Overview and Integration of Cellular Metabolism

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Lecture 51: Nucleotide Metabolism – II (Disorders of Purine Metabolism)

Hello everyone, welcome back to our lecture session on Overview and Integration of Cellular Metabolism. We are continuing with Nucleotide Metabolism and this class will focus on disorders of Purine metabolism. In the last class we have discussed how purine is synthesized. So in this class we will be discussing how they are degraded, how it leads to a disease of I mean uric acid production and hyperuricemia we will be discussing about uric acid, we will be discussing about diagnosis and treatment of gout, we will be discussing other inbounders of uric acid metabolism, diseases that are produced due to defective purine catabolism as well as the salvage pathways will be covering it all. So regarding nucleotide degradation right we discussed how nucleotides are being synthesized in the last class purine nucleotides. So regarding degradation mainly what we need to know is nucleotides actually ultimately nucleotides are monomers of big DNA or nucleic acids right.

So whenever we are eating any animal protein any plant product they have got all DNA and RNA inside them right. So when they are degraded ultimately they are nucleic acids right. So nucleic acid actually can survive the acid of the stomach. However they cannot when they go into the pancreas they are acted upon by pancreatic nucleases.

Nuclease means the enzyme which cleaves this nucleic acids right and also intestinal phosphodiesterase you know DNA RNA those are basically nucleotides connected by 3 prime 5 prime phosphodiester bond. So the enzymes that breaks those bonds are known as phosphodiesterase. So when these nucleases and phosphodiesterase enzyme acts on them they are hydrolyzed basically they are hydrolyzed and they are broken into small nucleotides. However since they are they cannot pass through the cell membranes the phosphate group is actually broken of further and they are ultimately turned to nucleoside. Very important last class we already discussed about nucleic acid chemistry what are nucleobase nucleotide nucleoside it is a very fundamental thing you should remember both using synthesis and degradation.

Next nucleosides may be directly absorbed by the intestine or may undergo further degradation to free bases right. So, 2 enzymes mainly act on that number 1 nucleoside days enzyme which can cover the I mean convert the nucleoside to free base and ribose sugar basically these are the 2 things that make up nucleoside. There is another enzyme that is nucleoside phosphorylase what it does it requires an inorganic phosphate which acts with the nucleoside and it converts the whole thing to a base and one ribose 1 phosphate all right. So, these are the 2 basic mechanism right that it is true for all nucleoside. Now if we look into the I mean biochemical path where these 2 enzyme fits this will be it all right.

So, you can see via the in the first step all the nucleo they are being first broken down by nucleotidase all right. So, now, what is happening nucleotidase is breaking down all of them to their corresponding nucleosides all right. Next what is happening nucleoside phosphorylase is again breaking down these nucleosides to ribose 1 phosphate as well as simple bases. Over here this pathway shows the application of nucleoside phosphorylase, but know this there are also nucleosidase enzyme that can directly convert this nucleoside into base and ribose that is not shown here we are showing nucleotidase because when there is phosphate these are nucleotides all right. One very important thing over here you can see all of this pathway right they are converging to this molecule that is xanthine which is actually acted upon by the enzyme xanthine oxidase to produce uric acid.

You know the xanthine oxidase enzyme has got some specialty what you need to remember it contains an FAD molybdenum metalloenzyme and iron it also requires iron as a cofactor. And this reaction is one of the reaction rare reaction that produces reactive oxygen species all right. So, H_2O_2 is produced in this reaction. What else do we need to observe in this or remember from this chart xanthine oxidase acts not only once, but also twice you can see hypoxanthine to xanthine conversion also occurs by the same enzyme that is xanthine oxidase this reaction also produce hydrogen peroxide. And adenosine to inosine this conversion is done by the enzyme adenosine baminase which is also abbreviated as ADA.

