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Tyrosinemia Webinar

NEUROLOGIC COMPLICATIONS OF TYROSINEMIA

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Case 1

A 5 month old infant present with seizure and decreased LOC

Brain CT :intra cranial hemorrhage

Lab data : PT prolonged

Succinylacetone of urine :positive

Final DX : tyrosinemia type 1

Case 2

A infant 9 month old present with vomiting
Physical exam :bulging fontanel
Lab data : ca : 8.5 Ph : 2.8 PT : 19
CSF pressure : high
DX : pseudotumor cerebri ,rickets , RTA ,high liver enzyme
Succinylacetone of urine : positive
Final DX : tyrosinemia type 1

Case 3

A 5 years old girl present with paralysis of lower extremities since 1 week ago
Physical exam : high blood pressure , hepatomegaly , weakness of lower extremities DTR hypo
Abdominal sono : hepatomegaly with multiple mass
EMG NCV : poly neuropathy axonal
Succinylacetone of urine : positive
Final DX: tyrosinemia type 1

Case 4

A 9 years old boy with epilepsy and intellectual disorder

Family history of like problem in brother

Metabolic work up : increased tyrosin

succinylacetone : negative

Final diagnosis : tyrosinemia type 3

CASE 5

- ***A 2 yr old boy with diagnosis tyrosinemia since 1 months of age. Low tyrosine and low phenylalanine diet started for him, but NTBC treatment was started at 6 months of age due to lack of access***
- ***At follow up, abdominal ultrasound showed a few small hypoechoic nodules in both lobes of liver. NTBC treatment interrupted by his parent and after 3 wk, he developed abdominal pain, irritability, muscle weakness, diaphragmatic paralysis, and two episodes of convulsion. Due to respiratory failure, the patient underwent intubation and mechanical ventilation and NTBC treatment started again with a dose of 2 mg/kg/day. After 2 wk, the patient weaned from ventilator, and neurological functions became normal***

Neurologic presentation of tyrosinemia

- ***Paresthesias,***
- ***Opisthotonic-like posture***
- ***Bruxism and tongue biting***
- ***Neurologic crises occur in up to 42% of individuals with tyrosinemia***
- ***These crises are biphasic, with an active period of pain, autonomic dysfunction, and sometimes paralysis lasting 1 to 7 days, followed by a period of recovery***
- ***Succinylacetone blocks the heme biosynthetic pathway, and the neurologic crises—a major source of morbidity—therefore have a physiologic basis similar to those in porphyria***
- ***Acute neurologic crises can occur at any age***
- ***Typically crises follow a minor infection associated with anorexia and vomiting***

Pathophysiology of neurologic symptoms

- ***Succinyl acetone is a potent inhibitor of the enzyme 5 aminolevulinic acid (5 ALA) dehydratase***

- ***5 ALA ,a neurotoxic compound believed to cause the acute neurological crises***

Acute management of neurologic crises includes

- ***Analgesia***
- ***Glucose (which inhibits ALA (aminolevulinic acid) synthetase)***
- ***Symptomatic treatment of hypertension***
- ***Repletion of sodium, potassium, and phosphate is necessary***
- ***The use of barbiturates and other medications that aggravate porphyria should be avoided before stabilization on NTBC***
- ***NTBC***

Long term neurologic manifestation

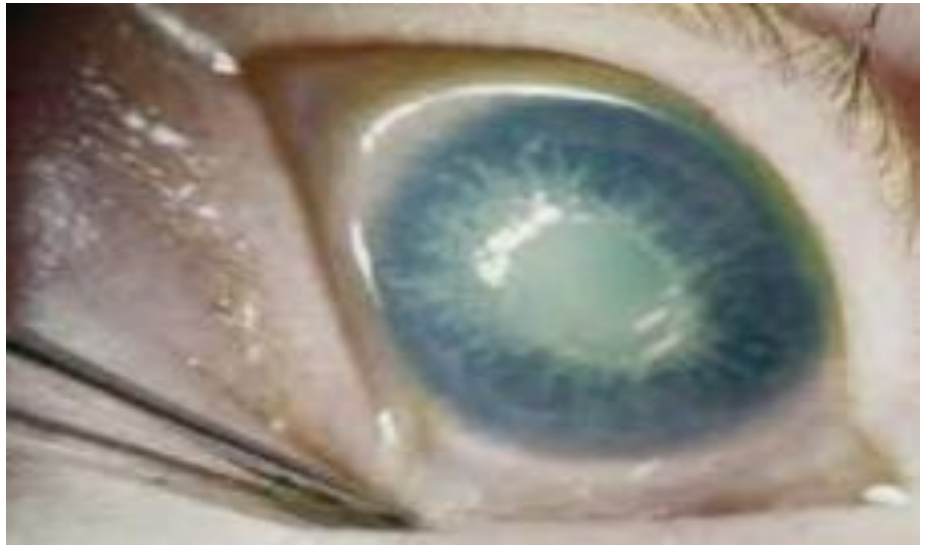
- ***Learning difficulty***
- ***Cognitive deficits performance abilities more than verbal abilities***
- ***Etiology : unknown (nitisinone therapy ?, high tyrosin level ?,low phenylalanine level ? or liver failure ?)***

Tyrosinemia type 2
Occulocutaneous tyrosinemia
Richner-Hanhart syndrome

- ***Ocular lesion 75 %***
- ***Skin lesion 80 %***
- ***Neurologic complications 60 %***
- ***The disorder usually present in infancy but can become manifest at any age***

