Overview and Integration of Cellular Metabolism

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Lecture 53: Inborn errors of Metabolism

Hello everyone, welcome back to lecture series on Overview and Integration of Cellular Metabolism. Today our discussion will be on Inborn Errors of Metabolism. So, we will be briefly covering these topics in few headings, I mean we will be discussing the demographics, we will be discussing the important symptoms and examples of IEM, we will be discussing few undiscussed disorders in our course like Lysosomal storage disorder, mitochondrial disorder, mucopolysaccharidosis and we also discuss the newborn screening criteria and method. So, to start with the demographic why we are so concerned, I mean this is why so important. First of all due to the shear number, the number of inborn of metabolism disorder that is possible and the number is increasing as the medical science is advancing and more and more diseases are discovered every year if not every month and every week, there are more than 500 such diseases that are existent due to a defect in intermediate metabolic pathway. So, somewhere in the other due to some defect a disease is formed and there are more than 500 varieties of them.

And to be honest those are not very common for example, a disorder like diabetes is almost hypertension or thyroid disorder for example, these are very common they can be found in almost every in my family neighbors and who not all right, every one person in 10 may have those disorders, but these are not that much common. For example, individually they might be very rare when we are collectively considering all the commonest and rarest disorder generally it may the incidence may be one in 800 to one in 2500 birth globally worldwide. However, the country that we are staying in is the highest in population right. So, we have cross China we all know 24 million births in India happened in the year 2011 that roughly corresponds to more than 65000 per day right first leading numbers.

Due to this issue suddenly the number actually rises up to a grave problem in Indian scenario. So, we are very much concerned about this disease in spite of its rare incidence ok. We need to thank Sir Archibald Garrod who coined the term inborn error of metabolism as early as nineteen hundred and ninety these are not new disorders they

existed human metabolism or any metabolism in animals they existed right, but the fact that the disease of the symptoms of the presentation. So, due to a defect in metabolism he was the one to pioneer that concept in 1909. He had many areas of research and there is a term which is as Garrod state rut right it consists of certain inborn error of metabolism combined together alcaptonuria, albinism, pentosuria and cystinuria all right.

Of this three you have already heard pentosuria can you tell me it is a disorder of what I mean what is exterior in urine pentose sugars all right carbohydrates are exterior in urine. So, pentosuria along with alcaptonuria albinism and cystinuria forms Garrod's tetrad MCQ question one of them might be taken out and you need to correctly identify what are the components what are the four components of Garrod's tetrad, but that still does not answer why we are so much concerned that we need to study these disorders in detail. So, much detail we are investing so much time in learning because of one very important thing permanent mental retardation unless these disorders are treated. Most of these disorders if not all if are not diagnosed early if not treated early will result in intellectual disability which is also termed as mental retardation. So, these are the disorders of babies undiagnosed the babies will not grow up intellectually sound they will be mentally retarded they will become imbecile and their IQ scores will be lower which is a very much concern for the parents as well as the entire society.

So, we need to identify and treat these disorders, but before identifying and treating we should at least know what are these disorders right anyway. So, we have got methods now that we have studied the entire metabolism we all know path we all know the nitty gritties of what is happening from where to where we can have I mean we can categorize them and we can have some common approach by which we can have an idea whether this problem is due to phenylketonuria or methyl syrup urine disease or galactosemia because early identification of these condition will avoid fatalities or irreversible clinical effects alright. So, if we can identify them early and treat early the baby will grow up into adolescent adulthood and will live a normal life. So, early detection is very important alright. In some cases there might be a triggering factor that is lead to acute symptoms for example, acute porphyria hemochromatosis glucose 6 phosphate dehydrogenase deficiency these are all these are also important of metabolism mind it, but there may be a triggering factor for example, acute porphyria comes with I mean leads to very much pain alright and we have seen we have discussed how administration of glucose will alleviate that pain in case of hemochromatosis repeated blood transfusion leads to that disorder.

So, we all there might be triggering factor for all of the diseases that we can identify and if we can stop them further deterioration of these diseases will also be stopped right. So, these are the various importance of early detection. So, we are very much concerned.

