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TYROSINEMIA TYPE 1; FAH DEFICIENCY A RARE GENETIC DISORDER, ITS ETIOLOGY, CLINICAL STUDIES AND DISEASE MANAGEMENT

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ABSTRACT

Tyrosine, an aromatic amino acid that is derivative obtained by hydrolysis of alimentary protein, or from the hydroxylation of phenylalanine, and plays essential role for the synthesis of catecholamines, melanogenesis and thyroid hormones. Many genetic and acquired liver disorders results due to reduced degradation of tyrosine. Hypertyrosinemia in humans is termed when tyrosine in blood elevated by >200 µM. The case of hypertyrosinemia in live births is reported to be 1 in 100,000. Both sexes have equal chances for tyrosinemia type I as it is an autosomal recessive disorder. The defect results in aberrations in gene expression, enzyme activity inhibition, apoptosis and instability of chromosomes. Tandem mass spectrophotometry for screening of TT1 in new borns. Tandem mass spectrometry is a precise technique which tells about the markers of disease in blood spot specimens of newborns. Inhibitor nitisinone and dietary therapy (diet without tyrosine and phenylalanine) is used to prevent liver dysfunction in type I tyrosinemia.

KEYWORDS: Tyrosine, Tandem mass spectrophotometry for screening of TT1 in new borns.

INTRODUCTION

Tyrosine, an aromatic amino acid that is derivative obtained by hydrolysis of alimentary protein, or from the hydroxylation of phenylalanine, and plays essential role for the synthesis of catecholamines, melanogenesis and thyroid hormones. Semi essential tyrosine in humans is mainly synthesized in the liver (Russo, 2001). Many genetic and acquired liver disorders results due to reduced degradation of tyrosine. Hypertyrosinemia in humans is termed when tyrosine in blood elevated by >200 µM. Tyrosine in mammals is glucogenic as well as ketogenic. Degradation of tyrosine is done in five enzymatic reactions that occur in series producing acetoacetate and fumarate. The hepatocytes and renal proximal tubules are only types of cells in body that are capable of tyrosine catabolism as they have sufficient quantities of all enzymes needed (Grompe, 2001). Reasons for Hypertyrosinemia doesn't only include innate errors in the degradation of tyrosine but also include liver failure, sometimes blood sampling, vitamin C deficiency and hyperthyroidism (Russo, 2001).

The case of hypertyrosinemia in live births is reported to be 1 in 100,000. Newborns having the problem often have a severe and sudden onset of disease which results in hepatic cirrhosis and then liver failure. The hepatic failure results in infant having a serious bleeding disorder (coagulopathy). Those who however survive at initial stage have a high risk of hepatocellular carcinoma. With the usage of both medical and surgical techniques, the death rate was abridged to <15% with the usage of both medical and surgical techniques. Both sexes have equal chances for tyrosinemia type I as it is an autosomal recessive disorder. The severity and chances of onset of disease are also equally distributed. The defect in the last enzyme fumarylacetoacetase in the degradation pathway of tyrosine results in tyrosinemia type 1 as indicated in figure 1. This defect results in accumulation of toxic metabolites succinylacetone, maleylacetoacetate and fumarylacetoacetate. This causes problems in intracellular metabolism of the liver and kidneys.

