Case Report

Tyrosinemia Type 1: Clinical and Biochemical Analysis of Cases with Poor Treatment Outcome

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Abstract

Background: Tyrosinemia Type I (TT1) is a metabolic disorder with impaired activity of fumarylacetoacetate hydrolase enzyme. The causes of death are liver failure, pseudo porphyric crisis and hepatocarcinoma. The treatment is based on diet restriction, liver transplantation and the NTBC.
Aim: To review the clinical presentation, biochemical analysis and expose the causes of failure of treatment in 3 patients with TT1**.**

Patients and Method: By studying the clinical and biochemical data of 3 dead patients with TT1 (part of the total 15 patients with the same diagnosis), during (October 2001 to October 2009).The diagnosis was established by high tyrosin in the blood and succinylacetone in the urine. Monitoring was based on the combination of liver imaging, and alpha feto protein as tumor marker. Two patients were treated by NTBC and diet restriction (patients 1 and 2) while the 3rd patient was treated by diet restriction only.

Results: Overall survival rate was 80% (85.7% in those treated by NTBC). The age at onset was respectively 8, 5 and 1.5 months .The age at diagnosis was 40, 6 and 6 months. All three patients were presented with severe liver failure. (PT ranged from 21% to 24%), patient 1 was treated with NTBC for 4 months and died after 2 months of stopping NTBC. The second patient did not respond to NTBC and died after 5 months of treatment. The third patient died after 2 months of treatment.

Conclusion: **A.** Poor prognosis in patient 1 and 2 could be explained by (1) The dose was less than 2mg/kg/d (2) Late diagnosis in patient 1. (3) Difficulty of management and monitoring. **B.** Poor prognosis in patient 3 was on diet restriction as in the literature. **C.** Slow decrease of alpha feto protein can explain the possibility of hepatocarcinoma in patient 1 and 2 but the duration of the treatment was short to conclude, the increase in patient 3 is well known as a part of hepatocarcinoma mechanism.

Recommendations: (1) Early diagnosis and starting NTBC with diet restriction give good prognosis. (2) Starting neonatal metabolic screening.

Keywords: Tyrosinemia 1, NTBC, HCC, AFP.

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Introduction

Tyrosinemia Type I (TTI) is an autosomal recessive multiorgan disorder, fatal liver disease, ranging from acute liver failure to chronic liver failure, renal tubular dysfunction, and intermittent porphyria like hepatocellular carcinoma. The term tyrosinemia was given to various disorders

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based on clinical observation and high blood level of tyrosine: **1**. Transient Tyrosinemia of Newborn (TTN) a benign condition due to delayed enzyme maturation; resolve spontaneously without complication. **2.** Hereditary tyrosinemia type1 hepato renal type. **3**. Tyrosinemia type 2 Richnar Hanhart syndrome, is a disease with the presentation of skin lesion of hyperkeratosis of palms and soles, mental retardation with herpitiform cornel ulcer. **4**. Tyrosinemia type 3 is a very rare disease presented by intermittent ataxia without the involvement of liver, kidney, skin or ocular lesion. [1, 2] The underlying defect in tyrosinemia type 1 is a mutation in the gene for furmaryacetoacetate which accounts for known liver and kidney damage, accumulation of succinylacetone responsible for local and systemic toxicity damage. [1, 2] Circulating of succinylacetone leading to increased delta mino levulimic acid which gives the presentation of porphyric like crisis, traces of this element in the urine are diagnostic. [3]