So, when we should actually concerned I mean consider a disease to be a metabolic disorder or I mean when we should at all consider that this disease should be included in our newborn screening program alright. Number one the criteria of those diseases are those disease have got serious neonatal presentation and mind it any presentation in babies are serious, but among them there are few complaints for example, failure to thrive failure to suckle growth retardation mental retardation abnormal social smiling these are all phenomena that are called ammonia toxicity that is leading to increase in intercranial tension.

For example, conductors linked to severe brain problem or I mean brain development is hampered. So, those are all serious neonatal presentation that are one of the check mark to consider a metabolic disorder biochemical abnormality liver dysfunction neurological features multiple amino acid have got neurological features I got all those focal central neurological features like abnormal movement athetosis jerks spasticity opisthotonous all those have been discussed. So, all you can relate and connect this lecture is all about revision alright if you are expecting me to teach and discuss every disorder in detail that is not possible because I already know I have taught it and you have learnt it with me and I trust you that you have already remembered whatever is new I will be definitely discussing. So, multiple skin and eye symptoms there are disorder like galactosemia fructose intolerance where we get cataract right course faces. So, science of storage diseases.

So, all of them are concerned when a disease should be considered as a metabolic disorder these features common features classifies a disease under metabolic disorder. So, what is the metabolic pathophysiology that we know alright. So, here is a condition where A is supposed to be converted to B, B is supposed to be converted to C, C is supposed to be converted to D, but and these all requires enzymes right. However, there is a block in thus this step that is really hampering the formation of C to D ok. So, what will happen accumulation of substrate.

So, all of these cannot be converted the products that is specifically if you are considering this step the C will be raised you agree with me you have to. Next accumulation of the precursors because C is raised A and B ultimately will also be raised because they cannot be converted to C and then downstream to D right. So, A and B will also be raised ok that will lead to direction or redirection or misdirection of the substrate into alternate pathway. One such example is phenyl ketone India where phenyl aniline instead of being converted to tyrosine was getting converted to phenyl pyruvate, phenyl acetate, phenyl lactate right very easy to example and you should be able to relate this analogy now otherwise go back revise come back listen. Next deficiency of the product definitely D will be deficient and that will lead to deficiency symptoms of D if D is a

metabolic product for example, again in case of phenyl ketone India tyrosine will be deficient products from tyrosine will be deficient melanin, thyroid hormone, catecholamine that will lead to multiple symptom the analogy the mechanism is same for almost all metabolic disorders and ultimately not only that unwanted or secondary side effect by any one of the metabolites they can get accumulated and they can exert any unwanted or damage jury effects in the system.

So, this is the basic pathophysiology of all inbonder of metabolism. Now, if you get a descriptive question regarding categorization or classify inbonder of metabolism you should be able to mention at least 5 or 6 of this classification. So, disorders of carbohydrate metabolism, disorders of amino acid metabolism, disorders of lipid metabolism, mitochondrial disorder, paroxysmal disorder, lysosomal storage disorder, disorders of heme metabolism, trace metal disorders mind it this lecture series did not cover vitamins and minerals, but there are disorders that also exist in vitamins and minerals that can be I mean classified together ok. So, you can give a read of that in order to comprehensively answer a question if it has got more marks and if vitamins and minerals are included in your syllabus or maybe we will we will cover that in upcoming course alright in a future course. So, that is beyond the purview of this lecture, but mind it you should be able to name at least 2 or 3 disorders among I mean under each heading ok at least 2 or 3 there are 500 you are not expect to write a book or even a if your question has got 15 marks right mention the important ones about which you know ok and we have discussed more than that in the lecture series ok.

