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Assesment Of Clinical Importance Of Adenosine Deaminase Levels In Gestational Trophoblastic Disease

Gestasyonel Trofoblastik Hastalıkta Adenozin Deaminaz Düzeylerinin Klinik Öneminin Değerlendirilmesi

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ABSTRACT

Aim: To determine the effect and role of Adenosine Deaminase which is an indirect marker of T cell mediated immunity and also determine the possible effects of oxidative stress in Gestational Trophoblastic Diseases.

Material and Methods: The study was performed among 88 patients. 31 patients with Gestational Trophoblastic Disease diagnosis, 29 pregnant women in their first trimester and 28 healthy patients as control group. Adenosine Deaminase levels were detected in all patients.

Results: According to definitive analysis there is no significant difference between three groups for age, gravid and parity. 1st trimester pregnancy group had the highest ADA levels. (Median=30,125) Gestational trophoblastic disease group had the lowest ADA groups (Median=3.491). The differences between three groups were statistically significant ($p< 0.001$).

Conclusion: However the exact mechanisms of Adenosine Deaminase activity and the effect of mediators that are released from fetus during pregnancy have not clearly identified yet. The results of this study suggest that the adenosine deaminase is associated with Gestational Trophoblastic Diseases According to our results ADA have a different mechanism in gestational trophoblastic disease from normal pregnancies. Future studies should be focused on revealing the impact of adenosine deaminase in molar pregnancy and may be in other intrauterine pathologies.

Key Words: Adenosine deaminase, ADA, gestational trophoblastic disease

ÖZET

Amaç: Çalışmada T-hücre aracılı immünitenin dolaylı bir göstergesi olan Adenozin Deaminaz seviyelerinin gestasyonel trofoblastik hastalıklı olan bireylerdeki seviyelerinin saptamak ve mevcut oluşan bir oksidatif stres mekanizmasının gestasyonel trofoblastik hastalığın etiyolojisinde ve patogenezinde rolunu açığa çıkartmak olacaktır.

Gereç ve Yöntemler: Çalışma, molar gebelik tanısı ile kabul edilen 31 hasta, yaş dağılımı molar gebelik hastaları ile benzerlik gösteren 29 birinci trimester gebeliği olan ve jinekoloji polikliniğine çeşitli şikâyetlerle başvuran 28 reprodüktif çağdaki kadın üzerinde yapıldı. Çalışmaya dahil edilen tüm hastalardan serum Adenozin Deaminaz düzeyleri çalışıldı.

Bulgular: Gruplar arası yapılan tanımlayıcı analizler sonucunda yaş bakımından gruplar arasında bir fark olmadığı saptanmıştır. Gruplar arasında Adenozin Deaminaz değerleri karşılaştırıldığında gerek gebe hasta grubu ve GTH hasta grubu, gerek gebe hasta grubu ve kontrol grubu, gerekse de GTH ve kontrol grubu arasında istatistiksel olarak belirgin bir fark bulunmuştur. ADA değerlerinin gebe grupta en yüksek değerlerde olduğunu gözlenirken, GTH grubunda en düşük değerlerde olduğu izlenmiştir.

Sonuç: Adenozin Deaminaz serum adenozin seviyelerini değiştirerek normal gebeliklerin devamında önemli bir rol oynar. Gebelikte bu fonksiyonların gerçekleştirilebilmesi için özellikle plasentadaki Adenozin Deaminaz aktivitesi kritik rol oynar. Plasental Adenozin Deaminaz aktivitesinin sağlanmasında fetusun de bir etkisi olduğu şüphe götürmeyecek bir gerçektir. Ancak bu enzimin sentezinde veya işlev görmesi sırasında fetusun ve fetusten salınan biyokimyasalların plasenta ADA oluşum ve fonksiyonundaki rolü henüz bilinmemektedir. Çalışmamızın sonuçlarına göre ADA GTH'de normal gebeliklerden farklı bir mekanizmayla etki göstermektedir. Bundan sonraki çalışmalar ADA'nın sadece GTH'de değil tüm gestasyonel patolojilerdeki rolü üzerine yoğunlaşmalıdır.

