Reduced Plasma Cholinesterase Activity in Patients With Gestational Trophoblastic Neoplasia

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Abstract

Objective: The objective of this study was to determine the relationship between plasma cholinesterase activity and stage of gestational trophoblastic neoplasia (GTN).
Materials and Methods: Plasma cholinesterase activities were studied in 47 women with GTN, 30 healthy women in the first trimester of pregnancy, and 44 non-pregnant, healthy women.
Results: Mean (±SD) plasma cholinesterase activities in healthy pregnant women (7738±2291 units/ml) and in GTN patients (7719±2262 units/ml) were significantly lower than in healthy non-pregnant women (10379±2380 units/ml) ($p<0.05$). Mean plasma cholinesterase activities in GTN patients did not differ ($p>0.05$) between low-risk (good prognosis) and high-risk (poor prognosis) groups as assessed by the revised International Federation of Gynecology and Obstetrics (FIGO) classification of trophoblastic neoplasia.
Conclusions: Patients with GTN and healthy pregnant women have reduced plasma cholinesterase activity compared with non-pregnant women. This is the first published report of reduced plasma cholinesterase activity in patients with gestational trophoblastic neoplasia according to FIGO staging.

Keywords: plasma cholinesterase, gestational trophoblastic neoplasia, FIGO staging

Özet

Gestasyonel Trofoblastik Neoplazili Hastalarda Azalmış Plazma Kolinesteraz Aktivitesi

Amaç: Bu çalışmanın amacı gestasyonel trofoblastik neoplazinin (GTN) evresi ile plazma kolinesteraz aktivitesi arasındaki ilişkiyi belirlemektir.
Materyal ve Metot: Kırk yedi GTN'li kadın, 30 sağlıklı, ilk trimestr gebe ve 44 gebe olmayan sağlıklı kadında plazma kolinesteraz aktivitesi çalışıldı.
Sonuçlar: Sağlıklı gebe kadınlarda (7738±2291 ünite/ml) ve GTN hastalarında (7719±2262 ünite/ml) ortalama (±SD) plazma kolinesteraz aktivitesi, gebe olmayan sağlıklı kadınlardan (10379±2380 ünite/ml) belirgin olarak daha düşük bulundu ($p<0.05$). Uluslararası Jinekoloji ve Obstetri Federasyonu (FIGO) sınıflamasına göre düşük riskli (iyi prognozlu) ve yüksek riskli (kötü prognozlu) olarak değerlendirilen GTN hastaları arasında ortalama plazma kolinesteraz aktiviteleri farklı değildi ($p>0.05$).
Tartışma: Gebe olmayan kadınlarla karşılaştırıldığında, GTN'li hastalar ve sağlıklı gebe kadınlarda plazma kolinesteraz aktivitesi düşük bulunmuştur. Bu çalışma, FIGO evrelemesi yapılmış gestasyonel trofoblastik neoplazili hastalarda, plazma kolinesteraz aktivitesinin azaldığını bildiren ilk yayındır.

Anahtar sözcükler: plazma kolinesteraz, gestasyonel trofoblastik neoplazi, FIGO evrelemesi

Introduction

The enzyme cholinesterase, also called pseudocholinesterase, butyrylcholinesterase, non-specific cholinesterase or S-type cholinesterase, is biosynthesized in the liver, and found in most tissues of the human body (1). Plasma cholinesterase has been given the systematic name acylcholine acylhydrolase with the code number EC 3.1.1.8. Cholinesterase has a tetrameric glycoprotein structure of which the molecular weight of the tetramer is approximately 342 000 Da. It occurs in the plasma as a number of distinct isoenzymes. In man, the biosynthesis of the 574 amino acid subunit is controlled by the cholinesterase-1 locus on chromosome no. 3 (2).

The physiological importance of cholinesterase is not clear, since congenital absence has no apparent ill effect (1). The

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enzyme has clinical interest because of its role in metabolizing depolarizing and non-depolarizing muscle relaxants such as suxamethonium and mivacurium. When these agents are used as neuromuscular blockers, decreased activity of plasma cholinesterase is responsible for prolonged apnea during anesthesia (2,3).