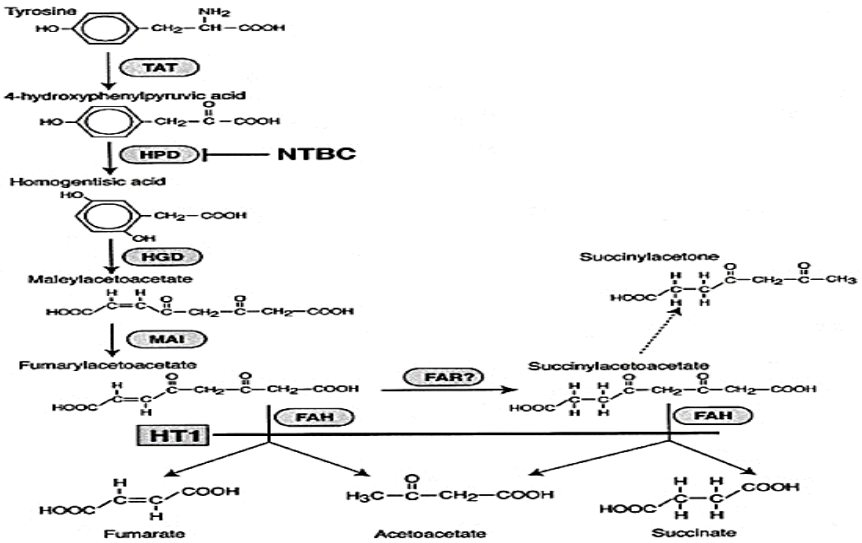

Figure 1: Degradation pathway of tyrosine in mammals: HT1 is caused by a defect in the fumarylacetoacetase

The catabolic sequence of tyrosine metabolism is illustrated in Figure 2. The mammalian tyrosine catabolic pathway was worked out in the early 1950s by Edwards and Knox. The FAH enzyme assay first described then is still used today. FAA is considered the natural substrate of FAH, but the enzyme also uses succinylacetoacetate (SAA) as a substrate, and both FAA and SAA accumulate in FAH deficiency. The mechanism of the reduction of FAA to SAA has not been established, but it is likely catalyzed by a yet uncharacterized enzyme, FAA-reductase. Neurologic crisis and respiratory distress are caused as a result of Fumarylacetoacetate hydrolase (FAH) deficiency or tyrosinemia type 1 (TT1) and it is an inherited metabolic disorder as described in table 1 (Barnby, 2014).

Table 1: The several inborn errors with their corresponding enzyme defects.

Enzyme	Defect	Major manifestations
Tyrosine aminotransferase	Tyrosinemia type II (oculocutaneous tyrosinemia)	Corneal thickening, developmental delay, hyperkeratosis of palms and soles
4-hydroxy phenylpyruvate dioxygenase	Transient tyrosinemia of the newborn	Transient immaturity of enzyme, usually resolves spontaneously
	Hawkinisinuria	Abnormal function of enzyme results in metabolic acidosis and failure to thrive in some patients
	Tyrosinemia type III	Primary deficiency of enzyme; asymptomatic to severe mental retardation and neurologic abnormalities
Homogentisate oxidase	Alcaptonuria	Arthritis in older patients Dark urine when exposed to air
Maleylacetoacetate isomerase		Reported in two siblings with liver failure and renal disease
Fumarylacetoacetate hydroxylase	Hepatorenal tyrosinemia Tyrosinemia type I	Liver, renal, and neurologic disease

Pathophysiology

Until the end of 1970s the biochemical reasons behind tyrosinemia type 1 remained unknowable. Then succinylacetone was found by researchers in the urine of defected infants. Later it was found by study (figure 2) that succinylacetone was produced by decarboxylation of succinyl acetoacetate which is a derivative of fumarylacetoacetate, a catabolic intermediate of tyrosine (Roth, 2015). The defect results in aberrations in gene expression, enzyme activity inhibition, apoptosis,

instability of chromosomes. Abnormalities in gene expression in patients with tyrosinemia type I may result in hypoglycemia, problems in metabolism of amino acids. Instability of chromosomes increase the risk of infantile liver cancer, and death of liver cells by apoptosis can cause liver failure (Nakamura, 2014).