Now, the next 3 slides will be revising amino acid ureas right these are nothing new I will be just letting you watch the slides I will change so that you can take a snapshot you can make your own note you can pause the video you can memorize it in your own way if you have not yet memorized it by now ok. Moreover this is not the entire class for example, see tyrosinemia there are again 3 types of tyrosinemia 1 2 3 I have included the most important one ok. So, phenylketonuria, tyrosinemia, alcaptonuria, hyperhomocysteineuria, histidinemia, MSUD, maple syrup, urine disease, methylmalanic aciduria, cystathionuria, hyperprolinemia, believe it or not if you are if you missed any of the amino acid metabolism classes and if you are attending this class without attending that class this class will be daunting if it will be too much it will be over the board for you right, but I hope you have not done that and you have already completed a weekly assignments for that week ok. So, we can go on and on regarding the symptoms what you need to remember in each of these diseases basically the enzyme very important for MCQ the clinical manifestation that may or may not be that much important, but what substrates are getting accumulated this is also again very important. For the all the slides that I have shown you in the last 3 slides this abnormality in the enzyme and that abnormal substance that is found in either urine or that is raised in

blood basic because will be diagnosing the diseases with the help of those substances ok.

So, though that is why they are very important. This slide is also common slide that was shown in previous lecture of fatty acid disorders right specifically the third class of fatty acid oxidation. So, methylmalanic aciduria, propionic acidemia, medium chain acyl cohead dehydriness deficiency ok, long chain acyl cohead dehydriness deficiency, glutaric aciduria why this is red because this is the most common disorder I am not going into detail you can simply recap and move on ok. Again known slide glycogen storage disorders were shown to you ok Von Zier's disorder the most common disorder, glucose 6 phosphatase deficiency we also learnt why there is hyper uricemia in Von Zier's disease very important. Why can you tell me glucose 6 phosphatase deficient, glucose 6 phosphate excess will be deviated to HMP shunt, HMP shunt, excess purine, excess purine, excess uric acid, excess uric acid gout ok.

Regarding pompous disease one way you can remember you see pompous disease one see Von Zier's disease will be a short note in remember everything right from the clinical symptom disease treatment the enzyme name everything. In case of pompous disease remember the enzyme name it was already discussed I am again recapping. In pompous disease you can see heart failure happens ok. How we remember Pompe, pump failure heart is a pump like. So, pump failure happens in case of Pompe's disease type 2 glycogen storage disorders.

Again this was also discussed one easy way to remember Cori's and Anderson right. ABCD what is that Cori's disease debranching enzyme Anderson's disease branching enzyme ok. This is as much as I can give you in order to help you remember, but there are multiple things and you need to have a good memory or you need to practice it over and over again discuss with your friends form a study group. So, that you write it over and over again. So, that you can remember how you can remember M McArdle muscle phosphorylase M for M ok.

So, these are few important things that you can remember I am not going to text because I have exactly copied those slides that were discussed in the respective classes these have been discussed in glycogen metabolism ok. So, this is about it there are 10 types of glycogen metabolism, but though the names that are deficient over here type 8 type 9 and type 10 are not that much important compared to those that have got names. So, Von Jerks Pompe Cori Anderson McArdle's Hearst and Tarwis disease these are the 7 that you need to remember all right. And the rest are actually less severe the other ones that we have discussed are much more severe and why glycogen storage disease leads to hepatomegaly glycogen is stored in the liver cells liver enlarges ok. But there are few disorders that we have not discussed that will be discussing today ok.

Sphingolipidosis. So, what are sphingolipidosis? Sphingolipidosis mind it these are inherited metabolic disorder due to deficiency of enzymes that degrade sphingolipids ok. So, these are so, we discussed sphingolipid synthesis we did not discuss sphingolipid breakdown, but the diseases will be discussing ok. So, what happens the mechanism is same. So, since enzyme is deficient multiple intermediate products will be accumulated and they specifically cause damage to the nervous system, liver, spleen and bones sphingolipidosis. There are multiple example names that will be discussing very soon tabulated form for you nematoid disease, gochre disease, fabric disease, tesach, crabs those are important names that you should remember ok.