Plasma cholinesterase activity is influenced by a wide variety of pathological, iatrogenic and physiological conditions, including pregnancy (4). During pregnancy, a substantial decrease in cholinesterase activity occurs during the first trimester, and activity remains low throughout the second and third trimesters until the immediate postpartum period (5-7). The reason for this decline is unclear (8).

Gestational trophoblastic neoplasia (GTN) encompasses a unique spectrum of interrelated disorders derived from abnormally proliferating trophoblastic tissues that vary in propensity for spontaneous resolution, local invasion, and metastasis. These include complete and partial hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor, and miscellaneous and unclassified lesions. GTN is characterized by a pseudopregnancy state. Patients with GTN have similar metabolic changes to those seen in pregnancy, such as hemodilution, altered hepatic function, and elevated estrogen and human chorionic gonadotrophin (hCG) levels.

In 2001, the International Federation of Gynecology and Obstetrics (FIGO) Council adopted a revised FIGO classification of trophoblastic neoplasia, combining anatomic FIGO staging with a modified World Health Organization risk scoring system of treatment outcome (9). The revised FIGO risk scoring system assigns a numerical value to adverse prognostic features such as age, duration of disease, type of antecedent pregnancy (e.g. molar or term), number of metastatic sites and foci, tumor size, pre-therapy hCG levels, and prior chemotherapy. This analysis results in a 'high-risk' (poor prognosis) or 'low-risk' (good prognosis) score that helps predict treatment outcome. The revised FIGO system is capable of predicting patients who are likely to respond poorly to single-agent chemotherapy, and helps select optimal treatment protocols such as early use of combination chemotherapy.

The aim of the present study was to determine if plasma cholinesterase activity in patients with GTN varies with FIGO staging and prognostic risk.

Materials and Methods

The study included three groups of women: Forty-seven women with GTN; 30 healthy, first trimester pregnant women; and 44 non-pregnant gynecology outpatients of reproductive age serving as the controls. Metastases in GTN patients were assessed according to the revised FIGO staging criteria (9) as follows:

Stage I : Confined to uterus
Stage II : Outside uterus; limited to genital structures
Stage III : Extending to lungs and genital tract
Stage IV : All other metastatic sites

The diagnosis of GTN was confirmed by histopathological examination of the molar tissue.

Patients with GTN were also categorized as 'high risk' (i.e. had a poor prognosis, and would probably require combined chemotherapy) and 'low risk' (i.e. had a good prognosis, probably requiring only single-agent chemotherapy), according to the revised FIGO risk scoring system (9).

For all 121 subjects, samples of 10 ml heparin-stabilized venous blood were drawn from the antecubital vein. Plasma was separated from red cells and then stored at -20°C. Plasma cholinesterase activity was determined within 24 hours after withdrawal, using a commercial kit (Rocholinesterase, Germany) with a colorimetric method, using an automatic analyzer (Hitachi 911, Germany).

Informed, written consent was obtained from all subjects. All statistical calculations were performed using SPSS for Windows version 7.5 computer program (SPSS Inc., Chicago, USA). Differences between groups were analyzed with Kruskal-Wallis test and Student's t-test. Data are reported as the mean ± SD; differences were considered significant at $p<0.05$.

Results

According to the revised FIGO staging criteria (9) there were 4 GTN patients at stage I, 10 at stage II, 18 at stage III and 15 stage IV. According to the revised FIGO risk scoring system: 14 patients with GTN were categorized as 'low risk', and 33 patients as 'high risk'.

Mean plasma cholinesterase activities for all 121 subjects are shown in Table 1. Plasma cholinesterase activity was found to be significantly lower in pregnant women and in those with GTN compared with non-pregnant women ($p<0.05$).

Cholinesterase activities in GTN patients according to FIGO stages are given in Table 2. There were no significant differences between mean cholinesterase activities for the four different stages of GTN.