Tyrosinemia type **1** has worldwide distribution with high incidence in Quebec, [1,2,4,5] presented either as acute form or sub acute or chronic. **1**. Acute type: characterized by progressive liver disease, porphyria like crisis with hypophosphatemic rickets and hepatic insufficiency develops before 6 months of age as a result of micro and macro nodular cirrhosis. **2**.Sub acute type: hepatomegaly, irregular bleeding and rickets are presented after the age of 6 months. **3**. Chronic type with hepatomegaly, rickets and growth retardation are presented after the age of one year. [6] The major target organs are liver and kidney but heart as cardimyopathy, pancreas, and peripheral nerves can be affected. Nephropathy is frequently seen in patients of tyrosinemia type1 with renal impaired varies from mild tubular dysfunction to renal failure with manifestation of fanconi syndrome results in a vitamin D resistant rickets. [7, 8] The causes of death are liver failure, porphyria like crisis and hepatocarcinoma. [5, 16, 17] Since 1992, the treatment of tyrosinemia type 1 has changed completely and has transformed the prognosis of the disease when Lindstedt et al. reported their first results with NTBC (2-(2 nitro- 4- 3trifluoro-methybenzoyl)-1, 3-cyclo hexanrdione. NTBC "Nitisinone, Orfadin" inhibits the second step in the tyrosin pathway and prevent accumulation of toxic metabolites. [9] With NTBC as treatment (in a usual dose of 1mg/kg/d to 2mg/kg/d in severe cases) can prevent liver failure, renal tubular dysfunction and porphyria like crisis but potential risk of developing of Hepatocelullar Carcinoma (HCC) still present, also patients treated with a restricted diet carries a high risk of HCC, combination diet restriction and NTBC have now become the best treatment of TTI. [10] Liver transplantation is the only long time curative therapy but is now limited to patients who failed to respond to NTBC treatment. [11]

Patients and Methods

The patients enrolled in this study were 3 patients who died (out of 15 patients who have the same diagnosis) during 8 years between Oct. 2001 and Oct. 2009. The medical records were analysed, the clinical diagnosis was confirmed by measuring tyrosin in the blood and succinylacetone in the urine, which were done by Bioscentia and Laboratoire Merienx. Investigations were performed and monitored and the outcomes of treatment were observed until death, following the tumor marker alpha feto protein and liver imaging. Enzyme assay, Genotype study was not available and liver biopsy was not done due to the critical situation of the patients. Two patients received NTBC, the dose was 1mg/kg/day and diet restriction as low as tyrosine/ phenylalanine diet aiming to maintain urine succinylacetone free, the third patient was treated by diet restriction and we kept her on breast feeding because the NTBC was not available.

Patient 1: A boy was presented to us at the age of 3 years and 2 months, referred from Orthopaedic department as a case of recurrent fractures, presentation was with huge ascites and bruises. He is the second child to healthy parents, who are second and their marriage is consanguineous. The other patient was presented at the age of 8 months with progressive abdominal distension, progressed to bone deformity delay motor development, he started

walking at the age of 19 months, and was treated as nutritional rickets with poor response as never healed although high doses of vitamin D were given. On admission, routine investigation and metabolic evaluation were done. The treatment was started in a severely ill patient symptomatically and specifically with NTBC 1 mg/kg/d capsules and restricted diet for 6 months (4 months with NTBC and 2 months without NTBC because it was not available).

Patient 2: A Female patient was the second child to healthy parents who are first cousins. Abdominal distension with an early sign of rickets was detected at the age of 5 months, she was referred as a tyrosinemia with suspected of hepatic malignancy. She was treated symptomatically to correct hypophosphatemic rickets, and bleeding tendency, we started NTBC 1mg/kg/d and restricted diet at the age of 8 months for 5 months.

Patient 3: A Female baby was admitted at the age of 5 months with history of crying, irritability, poor feeding with abdominal distension, rickets, persistent of jaundice without dysmorphic features or cataract. She was the product of first cousins whose marriage is consanguineous, she was born with a below-average weight of 1.9 kg, she was admitted with an initial differential diagnosis of biliary atresia, galactosemia, glycogen storage disease, lysosomal storage disease, alph1antitrypsin deficiency and cholestasis. The blood tyrosine and urine succinyl acetone and high level of alphafeto protein were the diagnoses of tyrosinemia, with liver imaging which cannot rule out hepatocellular carcinoma. She was treated by diet restriction and symptomatic treatment in the same way as in all tyrosinemia cases, then she did not come for follow up until the day of her death, she came back with massive bleeding.

