Chapter

Successive Drug Therapy for a Very Rare Autosomal Diseases

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Abstract

It is very rare to find reports concerning a drug therapy successively treating chromosomal abnormalities. In this paper, we are reporting a successive use of nitisinone in treating a fatal and very rare autosomal disease called hereditary tyrosinemia type-1 [HT-1]. HT-1 is affecting about one person in 100,000 to 120,000 births worldwide. It is due to a genetic defect in the enzyme fumarylacetoacetate hydroxylase (FAH), which is responsible for the final degradation of tyrosine. Accumulation of tyrosine metabolites is responsible for tissue damage such as liver, kidney, and neural tissues, finally causing the death of the newborn babies in their early months of life if not treated. Fumarylacetoacetate hydrolase gen has mapped on chromosome 15q23-15q25. Since 1992, the initiation of treating HT-1 with nitisinone (NTBC) has become the medical therapy of choice in combination with diet. NTBC therapy has shown a direct correlation between age of initiation and subsequent clinical course. We are reporting three brothers treated safely and successively with NTBC in combination with diet. All of them are in very good conditions. The elder brother is on NTBC since 27 years ago.

Keywords: autosomal diseases, hepatocellular tyrosinemia, nitisinone, NTBC, hepatocellular carcinoma, newborn screening

1. Introduction

1.1 Tyrosine

Tyrosine (4-hydroxyphenylalanine) is a nonessential amino acid with a polar side group, 1 of the 22 amino acids that are used by cells to synthesize proteins. Tyrosine is also a precursor to neurotransmitters (catecholamines) and hormones (thyroxine and melatonin) [1–3]. In humans, tyrosine is obtained from two sources, dietary intake and hydroxylation of phenylalanine [4, 5]. Tyrosine degradation as shown in **Figure 1** is catalyzed by a series of five enzymatic reactions that yield acetoacetate, which is ketogenic, and the Krebs cycle intermediate fumarate, which is glucogenic [4, 6, 7]. Although tyrosine degradation occurs mainly in the liver but to a lesser extent, it occurs in the proximal renal tubules [5, 8, 9]. Impaired catabolism of tyrosine is a feature of several acquired and genetic disorders. Four autosomal-recessive disorders result from deficiencies in specific enzymes in the tyrosine catabolic pathway: hereditary tyrosinemia (HT) types 1, 2, and 3, and alkaptonuria (AKU). These disorders result in elevated blood tyrosine levels except for AKU [4, 7, 9–11].

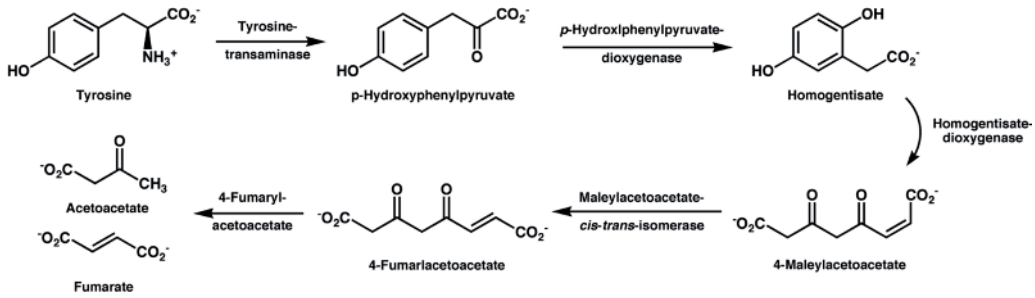

Figure 1.
The steps of tyrosine degradation.

2. Hereditary tyrosinemia type 1 (HT-1)

Synonyms: hepatorenal tyrosinemia (HRT), tyrosinemia type-1, hereditary infantile tyrosinemia, congenital tyrosinosis, and fumarylacetoacetate hydrolase (FAH) deficiency (FAHD), and is assigned OMIM 276700.

2.1 History

Inborn errors of metabolism (IEMs) are a group of diseases involving a genetic defect that alters a metabolic pathway and that presents during infancy.

The tyrosine degradation pathway contains five enzymes, four of which are associated with IEMs. The most severe metabolic disorder associated with this catabolic pathway is hereditary tyrosinemia type 1 (HT-1; OMIM 276700) [10].

In 1932, American biochemist Grace Medes, at the University of Minnesota Medical School in Minneapolis, first described "a new disorder of tyrosine metabolism" and called it "tyrosinosis" after observing 4-hydroxyphenylpyruvate in the urine of a 49-year-old man with myasthenia gravis [12]. She proposed that the metabolic defect in this patient was a deficiency of 4-hydroxyphenylpyruvate dioxygenase.