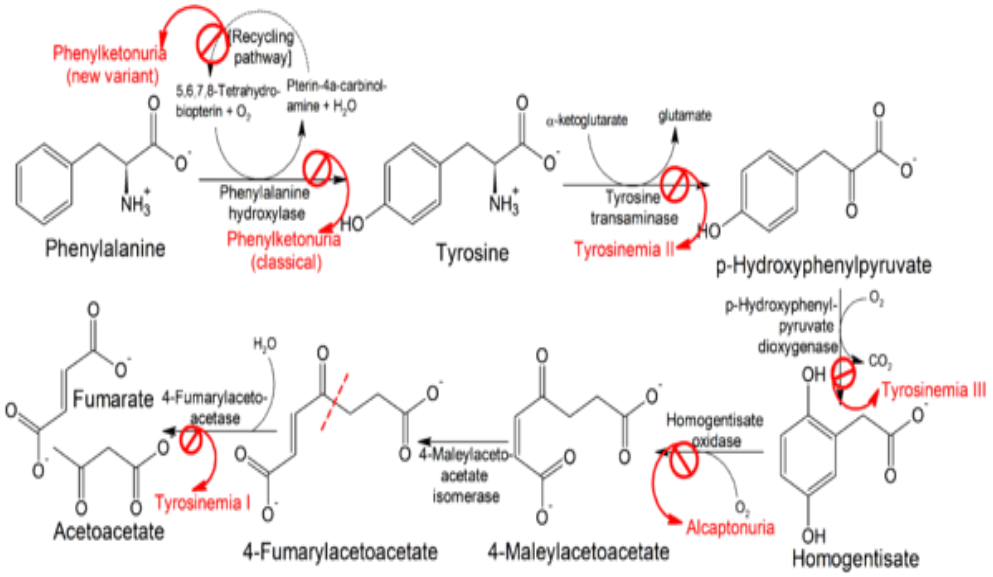

Figure 2: pathophysiology of tyrosinemia

Etiology of disease

Researchers found out the deficiency of fumarylacetoacetase to be the reason for enzymatic defect, which facilitates production of fumaric acid and acetoacetate in both liver and kidney. Later, studies proved it to be correct as accumulation of succinyl acetoacetate was because of this defect. succinylacetone was produced because of its decarboxylation, and was excreted in the urine. Naturally tyrosinemia type 1 is characterized by severe liver damage, which results in death. in initial stages symptoms of the disease are found with a critical rapid progress, or sometimes progress is chronic (Markus, 2001).

This condition is inherited in an autosomal recessive manner. It affects both boys and girls equally. Everyone has a pair of genes that make the FAH enzyme. In children with tyrosinemia 1, neither of these genes works correctly. These children inherit one non-working gene for the condition from each parent. Parents of children with tyrosinemia 1 rarely have the condition themselves. Instead, each parent has a single non-working gene for the condition. They are called carriers. Carriers do not have the condition because the other gene of this pair is working correctly. When both parents are carriers, there is a 25% chance in each pregnancy for the child to have tyrosinemia 1 (figure 3). There is a 50% chance for the child to be a carrier, just like the parents. And, there is a 25% chance for the child to have two working genes.