Results

The results of the three patients (Table 1) who were diagnosed with tyrosinemia type 1, who are highly susceptible of development of liver cancer, 2 patients were females and 1 was male. Two of them were treated with NTBC and diet restriction but they did not respond to NTBC treatment, the third patient was treated with a diet restriction only. In all the three patients the coaguolopathy and abnormal liver function progressed with clear deterioration in the general condition which ended by death. The clinical manifestation started before the age of one year in all patients, patient 1 was presented as a sub acute form at the age of 8 months while patients 2 and 3 have had earlier presentation as an acute form before 6 months of age. Age at diagnosis was too late in patient 1 with severe bone deformity, fractures and abdominal distension, the other 2 patients were presented by the classical picture of tyrosinemia with early rickets, liver abnormality and tubulopathy. None of them presented with porphoyria like syndrome or cardiomyopathy. All 3 patients started treatment after the age of 6 months. Between the conformation of diagnosis and starting treatment it took one to three months. Initially, all 3 patients started by diet restriction. The duration of treatment was between 2 to 6 months without clinical or significant biochemical general improvement. The treatment failed to reverse the coagulopathy defect without curing the underlying hepatic diseases, dropping in haemoglobin and platelets were significant. At the day of death, all were anaemic and thrombocytopenic with prolonged PT and PTT.

Alpha fetoprotein was markedly high in patients 2 and 3, also in patient 1 with a variable response but in all patients the case was persistent to be high and never normalised (Fig.3). Total serum bilirubin was very high in the third patient who is the youngest one (14 .6mg /dl at diagnosis) with an earlier presentation of deep jaundice (23.6mg/dl) during the last week before death, while the older one was the first patient with normal serum bilirubin (1.1 mg/dl) before starting treatment ending with jaundice before death (8.1 mg/dl). Patient two did not have much change in total bilirubin and jaundice was slight between (1.3-3.3 mg/dl) throughout the course of the disease. Liver transaminase GPT or ALT alanine aminotransferase is liver specific was significant high in all three patients specially in the third patient. ALP alkaline phosphatase is a good

marker of active rickets, initially it was high in all 3 patients and normalised in patients 1and 2 post treatment while still high in the third patient on diet restriction treatment. Phosphate level was low and normalised later with improvement in urine fanconi sign. S. calicum was low and normalized in patients 1and 2 but the third patient did not normalize the sign of rickets. Metabolic acidosis was present in patient 3 and was normal in the other patients.

S. protein was always low in all 3 patients. S. Na, K and blood sugar have shown a tendency to hyponatremia and hypoglycaemia in all 3 patients.

Variable sign of active rickets with an increased severity in delayed diagnosis. Liver image by ultrasound and CT scanning was abnormal at presentation with multiple focal spots and hepato splenomegaly without renal image abnormality which has been seen in all 3 patients. The more severe the illness have been seen in patient 3 with earlier presentation without NTBC treatment, severe liver deterioration with sign of liver failure, bleeding tendency, metabolic acidosis, ascites, oedema persistence sign of rickets with low phosphate, hypoglycaemia and hyponatremia.

Table (1): The general result of the patients.