We will be showing you a chart where it will be much easier for you to visualize. So, the symptoms are more or less common the very first symptom that we are concerned about all metabolic disorder are neurodegeneration developmental delay combined with hepatosplenomegaly, liver and spleen will increase in size, bone abnormality, processive loss of motor and cognitive function the main neurological function and storage functions are hampered. Apart from that how we can diagnose so, the general features have been discussed the diagnosis also falls in line with various other metabolic disorders that we have discussed clinical evaluation, biochemical testing, genetic testing and also imaging study radiological studies in some cases ok. Newer treatments like enzyme replacement therapy, substrate reduction therapy, hematopoietic stem cell transportation may be considered in specific cases, but not all cases alright and as I told you in all metabolic disorder the ultimate goal or cure is gene therapy, but that is under trial in most of the diseases ok. However, we can prevent these diseases by genetic counseling if the family there is a previous familial history of these disorders a genetic counseling by proper matching up of individuals if they have got a familial history they should be warned that the baby might have the disorder.

So, in that way we can prevent that ok. So, the prognosis actually may vary from case to case depending on at what age is detected at what time the treatment options are offered the prognosis may vary with management and care. So, now, you can see this is the pathway of sphingolipid metabolism we discussed about sphingolipid synthesis. So, we discussed our discussion up to here where I told you depending on the we discussed how head group is attached or tail group is attached and depending on the x it can be either ceramide if it is only hydrogen it can be choline it can be ethanollamine. So, choline ethylene belong to sphingomylin we extend that knowledge to let you know that if that is glucose it is referred to as glucosariboside if it is galactose it is referred to as galactosariboside if they are other sugars for example, glucose galactose n acetylgalactosamine they can be called globosides as well as if it combines with complex carbohydrate is known as ganglioside.

These names are important for chemistry part alright and for metabolism path knowing each of this step and intermediate in detail is not recommended compared to the synthesis part. Of course, everything is recommended if you have already covered the basics the must know and good to know area it is always nice to know because every other the now and then one rare question may be framed from this chapter or specifically this cycle and that will help to differentiate you from every other average student who may not have touched this area. So, studying a rare thing is good only if you have covered the very basics alright. So, with that in mind this is the chart that you need to remember. Neman pig disease again I told you in this case what is important this inheritance is important of course, the name of the disease and deficient enzyme is important right the symptoms are more or less common to all.

So, you may choose to not remember the symptoms ok. The accumulated products are important, but more important is the deficient enzyme and the name inheritance why it is important as you can see all of these disorders are inherited in an autosomal recessive fashion except Fabry's disease or Fabry disease which is X linked ok. So, for example, T-shax disease is due to cause due to deficiency of hexazaminidase A what accumulates GM to gangliosides ok. In case of Neman pig disease so, you may choose sphingomyelinase is deficient mind it T-shax is due to the deficiency of hexazaminidase A and Sandhoff's disease is due to the deficiency of hexazaminidase A or B. So, if the question says deficiency of hexazaminidase A leads to production of T-shax and Sandhoff will both be considered as an MCQ option.

So, this is more important for multiple choice questions in case of competitive exams ok. Next Neman pig disease sphingomyelinase now one thing is very important there may be specific clinical features you may not choose to remember all because most are common specific clinical features are important for example, acroparasthesia acroparasthesia means tingling and numbness or loss of sensor and tingling and numbness of fingers this happens in Fabry's disease finger Fabry easy to remember acroparasthesia in case of Fabry's disease. Erlenmeyer flash deformity, Gottschalk disease very what is Erlenmeyer flash deformity if you are I mean interested it is a radiological. So, basically if you take a straight x-ray there is a thinning of the femur. So, this is known as diaphysis is known as epiphysis these are from your anatomical knowledge thinning of diaphysis leads to a formation where the distance between the two meet femur is much more compared to that of the.

So, the distance is actually there is a index that is compared to knee distance and this whole thing looks like a flask Erlenmeyer flask right. So, this is known as Erlenmeyer flash deformity and it is a characteristic of Gottschalk disease and among them if you I

mean encounter a short note if you include all of these key points your short note will be done and if you still ask me is there any single important disease which we should know from all of them answer is yes you should know Tashak's disease because if you know Tashak's disease and if you remember the other names and enzymes you can relate the symptoms because they are more or less similar ok. So, this is about sphingolipidosis. Next we will discuss about mitochondrial disorders mind it mitochondrial disorders it is not specifically an inburner of metabolism, but still we are discussing or broadly discussing all inborn errors. So, I thought why not discuss in this context.