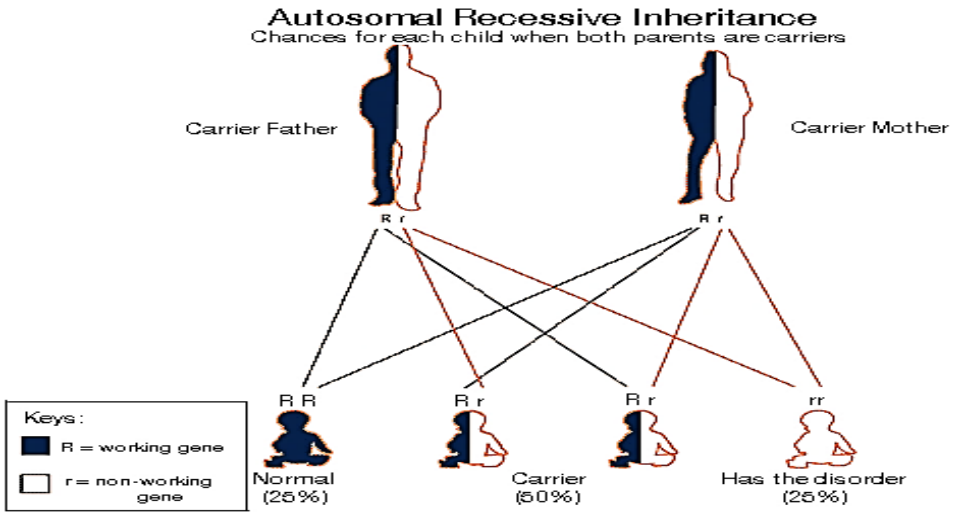

Figure 3: autosomal recessive inheritance in tyrosinemia

TT1 is basically the inability of child to degrade tyrosine. Tyrosine is a semi essential amino acid that is required by the body for normal functioning. Tyrosine is degraded by the enzyme fumarylacetoacetate hydrolase (FAH), but deficiency of this essential enzyme results in HT1. a mutation on chromosome 15q23-25 results in deficiency of this enzyme (Nyhan, 2005). It is autosomal recessive disorder it is expressed when the trait or mutation from both parents are passed onto child. When only passed by one parent, it is harmless but there are chances of disease in offspring (Barnby, 2014).

Effects and symptoms revealed by clinical studies

Clinically TT1 is characterized by dysfunction of liver and defected renal tubules. The liver dysfunction is of 3 types: acute, subacute, and chronic. After some weeks of birth the acute type begins with hepatomegaly, poor development, diarrhea, vomiting, and jaundice. Severe condition of dysfunction progress to liver failure; if it is not treated, ultimately results in death within 2–3 months. The subacute type reveals by dysfunction of liver after birth from quite a few months to about 1 year (figure 3). In the chronic type, slow progression of liver dysfunction, ultimately resulting in liver failure. Many cases lead to Liver cancer having multiple tumors. In kidneys, dysfunction of renal tubules results in diseases such as vitamin D-resistant rickets and hypophosphatemic rickets. Moreover, aminolevulinate dehydratase is inhibited by succinylacetone, which causes attacks of abdominal pain.

Figure 4: Newborn having tyrosinemia

Tyrosinemia mainly affects the liver, kidney and peripheral nerves.

Hepatic disease: Liver is the organ that is generally most severely affected. Fumarylacetoacetate, the compound that accumulates in FAH deficiency, is a potent alkylator, causing oxidative damage to the cells in which it is generated by re- acting with glutathione and sulfhydryl groups of proteins. Importantly, FAA acts cell autonomously, directly damaging only the hepatocytes and renal proximal tubules in which it is produced and not adjacent cells.48 Because of its rapid reactivity, FAA itself is not found in body fluids of HT1 patients. Succinylacetoacetate and Succinylacetone (SA) derived from reduction of FAA are the principal metabolites of FAA. FAA is strongly mutagenic and induces not only point mutations (20%), but small insertions and deletions (30%) and large genomic re- arrangements (50%). It may react and damage (alkylate) DNA directly, in which case point mutations would be the most expected result. Alternatively, FAA may act indirectly by damaging cellular proteins involved in maintaining genomic stability. In the first few weeks or months after the start of disease acute liver dysfunction occurs with anomalies in clotting, ascites and oedema along with hypoalbuminemia. Hemorrhage is common. mild jaundice may occur and the plasma aminotransferases may be raised up. These all condition results in liver carcinoma. in some cases, condition may prevail up to later age without liver failure. clinical examination shows, the liver is firm or even hard. Hypoglycemia can also be caused. Clinical manifestations of enzymes deficient in tyrosinemia is described in table 2.

Renal disease

Fanconi syndrome is caused because of renal tubules damage. the problems include aminoaciduria, glycosuria, phosphaturia and renal tubular acidosis, all may not be present. Hypophosphataemic rickets is caused in some patients and it can be severe. The renal disease may result in nephrocalcinosis, glomerulosclerosis and chronic renal failure. Along with renal disorder liver is also damaged to varied extent. Many infants with tyrosinemia type I develop kidney (renal) abnormalities such as renal Fanconi syndrome, a rare disorder characterized by kidney dysfunction that often leads to progressive softening and weakening of the bone structure (rickets). Fanconi syndrome is also associated

with episodes of vomiting, dehydration, weakness, and fever.