Type of Evaluation	***Patient 1***	***Patient 2***	***Patient 3***
Clinical form	*Sub acute*	*Acute*	*Acute*
Age at onset	*8 months*	*5 months*	*1.5 months*
Age at diagnosis	*3 years 4 months*	*6 months*	*6 months*
Age at start treatment	*3 years 7 months (NTBC+ diet)*	*8 months (NTBC+ diet)*	*7 months (Diet only)*
Duration of treatment	*4 months (then 2 months on diet only)*	*5 months*	*2 months*
Dose of NTBC	*1 mg/kg/d*	*1 mg/kg/d*	*Not used*
PT			
- ***At diagnosis***	*-22*	*-24*	*-21*
- ***At death***	*-23*	*-17*	*-22*
Alkalinephosphatase			
- ***At diagnosis***	*1860 u/1*	*2185 u/1*	*2790 u/1*
- ***At death***	*215 u/1*	*203 u/1*	*1933 u/1*
Á Feto protein			
- ***Diagnosis***	*9448 IU/ml*	*7160*	*82157*
- ***Death***	*6650 IU/ml*	*40105*	*88200*
Clinically at onset ***Hepatomegaly*** ***Jaundice*** ***Oedema Ascites*** ***Rickets***	*All present in severe form*	*All present*	*All present*
U/S and CT scan abdomen	*With evidence of liver cirrhosis*	*Liver multi focal lesions*	*Hepatosplenomegaly with hepatic lesions*

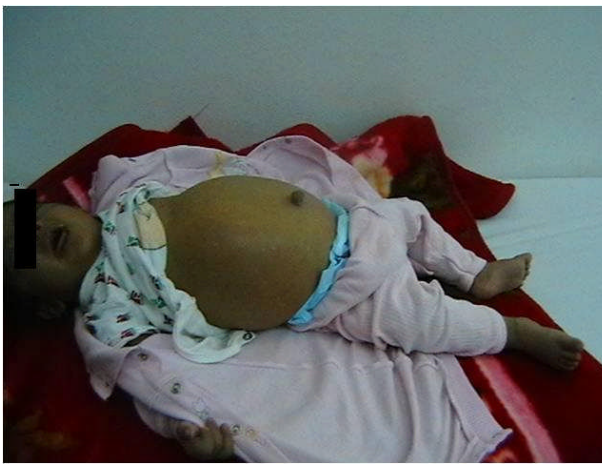

Figure (1): Presentations of patient 3.

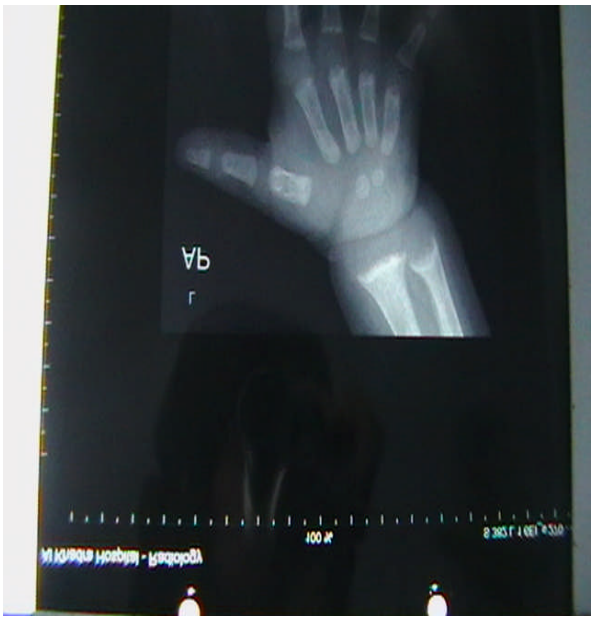

Figure (2): X ray of the wrist of patient 2.