Whenever we are later in the later in the slide when we are discussing various disorders all these names will be very handy. So, adenosine baminase, purine nucleoside phosphorylase, xanthine oxidase all of them are very important right. So, why at all we are bothered about these disorders of purines all right purine metabolism disorders why they are so important is very important because these disorders may present with many variable symptoms right. So, they can range from a simple rise of uric acid to kidney failure to a condition where uric acid rise leads to inflammation of joint known as gout it may lead to neurological effect like seizure muscle weakness it can do developmental

disorder mental retardation. It also all of these some or the other purine metabolism disorders exhibit these features compulsive self injury and aggression I mean self harm right immune deficiency deafness.

So, there is a varied range of symptoms the problem may lies in the purine metabolism defect all right. So, we should know that both purine synthesis and purine degradation may lead may have some problems due to which there may be many diseases which will be discussing very soon will have these features which are also overlapping among many symptoms. Now, what are the main mechanism the basic mechanism? So, two types of disorder may happen right specially that is one that may arise from blockage in purine nucleotide degradation pathway when you are considering the catabolic disorders of purine right. So, when purine is blocked from degradation next is increased activity of nucleotide degradation. So, either it is blocked from degradation or there is increased activity I mean there is excess production of waste products of purine all right.

So, under these two headings it may be classified broadly we will again be looking into the mechanism. So, the common symptoms that are produced when there is a block in degradation are immune deficiency all right myopathy that is muscle disorder and stones renal calculin means stones in the kidney. Whenever the opposite is happening that is excess or increased degradation of nucleotide the symptom are characterized by hyperuricemia and gout a common symptom that is renal stones and anemia or acute hypoxia all right. So, one of them may come as a multiple choice question and an all except symptom may be given. So, you need to be very mindful for example, immunodeficiency does not occur in diseases which are characterized by increased degradation of nucleotides all right it only occurs in a block of degradation pathway.

So, be careful. So, we need to know about uric acid we saw the final product in purine catabolism was uric acid right is the end product of urine metabolism in humans and whenever there is excess accumulation of uric acid in blood it is known as hyperuricemia all right. So, why what is the problem see uric acid is 268 trioxy purine now you already know how to number the purine nucleotide you can easily number this and you will find out the oxo or the keto group is in the 268 position right. Uric acid is actually highly insoluble therefore, a slight alteration in the production or solubility will increase blood level. See humans prefer urea as an excretary material uric acid we are not uricotelic we are uriotelic uricotelic are birds that especially those animals where they have got they have adapted in such a way that there is less water intake they prefer uric acid excretion uric acid is highly insoluble.

So, even if there is slight increase there will be problem in solubility and that is why due to pure solubility blood levels are usually at the maximum tolerable the our internal

homeostasis is in such a way. So, that the maximum uric acid that is produced is actually physiologically soluble any excess production or any problem that leads to an over level of uric acid I mean above normal will lead to insolubility and what will happen if there is insolubility we will be discussing very soon. Now you see uric acid is actually filtered through the proximal convoluted tubule and it is also reabsorbed I mean it is filtered through the glomerulus right it is coming out, but majority is getting reabsorbed in the proximal convoluted tubule. However, urine has got uric acid uric acid is a normal constituent of urine. So, where is that uric acid coming from if more than 90 percent is absorbed it is because it is also secreted.

So, uric acid is also secreted in the tubule. So, mind it in the renal tubule there is a process called reabsorption in renal physiology you must have read where the element or the compound of interest is being reabsorbed into the circulation and what is secretion when it is secreted by the tubular lining into the renal tubule something which is not filtered ok. So, uric acid is filtered reabsorbed as well as secreted right and this renal secretion it may be enhanced by some 10 drugs for example, probenecid sulfine pyrazone these are drugs that actually block tubular urate reabsorption and hence once it is secreted it cannot be reabsorbed and thus uric acid is excreted in urine this is one mechanism we should know and this concept will come handy later on whenever we are discussing treatment of hyperuricemia. Anyway 75 percent of living urate that is I mean living the bodies in urine the remaining 25 percent of uric acid is broken down by the intestinal bacteria that process known as uricolysis. So, again uric acid filtered majority reabsorbed again most uric acid is also secreted a high amount is secreted and of them I mean that the secreted amount is actually almost three-fourth of the uric acid is living the body by urine and one-fourth is actually metabolized or broken down in the gut via intestinal bacteria.