In 1957, Japanese scientists, Kiyoshi Sakai and colleagues, published three reports describing the clinical, biochemical, and pathological findings of a 2-year-old boy with hepatorenal tyrosinemia who was then thought to have an "atypical" case of tyrosinosis ("atypical" because it differed from the supposedly prototypical case reported by Medes) [13–16].

Then, between 1963 and 1965, Swedish pediatrician Rolf Zetterström and associates published the first detailed descriptions of hepatorenal tyrosinemia and its variants, a disorder then hypothesized to be caused by a defective 4-hydroxyphenylpyruvate dioxygenase enzyme [17–20]. Furthermore, in 1964 several pediatricians in Chicoutimi (Quebec-Canada) became aware of an increased incidence of infantile liver cirrhosis that was later recognized to be due to hereditary tyrosinemia type [21, 22]. Both the Scandinavian and Canadian groups suggested that the Japanese patients described earlier by Sakai and colleagues had the same disorder, that is, HT-1 [16]. Therefore, it has been considered that the first definite case report in the world of HT-1 was in Japan by Sakai and colleagues in 1957 [23].

2.2 Pathophysiology

Hereditary tyrosinemia type 1 is an inborn error of metabolism, inherited as an autosomal recessive disorder. The biochemical defect was shown to be

due to a genetic defect causing a deficiency (weak activity) or absence in the enzyme fumarylacetoacetate hydrolase (FAH), the enzyme catalyzing the final step of tyrosine catabolism pathway as shown in **Figure 2** [24, 25]. Fumarylacetoacetate hydrolase gen has located on chromosome 15q23-15q2515q23 and is composed of 14 exons [26]. This enzyme defect leads to subsequent accumulation of the amino acid tyrosine and its toxic metabolites such as succinylacetone, maleylacetoacetate, and Fumarylacetoacetate in the blood and tissues such as the liver, kidney, heart, and peripheral nerves, leading to dysfunction of these organs [24, 27–30]. The patient may develop acute and severe liver failure that is life-threatening in early infancy (<6 months of age). The survivors of the acute failure show before two years of life liver cirrhosis, complex renal tubulopathy, rickets, cardiomyopathy, and hemorrhagic syndrome. Hepatocellular carcinoma (HCC) is a frequent complication of this form of HT1, which is often the cause of death in early life in an untreated individual [22, 25, 31, 32].

2.3 Prevalence of HT-1

In general, hereditary tyrosinemia type-1 is a very rare inborn genetic disease affecting about one person in 100,000–120,000 live births worldwide [29, 31, 33, 34]. In some areas, the incidence of HT1 is noticeably higher. In Norway, Finland, and Tunisia, the frequency of HT1 is 1:74,800, 1:60,000, and 1:14,804, respectively [35–37]. The highest prevalence of the disorder is observed in Canada (the Province of Quebec), which is about 1 in 16,000 live births [32, 33, 38, 39], and even in a certain region of Quebec near Saguenay-Lac Saint-Jean Jean, it is estimated to be 1:1846 live births [32], and the carrier rate has been estimated to be between 1 in 20 and 1 in 31 [39].

The estimated incidence of tyrosinemia in the Eastern Province of Saudi Arabia is 3 in 100,000 live births, although the authors concluded that data obtained from their study underestimate the true number [40].

