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The Diagnosis and Management of Ornithine Transcarbamylase Deficiency in Pregnancy: A Case Report

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Abstract

Objective: Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle disorder. In our case, we discussed the follow up and the management of the OTC deficiency patient, diagnosed during pregnancy.

Case: 32-year-old patient, OTC deficiency was diagnosed during pregnancy which was resulted with missed abortion. In the next pregnancy, the patient treated with phenyl butyrate, arginin ornitin lisin and carbamazepine. Coryon villus sampling (CVS) was done in the first trimester. There was not any mutation in the fetal gene locus. In the 39. gestational week, healthy female baby was delivered by caesarean section.

Conclusion: OTC deficiency is a rare disease. To make the followup and the management of these patients during pregnancy, may require knowledge and experience about complications. The treatment must be carried out with multidisciplinary approach. The genetic counseling should be given to the family about the prenatal diagnosis of OTC deficiency (CVS, amniosentesis).

Keywords: Ornithine transcarbamylase deficiency, pregnancy, prenatal diagnosis, multidisciplinary approach.

Gebelikte ornitin transkarbamilaz eksikliği tanısı ve yönetimi: Olgu sunumu

Amaç: Ornitin transkarbamilaz (OTC) eksikliği, en sık rastlanan üre döngüsü bozukluğudur. Olgumuzda; abortus ile sonlanan gebeliği sırasında OTC eksikliği tanısı alan hastanın, sonraki gebeliğindeki takip ve yönetimini literatür bilgileri ışığında tartıştık.

Olgu: 32 yaşında hastaya, abortus ile sonuçlanan gebeliği sırasında OTC eksikliği tanısı konuldu. Takip eden gebeliğinde; oral sodyum fenilbutirat, arginin ornitin lizin ve karbamazepin tedavisi başlandı. Birinci trimesterde koryon villus örneklemesi yapıldı. Fetal gen lokusunda mutasyona rastlanmadı. 39. gebelik haftasında, sağlıklı kız bebek sezaryen ile doğurtuldu.

Sonuç: OTC eksikliği nadir görülen bir hastalıktır. Bu hastaların gebelik süresince takip ve yönetimini yapmak, olabilecek komplikasyonlar hakkında bilgi birikimini ve tecrübeyi gerektirmektedir. Tedavi multidisipliner yaklaşımla gerçekleştirilmelidir. OTC eksikliğinin prenatal tanısının (CVS, amniyosentez) mümkün olduğu konusunda aileye gerekli genetik danışmanlık verilmelidir.

Anahtar Sözcükler: Ornitin transkarbamilaz eksikliği, gebelik, prenatal tanı, multidisipliner yaklaşım.

Introduction

Urea cycle disorders are seen once in every 30000 living delivery. All such disorders are autosomal recessively inherited except transcarbamylase deficiency (OTC) displaying inheritance via X.[1,2] OTC deficiency is the most frequent urea cycle disorder.[1] Homozygote males are affected more severely by the disease than heterozygote females. Citruline level is distinctively low while glutamine, glycine, and alanine levels are high. Orotic acid levels in urine increase notably. Enzymatic deficiency is shown by liver biopsy.

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Mutation in OTC gene locus supports the diagnosis. Different alleles more than 20 have been defined.[2]

The symptoms of OTC deficiency are characterized by cyclic vomiting, lethargy, coma attacks and intermittant hyperammoniemia (Table 1). Neurological problems may occur as palsy, cerebral atrophy, and other encephalopathic diagnoses. Also epileptic seizures may be seen frequently.[3] Diet rich in protein, stress or infection cases may initiate hyperammoniemia attacks. Hyperammoniemic coma and death may occur during these attacks. Light-mild mental retardation is frequent in patients. The prevalence of gallstone increases in those reaching adult age. Acute hyperammoniemia attacks were reported in postpartum period. Vomiting and lethargy attacks are characterized with the late form of OTC deficiency.[4] Only 20% of heterozygote girls are symptomatic.[5] Diagnosis may be late as symptoms in some heterozygote patients are non-specific.[6] The general purposes of the treatment in urea cycle disorders are to fix biochemical disorder and to provide body balance by meeting nutrition requirements. It is aimed to keep plasma ammoniac levels below 80 micromole/L and plasma glutamine levels below 800 micromole/L and essential amino acids at normal levels. It is required in the most diet patients with poor protein. Natural protein amounts recommended for adults are below 0.5 g/kg/day. Changes should be done according to individual requirements. Essential amino acids can be given up to 0.7 g/kg/day. Sodium benzoate and sodium phenylbutyrate may be used to provide nitrogen excretion alternatively.[2] Also arginine which is an essential amino acid synthesized in urea cycle should be replaced. Arginine dose (free-base) should be 0.4-0.7 g/kg/day (8.8-15.4 g/m²/day).[2]

OTC deficiency cases in pregnancy appear in the literature only as case reports. In our case, we discussed the follow-up and management of next pregnancy of the patient who got OTC deficiency diagnosis during her pregnancy ended with abortus.