So, we have discussed hyperuricemia. So, what is hyper what is the cut off level beyond which we will claim it to be hyperuricemia the level you should all remember it is more than 7 mg per dl in male and more than 6 mg per dl in women. So, it varies the normal value in males and females are the reference range or the reference cut off value is different in male and female males generally have got higher level of uric acid why again the answer lies very soon. Now, how uric acid can be increased in blood right? If you conceptually think there are only two ways number one it is produced in excess right and number two the outflow is stopped. So, decreased excretion.

So, over production or under excretion these are the only two possibilities by which in uric acid level can be increased in blood right. So, what are the factors that contribute to uric acid I mean hyperuricemia very easy you can conceptually guess number one increase synthesis of purine which is also known as primary gout all right that is the

process by which the normal metabolism of nucleotides are enhanced all right. What is secondary gout? Secondary gout means the there is over production of uric acid not due to a I mean change in the pathway all right it is rather more and more destruction of purines related to some other cause all right there is more available material to be converted to purine that is the concept of secondary gout. Primary gout means over production of uric acid just like that without any underlying reason ok. Next excess intake of purine increase turnover of nucleic acids these are all reasons which will ultimately be degraded to produce excess purine.

So, generally what are the factors that are contributing to hyperuricemia? Number one as I have discussed sex plasma uric acid is higher in male than in females all right. So, males are more predisposed naturally to hyperuricemia. Next obesity if the person is obese people tend to have higher level of uric acid or urate in plasma remember in plasma it is present as urate crystals specially I means urate salt sodium urate right. Next diet it is a very important factor which contributes to hyperuricemia subject to it higher protein diet all right. For example, a person who is trying to build his body all right build muscle or due to any reason his dietary habit includes western diets these are there are more protein component in the balanced diet.

Those diet ultimately are broken down and also and naturally since it is high protein also produce high nucleic acids also rich in high nucleic acid and all persons who also consume alcohol chronic alcoholism specially all of these because alcohol the edible alcohol you can name any beer whiskey all any form of alcohol are also fortified with purines and they increase the amount of purine consumption purine will be degraded to form uric acid. So, all of these factors sex obesity diet they contribute to the hyperuricemia right genetic factor very important apart even if all these factors are controlled still it has been found the two different person will have different level of uric acid depending on something which is unexplained. So, it generally it is thought to be a polygenic mechanism by which uric acid or specially primary gout is performed right I mean is I mean exhibited as a clinical disorder. Next what are the conditions you can say disease condition that leads to increase uric acid production malignancy why malignancy increase more and more cancer cell production cancer cells degrade to form the nucleus degrades and then excess purine that leads to increase uric acid production. Ray's syndrome, dine syndrome, sickle cell anemia all are increased with increased cell turnover we will be discussing glycogen storage disease type 1 later.

Next again hereditary fructose intolerance what happens you know in hereditary fructose intolerance the enzyme that is deficient is that is your homework you should be able to tell us by now what is the enzyme that is deficient in hereditary fructose intolerance. Remind it is time that you start revising all your lessons because very soon

we will be starting integration of metabolism which needs mandates you to have a comprehensive idea about all metabolism carbohydrate protein lipid nucleotide right. So, that we can tie all together it is easier for you to understand. So, hereditary fructose intolerance should be something that you revise anyway I let me tell you in hereditary fructose intolerance the fructose is trapped as fructose 1 phosphate ultimately what happens since excess fructose is converted to fructose 1 phosphate there is depletion of ATP and more and more AMP needs to be produced to form ATP and more AMP production ultimately leads to more AMP destruction. So, increase production of nucleus types again the whole thing each and every one of them can be again due to a side medium chain acyl-CoA dehydrogenous deficiency excess production and decreased excretion all of these have got similar mechanism by which it can contribute to a higher uric acid production and leading to hyperuricemia.