Anahtar Kelimeler: Adenozin deaminaz, gestasyonel trofoblastik hastalık

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Introduction

Gestational trophoblastic disease is an abnormality of human gestation which is characterized by abnormal proliferation of trophoblastic tissue. It includes partial and complete hydatidiform mole and gestational trophoblastic neoplasia (invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor). The pathology itself has propensity to become malignant which there is abnormal embryonic development and proliferation of placental villi (1,2). The incidence of hydatidiform mole appears to be about 1 per 1,000 pregnancies in most parts of the world and perhaps twice as high in Asia (3). This difference can be explained by discrepancies between hospital-based and population-based data, or disparity in availability of central pathology review in the researches. The pathogenesis and factors predicting the progress of these diseases remain to be clarified (4).

Adenosine deaminase (ADA) is an enzyme of purine metabolism that catalyzes the deamination of adenosine to inosine and 2'-deoxyadenosine to 2'-deoxyinosine.(5)Catalytic activity of ADA is especially remarkable in T lymphocytes. Therefore it can be defined as an indirect marker of cellular immunity.(6) There have been incoherent reports about the serum ADA levels in normal pregnancy. In the literature there have been reports claimed that an increase (7) or a decrease (8) of ADA levels in normal pregnancies. Most definitive study about ADA levels in pregnancy was published by Lee et al. in 2007. In this study no significant correlation was shown between the serum ADA activity and gestational age in normal (9). The median serum ADA levels in the 1st trimester of pregnancy are detected as 20.1±6.9 IU/ L in this study.

In the present study, we aimed to compare maternal serum ADA levels in normal uncomplicated pregnancies and in gestational trophoblastic diseases with non-pregnant women

Material and Methods

A total of 88 women comprising 31 women with the diagnosis of gestational trophoblastic disease, 29 singleton non-complicated pregnant women at first trimester which were matched with regard to their age and gestation weeks with GTH patients and 28 normal non-pregnant women at reproductive age with no known chronic disease were recruited into the study. After having received informed consent from all the patients and controls, venous blood samples were obtained from all patients following an overnight 8 hours of fast. Blood sampling was performed before evacuation of uterine cavity from GTD group. Heparinized blood was centrifuged and the plasma was separated and frozen at -70 °C until analyzed. GTD patients are called back for control serum sampling after 6 months of evacuation for ADA levels and venous blood samples were also obtained. Serum Beta-HCG and ADA levels were measured by ELIZA method.

The data collected were analyzed by SPSS 14.0 for Windows software (SPSS, Chicago, IL, USA). One-Way ANOVA, Mann-Whitney, Wilcoxon Signed Rank Test tests were used for comparing quantitative data. P value less than 0.05 was considered statistically significant within the % 95 Confidence Interval.

Results

Demographic data of molar group and normal pregnant group are shown in Table 1. There were no statistically significant differences among the groups with regard to age, gravida, parity and pregnancy period.

Table 1: Evaluation of the groups according to demographic characteristics

	GTD (Mean±SD) n =30	1st Trim. pregnancy (Mean±SD) n=29	Control (Mean±SD) n=28	p values
Age	28,25±3,63	29,34±3,16	28,96±4,20	0,512
Gravida	2,35±0,71	2,75±0,83	2,42±0,99	0,157
Parity	1,25±0,68	1,44±0,68	1,50±0,83	0,412
Pregnancy age (day)	63,38±16,44	60,62±14,780	---------	0,398

The mean of plasma ADA levels of the GTD, normal pregnancy and control group are summarized in Table 2. Patients with GTD had lower mean of plasma ADA levels (3,491±0,511) when compared with pregnant (30,125± 16,327) and control groups (8,279±2,318) and the difference was statistically significant ($P < 0.001$). 1st trimester pregnant group has the highest ADA levels among three groups.