So, mitochondrial disorders involve mutation these are genetic disorders they involve mutation in mitochondrial DNA and you should know that these follow a maternal pattern of inheritance mitochondrial DNA mitochondria comes from mother ok. So, you can see in this case where the senior progeny the father and mother was affected and all of the sibling children are unaffected because mitochondria and all of the children are because they are mother is unaffected and mitochondrial diseases come from mother here the father was affected and in this case the mother is affected and the father is unaffected, but the all of the children are equally affected because they are inheriting the mitochondrial DNA from the mother. However, there is one thing they are affected, but symptomatically they may not be the same because of something I discussed earlier that is called genetic penetrance. Even if we have got the mutant gene that disease may not choose to express fully or partially depending on this is known as penetrates that is expression of genotype into phenotype that is the concept which you should be able to clear yourself on your own from any text book of genetics alright or from your fundamental concepts in plus 2 lessons classes right. So, what are the mitochondrial disorders that you need to know for multiple choice question ok I am not going into the much details the mitochondrial disorders are actually collection of combined disorders that are abbreviated depending on I mean abbreviated because of the disease.

So, see the name MELAS or we often say MELAS why because it consists of myopathy, encephalopathy, lactic acidosis and stroke like episodes. Similarly, morph myoclonic epilepsy with ragged red fibers, nerve, neurogenic weakness, ataxia and retinitis pigmentosa. So, you see so, if you just remember the name in detail you will be able to easily write what are the clinical presentations ok, but specifically for competitive exams you should remember this mitochondrial DNA mutation and tRNA mutation the numbers these are difficult to remember, but some of them have appeared in higher competitive exams and they might help you if you can choose to remember mind it this is one such chapter that you should revise at the last moment. There are multiple chapters that needs to be revised just before exam because these are very volatile information and it will go up because human mind behaves in that way we need to revise at the last moment. So, that you can easily remember and you need to write this over and

over again form a study group and discuss with your friends.

So, that you can easily remember. So, ragged red fibers in muscle biopsies the name suggests is found in MARF and peripheral neuropathy is found in NARF. Eye problem retinitis pigmentosa eye problem that may lead to blindness is also found in NARP ok. Next we move on to mucopolysaccharidosis again these are storage disorders ok. So, inherited metabolic disorders due to the effect due to which the defective ability of the body to break down complex carbohydrates ok that are also known as glycosaminoglycans. So, when these glycosaminoglycans the enzymes that are actually degrading the glycosaminoglycans or GAGs are deficient what will happen the intermediate products of glycosaminoglycan breakdown will be accumulated the rest of the pathologies very same even if I do not proceed I think most of you will be able to tell on your own what is going to happen.

So, they will be accumulated the level will be high and they will lead to various problems. What are the problems you can just simply close your eyes at this point and say there will be neurological problem organ enlargement skeletal abnormality bone deformity and bone deformity in specially in this case of mucopolysaccharidosis leads to facial dysmorpation there is a characteristic phase that is present in mucopolysaccharidosis apart from that neurological problem hepatosplenomagaly bone development defect are common to all other just like all other disorders. So, they are actually depending on the enzyme variety they are classified as number one my my mucopolysaccharidosis type 1 type 2 type 3 and type 7 like that we will be studying it in a next chart. So, symptoms might appear in very early childhood however, the severity varies from person to person individual to individual cases to cases. So, this is one specific appearance of a mucopolysaccharidosis case.