Well the often we use the term hyperuricemia and gout synonymously mind it hyperuricemia is a clinical condition that is characterized by excess uric acid in serum that is more than level of normal. It can be a finding in routine examination suppose I have given my blood for routine screening I am a very health conscious person my blood glucose level is normal urea creating those parameters liver functions are normal suddenly I see my uric acid level is very high the what is the diagnosis I have got hyperuricemia, but do I have got gout no because gout is completely it it is used synonymously in most cases because hyperuricemia leads to gout, but gout is actually the disease where there is accumulation of monosodium murate crystal that are deposited resulting inflammation in joints and synovial membranes and I am basically joints all right. So, synovial joints are lead characterized by deposition of needle like monosodium murate crystal leading to acute inflammation excessive pain leads to production of this disease that is known as gout. What are the characteristic hyperuricemia, acute inflammatory arthritis means pain in joints also uric acid nephrolithia means formation of uric acid stones in the kidney all right. So, often it is a mono articular disease there are multiple reasons of joint pain there are multiple systemic disorders for example, rheumatoid arthritis osteoarthritis psoriatic arthritis there are multiple reasons you can find the reasons of arthritis in any standard textbook or you can even search online and you will get the answers, but most of them are characterized by multiple joint involvement.

Whereas, initially to start with gout almost always presents with involvement of a single joint and due to the gravity that is known as physiology uric acid crystals tend to get deposited in the lower part of the body and what is the most important joint in the lower limb that is great toe all right. So, metatarsophalangeal joint of great toe is most commonly the first affected joint is generally the first affected joint and pain isolated pain in right or left great toe with all the symptoms suppose age, hypurine diet, chronic

alcoholism should have a strong suspicion for gout all right. So, uric acid level should be checked. However, monosodium urate crystal which are also known as tophi are can be deposited in elbow, knee, feet, helix of the ear as you can see in the photos in interphalangeal joints. Now this disease was discovered very early it is not a recent disease because we have got purines in our system alcohol has been consumed since ages and purine degradation is also since ages, but even before it was discovered the pain in great toe was there and there have been references even ancient inscriptures that the disease where invisible demon is biting the great toe all right this is a illustration by James Gilroy in early 18th century 1799 all right.

So, mind it the pain in great toe is almost synonymous with gout this is a nice history of gout that you should keep in mind. Anyway as I discussed primary gout and secondary gout primary gout means again caused by either over production or decreased renal excretion or both mainly occurs in middle aged men, men are more predisposed, but the biochemical etiology is not known it is considered a polygenic disease. We cannot clearly pin point what problem I am having suppose I have been diagnosed with hyperleucomy just like that many individuals get diagnosed with more uric acid just like that males females irrespective, but males are more predisposed, but we cannot pin point a single reason if all other findings are all right ok. Whereas in secondary gout it can happen in both children and adult and it is characterized I mean there are underlying reasons that lead to in rapid tissue breakdown or cell turnover and that can also lead to I mean mechanism of gout by two reasons increased production or decreased clearance all right, but know this in primary gout there is no such obvious reason whereas, in secondary gout we can pin point this is the reason that has lead to increased cell turnover, increased nucleic acid turnover or some drugs that has lead to gout all right that is secondary. So, whenever you can pin point some reason due to which it is happening it is secondary to that disorder and in case of primary gout just hyperleucomy and gout is there, but no single etiology can be pin pointed.

So, what are the hereditary disorders that are associated with gout means these are the disorder that are in lying in the nucleotide metabolism pathway all right or there is some enzyme defect that is present since childhood. So, hereditary inherited those are number one AEG PRT deficiency hypoxanthine guanosine phosphoribosyltransferase we have discussed in purine salvage pathway. Superactivity that is more activity of PRPP synthase this is an enzyme that was regarded as the step 0 of both purine synthesis purine salvage pathway de novo synthesis salvage pathway as well as it will be required in pyrimidine synthesis. So, step 0 that enzyme PRPP superactivity or rather it is synthetase all right. Next glucose 6 phosphatase deficiency you already know Von Jerks disease or glucose glycosine storage disease type 1.