Neurological disease

A porphyria-like syndrome is usually occurring neurological disorder. The severe conditions cause pain, weakness and hypertension. motor neuropathy may occur in some patients also with respiratory distress which may require ventilation (Laet *et al.*, 2013). The most prominent is the inhibitory effect of SA on aminolevulinic acid dehydratase, the first step of heme biosynthesis. This leads to neurologic crisis, as seen in acute intermittent porphyria. In approximately 40 percent of cases, affected infants also experience episodes of disease affecting many nerves (polyneuropathy) often following a minor infection. These episodes, which may be referred to as neurological crises, are associated with severe pains in the legs and stomach, increased muscle tone (hypertonia), vomiting, obstruction of the intestines (ileus), an irregular heartbeat (tachycardia), and high blood pressure (hypertension). Some affected individuals may also exhibit self-mutilating behavior (e.g., biting one's tongue or grinding the teeth) during these episodes. In some cases of neurological crises, respiratory failure may occur.

Table 2: clinical manifestation in enzymes deficient in tyrosine catabolism

Defective Enzyme	Disease Names	Elevated Blood Tyrosine	Corneal Ulcers	Hyper-keratosis	Mental Retardation	Arthritis	Liver Failure	Renal Fanconi Syndrome
Tyrosine aminotransferase	Tyrosinemia type II Oculocutaneous tyrosinemia Richner-Hanhardt syndrome	+++	+++	++	+/−	Ø	Ø	Ø
4-OH-phenylpyruvate dioxygenase	Tyrosinemia type III	++	+/−	+/−	+/−	Ø	Ø	Ø
Homogentisate dioxygenase	Alkaptonuria	Ø	Ø	Ø	Ø	+++	Ø	Ø
Maleylacetoacetate isomerase	No human patients described	?	?	?	?	?	?	?
Fumarylacetoacetate hydrolase	Tyrosinemia type I Hepatorenal tyrosinemia	++	Ø	Ø	Ø	Ø	+++	++

Ø, symptom absent; +/−, symptom present in some patients; +, ++, +++, symptom always present, ranging from mild (+) to moderate (++) to severe (+++).

Diagnosis

Tandem mass spectrophotometry for screening of TT1 in new borns. Tandem mass spectrometry is a precise technique which tells about the markers of disease in blood spot specimens of newborns (Barnby, 2014). Test for succinylacetone is very useful that can be measured in plasma, dried blood spot (DBS) or urine. This test is sensitive and accurate. Succinylacetone is difficult to be measured if it is very less concentrated or the urine is very dilute so it is done through special assays. if tyrosinemia type 1 is supposed tests should be done as early as possible (Laet, 2013). Assay of enzyme activity of FAH in skin fibroblasts is possible but not readily available. Sequence analysis of the entire coding region and molecular genetics for the common pathogenic variants of FAH can distinguish pathogenic variants in over 95% of affected persons (King, 2014). The occurrence of succinylacetone (SA) in urine and blood is the sensitive and specific indicator for tyrosinemia type I. For all types of tyrosinemia, plasma amino acids and urine for amino and organic acids are to be tested, for checking the rise of plasma tyrosine, tyrosine-derived urinary metabolites, aminoaciduria, and presence of urine and/or blood succinylacetone. Tandem mass spectrometry is used for rapid diagnosis of Succinylacetone in the blood. The presence of succinylacetone (SA) differentiates tyrosinemia type I from types II and III. For diagnosis of the later types, usually plasma hypertyrosinemia with absence of SA in both urine and blood samples is sufficient for diagnosis. Gene sequencing of the TAT (for type II) and 4-HPPD (for type III) genes are only occasionally necessary for confirmation of these disorders.

Imaging studies

For initial diagnoses, imaging studies are not usually helpful but are necessary in follow-up considerations of tyrosinemia type I. Ultrasound surveillance studies of liver homogeneity are important to determine if there are early signs of either nodular development or infiltrate associated with the known complication of development of hepatomas and/or hepatocellular carcinoma (Chinsky, 2017).

