. Now, from this endoneurium area, it starts to secrete different molecules, for example, serotonin and histamine, that attract immune cells like macrophages. And once this macrophage comes, basically it will start to kind of chop off a lot of this cellular debris. So, eventually a lot of this cellular debris will be chopped off, all this axonal-like debris, so this whole part will eventually be chopped off. So, once all this part is chopped off, what will be left? So, once all parts are chopped up, we will be left with the distal segment, and there is basically some amount of Schwann cells, a little bit of myelin sheath, but all these damaged areas in the distal part will be completely degenerated by the activity of the macrophages.

So, this whole process of degeneration is called Wallerian degeneration. So, we thoroughly discussed a few steps. Before we go to the degeneration, try to recapitulate again from the last slide. So, in cases of injury, what we say is that the first step is chromatolysis. In the case of chromatolysis, what happens? First, the cell body becomes larger.

The nucleus comes near the membrane area, and then the nucleoli, ribosomes, and Golgi bodies concentrate around the nucleus, which, in response to the injury, starts to secrete different growth factor proteins, such as anti-inflammatory factors. And after that, changes happen in the proximal segment, which means that the surrounding myelin sheath may completely degenerate. So, changes happen in the initially proximal segment. After the change in the proximal segment, the change in the distal segment happens. So, basically, on the distal side, what will happen initially is that degeneration will occur: degeneration of myelin sheath will occur, degeneration of the axon will occur, leaving different cellular debris with a few Schwann cells.

Now, the endometrium layer or the endoneurium layer will basically secrete different molecules, for example, serotonin and histamine, that will activate or attract macrophage cells, which are immune cells, and these immune cells will basically remove all the cellular debris from the distal segment area, along with some of the Schwann cells as well. Eventually leaving like the clean part of the distal segment. So, we now have a clean part of the proximal segment. So, basically, what are we left with? We are left with the clean part of the proximal segment. With myelin sheath and so on, cells will also be left with a distal segment containing some myelin sheaths and so on.

And in this last stage, finally, the cell body will become normal in shape. So, the cell body will also become normal in size and shape from the initial enlargement. So, whenever this Wallerian degeneration happens, the last step is regeneration. So, you can see what we now have: we have one proximal segment, right, and also we have this distal segment. So, we now have both the proximal segment and the distal segment, right? And these have myelin sheaths with the Schwann cells, okay? So, this has the myelin seed with one cell switch.

Now, you can see from these two areas that it starts to generate some axonal sprouts. So, you can see that it starts to create the axonal sprout, and this axonal sprout can eventually, very slowly, migrate from the proximal area to the distal segment area. So, once in the last stage of regeneration, this different growth factor and the protein eventually emerged. So, basically, different growth factors or different healing proteins. So, different growth factors and healing proteins that are synthesized from the nucleus are packaged in vesicles and go to the injury area, promoting the release of axonal sprouts.

So, basically, it promotes the release of axonal sprouts. And these sprouts basically migrate from the proximal segment to the distal segment area. And very interestingly, you can see that these Schwann cells—the green ones—direct the axonal sprout migration. So, Schwann cells are basically acting to give them directionality so that the sprouts can eventually migrate from the exact proximal area to the distal segment area in order to complete this gap. Once this axonal sprout reaches the distal segment area, what happens is that slowly those healing proteins eventually start to act together, causing the axon to be regenerated and the myelin sheath, like the Schwann cells, to proliferate. After the axonal sprout generation and once it migrates to the distal area, the next step that has been seen is similar to axonal regeneration occurring.

So, basically the axonal regeneration happens. Then the Schwann cells get proliferated, and new myelin sheath formation occurs. So, new myelin sheath formation happens. So, in this way, the regeneration step is complete, and you can see that eventually the axon is basically regenerated. So, basically, the axon is regenerated, and the whole regeneration process is complete. One very interesting thing to remember is that this axonal sprout migration.

So, basically, this axonal sprout migration is a very slow process; it happens at a rate of about 1 to 3 millimeters per day. So, this movement of axonal sprouts from the proximal to the distal area is very slow; it takes about 1 to 3 millimeters per day. A few important things before we go to this table, and some more things to remember. So, basically, let us consider that this is our action, this is our action, right? And this is the proximal area; this is the proximal area. Now, if the injury happens, basically between these are the myelin sheaths, right? These are the myelin sheaths, and in between the myelin sheaths is what we call the node of Ranvier, right? If the injury happens here, what will happen? Initially, this will get degenerated, right? So, it will degenerate, creating like the proximal segment, and of course, the process will happen in the distal segment also.

But let us consider the injury that happens here. Let us consider the injury that happens here, and as you can see, if the injury happens, then it will eventually degrade the adjacent myelin sheath, right? It will eventually degrade the adjacent myelin sheath, and that means if it degrades the adjacent myelin sheath, in these cases there will not be any Schwann cells left. There would not be any Schwann cells left, and what may eventually happen is that the whole cell body could get damaged. So, the whole cell body may get damaged and degenerated; the whole cell body may get damaged or degenerated. So, it is very important to know exactly where the injury happens; if the injury occurs a little far from the cell body, then only regeneration and healing are possible. If the injury happens very close to the cell body, it is highly risky that regeneration might not still happen in the peripheral nervous tissue.

So, in cases of CNS and PNS nerve regeneration, you have to remember that in the case of CNS, the glial cells, which create this myelin sheath cover called oligodendrocytes, inhibit regeneration and cannot remyelinate. And in this case, because of that particular reason, the CNS nerve finds it difficult and cannot regenerate. But in cases of PNS, the glial cells, which are called Schwann cells, can eventually proliferate and promote regeneration. In cases of growth factors in the CNS, it doesn't secrete too many growth factors; basically, it limits the growth-promoting factors, but in cases of the PNS, it forms a lot of different growth factors, for example, neuronal growth factor and other types of growth factors, which can promote regeneration. So basically, in cases of the CNS, a lot of myelin-associated inhibitory factors, like Nogo, can be seen.

So, basically, a lot of inhibitors, a lot of inhibitor molecules like NOGO, can eventually inhibit the myelin-associated regeneration. But in the case of PNS, there is no such inhibition that can be seen. In cases of immune response, a robust inflammatory response can hinder regeneration. In cases of PNS, there is a very controlled inflammation to clear the debris. Further, there are astrocytes from this dense scar tissue that block the axon extension.

But in cases of this PNS, very few astrocytes are present. So, this dense layer of astrocytes cannot block the axonal sprout movement or axon extension. So, this is very important for your exam: we need to remember that in cases of a CNS injury, it is highly difficult or almost impossible to regenerate the nerve. A lot of recent studies are going on in order to develop neuroregenerative reagents or neuroregenerative therapies. That may be successful in the near future, but naturally, injuries in the CNS are not possible to repair, while injuries to the nerves or neurons in the PNS are very well possible to repair. So, do you know that electrical stimulation can enhance regeneration? Also, do you know that the glial scar is a double-edged sword, and it can be both beneficial and harmful? So, activity question: which type of nerve injury involves Wallerian degeneration, PNS or CNS? Which type of nerve injury has the best prognosis for recovery? Which type of nerve injury often requires surgery? So, hopefully you are enjoying the human physiology classes.

If you have any further questions, please discuss them with us during the live session. You can also submit your question by email. So, hopefully, you like the classes on nerve injury and repair. So, we will meet with you very soon for another new class of human physiology. Thank you very much.