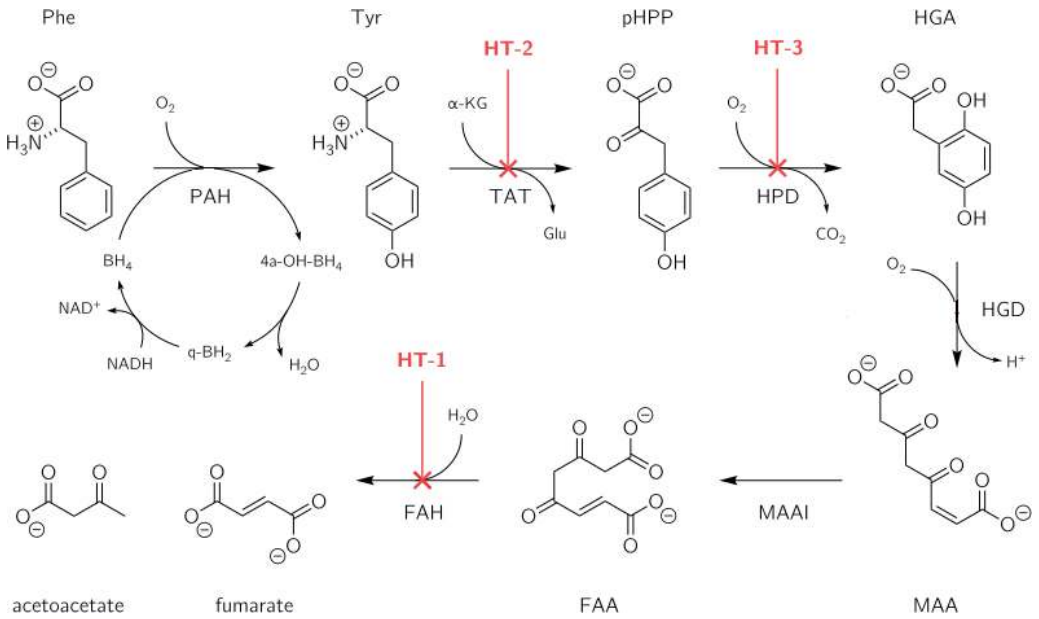

Figure 2.
Steps of tyrosine and its inborn enzymatic error of metabolism causing tyrosinemia type I, II, and III.

2.4 Diagnosis

A diagnosis of HT-1 is made based upon thorough clinical evaluation, a detailed patient history, and specialized tests.

Elevated blood tyrosine level in newborns should be seen as soon as possible for clinical and laboratory evaluations for the possibility of HT-1. The diagnosis of HT-1 is based on elevated succinylacetone (SA) levels in the blood and or urine, as tyrosine elevation is an unreliable marker. There are many false-positive and false-negative results when tyrosine is used as the only diagnostic parameter [41]. In the US, Canada, and some of the European countries, they use the detection of plasma SA as a newborn screening test for the detection of HT-1 [42].

If there is a high suspicion for HT-1, plasma amino acids (PAA) and liver function tests including prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and α-fetoprotein (AFP) should be evaluated at the first visit. [43].

Clinical symptoms typically begin before two years of age, with the majority of children presenting before the age of 6 months with hepatosplenomegaly and evidence of acute liver failure and renal dysfunction. A few affected children may present over the age of 2 years with isolated coagulopathy or other signs of liver dysfunction, renal tubular disease, hypophosphatemic rickets, and failure to thrive. All children with HT-1 are at high risk for hepatocellular carcinoma (HCC), and this also may be the first recognized clinical event [44].

Molecular genetic testing for FAH gene mutations is available to confirm the diagnosis [45, 46].

2.5 Differential diagnosis

HT-1 should be differentiated from another inherited inborn autosomal recessive disorders with dramatically elevated blood tyrosine levels such as:

Tyrosinemia type II, which is due to tyrosine aminotransferase (TAT) deficiency as shown in **Figure 2**, causing accumulation of tyrosine that produces a severe dermatologic and ophthalmologic abnormalities. Type II tyrosinemia occurs in less than 1 in 250,000 individuals [47–49].

Tyrosinemia type III is due to 4-hydroxyphenylpyruvate dioxygenase (HPD) deficiency as shown in **Figure 2**. It is the rarest of the three conditions, with only a few cases ever reported. Most of those cases have included intellectual disability and neurologic dysfunction. It also has highly elevated blood tyrosine levels but does not manifest liver disease or renal tubular disease [50–53].

Tyrosinemia types II and III variably respond to phenylalanine and tyrosine dietary restriction therapies, unlike HT-I, the dietary restriction, even if begun within the first month of life, did not eliminate the development of hepatic, renal, or neurological complications.

Plasma amino acids (PAA) will help to differentiate tyrosinemia types II and III from HT-1 in those cases where the children are detected by an elevated tyrosine level but do not have detectable succinylacetone (SA).

2.6 Management of HT-1

2.6.1 Nitisinone drug therapy

Nitisinone, orfadin, **or** 2-(2-nitro-4-trifluoromethylbenzoyl)-cyclohexane-1,3-dione (NTBC). Its structure is shown in **Figure 3**.