Table 1. Genetic diseases causing hyperammoniemia.[13-15]

Urea cycle defects
N-acetylglutamate synthetase deficiency
Carbamoylphosphate synthetase 1 deficiency
Ornithine transcarbamylase deficiency
Argininosuccinate synthetase deficiency
Argininosuccinate lyase deficiency
Arginase deficiency
Amino acid transport defects
Mitochondrial ornithine transport defect: hyperornithinemia
Hyperammoniemia, hypercitrulinemia (HHH) syndrome
Dibasic amino acid transport defects: Lysinuric protein intolerance
Aspartate-glutamate transport defects: Citrine deficiency (citrulinemia type 11)
Glutamine synthetase deficiency
Organic acidemias

Case Report

Thirty-two years old, G 1, P0 patient applied to the Internal Diseases Department of Cerrahpaşa Medicine Faculty with the complaints of ammonia odor from mouth and having fainting seizures. The patient was using 400 mg/day carbamazepine for epilepsy treatment since 15 years old. 5 weeks of intrauterine pregnancy was detected in the general physical examination and abdominal ultrasonography of the patient, no additional pathology was observed. Ammoniac level in the blood of patient was found as 179 microgram N/dl (normal value over 2 years old is 19-60 microgram N/dl). It was found in the organic acid analysis performed on the urine of the patient that lactic acid, pyruvic acid, 3- OH butyric acid and 3- OH isovaleric acid increased. In the amino acid analysis, it was found that tyrosine, taurine, cystine and cystathionine levels were low and tryptophane and methionine levels were on the lower limit of normal values. Fetal cardiac movement was not observed in the obstetric examination of the patient at her 6th gestational week. Dilatation and curettage were applied. In the genetic evaluation of abortus material, male fetus was found which did not have polymorphism and mutation.

It was found in the blood of the patient that citruline level was 10 micromole/L (normal value is 10-60 micromole/L), alanine level was 130 micromole/L (normal value is 100-460 micromole/L), glycine level was 89 micromole/L (normal value is 60-490 micromole/L), glutamine level was 134 micromole/L (normal value is 48-820 micromole/L). Orotic acid level in the urine was detected as 1.3 micromole/mole creatinine (normal values above 10 years old are 0.4-1.2 micromole/mole creatinine).

Mutation was not observed in the genomic amplification process of the patient performed by polymerase chain reaction (PCR). However, in the Xp21.1 gene locus, K46R, lus3- 8A> T, Q 270R heterozygote polymorphism was detected. In the light of findings, the patient was diagnosed as gene defect of OTC heterozygote enzyme deficiency.

As the result of the diagnosis, 15.8 g/day (6 x 2.500 mg) sodium phenylbutyrate, 6.600 mg/day (2x3.300 mg) arginine – ornithine – lysine and 400 mg/day (2x200 mg) carbamazepine were given to the patient.

Spontaneous single pregnancy was detected 5 months after the treatment of the patient was arranged. It was accepted suitable to perform the follow-up of the pregnancy by multidisciplinary approach together with the Perinatology and Internal Metabolism Diseases. Upon the joint decision, arginine – ornithine – lysine amino acid complex (AOL), sodium phenylbutyrate and carbamazepine treatments were carried on during the pregnancy. Genetic consultation was provided to the patient about the prognosis of urea cycle disorder and the carbamazepine treatment during pregnancy. The patient stated that she wanted prenatal diagnosis, but she could not use the drug by taking teratogenic effects of carbamazepine into consideration. Carbamazepine treatment was ceased on 8th gestational week and it was planned to do a chorionic villus sampling (CVS) on 13th gestational week.

Nuchal thickness (NT) was measured as 1.8 mm and nasal bone was screened on the first trimester scanning. A wave was positive on ductus venosus and regurgitation was not detected on tricuspid valve.

Ammonia level was 157 microgram N/dl at 12th gestational week. Numerical anomaly was not observed in the microscopic evaluation performed by GT 6 band technique of metaphase plates obtained by direct and long-term cultures of CVS sample. Chromosome establishment was found as normal. No mutation was seen in OTC gene locus.

In the 22nd gestational week examination, bipariteal diameter (BPD) was measured as 52 mm, head circumference (HC) as 195 mm, abdominal circumference (AC) as 177 mm, femur length (FL) as 35 mm, peak heart rate as 158 beat/min, and placenta anterior wall located nasal bone was measured as 6.2 mm. Right uterine artery pulsatility index (PI) was found as 0.96 and resistance index (RI) was 0.54, but no notch was observed. Left uterine artery PI was 0.76 and RI was 0.53 but no notch was observed. In the detailed ultrasonography, fetal anatomy and development was observed appropriate to gestational week. Ammoniac level of the patient was 148 microgram N/dl. Fetal anatomy and development was found as normal in the ultrasonography examination at her 28th gestational week. Estimated birth weight was measured as 1,529 g. As the patient had once tonic-clonic seizure in her history, she was consulted by Metabolism Diseases and carbamazepine was initiated as 200 mg/day and clonazepam drop as 7.5 mg/day. Ammoniac level of the patient was measured as 81 microgram N/dl.