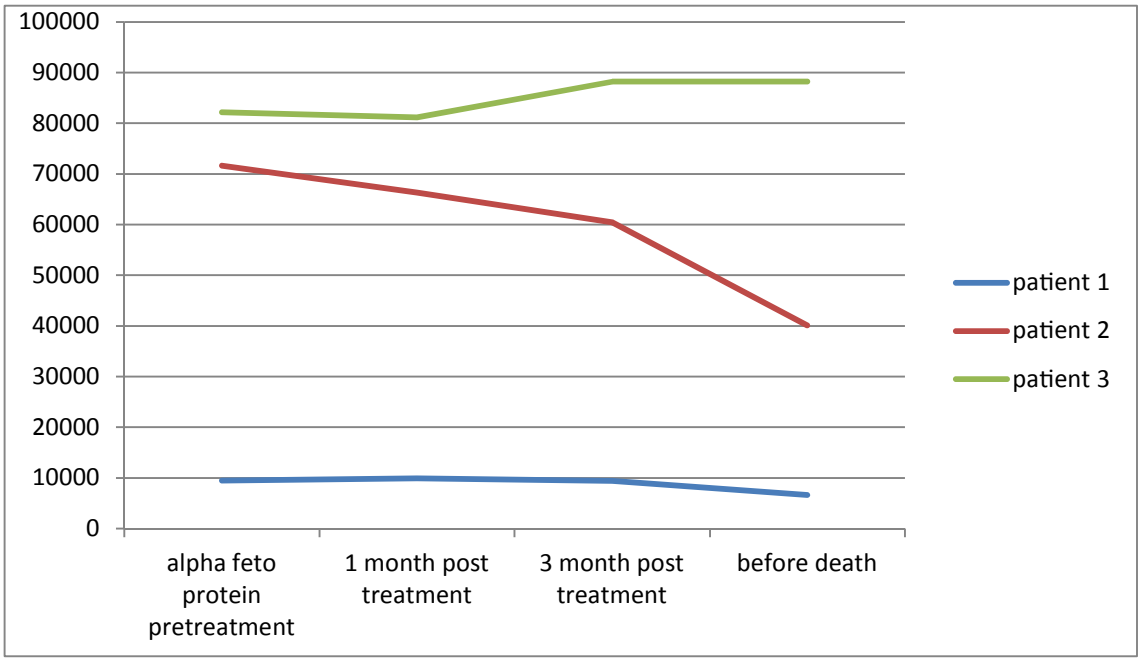

Figure (3): The level of alphafeto protein pre and post treatment.

Discussion

Liver and kidney damage are the main complications in TTI which are considered risk of the development of Hepatocellular Carcinoma (HCC) in some children [10-12] as HCC does not develop in all patients. Patients treated by diet results in poor prognosis with high risk of the development of liver malignancy, the survival rate was 38% at one year old when the onset of treatment began before 2 months, 17% of patients with HCC died according to an international study of 108 patients treated by diet restriction. [10]

Follow up of our 15 patients who were diagnosed as TTI patients at a single hospital, most of them

have good response proved by normalization of liver and kidney function except 3 patients who died, they had no significant response to treatment either by combination of NTBC and diet restriction or by diet restriction only, overall the survival rate was 80% (85.7% with the use of NTBC). Our belief is based on studies which indicated that the NTBC cannot stop the progress of hepatoma, however it seems there is no age exception in the possibility of HCC development. Delayed treatment caused higher risk of HCC, more than 13% of patients (8 of 60 patients) when the NTBC had been started after the age of 2 years developed HCC. [13] In older children with delayed diagnosis and advanced disease, the use of NTBC as a palliative therapy although the HCC developed one year later which does not look like NTBC could prevent the liver complication, [14] another prove in a murine model, long term NTBC treatment did not succeed in stopping HCC development. [15] The literature reported a late diagnosed 27 month old child with long term treatment of 6 years with NTBC with 2ry rising AFP and undetectable succinyl acetone in the urine which indicates an adequate amount of treatment but presence of HCC.[16] Development of HCC has been reported after a short period of NTBC introduction (10 months) in a 15 month old patient. [21]

High Persistence of AFP level is a good marker of the persistent risk of carcinoma. [5, 16- 18] AFP can be elevated in all types of benign chronic liver disease or in small HCC or in highly differentiated liver cancer, [19] in TTI normalization of AFP occurs within 4-12 months post NTBC treatment, but failure of dropping or 2ry rising is associated with liver malignancy. [11] Monitoring for HCC is based on a combination of liver imaging, liver histopathology and total AFP, the visualization of small HCC by ultrasound is difficult but finding of a hypo and hyperechogenic lesions with ill-defined margins and CT scan with parenchyma heterogenicity with low and high attenuation nodules is highly suggestive of HCC. [20]

Conclusion

The poor prognosis in patient 1 and 2 could be explained by 1) The dose was less than 2mg/kg/d in severe forms 2) The late diagnosis was typically in case 1. 3) Difficulty in the management and monitoring. The poor prognosis in patient 3 on diet treatment as in the literature. The slow decrease of alpha feto protein can explain the possibility of hepatocarcinoma in patients 1 and 2 but the duration of treatment was short. To conclude, the increase of this parameter in patient 3 who was on diet restriction is well known as a part of hepatocarcinoma mechanism.