The problem in all of these what is the exact etiology we will be discussing later ok. So, we will be touching all of them one by one, but this is the rare variety of since we are discussing gout these are all the reasons that can lead to gout ok. So, there is one rare variety that is familial juvenile gout also termed as familial juvenile hyperuricemic nephropathy. So, it is a autosomal dominant type of disorder in which there is severe renal hypo excretion of uric acid. So, the clearance is actually defective all right due to problem in transporters of uric acid.

At first what happens the hypo excretion of uric acid is reported in the childhood and by the time the patient goes to adulthood renal failure can happen. So, ultimately the symptom of renal failure are presented in adult to generally at the third decade of life. However, in some cases it has also been reported that the disease has expressed itself in infancy. The main problem lies in hyperuricemia and gout since uric acid cannot be excreted properly it leads to accumulation in the serum leading to hyperuricemia and gout. Next it is a familial renal disease as it the name suggests since it is autosomal dominant the disease runs in family and generally there is low urate clearance with respect to the glomerular filtration rate.

So, normal clearance with respect to normal individual the urate clearance is actually very low. So, the common treatment for gout is actually inhibiting formation of uric acid. So, how can we inhibit formation of uric acid by attacking the enzyme that is responsible for uric acid formation and the most and the compound that are available with us to target that specific enzyme of uric acid degradation is allopurinol ok. It is a competitive inhibitor of the enzyme xanthine oxidase we have seen xanthine oxidase actually acts in a two phase. So, once xanthine oxidase is inhibited how in competitive inhibition the inhibitor is a substrate analog.

So, it actually so xanthine oxidase acts on hypoxanthine to produce xanthine. So, since allopurinol looks like hypoxanthine it can actually fool the enzyme. So, that it can uptake allopurinol and then uric acid will not be formed right generally alloxanthine is formed. So, see other than treatment with these xanthine oxidase inhibitor all right. So, there we also need treatment with so you can see there is also another inhibitor allopurinol and febuxostat febuxostat.

So, febuxostat so why we have got two drugs febuxostat has been discovered much later because one has got high renal clearance and one has got high hepatic clearance. There are scenarios in which there is hyperuricemia with renal failure. So, the excretion of allopurinol will be hampered and there are also situation in which there is hyperuricemia with liver failure then we to need to stick to febuxostat. So, depending on the patient condition we need to adjust the drug. So, both of them are actually xanthine oxidase

inhibitor.

However, in I mean apart from lowering the uric acid level we also need to control the pain and inflammation with the help of non-steroidal anti inflammatory drugs. We can also use uricosuric drugs like probenecid etcetera to increase the uric acid excretion right. Next those patients that do not respond to traditional therapy recently has been targeted with these drugs that is pegylated uricase. Uricase what it does it actually converts uric acid to allantoin which is easily excreted via the kidney. Not only that the tophi can also be surgically removed.

So, here you can see uric acid crystal is been present in the fifth proximal I mean carpal, phalangeal, metacarpal phalangeal joint and it has been removed ok. So, as I discussed what are the inborn errors of uric acid metabolism? Number one purine phosphoribosyl pyrophosphatase. So, PRPP synthetase ok this enzyme if it is more active what will happen there will be excess PRPP and as I told you PRPP positively affects uric acid production alright. Uric acid production and if uric acid production more it will be degraded more and more. So, this enzyme super activity can be can vary ok it can be very severe form which appears in infancy and there is a mild form which presents in adolescence in both the form kidney or bladder stone is the first symptom because of the excess production of uric acid apart from that gout impairment of kidney function may develop if they are not properly controlled alright.