Table 2: Distribution of ADA levels among GTD, pregnant and control groups

ADA	Mean	Standart Deviation	Minimum	Maximum
Pregnant	30,125	16,327	10,40	73,20
GTD	3,491	0,511	2,66	4,89
Control	8,279	2,318	4,23	13,88

p<0,001

6 months after proper treatment of GTD, 10 of 31 patients answer the recall for detection of ADA levels after treatment. Comparison between ADA levels before and after treatment of GTD is shown at Table-3. ADA levels of GTD group significantly increases 6 months after evacuation. (From 3,480 IU/L to 8,760 IU/L) ADA levels of treated GTD patients were similar to control group after 6 months of follow up. (8,760 IU/L and 8,279 IU/L respectively).

Table 3: ADA levels before and 6 months after treatment

ADA	Mean	Standart Deviasyon	Minimum	Maksimum
GTD before treatment (n=31)	3,480	0,369	2,81	4,06
GTD after treatment (n=10)	8,760	2,220	6,58	12,40

p=0,005

Discussion

Gestational Trophoblastic Diseases (GTD) is commonly viewed as a genetic disease and the pathogenic mechanism of which is obscure. Adenosine Deaminase (ADA) is a well known enzyme which is described as an indirect marker of cellular immunity. There are conflicting data about ADA levels in pregnancy in the literature. Most detailed study has been published by Lee et al. In this study ADA levels in 1st trimester of pregnancies are defined as 20,1±6,1 IU/L which is similar with our study (30,125±16,327 IU/L).

ADA is an essential enzyme for the differentiation of lymphoid cells, and changes in ADA activity reflect alteration in immunity. (10) ADA levels in other pregnancy related pathologies have been studied previously. Increase in ADA level was determined in preeclampsia (11) and gestational diabetes mellitus (12, 13) by Yoneyama Y. et al. and Mokhtari M. et al. respectively. Moreover, in the circumstances like absence of healthy conceptus in recurrent abortus Hitoglou S. et al. described a decrease in ADA levels when comparing to normal pregnancies (14).

ADA enzymatic role is defined as prevention of accumulation of potentially toxic oxidative material for baby in the placental environment. Placental ADA activity was demonstrated as essential for early post-implantation development in genetically engineered mice by Blackburn M. et al. They claimed in their study that embryos within gestation sites lacking both decidual and trophoblast ADA died during the early postimplantation period, whereas expression in trophoblast cells alone was sufficient for survival through this period (15).

As it can be seen previous studies, ADA has a complex and not fully understood mechanism in pregnancy. Adenosine Deaminase is an important molecule in persistence of normal pregnancies by changing the adenosine levels. There are strong evidences for the effects of healthy fetus on placental Adenosine Deaminase activity. ADA levels are seemed to be lower than expected in the absence of normal conceptus. This result indicates that embryo has also an important role in ADA response in placental environment.

In our study, 6 months after treatment of GTD patient's ADA levels increases to control group's ADA levels. (8,760±2,220 vs. 8,279±2,318) To the best of our knowledge, there is only one clinical study investigating ADA levels in molar pregnancies. This study shows an increase in ADA levels in patients with hydatiform mole which is the opposite direction of our study (16). There are many conflicting data about ADA levels in several studies. It can be explained as different measurement methods as ELISA and Giusti method based on measurement of the formation of ammonia by Berthelot's reaction which is known as less specific than ELISA. Moreover, increase of serum ADA levels to control group's ADA level after treatment of GTD which is discussed above increases the reliability of measurement of our study.

As a result, the change in the levels of ADA in obstetric pathologies demonstrates that ADA may play a critical role in placentation process. Defective trophoblastic activity like as in preeclampsia causes alterations in the immune response and oxidative stress level. As can be understood from the fact that decrease in immune response does not always indicate an increase in ADA levels. ADA enzyme level alterations in GTD have a complex mechanism of action.

Our hypothesis is that there is an alteration of immune response in GTD which is different from normal pregnancy. This difference in immune response can be a result of absence of fetal tissue or just the opposite, immune response changes can lead genetic alterations that can be a cause of development of molar pregnancy. Although our data are limited, the study shows that ADA levels in plasma of patients with GTD are decreased; suggesting that ADA may play a role in the development of this condition or it can be a result of the pathology. Further controlled prospective studies with higher number of participants are needed to determine the complex mechanism of GTD and immune response. Future studies should be focused on revealing the impact of adenosine deaminase in molar pregnancy and may be in other intrauterine pathologies.

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