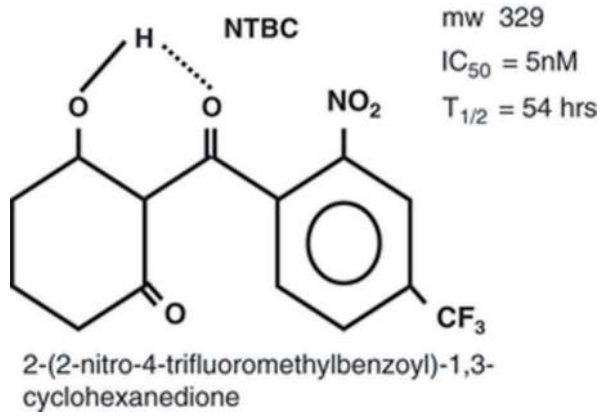

Figure 3.
The structure of nitisinone (NTBC).

2.6.2 History of nitisinone discovery

Nitisinone is a member of the benzoylcyclohexane-1,3-dione family of herbicides, which are chemically derived from a natural phytotoxin, leptospermone, obtained from the Australian bottlebrush plant (*Callistemon citrinus*) [29].

Nitisinone was discovered as part of a program to develop a class of herbicides called 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors. HPPD is essential in plants and animals for catabolism, or breaking apart, of tyrosine. In plants, preventing this process leads to the destruction of chlorophyll and the death of the plant [54].

In normal humans, fumarylacetoacetate hydrolase acts on the final step of tyrosine metabolism after HPPD does. The absence or weak activity of fumarylacetoacetate hydrolase as in HT-1 leads to very harmful products building up in the body [24, 27–30]. So scientists working on making herbicides in the class of HPPD inhibitors hypothesized that inhibiting HPPD and controlling tyrosine in the diet could treat this disease. A series of small clinical trials attempted with one of their compounds, nitisinone, were conducted and were successful, leading to nitisinone brought to market as an orphan drug Swedish Orphan International, which was later acquired by Swedish Orphan Biovitrum (Sobi). [55, 56]. Therefore, in HT-1, the mechanism of nitisinone action will involve reversible inhibition of HPPD preventing the formation of maleylacetoacetic acid and fumarylacetoacetic acid, which have the potential to be converted to succinylacetone, a toxin that damages the liver and kidneys. This causes the symptoms of HT-1 experienced by untreated patients.

Lock described nitisinone by a nice statement "From Weed Killer to Wonder Drug" [57].

2.6.3 The clinical trial of nitisinone

Sven Lindstedt recognized the potential value of NTBC for the treatment of HT-1. By blocking the proximal tyrosinemia pathway, NTBC minimizes the formation of FAA and maleylacetoacetic. It was this keen insight that led to the original clinical trial with five patients, which documented the rapid reversal of clinical symptoms [58].

NTBC dosing should be sufficient to completely suppress plasma and urine SA detection and normalize liver and renal function. SA, in either plasma or urine, should be below detectable limits (or within the limits of normal established by

the reference laboratory). The dose of NTBC should be increased if the SA level increases once patient adherence has been confirmed [43].

The standard recommended dosage of NTBC is 1 mg/kg body weight [43, 59, 60]. The half-life of NTBC has been measured in healthy human subjects and found to be approximately 54 h [61]. Because of this long half-life, a single daily dose of NTBC is satisfactory for maintaining inhibition of HPD [62, 63].

In the evaluation of its safety profile, rats and dogs exposed to NTBC developed elevated plasma tyrosine levels and ocular lesions. The ocular lesions (keratopathy) were caused by tyrosine crystals within the cornea, which on cessation of the diet recovered [43, 57].

The FDA approved NTBC in January 2002 [64].

2.6.4 Nutritional therapy

The combined nitisinone and low phenylalanine and tyrosine diet treatment should be initiated as soon as possible following the diagnosis of HT-1, to maintain PAA concentrations within the treatment range. Phenylalanine must be restricted in the diets of affected patients since approximately 75% of dietary phenylalanine is hydroxylated to form tyrosine [65, 66]. The combined diet restriction and NTBC treatment resulted in a greater than 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, and improvement in secondary rickets [67–69].

2.6.5 Liver transplantation

Before the availability of nitisinone for the treatment of tyrosinemia type I, the only definitive therapy was liver transplantation. The first case of HT-1 treated with liver transplant was in 1978 performed by Fisch and his colleagues [70]. The patient died 3 months later, but the biochemical derangements improved. Subsequently, the use of liver transplants in HRT cases has increased, and the benefits appear to be confirmed [71].

Liver transplantation should be reserved for those children who (1) have a severe liver failure at clinical presentation and fail to respond to nitisinone therapy or (2) have documented evidence of malignant changes in hepatic tissue [72]. Transplant recipients may also benefit from low-dose (0.1 mg/kg/day) nitisinone therapy to prevent continued renal tubular and glomerular dysfunction resulting from the persistence of succinylacetone in the plasma and urine [73].