The next enzyme deficiency that we need to know is adenylosuccinate lyase deficiency adenylosuccinate lyase as I told you I when we are discussing about purine synthesis you know purine synthesis this was a step 11. I told you by comparing it with urea cycle that aspartate is coming in fumarate is going out. So, this is the step where this enzyme if it is deficient the previous products will be accumulated AMP production will be hampered what we need to know is this is a disease which is characterized by neurological symptoms which includes abnormality, abnormal cognition, epilepsy, muscle wasting and feeding problems. So, mainly neurological symptoms are there in adenylosuccinate lyase deficiency alright. So, generally MCQ will hover around this the neurological symptom you cannot rule out adenylosuccinate lyase deficiency alright.

So, what that the in order of purine catabolism now we are strictly focusing on catabolism. The first disorder is adenosine deaminase deficiency or ADA. So, when adenosine deaminase is deficient what will happen adenosine cannot be degraded right. So, basically adenosine and deoxy adenosine both in ribo and deoxy ribosugars are handled by the same enzyme. So, what will happen their concentration will rise right ATP and DATP will rise.

What they do they actually inhibit the enzyme ribonucleotide reductase DATP in inhibits ribonucleotide reductase which is actually an essential element of DNA synthesis. Therefore, RBCs cannot proliferate that is cannot grow are WBCs white blood cells. So, major part of white blood cells are lymphocyte T cell B cell. So, their functions are defective and these white blood cells are actually cells that are imparting immunity to us. So, adenosine deaminase deficiency is actually named as severe combined immunodeficiency.

So, the immune system is highly compromised whenever the immune system is highly compromised can you name any other disorder in which immune system is highly compromised HIV AIDS is one such disorder in which in steroid therapy prolonged steroid therapy immune system is highly compromised. What happens those organisms which are normally residing in skin normal residing in air which cannot attack us now can cause infection those are known as opportunistic organisms. So, opportunistic infection are very common. Again symptoms may include pneumonia chest infection chronic diarrhea growth retardation apart from that neurological problems developmental delay can happen in ADA deficiency and if it is not treated if it is not diagnosed and treated a child can maximum survive up to 1 or 2 years otherwise he will die of infection right. Next purine nucleotide phosphoryl purine nucleotide phosphorylase this is the enzyme PNP right.

What it does it if this enzyme is defective. So, there will be a very ineffective conversion of IMP to hypoxanthine xanthine and guanine right. So, basically inability to metabolize guanosine and deoxyguanosine and ultimately it will lead to accumulation of their nucleotide. They also inhibit ribonucleotide reductase the mechanism is same like ADA deficiency, but it is much less severe. So, much so that only T lymphocyte function is affected alright whereas, in case of ADA deficiency both T and B lymphocyte are affected and there was severe immunodeficiency here it is mild immunodeficiency alright, but both of them nevertheless fall into immunodeficiency disorder characteristic. There is a minor enzyme that we should know that is known as myo adenylate deaminase deficiency also known as muscle adenosine monophosphate deaminase deficiency specially for MCQ.

This may not come as a question in descriptive exams, but for MCQ it is very important the disease disorder defect lies in the AMP D 1 gene which is the what happens basically that interferes with processing of ATP ok. You can see in the system what it is doing AMP is getting converted to inosine via AMP deaminase alright and ammonia is being produced. So, if there is lack of that enzyme that converts ATP to inosine and ammonia alright. So, you can see ammonia is actually produced with the help of this enzyme. Generally what will happen there is no such severe symptom generally it is characterized

by exercise induced muscle cramping right and the disorder is actually diagnosed through accumulation of ammonia or inosine monophosphate in the muscle ok.

This typically consists treatment typically consist of exercise modulation mind it most of these enzymes are actually reversible. So, the same enzyme also converts inosine and ammonia to this ok. So, if this enzyme is deficient ammonia will be accumulated, AMP will be accumulated AMP cannot be synthesized ok. So, you might be confused with the arrow, but these are reversible enzymes most of these enzymes are reversible. Next xanthine oxidase deficiency we know xanthine oxidase the enzyme which was appearing the last in purine catabolism is a rare hereditary disorder in which there is a deficiency of liver xanthine oxidase.