Next so, how we can diagnose same just like any other metabolic disorder genetic testing imaging testing enzyme activity clinical evaluation all those will give us answers that we are looking for. So, treatment option I mean if it is treatment is if it is implemented early it will lead to improvement of symptoms on affected individuals right. So, early treatment is early diagnostic treatment is very essential how we can treat enzyme replacement therapy hematopoietic stem cell transplantation those are commonly used intervention for mucopolysaccharidosis ok. And just like all other metabolic disorder supportive care physiotherapy pain management because there are bone pain respiratory support they often help in fighting the other complication that are associated with mucopolysaccharidosis ok. And final answer to all metabolic disorders gene therapy ongoing research once medical science progresses into a certain extent that gene therapy is available right a diagnosis may be these chapters will go into historical I mean historical archives and this will be of historical importance, but we are now not there yet.

So, at this point of time we only rely on early diagnosis medical care and comprehensive management and that plays a crucial role in improving the quality of life of these individual. So, this is how patient of mucopolysaccharidosis looks like typical faces bone deformity short height widespread pelvis teeth deformity facial dimorphism there will be internal organomegaly. And these are the this is the complete chart that needs to be followed ok. Again just the name of the disease specifically what are their types and what are the enzymes that are deficient ok. Regarding inheritance here also just like the previous disorder all are autosomal recessive except hunters disease which is X linked recessive.

So, you need to remember the exception ok. The gene location if it is too much to remember for exam not an issue, but for those who are into clinics who are already trying to diagnose the involvement of metabolism and who are already physicians and lab specialists who are undergoing these courses mind it these are the gene mutations that you should be looking for these are gene polymorphisms you should be looking for in order to diagnose all of these disorders. So, you can take a screenshot and memorize this and we move on to our next topic which is the common symptoms of IMDs in bond metabolic disorders IM those are same thing ok. So, they are often referred to as IMD. So, by now you should be able to tell what are the common symptoms. Symptoms means those are the things that a mother will complain for the baby, seizure, abnormal convulsion ok involuntarily movement, reduced heartbeat that is bradycardia, vomiting, diarrhea, dehydration very common presentation, fever up and down shooting of temperature instability, abnormal muscular tone the baby might be spastic or flaccid there may be skin rashes, there may be mental retardation this is the final common presentation regarding which we are so much concerned if untreated it will invariably lead to mental retardation and it is beyond repair because it is a permanent mental retardation.

So, in this context let us see how we can diagnose this involvement of metabolism based on very simple test because you see in India specially this is a huge problem public health problem and babies are being delivered in remote corners remote areas where there might not be advanced diagnostic facilities right. So, we need to be aware or these are the hence these are the few common physical features that have been found out by various scientist and physicians which can at least short list the case to a suspicious case which can be later sent to the laboratory. So, here we are discussing in order of metabolism and how a simply urine odor the odor of urine can distinguish them. So, glutaric acidemia glutaric aciduria is characterized by a sweaty feet odor all of these are MCQ these terms MCQ. Mapple syrup urine disease or burnt sugar you already know right boiled cabbage hypermethioninemia very important boiled cabbage

hypermethioninemia in some cases if hypermethioninemia is not an option often in case of tyrosinemia is an option ok.

So, mind it when hypermethioninemia is an option that will be the answer of choice in case of boiled cabbage odor moussey or musty odor in case of phenylketonuria rotten fish in case of trimethylamineuria. So, these are the few odor urine odors you should remember in context of inburner of metabolism diagnosis. So, when so, we have already discussed these slide discuss this slide, but mind it these symptoms may appear late. So, often the symptoms occur in a child who is otherwise healthy at birth. So, being a parent one needs to be need watchful if the baby I mean exhibits the symptom involved as a physician one needs to be watchful as well ok.

So, what are the studies that are directed by which we can classify these disorders ok, because in order to diagnose and treat these disorders we first need to know right that either these are disorders of urea cycle or these are disorders of carbohydrate metabolism or this is heme synthesis disorder. So, these are roughly few tests that can actually categorize those 500 disorder into a subclass plasma ammonia organic acid urea cycle, plasma lactate, beta hydroxy butyrate analysis, analysis of free fatty acid, quantitative and semi quantitative analysis of plasma and urine amino acid all right. Unary plasma organic acid urea, organic acid presence of organic acid can be detected, urinary mucopolysaccharides can be detected oligosaccharides treating test may be done and there are specific panel of test for galactosemia that should be implemented ok. So, I told you these genetic disorders can be prevented ok. So, in order to prevent we need to genetically counsel the parent specifically in the here I mean maternal screening is a common thing.