2.6.6 Low phenylalanine and tyrosine diet restriction

Diet restriction for the treatment of HT-1 patients was introduced by Halvorsen and Gjessing in 1964 [19] and for a long time was the only treatment available. It had a beneficial effect on the renal tubular defects but did not cure the liver disease. A girl with HT-1, diagnosed at 6 months of age, was treated with a diet restricted in phenylalanine and tyrosine. At 9½ years of age, she developed an acutely enlarged liver and spleen, and the diagnosis of hepatocarcinoma was made [70].

2.6.7 Genetic therapy

Gene therapy is a promising means to cure many monogenic diseases. However, traditional gene therapies are best suited to treat diseases of deficient or absent gene products rather than those diseases caused by aberrantly functioning proteins [74].

Adeno-associated virus (AAV)-mediated gene repair is feasible *in vivo* and can functionally correct a mouse model [74] and pig model of HT-1 [75] and concluded that further exploration of *ex vivo* hepatocyte genetic correction is warranted for clinical use. Although AAV-mediated gene therapy in a mouse model of HT-1 was successful as it has shown that none-treated FAH mutant control mice died within six weeks from fulminant liver failure, FAH adenovirus-infected animals survived 2–9 months. But this gene therapy does not obviate the tumor risk inherent in HT-1 as nine of 13 virus-treated animals developed hepatocellular cancer [76].

2.6.8 Family cases of HT-1 treated successively with nitisinone

We are reporting three Saudi siblings who have diagnosed as patients with HT-1. They are living in Najran city, the southern province of Saudi Arabia.

The first case is 27-year-old male patient. He has been diagnosed at the age of 4 months in Great Ormond Street Hospital (London-UK) and treated by nitisinone in combination with tyrosine and phenylalanine-free diet. For the next 15 years, he used to visit the clinic for regular checking. The final report showed that he has good general health, with normal liver and renal function test and normal alpha-fetoprotein. Since then and until now, he attends the National Laboratory for Newborn Screening, Department of Genetics, King Faisal Specialist Hospital and Research Centre for a routine checkup. Still, he is on nitisinone and diet restriction. He has graduated from Najran Technical College, and now he is doing very well in his job as the vice director of staff affairs at Al-Ghad International College for Applied Medical Sciences in Najran-KSA.

The second case is his brother, who is 20 years old. He has been diagnosed in the first few days after birth by the National Laboratory for Newborn Screening, Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. Since then he has been treated by nitisinone in combination with tyrosine and phenylalanine-free diet. He is having good general and mental conditions. He is now a 2nd-year university student and doing well in his study.

The third case is their younger brother, who is 15 years old. Diagnosed since birth by the National Laboratory for Newborn Screening, Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. Since then, he has also been put on nitisinone in combination with tyrosine and phenylalanine-free diet. He is also having a good general and mental conditions. He is a secondary school student, and he is also doing very well in his study.

The three brothers are now on nitisinone in a dose of 1 mg/kg/day. It is marketed under the brand name Orfadin by the company Swedish Orphan Biovitrum (Sobi). Also, they are on tyrosine and a phenylalanine-free diet supplemented with HCU Anamix Junior LQ [Nutricia Advanced Medical Nutrition Company].

They have a regular visit to the National Laboratory for Newborn Screening, Department of Genetics, King Faisal Specialist Hospital, and Research Centre, Riyadh, Saudi Arabia for regular checking, and the last visit was a few weeks ago.

Their elder two siblings (sister and brother) died in their early life of unknown cause. The sister died at the age of 26 months. From the history of her mother, it seems that the daughter developed abdominal distension, and their doctors told her that the baby has hepatosplenomegaly. She also developed jaundice and became reluctant to milk or food. Until the day of death at the age of 26 months, she could not sit or walk; she was very week as her mother described.

Then after, they have a boy who developed after birth hepatomegaly, and jaundice, abdominal distension with very thin extremities and died early after birth at the age of 4 months, as his mother said.

After the birth of the third baby (our first case), they went to Great Ormond Street Hospital and diagnosed as having tyrosinemia-1. At the same time, the parents diagnosed as a carrier of the disease.

The clinical history of their previous dead siblings suggested that they did have undiagnosed HT-1. Furthermore, the diagnosis of the parents that they are a carrier of the disease is highly supporting that the death of their two children early life was due to the lack of diagnosis and treatment of HT-1.