So, catabolism of purine stops stops at the xanthine hypoxanthine level which results in again formation of excess amount of xanthine and hypoxanthine and they hypoxanthine and xanthine stones are found. However, blood uric acid is very low right and there is high level of urinary excretion of xanthine that is why it is known as xanthine xanthine urea. So, reduce excretion of uric acid additionally this condition can also lead to muscle disorders myopathy because there is xanthine deposition in the muscle. So, xanthine stones xanthine crystal may be deposited in the muscle. So, treatment involves avoiding food and drink that contains xanthine derivatives such as coffee, tea, coca cola and maintain a high fluid intake.

So, that the amount of excess xanthine can be dissolved in urine right. And finally, we come to disorders of purine salvage pathway over there we mainly need to know about two enzyme number on hypoxanthine guanosine phosphoribosyltransferase that enzyme may be fully deficient in which it is known as Les Nihon syndrome or it may be partially deficient with similar symptoms, but reduced intensity will be discussing those symptoms and the second enzyme was APRT or adenine phosphoribosyltransferase alright. This results in accumulation of insoluble purine 2 a dihydroxy adenine and it results in only kidney stones and acute renal failure. APRT deficiency results in acute renal failure, but what does HGPRT deficiency or Les Nihon syndrome is it is a metabolic disorder which we already know characterized by the deficiency of HG hypoxanthine guanosine phosphoribosyltransferase enzyme HPRT or HGPRT as you may term it. It is inherited in an x linked recessive fashion again characterized by hyperuricemia and hyperuricosuria ok.

Why? Because the purine nucleotides cannot be resynthesized I mean nucleobases cannot be resynthesized to nucleotides. So, they have to be excreted by uric acid pathway leading to excess production of uric acid and the intermediates which lead to mental retardation. This is characterized very early it presents very early as early as in

the first year of life and the symptoms are many neurological since it is affecting the brain it includes facial grimacing involuntary writhing the baby calls on to himself aggressive behavior self mutilation the baby bites his or her fingers and repetitive movements. And the bad thing is there is no known cure however some cases with mild deficiency may proceed to adulthood here we can see a few cases where this is a mental retarded child the look it says so as well as the condition where a child who has bitten his or her own fingers. So, self mutilation aggressive behavior multiple choice question Lesney-Hans syndrome HGPRT is deficiency.

Now, one very important thing that was left out is Bonjour's disease why Bonjour's disease leads to hyperuricemia. You already know Bonjour's disease characterized by glucose 6 phosphatase deficiency therefore, glucose 6 phosphate cannot be converted to glucose. So, all I mean the majority since glucose 6 phosphate cannot be converted to glucose it will be diverted towards HMP shunt. HMP shunt we all know one of the important product is production of ribose which ultimately is to increase production of PRPP and purine and then uric acid. So, in case of glucose 6 phosphatase deficiency these are Bonjour's disease or glycogen storage disease one it leads to hyperuricemia alright.

In addition glucose 6 phosphate can be converted by anaerobic glycolysis to lactic acid we already know because this is V6P is also diverted towards glycolysis this lactic acid competes with uric acid for excretion. So, both overproduction and excretory defect that leads to hyperuricemia in case of Bonjour's disease. And lastly this is a very I mean we cannot call it a condition it or a disease it is a condition known as hypouricemia where there is less than 2 mg per dl of uric acid in blood. What is the problem again for MCQ? URAT1 gene is defective that leads to secretory and reabsorption defect alright. Again uricosuric drug a patient on uricosuric drug may actually develop hypouricemia mainly without any gene mutation defect alright without any gene mutation.

Again hypouricemia is also common in vegetarian because vegetarian diet have got low purine content, but it is a good thing that this has got no recognisable symptom and hence they do not require any treatment. So, to conclude we have discussed about the degradation pathway of nucleic acid we have discussed about uric acid hyperuricemia we have discussed in border of uric acid metabolism we have discussed disorders due to purine catabolism disorders due to purine salvage pathway the diagnosis and treatment of gout as well as hyperuricemia. So, these are my references and I thank you for your kind attention.