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Ornithine Transcarbamylase Deficiency in Iranian Children

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Abstract

Ammonia is a toxic material for mammalians. It is detoxificated and converted to urea in the urea cycle in liver. Each defect in the urea cycle cause increase in blood ammonia level. Ornithine transcarbamylase enzyme (OTC) is the second enzyme in the urea cycle that exists in mitochondria. OTC deficiency is the most common hereditary disorder in the urea cycle. In this study, 45 hyper ammonia patients were selected (2-13 years old) and assayed for serum OTC, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT). Four patients (n=45, 8.9%) suffered from OTC deficiency. One patient was male (n=29, 3.4%) and the others were female (n=16, 18.8%). About half of children (53.3) with hyper ammonia have liver disease. Further studies on OTC deficiency and OTC gene mutations in Iran are recommended.

Keywords: *Aspartate aminotransferase, Alanine aminotransferse, Hereditary disorder, Hyper ammonia, Ornithine transcarbamylase, Urea cycle deficiency*

Introduction

Ammonia is produced from deamination of amino acids. Ammonia is toxic for all animals. Ammonia could be converted to glutamine in tissues, and then glutamine is transported to liver. In liver, ammonia is converted to urea. Urea is a substance that is rich in nitrogen with less toxicity. Every disorders in the urea cycle cause elevation of ammonia and severe damages. OTC (EC 2.1.3.3) is the second enzyme of the urea cycle that exists in mitochondria. OTC was discovered by Grisolia and Cohen and purified from liver in 1952 (1). Approximately all of OTC in mammalian tissues exists in mitochondria of hepatocells (2). OTC gene exists in short arm of X chromosome in Xp21.1 (3). OTC gene has 73kb, 10 exons and 9 introns. Primary protein of OTC has 354 amino acids and 40 kDa (4). A perfect OTC polypeptide has 36KD (5). Active enzyme is a homotrimer that connected to mitochondria inner membrane (6).

Urea cycle disorders. The age of onset of OTC deficiency in males, is newborn and in females is childhood. Approximate incidence of OTC deficiency is 1 in 14000. Brusilow et al reported that OTC deficiency is the most common hereditary disorder in urea cycle (7). Estimated frequency of enzymes deficiency of urea cycle was shown in table I (7). Cause of approximately 15% of hyperammonemic coma in adults is OTC mild deficiency (8). A few mutations and deletions are observed in OTC gene (8). Major deletion in short arm of X chromosome is along with severe disorders in OTC activity. Spot mutation is the cause of other OTC gene disorders (8). OTC mild deficiency can be fatal or it may cause few defects (9). K46R polymorphism in axon 2 and Q270R polymorphism in axon 8 is found in 36% and 4% alleles (4). Condition of OTC deficiency carrier can be shown by increase in urotic acid and orotidine in urine after administration of aloporinol (9).

Clinical aspect of OTC deficiency. Normal level of ammonia in plasma is less than 100 μM. Ammonia level in plasma in heterozygote is over 100 μM and in homozygote over 500 μM. If ammonia level in plasma reaches to over than 100 μM, it may cause persistent vomiting, respiratory alkalosis, and edema of brain, coma and death. Homozygote males are usually normal at birth with onset of features 24-72 hours after feeding. In 10% of heterozygote female's onset of symptoms in childhood characterized by recurrent lethargy, hyperactivity and migraine like headaches. Severe disorders lead to 100% mortality if untreated. This is a direct correlation between the duration of hyperammonemic coma and morbidity (mental retardation, developmental delays, cortical atrophy) (10).

Materials and Methods

This study was carried out, between 1999-2000.Serum OTC was assessed by colorimetric method (11) in 45 children (2-13 years old) with hyper ammonemia who were referred to Children Medical Center of Tehran. AST (EC 2.6.1.1) and ALT (EC 2.6.1.2) activities were assessed as well. These tests (OTC, AST, and ALT) performed in 45 children with normal level of ammonia.

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Results

Average of OTC, AST and ALT in the patient group was 17 ± 13.9 U/L, 41.9 ± 26.5 U/L, 27.8 ± 17.3 U/L, respectively (Table 2). Results of OTC, AST and ALT in patients are shown in table III. In this study OTC normal level was estimated (in control group) from 3.8 to 16.6 U/L. OTC activity was defected in four of 45 patients (8.9%), out of these, one patient was male (n=29, 3.4%) and three were female (n=16, 18.8%). Normal level of OTC is 3.8-16.6 U/L, AST less than 25 U/L and ALT less than 23 U/L. There was no correlation between OTC, AST and ALT in both patient and control groups.