3. Discussion

HT-1 is a rare but clinically severe and fatal inborn error that principally affects the liver, kidney, and peripheral nerve [32]. In general, the most diagnosed patients of inborn errors of metabolism (IEMs) including HT-1, were born from consanguineous married parents. As HT-1 is a rare inherited autosomal recessive disorder, it explains why it is more common in population with a high rate of consanguineous marriages, such as in United Arab Emirates, Oman, Kuwait, and Saudi Arabia, in which the rate of consanguineous marriages reaches up to approximately 60% [33, 77–80], and even the first reported case of HT-1 in Japan (1957) was a child from parents of consanguineous marriage [13, 14]. Furthermore, in our study, the reported three family cases are also born from a consanguineous married parent.

In the sixties and early seventies HT-1 patients were treated by phenylalanine- and tyrosine-free died; it delayed the mortality and morbidity for a few years but it did not prevent the development of hepatic failure, renal complications and hepatocellular carcinoma (HCC) even if begun within the first month of life [43]. Then after, treatment with hepatic transplantation was the only option for survival. But it has been reported that the development of HCC was observed in 17–37% of affected children [81, 82]. Furthermore, after transplantation, urine and plasma SA decreases but is not completely suppressed [43, 63], and even other scientists reported that plasma succninylacetone is persistently raised after liver transplantation [73] presumably because of continued production in the kidneys which could cause damage to the liver and the kidney. Also, some of the patients died from the complications of hepatic transplant, whether the surgical or the immunosuppressive drug complications [43, 63, 69]. Therefore, in 1992, the introduction of nitisinone in combination with diet restriction was the ideal therapy for HT-1 patients especially if started in their early neonatal days [58].

The three HT-1 patients in our study used nitisinone in combination with phenylalanine and tyrosine diet restriction from early days of their neonatal life and till now, which is 27, 20, and 15 years, respectively. They are not only still alive but also doing very well in their living.

These results justify implementing prevention programs that incorporate genetic counseling and neonatal diagnostic screening tests, especially in the suspected families of consanguineous marriages to detect the neonatal patients with HT-1 as early as possible and then to start treatment which will minimize the lethal consequences of the disease.

All subsequent children of the parents of a child with HT-1 should have urine and blood succinylacetone analyzed as soon as possible after birth to enable the earliest possible diagnosis and initiation of therapy. Early detection of newborn babies with HT-1, followed by prompt treatment with nitisinone in combination with a low phenylalanine and tyrosine diet has improved the survival to over 90% and resulted in normal growth, improved liver function, prevention of cirrhosis, correction of kidney disease, and improvement in rickets [41, 42, 83, 84]. In 2012, Larochelle

et al. reported that patients who receive nitisinone treatment before 1 month had no detectable liver disease after more than 5 years [69].

These data suggested that early neonatal diagnosis of HT-1 and treatment with nitisinone and diet restriction not only keep the survival of the patients but also keep them in good general, physical, and mental conditions.

4. Conclusion

Nitisinone (NTBC) has been used since 1992 and proves to be an effective and safe pharmacological treatment for HT-1 in combination with phenylalanine- and tyrosine-free diet.

In this paper, we are reporting three cases (brothers) treated safely and successively with NTBC in combination with diet. All of them are in very good conditions. The elder brother is on NTBC since 27 years ago. He is one of the few cases worldwide treated since 1992 and till now, and he is living with a very good general health.

HT-1 is not only a rare and fatal autosomal disease, but it is a very rare genetic disease that can be successfully, effectively, and safely treated by drug therapy, which is nitisinone (NTBC).

4.1 Recommendation

We highly recommend establishing a national Newborn Screening Center, which provides newborn screening test for the diagnosis of HT-1, especially for the high-risk neonates in the suspected families. The use of tandem-mass-spectrometry could make an early diagnosis of HT-1 by measurement of succinylacetone in blood spot specimens.

Prenatal diagnosis is also possible by doing DNA analysis in addition to the detection of succinylacetone in the amniotic fluid of the suspected pregnancies.

Early diagnosis and treatment of this life-threatening disease provide an opportunity to intervene before symptom onset.

Furthermore, this report justifies implementing prevention program by doing genetic counseling and DNA analysis in the suspected families, where consanguineous marriages are prevalent.

Disclosure of conflicts of interest

None.

Ethical consideration

The protocol was submitted and approved by the Research Ethical Committee of Al-Ghad International College for Applied Medical Sciences-Najran, KSA.

Consent

Written informed consent was obtained from the family for the anonymized information to be published in this article.

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