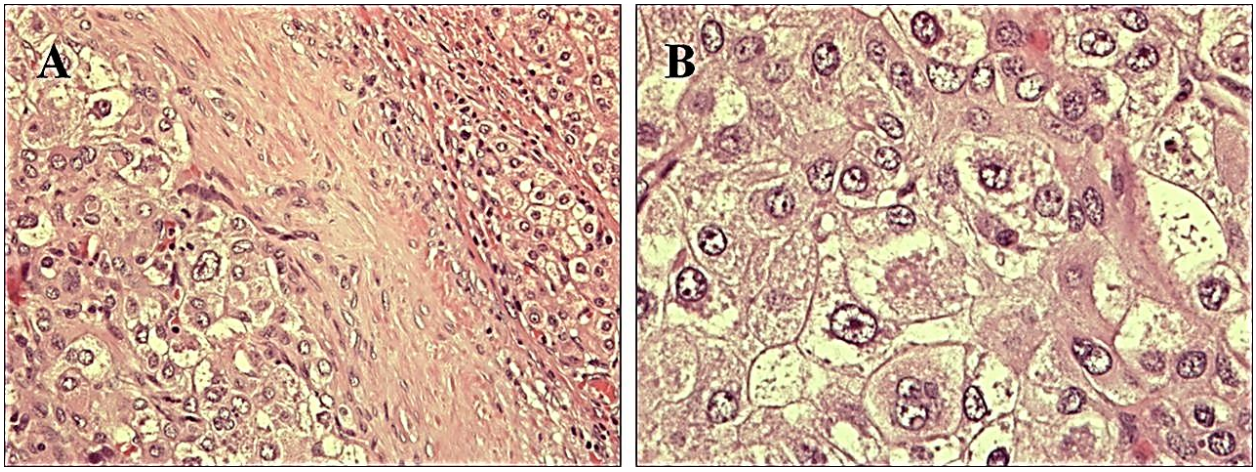

Figure 5: A) Hepatocellular carcinoma in tyrosinemia B) tumor cells

Once the diagnosis of tyrosinemia type I is established from blood and urine studies, liver imaging is performed on a routine, ongoing basis, usually with periodic ultrasound studies and occasional CT/MRI correlation.

Laboratory studies

Biochemical alterations include elevated plasma concentrations of tyrosine and methionine, as well as the excretion of tyrosyl compounds in the urine. The presence of succinylacetone in urine is diagnostic; therefore, urine organic acid analysis is the single most important diagnostic test for this disease. Highly elevated concentrations of AFP are seen, even before the elevation in tyrosine. Hypoglycemia may occur and coagulation defects are common. Plasma transaminase levels (ALT and AST) may be only mildly elevated and are in "disproportion" to the degree of coagulopathy. Fumarylacetoacetate hydrolase (FAH) enzyme activity can be measured in cultured skin fibroblasts or liver specimens to confirm the diagnosis (Laet, 2013).

Treatment

When a patient has high tyrosine either in tyrosinemia type I, type II and type III, or if there is another cause for tyrosinemia while instantaneously managing characteristic treatment. When there is no organ damage high tyrosine level in new borns lead them to be kept under observation. Inhibitor nitisinone and dietary therapy (diet without tyrosine and phenylalanine) is used to prevent liver dysfunction in type I tyrosinemia. Succinylacetone will decrease effectively under the action of nitisinone but with rising level of tyrosine so diet without tyrosine and phenylalanine is essential to decrease the level of tyrosine up to 9mg/dL. Nitisinone is effective on about 90% of patients if treatment is initiative at an early stage. LFTs (liver function test) and test of serum α-fetoprotein are used to evaluate the therapeutic effect of nitisinone. The standard range (<10 ng/dL) of serum α-fetoprotein test shows positive prognosis. Patients might experience liver failure if they do not take nitisinone and then only treatment is left liver transplantation. Sometimes liver cancer can develop in patients who are already taking nitisinone and lead to liver transplantation. Skin and eye problems improve with reduction in tyrosine level after the treatment in type II tyrosinemia. For this purpose, patients are recommended dietary therapy to maintain the tyrosine level for their bodies. Patients of Tyrosinemia type III are also recommended with diet low in tyrosine and phenylalanine tyrosinemia type one can easily treated. Tyrosinemia type 1 is a disease that can be treated. An experienced and well-coordinated team of physicians is needed for the treatment. Amino acids free diet along with nitisinone dose is needed for treatment. (Barnby, 2014).