Table 1: Stimation of the incidence of each urea cycle disorder based on its incidence relative to argininosuccinase deficiency (7).

Enzyme defect	Prevalence
Carbamyl phosphate synthetase	1 in 62000
Onetime transcarbamylase	1 in 14000
Arginino succinate synthetase	1 in 57000
Arginino succinase	1 in 70000
Arginase	1 in 363000
Total urea cycle defects	1 in 8200

Table 2: Comparison of OTC, AST, and ALT in the patient and control group.

	OTC U/L	AST U/L	ALT U/L
Hyper ammonemia patients N=45	17 ± 13.9	41.9 ± 26.5	27.8 ± 17.3
Control group N=45	10.2 ± 3.2	12.9 ± 3.5	10.8 ± 1.6

Table 3: Results of OTC, AST, and ALT in the hyper ammonia patients referred the children Medical Center of Tehran from 1999 to 2000.

	Male	Male %	Female	Female %	Total	Total %
Patient	29	64.4	16	35.6	45	100
AST ≤ 25 U/L	12	41.4	9	56.3	21	46.7
ALT≤ 23 U/L	12	41.4	9	56.3	21	46.7
AST> 25 U/L	17	58.6	7	43.7	24	53.3
ALT> 23 U/L	17	58.6	7	43.7	24	53.3
OTC 3.8-16.6 U/L	16	55.2	10	62.5	26	57.8
OTC> 16.6 U/L	12	41.4	3	18.8	15	33.3
OTC< 3.8 U/L	1	3.4	3	18.8	4	8.9

Table 4: Distribution of urea cycle disorder cases referred to the Johns Hopkins hospital from 1974 to 1994 (7).

Enzyme defect	Cases	Percentage
Carbamyl phosphate synthetase	69	12.7
Ornithine transcarbamylase	334	61.2
Arginino succinate synthetase	74	13.6
Arginino succinase	57	10.5
Arginase	11	2
Total	545	100

Discussion

Hepatic enzymes (AST and ALT) in patient group were above normal level (Table II). In addition, about half of children (53.3%) with hyper ammonemia had liver disease. In this study four children (n=45, 8.9%) were OTC deficient. We studied the frequency of OTC deficiency in children with hyper ammonemia, not in children with the urea cycle defect In a study, 61.2% OTC deficiency in urea cycle disorders was reported (table 4). Since OTC deficiency is an X-linked semi dominant, we expected that it was the most frequent disease in the urea cycle disorders, but in other study reported that the most frequent urea cycle disorder was citrullinemia (43.9%) and OTC deficiency as 21.1% (12). In one study in Japan, frequency of OTC deficiency 1 in 80000 was reported (13). In another study, OTC deficiency incidence has been reported as 1/30000 (10). In a retrospective survey done from 1978-1988 in Japan, 32 male patients with ornithine transcarbamylase deficiency were identified. They classified as neonatal and two late onset groups, depending on clinical manifestations and the age at onset, group 1 (0-28 days), group 2 (29 days – 5 years), and group 3 (greater than 5 years). Compared to findings in the group 2, there was a higher rate of mortality and a higher incidence of mental retardation in association with a great decrease in enzyme activity in group 1. In group 3, the mortality rate and enzyme activity were similar to those in group1 (14). We expected that OTC deficiency would be more frequent in males than females. In the genetic analysis in unrelated Italian patients affected by OTC deficiency, one was male patient and eight were female manifesting carriers (15). Women with OTC deficiency have a variable expression of their disease, the variability being determined by lionization (random inactivation) of the X chromosome. In on study reported a case of a 28-year-old woman who presented with hyperammonemic encephalopathy that was precipitated by a gastrointestinal bleed unmasking OTC deficiency (16). Male's newborn usually dies with OTC severe deficiency. Since this study was done in children with 2-13 years old, it was anticipated that we were confronted with OTC mild deficiency. Female heterozygotes have a wide clinical spectrum, ranging from asymptomatic to moderate or severe manifestations. The present article is the first study in the urea cycle disorders and OTC deficiency in Iranian population. For more analysis, it is necessary to do further studies on OTC deficiency and OTC gene mutations.

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