TTI is a treatable disease, NTBC is a magic drug. It is important to diagnose and introduce NTBC as early as possible, treatment by diet restriction carried poor prognosis.

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التيروسنيميا 1:التحليل الكلنيكي والبايوكمياوي للحالات ذات نتائج العلاج الضعيف

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الملخص

الخلفية: التيروسينيميا احد أمراض الايض نتيجة خلل في نشاط الانزيم فيوميرال اسيتو اسيتيت. اسباب الوفاة فشل الكبد، نوبات شبيه بالبورفيريا وسرطان الكبد. العلاج يعتمد على الحمية الغذائية ونقل الكبد وNTBC .

الهدف: توضيح الشكل المرضي دراسة التحاليل لتوضيح مسببات فشل العلاج في 3 أطفال شخصوا بهذا المرض.

المرضى وطريقة البحث: دراسة لثلاث حالات توفوا (من اصل 15حالة شخصوا بهذا المرض) في الفترة من 2001/10 إلى 10/ 2009. اعتمد التشخيص على ارتفاع التيروسين في الدم مع وجود سكسنايل استون في البول، مراقبة مؤشرات سرطان الكبد كانت بفحص البطن بالموجات فوق الصوتية وبالتصوير المقطعي ونسبة الفا فيتو بروتين في الدم. العلاج في حالتين كان بـ NTBC مع حمية غذائية اما الحالة الثالثة فكانت على الحمية الغذائية فقط.

النتائج: المحصلة النهائية لعلاج 15 حالة كانت 80% كحالات تيروسنيميا النوع الاول و85.7% للحالات التي استعملNTBC كجزء من العلاج، عمر بداية المرض كان 8 و5 و1.5 شهور بالتتابع لكل مريض.عمر التشخيص 40 و6 و6 شهور بالتتابع جميع المرضى كانوا قبل العلاج يعانون من فشل في الكبد (نسبة البروثرمبين كانت بين 21%–24%). الحالة الاولى استعمل 4 اشهر علاج بNTBC مع حمية توفى بعد شهرين من توقف الدواء. الحالة الثانية عولجت بالدواء والحمية لمدة 5 شهور ولم تستجب للعلاج وتوفيت. الحالة الثالثة توفيت بعد شهرين من الحمية الغذائية.

الملخص: 1–فشل العلاج في المريض 1 و2 قد يكون بسبب – الجرعة إذا كانت اقل من 2 ملغم/كغم/اليوم. التشخيص المتأخر في المريض الاول، صعوبة توفير العلاج وتحاليل المتابعة. 2– المريضة الثالثة كانت على حمية غذائية وهذا معروف حسب المصادر العلمية. 3–الانخفاض البطى في الفا فيتوبروتين في المريض 1 و2 يعطي مؤشراً على احتمال وجود سرطان الكبد لكن يصعب تأكيده لقصر مدة العلاج لكن استمرارية الإرتفاع في المريضة الثالثة مؤشر معروف في مراحل وجود السرطان.

التوصيات:1) التشخيص المبكر للحالات وبدء العلاج بـ NTBC مع حمية غذائية في مرحلة مبكرة يضمن مستقبلاً علاجياً جيداً. 2) بدء المسح الايضي للمواليد.

الكلمات الدالة: التيروسنيميا، التحليل الكلنيكي والبايوكمياوي، نسبة الفا فيتو بروتين في الدم.