Case Reports

Tyrosinemia - Titration of Dose of Nitisone (NTBC) based on Blood Levels

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Tyrosinemia type 1 is caused by a defect in enzyme fumarylacetoacetase which is final enzyme of the pathway of the degradation of tyrosine. As a result of the metabolic block, toxic metabolites are formed including succinylacetone (SA), maleylacetoacetate and fumarylacetoacetate. These are responsible for severe disruption of intracellular metabolism of the liver and kidney. NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione) is the only drug which is used in management of tyrosinaemia type 1[1]. It is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD), an enzyme that is upstream of fumarylacetoacetasehydrolase (FAH). As a result the flux through the pathway is markedly reduced and in most patients there is a rapid decrease in the concentrations of succinylacetone (SA), an increase in tyrosine and a clear clinical improvement. As NTBC has adverse effect like corneal opacity, leukopenia, thrombocytopenia, convulsions, there is a need to monitor the levels of NTBC in the blood and adjust dose accordingly. We present a child with tyrosinemia diagnosed in May 2012, started on NTBC in July 2012 and needed a dose adjustment based on serum NTBC levels as serum tyrosine was very elevated in January 2016.

Case Report

A 1 year 9 month old girl was diagnosed to have tyrosinemia in May 2012. She had hepatosplenomegaly with renal tubular acidosis (RTA), alpha fetoprotein (AFP) was 6793 IU/L and urine SA was elevated (0.802mmol/l, Control = 0.001). She has been started on tyrosine and phenylalanine low diet along with bicarbonate supplement and NTBC (1 mg/kg/day)from July 2012(Shah I, Shah F 2006). Her serial AFP and Urine SA as well as serum tyrosine levels aredepicted in **Table 1**. She had a first episode generalised tonic clonic convulsion in Feb 2014 along with fever and was diagnosed to have febrile convulsion. Subsequently, she had a left focal convulsion in June 2015 without fever. EEG showed abnormal focal slowing in the right occipital region. She was started on leviracetam and advised serum levels of NTBC. In January 2016, her NTBC levels were 50 umol/L (normal

Table 1: Serial monitoring of parameters.

	May 2012 (prior to NTBC)	Oct 2012	Dec 2012	Nov 2013	Dec 2014	Jan 2016	Feb 2016
Plasma tyrosine (umol/L)	568	480	475.5	562	597	987	708
Urine succinyl acetone (umol/L)	0.802	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
NTBC (umol/L)						50	30
Alpha feto-protein (IU/L)	6793	57.5	16.41	5.26	2.8	2.41	-

range 30 to 50 umol/L) and simultaneous serum tyrosine levels were 987 umol/l. Her dose of NTBC was decreased to 0.8 mg/kg/day. Repeat tyrosine in February 2016 was 708 umol/l and serum NTBC levels were 30 umol/L. She was advised same dose and regular follow-up. Her liver function tests, venous blood gases and hemogram continue to remain normal. Her milestones and growth are also appropriate for age.

Discussion

With the introduction of NTBC (nitisinone) the prognosis for thosewith tyrosinemia type 1 has improved greatly. Nitisinone treatment has significantly improved the outcomesof patients with tyrosinemia type I, while decreasing utilization of healthcare resources, liver transplants, and associated costs[2].

As soon as the diagnosis of tyrosinemia 1 is confirmed, NTBC is started in adose of 1 mg/kg/d once a day as the half-life is 54 hrs[3]. A dose of 2 mg/kg/d should be given for 48 hoursfor those in acute severe liver failure. An alternativeapproach is to give all patients in liver failure, nitisinone ata dose of 2 mg/kg/d from the start and allow the dose tofall with growth to 1 mg/kg/d before increasing it. NTBCcan only be given orally (or by naso-gastric tube). It is imperative to do so quickly to prevent further liver and kidney damage and avoid potentially major complicationssuch as haemorrhage. The risk of long term complicationsis also reduced[4].The response to nitisinone is usually rapid. Coagulationusually improves within 48 hours and all patients shouldrespond within a week. Succinylacetone in the urine andblood should no longer be detectable after the first 24 hours. Nitisinone must be continued without interruption. If not continued may precipitate serious complications including acute liver failure, a neurological crisis[4] or even hepatic malignant change. On the standard dose of 1 mg/kg/d, the plasma concentrationsin individuals that suppress SA are variable[3,4]. Adjustments of the dose based on plasma NTBC concentrations may be indicated. However the target NTBC concentrations in plasma are uncertain andvary from 30-50 μM[5]. Some prefer to maintain the concentration above 50 μM[5]. However lower doses of NTBC have been found tobe effective[8]. In one case the serum nitisinoneconcentration was only maintained above 30 μmol/l[8] with apparently good metabolic control. Whatever the dose, complete suppression of succinylacetone concentrationsis essential. Our patient was on 1 mg/kg/day dose of NTBC for 3years 5 months. Then in January 2016 her plasma levels of NTBC were done as the serum tyrosine levels had increased and subsequently dose of NTBC was titrated to maintain at the lower limit of normal so that plasma tyrosine levels decrease. Also whether the seizure disorder in our patient was due to NTBC or a sequelae of febrile convulsion remains undetermined.