By cesarean on her 39th gestational week, the patient gave a 3,820 gr girl baby who had cephalopelvic disproportion indication, 7 APGAR score at 1st minute and 9 APGAR score at 5th minute. Ammoniac level after delivery was found as 116 microgram N/dl.

The patient was followed up at postpartum period in terms of clinical findings of hyperammoniemia (anorexia, vomiting, lethargy, respiratory alkalosis, tremor, feebleness, ataxia, hypothermia, epileptic attacks). 250 mg/kg sodium benzoate and sodium phenylacetate, and 500 mg/kg/day (intravenous) arginine were kept available in order to use on hyperammoniemia seizure. However, no symptom requiring emergency treatment appeared after cesarean.

Mother and baby did not require intense care after delivery. Mother and baby were discharged from the hospital on postoperative 4th day. No mutation was found in OTC gene locus of the baby via the genomic amplification process by PCR. The baby was taken into routine follow-up in Healthy Child Polyclinic.

Discussion

OTC deficiency is inherited via X and is the most frequent urea cycle disorder. Its diagnosis is based on inheritance via X, concentration of high serum ammonia, glutamine and alanine, and high orotidine existence within urea after taking allopurinol.[7]

Mental deficiency is frequently seen in patients and generalized tonic-clonic or focal seizures are seen in those with hyperammoniemia.[7] The level of relative lyonization (random X chromosome inactivation) of normal and abnormal OTC genes in hepatocytes determines the severity of disease.[2]

The diagnosis in our case was late until 32 years old since she had heterozygote mutation. Establishing certain diagnosis during pregnancy is a rare case.

Citruline level of our case was found as 10 micromole/L, alanine level as 130 micromole/L, glycine level as 89 micromole/L and glutamine level as 134 micromole/L. Low citruline level was found as compatible with the literature. However, normal values of alanine, glycine and glutamine levels were not parallel to the literature.

Orotic acid level in urine was found as 1.3 micromole/mole creatinine in our case. High orotic acid level in urine was compatible with the literature. High orotic acid level in urine also together with Carbamyl Phosphate Synthetase is a significant marker in distinctive diagnosis.

The disease is observed as acute metabolic encephalopathy attacks in adult age group. Attacks generally appear as a result of metabolic stresses such as infection, anesthesia, pregnancy, delivery. Triggering factor may not always be detected. When acute encephalopathy attacks (due to hyperammoniemia) are not treated, deterioration advances, patient is lost due to coma or patient continues to live with neurological sequel. Death reason is frequently cerebral edema.[2] Cases with hyperammoniemia attack and atonia bleeding in postnatal period were reported in the literature. We did not observe such a complication in antenatal and postnatal follow-up of our case. Since postpartum 1st hour ammoniac value was 116 microgram N/dl, emergency treatment of hyperammoniemia was not required (emergency treatment applications are initiated when plasma ammoniac value is three times higher than the normal value).

CVS was applied to our case as prenatal invasive diagnosis test. Numerical and structural anomaly and mutation in OTC gene locus were not detected when evaluating the sample.

AOL amino acid complex and sodium phenylbutyrate treatment carried on during pregnancy of our case. Though anti-epileptics were not used until 28th gestational week, no seizure occurred. Upon tonic clonic epileptic seizure at 28th gestational week, carbamazepine treatment was initiated. The patient was followed up under anti-epileptic treatment in the rest of the pregnancy period and no seizure occurred.

Consequently, OTC deficiency is a rare disease. Performing follow-up and management of these patients during pregnancy requires knowledge and experience about possible complications. Patients should be protected as much as possible against metabolic stresses such as hunger, excessive protein loading, infection etc. in order to prevent acute hyperammoniemia attack, and surgical applications such as normal delivery and cesarean should be followed up carefully. In such cases, protein intake should be lowered and more carbohydrate should be given as a precaution. It should always be prepared against acute encephalopathy attack. Intravenous treatment (Sodium benzoate, sodium phenylbutyrate, arginine) should be applied to patients who have vomiting and progressive encephalopathy which can not tolerate oral intake.

As seen in our case, management of patients should be performed by multidisciplinary approach (Internal Endocrinology Department and Gynecology and Obstetrics Perinatology Department) and tertiary centers.

Required genetic consultancy should be provided to family that prenatal diagnosis (CVS, Amniocentesis) of OTC deficiency is possible. In the first 24 hours, protein should be removed from the diet of prenatally diagnosed newborn. Also, female relatives of patient should be checked for heterozygote inheritance of OTC deficiency. Detection of inheritance helps the early diagnosis of women who have acute hyperammoniemia attack risk. Early diagnosis of these people decreases complication possibility and provides prenatal diagnosis possibility in a pregnancy.

Conclusion

OTC deficiency is a rare disease. Making the follow-up and the management of these patients during pregnancy may require knowledge and experience about complications. The treatment must be carried out with multidisciplinary approach. The genetic consultancy should be given to the family about the prenatal diagnosis of OTC deficiency (CVS, Amniocentesis).

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