So, one of the concerns when an inbonder of metabolism might happen that is advanced maternal age all right. There are triple and quadruple markers in maternal screening if those markers are positive we consider positive maternal screening that may increase the probability of a new inbonder of metabolism. Familial history, prior pregnancy with such chromosomal disorder, familial history of mental deterioration of birth defect, any abnormal ultrasonography, recurrent draws of pregnancy, previous still birth, infertility, ethnic based carrier screening and consanguinity these are all situation when we should refer a mother to a genetic counselor ok. And one and why we are doing this? We are doing this to prevent any inborn error an inborn error of metabolism can be one such inborn error ok. So, these points may be quoted in a multiple choice question you need to wisely select the answers ok.

So, prenatal diagnosis of IM prenatal means even if they are born. So, the sample should be obtained from the trophoblastor amniotic fluid cell culture it can be done by amniotic

fluid amniocentesis amniocentesis or chorionic villus sampling chorionic villus sampling. These are the two techniques by which fetus fetal material can be obtained and direct detection of a gene deficiency by molecular techniques or the gene product that is the enzyme deficiency biochemical techniques is the preferred diagnostic approach direct proof always proves the disease ok. So, what are the criteria for which any disease can be included in the newborn screening program? We first discuss what are the criteria for disease to be considered as a metabolic disease. Now, we are already knowing it is a metabolic disease why should we screen them? So, number one the disorder should be an important health problem there are many milder disorder that might not possess any problem right that should not be the case ok.

The disease should have a latent or pre symptomatic stage means what that can be a window where we can actually suspect or detect the disorder ok. The natural history of disease should be well known we should the physician should be able to know what happens up next. Then when the natural history of disease is known it is much easier to diagnose and lastly there should be an accepted treatment we are trying to find out the disease only because we can treat the disease right. So, there should be an accepted treatment. So, if all these criteria are falling into place then the disease can be considered for newborn screening.

So, what is the specimen recommendation? The specimen should be obtained if it is a neonatal disorder we are suspecting especially in it should be in case of all newborns in tertiary care center for all newborns in the first one or two days of birth it is generally obtained by a heel trick and it should be repeated after two weeks in case of premature babies. For example, in premature babies I discussed that liver the conjugation system is not functional. So, they may have got unconjugated hyperbilirubinemia, but that will wane off as the baby matures right and there are few diseases which needs blood transfusion. So, if transfusion is a method of management since the sample should be achieved prior to transfusion. So, what are the initial screening test? Initial very basic tests that can be done are electrolytes to evaluate the anion gap and acidosis ok, because in many such cases the metabolic acidosis leads to a high or raised anion gap or even in case of normal anion gap we can actually classify the disease based on their findings.

Glucose hyperglycemia is the feature of most in border of metabolism ok. Ammonia, hyperammonemia is common in case of urea cycle disorders and organic acidemia. So, if plasma ammonia is one important parameter that we should be considered in initial screening also lactate to pyruvate ratio happens I mean lactate elevation occurs in case of energy metabolism disorders and high amount of lactate to pyruvate ratio should raise a suspicion right. There are actually kits available by which a urine sample can be tested for almost 35 odd disorders. Few of them we have already discussed right and the names

which are not common you can actually take a note from here we have discussed Rothera's test, cyanide nitroprusside test, ferric chloride test, Benedict's test, 2, 4-dinitrophenylhydrazine test for qualitative analysis of aldehyde or ketone group alright.

What is CPC test? Cetyl pyridinium chloride for muicopolysaccharidosis we did not discuss it is not a metabolic disorder, but we should know that. Minhydrin test will take any amino acid. Arlix aldehyde test for porphybelinogens, arlix aldehyde test, test for methyl mannolic acid nitrosophenol test for tyrosine which gives a pulp halide color. So, basically what should be done is screening for all newborn disease can be done in small laboratories because it is urine ok.