Not all centres monitor NTBC levels in patients. While metabolic control can be judged by SA levels/ excretion in urine overdosing and compliance can only be judged by measuring NTBC levels. Monitoring of NTBC plasma levels is therefore useful and permits individual dosing. Thus, treatment costs and side effects can be minimized without hampering metabolic control.

In conclusion, monitoring of NTBC levels is essential in patients with tyrosinemia 1 to titrate the dose so that maximum effect can be achieved by minimising adverse effects of NTBC.

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Unusual Presentations of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) constitutes more than 90% of primary liver cancers and is a major global health problem[1]. Peritoneal dissemination of hepatocellular carcinoma (HCC) is a rare presentation, with an incidence of 2% to 6% detected during autopsy or laparoscopy[2].Gastrointestinal tract involvement is noted in 4-10% of cases and mostly via direct invasion and hematogenous metastasis and is rather rare[3]. To the best of our knowledge, HCC with peritoneal metastasis diagnosed by trans rectal endoscopic ultrasound guided biopsy has not been reported previously. The current report is of 2 cases of metastatic HCC one each to peritoneum and stomach presenting with abdominal mass and gastrointestinal bleeding.

Case Report

Patient A: A 63 year old male diagnosed case of decompensated chronic liver disease presented with abdominal pain and significant weight loss of 10 kgs for 1 month duration. On examination, he had palpable liver without any bruit, ascites and an ill-defined pelvic mass. Ultrasound abdomen followed by contrast enhanced computed tomography (CECT) abdomen revealed multiple lesions in both lobes of liver enhancing in the arterial phase- largest measuring 2 X 1.8 cm. There were multiple enhancing pelvic deposits- largest measuring 15 X17 cm and moderate ascites (**Figure 1**). He was non reactive for hepatitis B surface antigen and hepatitis C virus. Alpha fetoprotein (AFP) levels were elevated-414 ng/mL (normal:<10ng/mL). Large pelvic deposit is unusual in HCC, so an endoscopic ultrasound (EUS) guided biopsy was done. Transrectal EUS revealed 7x5 cm heteroechoic pelvic mass with moderate ascites in pararectal area. Fine needle aspiration biopsy was done and cellular smears comprising of sheets, clusters and trabeculae of round to polygonal neoplastic cells with abundant clear cytoplasm were seen. Immunohistochemistry (IHC) revealed Hepatocyte

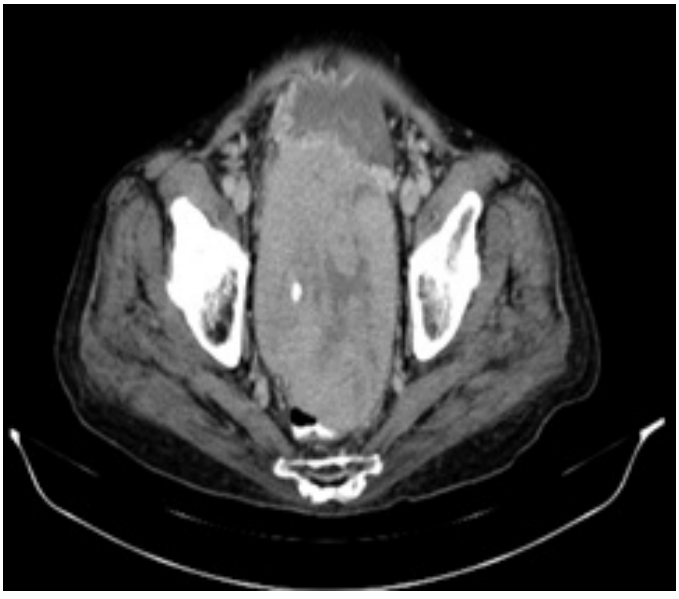

Figure 1: CECT abdomen showing multiple enhancing pelvic deposits.