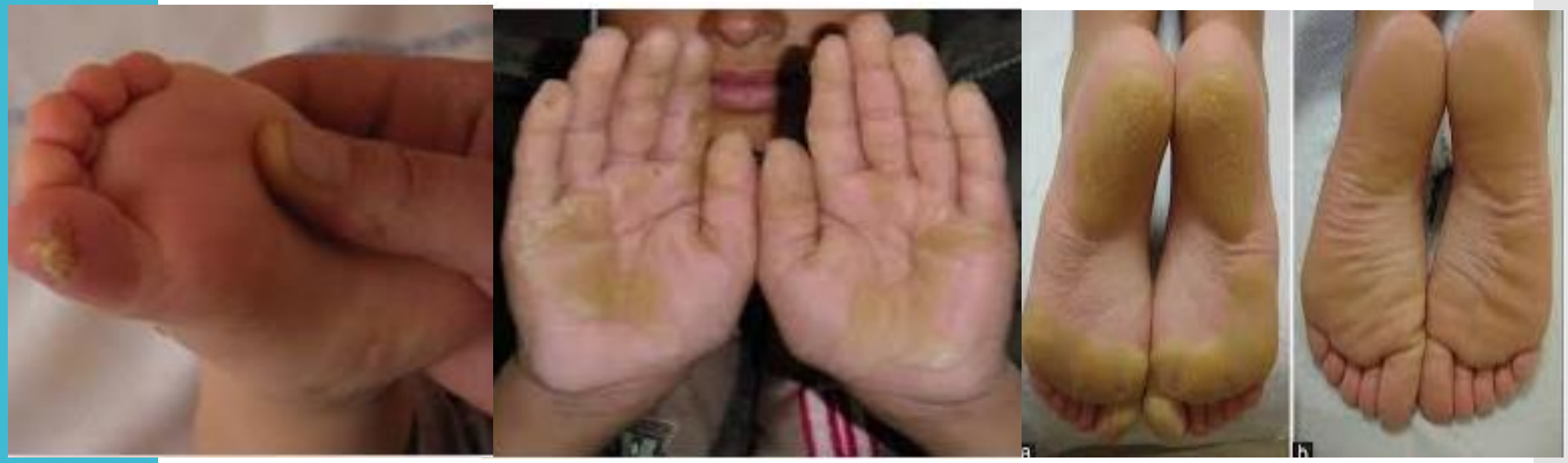
Clinical manifestation of tyrosinemia type 2

Eye symptoms : photophobia ,lacrimation ,intense burning pain
Inflamed conjunctiva ,herpetic like corneal ulcer (bilateral)
If not treated : scar ,visual impairment ,nystagmus ,glaucoma



Skin manifestation of tyrosinemia type 2

Blister or erosion of palms and soles progress to crust ,painful hyperkeratotic plaque with erythematous rim typically 2 mm to 3 cm



Neurologic manifestation of tyrosinemia type 2

- ***Neurologic complications : highly variable***
- ***Normal development in some cases***
- ***Some degree of developmental retardation***
- ***Sever form : microcephaly, seizure, self mutilation, behavior problems***

Diagnosis and treatment of tyrosinemia type 2

- ***Diagnosis*** ***: plasma tyrosine level > 1200***
- ***High level urinary excretion of the phenolic acid 4-hydroxyphenylpyruvate , 4hydroxyphenyllactate , 4-hydroxyphenylacetate***

- ***Diagnosis confirmed*** ***: mutation analysis***

- ***Treatment*** ***: restriction of tyrosine and phanylalanine in diet (tyrosine level 200 -500)***

- ***Pregnancy*** ***: fetal neurologic abnormalities reported in some untreated cases ,such as :microcephaly ,seizure ,mental retardation***

Tyrosinemia type 3

- Rare
- Patients mostly present with neurologic symptoms :
- Ataxia increased DTR ,tremor ,intellectual disorder , microcephaly ,and seizure
- No liver ,skin and eye involvement

- Diagnosis : neonatal screening ,high level tyrosine 300 -1300
- Diagnosis confirmed : enzyme study or genetic

- Treatment : restriction tyrosine and phenylalanine
- Plasma tyrosine level 200 -500

Neurological Crises after Discontinuation of Nitisinone (NTBC) Treatment in Tyrosinemia

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Abstract

Objective

Tyrosinemia type 1 is a hereditary disorder with liver, kidney and nervous system involvement. Neurological crises can occur in tyrosinemic patients without treatment or when treatment stops. Here we report three children that developed diaphragmatic paralysis after discontinuation of nitisinone. In patients with tyrosinemia type 1, combined treatment with nitisinone and a low-tyrosine diet have prevented neurological crises. The purpose of this article was to express the importance of taking nitisinone (NTBC) for tyrosinemia diseases and risks of inadvertent discontinuation.

Materials & Methods

We describe three children referred to emergency department of Nemazee Hospital, Shiraz, Iran in December 2015 with tyrosinemia type 1 who stopped NTBC treatment, presenting with respiratory. Clinical findings, laboratory results, and imaging study were assessed in three patients on admission and after starting nitisinone.

Results

All patients developed diaphragmatic paralysis and respiratory distress after interruption of nitisinone treatment. Two of the patients were improved after starting nitisinone. One patient expired due to respiratory failure. Full recovery occurred about 2 months after starting nitisinone.

Conclusion

Discontinuation of nitisinone can induce diaphragmatic paralysis and respiratory failure. Therefore, we should advise patients to use NTBC for the long term and not interrupt it.

Keywords: Tyrosinemia type 1; Diaphragmatic paralysis; Nitisinone; Neurological crises; Respiratory failure

Thanks for your Attention