For all the hypertyrosinemias, dietary restriction of tyrosine (and phenylalanine from which it is derived) is indicated. Often this involves the use of synthetic amino acid formulas that contain limited or no amounts of phenylalanine or tyrosine, combined with a lower than normal (restricted) natural protein diet. For some patients with type II tyrosinemia, a low natural protein diet without using tyrosine/phenylalanine -free amino acid supplements may be adequate. For type I tyrosinemia, usually both a restriction in natural protein and supplementation with tyrosine free amino acids mixture are required and must be monitored by a metabolic nutritionist or equivalent for ongoing changes based on results of the plasma amino acids. Patients with acute signs of hepatic dysfunction likely due to tyrosinemia type I should be treated with high dextrose containing intravenous fluids. This will avert or correct the hypoglycemia due to metabolic liver dysfunction, and, in the case of tyrosinemia type I, directly inhibit the porphyrin synthetic pathway that produces delta aminolevulinic acid, the toxic compound associated with neurologic crises.

NTBC (2-nitro-4-trifluoro- methylbenzyol)-1,3 cyclohexanedione has the potential to be used as treatment of HT1. In 1992, NTBC's potential for the treatment of human tyrosinemia and used it successfully in five patients. The principal underlying this treatment is to reduce metabolic flow through the tyrosine catabolic pathway and to prevent the formation of the toxic

compounds maleylacetoacetate (MAA) and fumarylacetoacetate (FAA) (Grompe, 2015). During these neurologic crises, not only high dextrose infusion but also saline supplementation will likely be needed since hyponatremia is common. NTBC is usually prescribed at 1mg/kg day in divided bid dosing, but some patients may require 25%-50% more, especially during infancy and early childhood. In some sites, plasma NTBC levels can be monitored to correlate both compliance and clinical efficacy of current dosing. As with all amino acid restricted diets, appropriate nutritional monitoring and ongoing dietary recommendations are mandated to ensure optimal growth (Chinsky, 2017). Tyrosine level increases with nitisinone, thus diet low in tyrosine is necessary to prevent formation of crystals of tyrosine in cornea. Patient should go for a vegetarian diet that is low in protein along with a medical formula. Exact information is not available about use of nitisinone in pregnancy and its side effect but developing fetus might be at risk due to increased tyrosine level (King, 2014).

Management

Management of tyrosinemia is described in figure 6, after the diagnosis of tyrosinemia the patient is referred to start a diet without tyrosine and usage of nitisinone. Dietary restriction of phenylalanine and tyrosine remains an important aspect of treatment, even with the use of nitisinone. Because nitisinone blocks p- HPPD, tyrosine values in blood can rise to levels that cause tyrosine crystals to form in tissue. Tyrosine has low solubility compared to most amino acids and readily crystallizes in tissues at concentrations that exceed solubility. The major complication from nitisinone therapy is tyrosine crystal deposition in the cornea, causing photophobia and an ocular inflammatory response. To prevent this, it is recommended that tyrosine concentrations be monitored and that children utilize a phenylalanine- and tyrosine-restricted diet.