Table 1. Plasma cholinesterase activity

Patients	n	Cholinesterase activity ± SD (units/ml)	p value*
With GTN	47	7719±2262	<0.05
Healthy pregnant	30	7738±2291	<0.05
Healthy non-pregnant	44	10379±2380	-

*Versus healthy, non-pregnant women
GTN, gestational trophoblastic neoplasia

Table 2. Plasma cholinesterase activity in GTN patients according to FIGO stages

FIGO stage	n	Cholinesterase activity ± SD (units/ml)	p value*
I	4	8944±2927	NS
II	10	7804±2670	NS
III	18	7658±2514	NS
IV	15	7409±1477	NS

*Versus healthy, pregnant women
GTN, gestational trophoblastic neoplasia
FIGO, International Federation of Gynecology and Obstetrics
NS, not significant

Table 3 shows plasma cholinesterase activity in GTN patients according to low risk (good prognosis) and high risk (poor prognosis), as assessed using the FIGO risk factor scoring system. There was no evidence of any distinction between low-risk and high-risk GTN subjects in terms of cholinesterase activity.

Table 3. Plasma cholinesterase activity in low- versus high-risk GTN patients

Patients	n	Cholinesterase activity ± SD (units/ml)	p value
Low risk* (good prognosis)	14	7714±2344	
High risk* (poor prognosis)	33	7306±1033	NS

*Assessed according to revised FIGO classification of trophoblastic neoplasia (9)
GTN, Gestational trophoblastic neoplasia
FIGO, International Federation of Gynecology and Obstetrics
NS, not significant

Discussion

Physiological alterations develop during the course of pregnancy. Early changes are due, in part, to the increasing levels of pregnancy hormones. A well-characterized glycoprotein hormone secreted by the syncytiotrophoblast, hCG is involved in trophoblast production, and essential for maintaining normal function of the corpus luteum during pregnancy.

GTNs arise from abnormal union of sperm and ovum, and appear as a spectrum of neoplasms that resemble pregnancy in terms of the hormonal milieu and metabolic changes. Abnormalities of the trophoblast result, and probably an early embryo death. Most commonly, GTN results in a hydatidiform 'molar' pregnancy characterized by the lack of a fetus, trophoblastic hyperplasia, edematous chorionic villi, and loss of normal villous blood vessels (10).

Metabolic changes occurring with GTNs might be related to altered metabolic functions and other interrelated changes occuring in pregnancy. Several clinical features of GTNs can mimic the symptoms and findings of normal pregnancy. Early toxemia (hypertension, proteinuria, and edema), hyperemesis gravidarum, hyperthyroidism, and the extrinsic coagulation pathway activation are not uncommon in patients suffering from GTN. Plasma hCG levels are abnormally elevated in a molar pregnancy, and this hormone serves as marker for tumor activity in the GTN patient.

Normal pregnancy is associated with a significant reduction in plasma cholinesterase activity (11-14), as is the pseudopregnancy state GTN (15); the reasons remain unclear. Several interrelated factors have been postulated to produce the decrease in plasma cholinesterase activity in normal pregnancy and in a pseudopregnancy state such as GTN. These mechanisms are nutritional factors, hemodilution, hypoalbuminemia, high estrogen levels, altered lipid and lipoprotein levels, specific inhibition of hepatic function or induction of hepatic microsomal function. Altered hormonal balance, related to elevation of hCG may account for the decreased cholinesterase activity (5,15).

A negative correlation between cholinesterase activity and duration of neuromuscular blockade following suxamethonium has been reported (16). Thus, deficiency of plasma cholinesterase can result in prolonged apnea during anesthesia, delaying postoperative recovery and presenting a potentially life-threatening complication in extreme cases (17).

Data from the present study show that plasma cholinesterase activity was decreased in pregnancy and in GTN. There was no significant difference between cholinesterase activity in GTN patients and healthy pregnant women, and cholinesterase activity did not differ between low- and high-risk GTN patients. This is the first published report of reduced plasma cholinesterase activity in patients with GTN according to FIGO staging.

In conclusion, GTN resembles a gestational state that can mimic pregnancy both clinically and biochemically. Plasma cholinesterase levels were lower in patients with GTN than in non-pregnant women, and similar to those seen in normal pregnancy. No relationship was detected between plasma cholinesterase activity and prognosis risk associated with GTN. Like pregnant patients, GTN patients are susceptible to prolonged neuromuscular blockade with depolarizing and non-depolarizing muscle relaxant drugs.

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