We do not need expertise to collect heel blood heel prick. So, urine simply apply urine sample and test the kids so that to test what diseases are positive and if suspicious results are found samples are sent to higher central laboratories. So, these are the very basic preliminary test. So, what are the advanced techniques for detecting inbounder of metabolism? Thin layer chromatography that requires actually expertise. Thin layer chromatography, high performance liquid chromatography, HPLC for amino acid ureas, gas chromatography and MS for detection, mass spectrometry for detection of organic acid urea and tandem mass spectrometry which after discovery in 1998 have revolutionized the disorder I mean diagnosis. So, mind it I have told you in multiple class this lectures that if you are asked that tell me one method by which you can easily or confidently diagnose organic acid urea or any product of metabolism answer should be tandem mass spectrometry which is often abbreviated as MS MS.

If this option is presented in MCQ this will be your answer ok. And what are the genetic advanced techniques? I mean these are newer techniques compared to small labs, but these are also becoming common in higher tertiary care centers ok. But DNA hybridization probe analysis that is by directly designing a hybridization probe which can go and attach to the gene that is malfunctional. So, by that we can actually directly prove that the genetic disorder exists ok. However, that might be a definitive test, but and this advantage they are very sensitive and specific.

Only the person who have got the positive disease will give that test. If there is no negative test it means we do not have the disease and if the disease is positive it means we have if the test is positive we have the disease it means sensitive and if we do not have the test positive we do not have the disease. So, the test is highly sensitive and specific prenatal diagnosis is possible. So, samples I told you which is achieved from chorionic villus sampling amniocentesis can be analyzed genetically and even with small sample volume this definitive test can be done. However, it is not always feasible

because the infrastructure cost is very high we require dedicated and trained personnel it is very expensive to sustain all right. So, definitely diagnostic diagnostic tests are specific enzyme assay, nucleoside, leukocyte, plasma, serum or red cell.

So, specific enzyme assay if they are found to be differ I mean problematic or decreased eruption then definitively the inbound of metabolism is proved. And lastly we come to therapeutic modality. So, therapeutic modality again that may come as a long question and you need to classify your answer under several headings giving one mode of treatment at least two or three disorder under that heading. So, substrate deprivation modality of treatment can be done in phenylketoniolegalactosemia, MSUD, fructoseuria. High dose of coenzyme remember in case of phenylketoniolegalactosemia also tetrahydrobioprene was a coenzyme that deficiency was leading to hyper phenylalanemia ok.

So, again high dose of coenzyme can be a modality of treatment enzyme replacement therapy in almost all of the diseases where enzyme is deficient enzyme can be replaced often abbreviated as ERT. Inhibition of substrate synthesis in case of glycosvingolipidosis, bone marrow transplant or hematopoietic stem cell transplant HSCT is the abbreviation can be done in case of mucopolysaccharosis, leukodystrophin, imac peak disease, liver transplant in case of diesel duct Milson's disease, alpha or antiseptic deficiency, Kriglian-Nazars syndrome I discussed in Kriglian-Nazars syndrome definitive cure is liver transplant ok. Milson's disease is a trace metal disease in case of copper, but you should know Milson's disease treatment is also liver transplant. However, the final answer the most definitive treatment of any enzyme deficiency because the gene is defective is gene therapy and this is the holy grail that goal that we are trying to achieve. Once we achieve that we will be done worrying about the dreaded sequences of inborn error of metabolism.

So, to conclude the we have discussed the demographics of IEM, we have discussed why early diagnosis very important, we have discussed the symptoms, we have given multiple examples, we have studied newly the disorders of lysosomal storage, mucopolysaccharosis, mitochondrial disorders I told you where newborn screening criteria is applied, what are the diseases that are criteria where the diseases will fit to be in screening program and also the therapeutic modality for inborn error of metabolism. These are my references for today's class and I thank you all for your patient hearing and get ready to revise all of the lessons because we will be coming to the end of the course very soon.