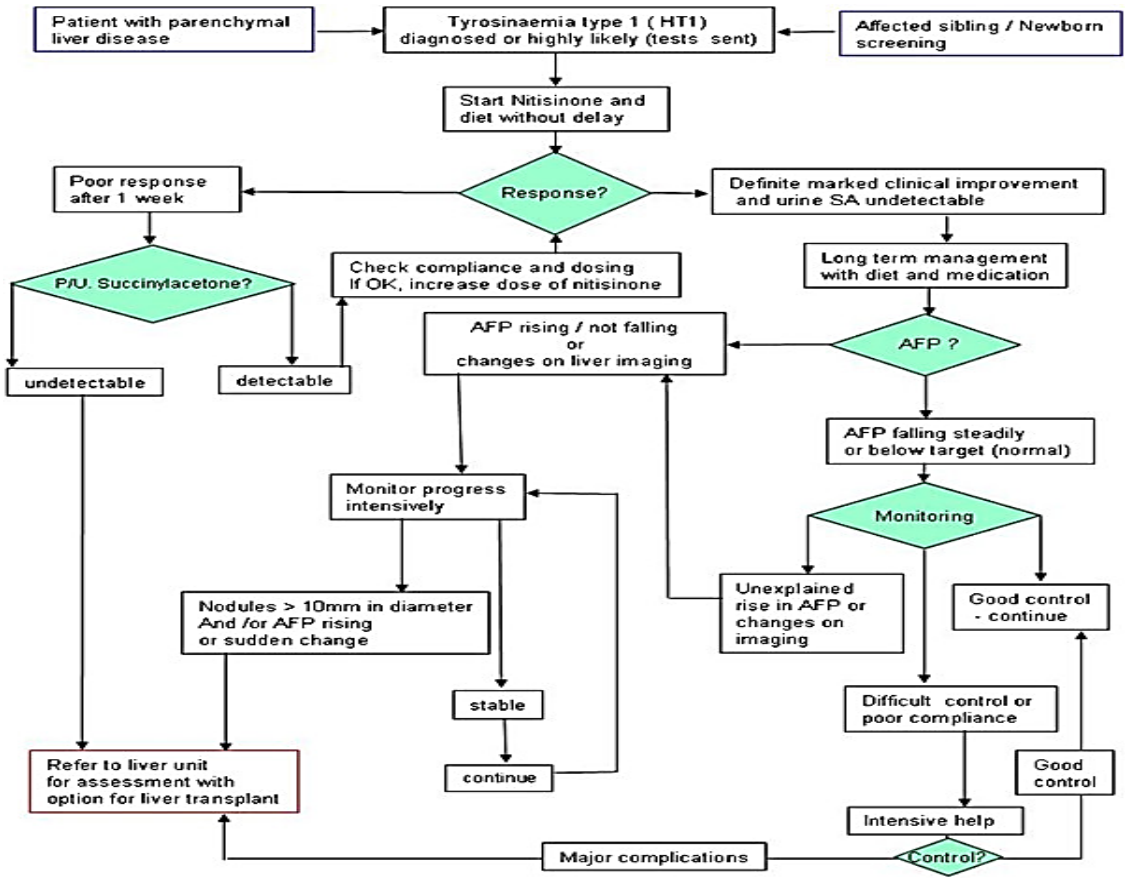

Figure 6: management of tyrosinemia

Prognosis

Even in early treatment with nitisinone for tyrosinemia type I, there are chances of liver cancer and rickets. About 5% of children who started treatment before 2 years old were later diagnosed with liver cancer by the age of ten. Therefore, regular imaging and other checkups should be performed during treatment so that liver cancer can be exposed early. Enduring survival can be expected for patients with type I if nitisinone treatment is effective. Types II and III have relatively good prognoses (Nakamura, 2015).

CONCLUSION

The examination of "rare" diseases, such as tyrosinemia, can result in productive explorations with some significant therapeutic consequences for the patients with these diseases and insights into the biological processes. To be part of this process, even in a limited capacity, is

truly the greatest reward of our specialty. With the introduction of nitisinone the prognosis for those with HT1 has improved greatly. However, because newborn screening is only available in a few countries most patients still present clinically. Early treatment with nitisinone and strict diet is essential. Careful long term intensive care and supervision is required. Potential, controlled treatment studies are needed to develop evidence-based guidelines for the future management of Hypertyrosinemia Type 1.

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