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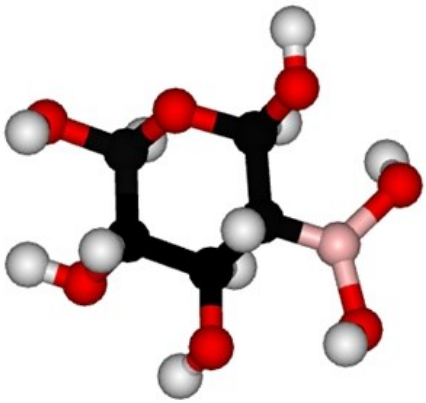

High Lights

Complexion of Boric Acid with 2-Deoxy-D-glucose (DG) as a novel boron carrier for BNCT
1984A/G adrenomedullin (rs3814700) gene polymorphism
Histopathological Review of Male Breast Cancer Cases
The analysis of Doppler flow alterations in intrauterine growth restricted pregnancies
Familial Recurrent Hydatidiform Moles

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Contents

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Letter to Editor
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Toxoplasma IgM positive in pregnancy: what does it mean from the perspective of the gynecologists?

Burcu Artunc Ulkumen[1], Halil Gursoy Pala[1]

Sir,

Toxoplasma gondii infection in pregnancy occurs with maternal ingestion of cysts in undercooked meat or with maternal ingestion of oocysts found in water, food and soil (1). Contaminated under cleaned green salads (like garden rocket, parsley) and water may be important sources for women in Turkey. Although routine screening for toxoplasmosis in pregnancy is not recommended, this is not the case in daily practice and due to unnecessary screening and confounding test results, gynecologists should be also familiar with patients having the results of Toxoplasma IgM(+). One key-point for evaluation the toxoplasmosis-suspected pregnant woman is to know that congenital infection risk for the fetus is higher in third trimester; however, the risk of the injury for the fetus is greater in the first trimester (2). Pregnant women with IgM(+)/IgG(-) should be screened in 1 to 3 weeks again. If seroconversion in Ig G occurs, then infection is probably acquired during pregnancy and there is risk for congenital infection (3). Treatment is to be initiated with Spiramycin. Amniocentesis for amniotic fluid PCR should be performed after 16 weeks. A detailed fetal ultrasonography should be also performed. In case of IgM(+)/IgG(+), the results should be confirmed. *Toxoplasma Gondii* avidity testing is reasonable at this stage (4). High-avidity IgG antibodies are detected at least 12-16 weeks after infection, so high-avidity IgG results show that the infection was started 16 weeks before. Low-avidity results may persist for a long period (even more than one year after acute infection), so only avidity tests should not be used (1, 5).

In our daily practice, we account the gestational week, the Ultrasonograhic findings with maternal serum results into account. In case of IgM(+)/IgG(+); we also perform IgG avidity test. We initiate medical treatment and repeat the tests in 3 weeks. A significant increase in IgG titers (3-4 times) together with low-avidity IgG is suggestive for an acute infection. Fetal infection should be checked with amniocentesis

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Conflict of Interest: The authors declared that they had no conflicts of interest.

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Complexion of Boric Acid with 2-Deoxy-D-glucose (DG) as a novel boron carrier for BNCT

Zafer Akan[1], Hasan Demiroglu[2], Ugur Avcibasi[2], Gokhan Oto[3], Hulya Ozdemir[3], Sabahattin Deniz[4], Ali Sadi Basak[5]

Abstract

Objective: Boron neutron capture therapy (BNCT) is an intensive research area for cancer researchers. Especially the side effects and inabilities of conventional therapies in some cases, directs researchers to find out a new cancer therapy methods such as BNCT. One of three important problem of BNCT is targeting of boron to tumor tissue. Borono Phenyl Alanine (BPA) and Borono Sodium Borocaptate (BSH) are already using in clinical studies as boron carriers. New boron carriers are searching for high yield boron accumulation in the tumor tissue.

Methods: In this study, a novel ^{10}B carrier was synthesized, ((2*R*)-4,5,6-trihydroxy-2-(hydroxymethyl)tetrahydro-2*H*-pyran-3-yl)boronic acid (**^{10}**B-DG), for BNCT studies. ^{10}Boric Acid and 2-Deoxy-d-Glucose was complexed (^{10}B-DG) through a low-high pH reaction and yield of complexion was tested with FTIR ATR and Liquid Chromatography Mass Spectrometry (LC/MS).

Results: Confirmation studies have been carried out by HPLC and chromatograms have confirmed that Borono-2-Deoxy-d-Glucose synthesized with % 80 yield.

Conclusions: This compound appears to be an alternative boron carrier for BNCT applications

Keywords: ((2*R*)-4,5,6-trihydroxy-2-(hydroxymethyl)tetrahydro-2*H*-pyran-3-yl)boronic acid, 10B-DG, BDG BNCT, HPLC, FTIR-ATR, LC-MS

Introduction

Radiotherapy is a long-standing treatment method which makes use of ionizing radiation for the treatment of patients with malignancies. Ionizing radiations are absorbed by the all encountered tissues during radiotherapy. Side effects of ionizing radiation are unavoidable [1] Even different modalities and approaches are advancing the radiotherapy more radical changes such as BNCT are needed for patient life quality.

$^{10}B+^{1}n \rightarrow ^{7}Li(0.84\ MeV)+^{4}He\ (1.47\ MeV)+\gamma\ (0.48\ MeV)\ 93.7\%$
$^{10}B+^{1}n \rightarrow ^{7}Li\ (1.01\ MeV) + ^{4}He\ (1.78\ MeV)\ 6.3\%$

The cornerstones of BNCT are the targeting of ^{10}boron to tumor tissue (15-30 ppm), pure neutron radiation sources with high intensity (≤10 KeV; ≈10^{9} n^{0} sec/cm^{2}) and simultaneously neutron radiation dose measurements during therapy.

Although development of different carriers such as monoclonal antibodiesdendrimers, liposomes, dextrans, polylysine, avidin, folic acid, and epidermal and vascular endothelial growth factors (EGF and VEGF), ideal alternative carriers are needed for BNCT application [2] As known, tumorigenic cells on mitosis process, needs constantly energy. Energy requirements are supplying from aerobic and anaerobic ways in the normal cells.

However in cancer cells oxygen supplies not enough due to delayed angiogenesis in the tumor tissue, there for, cells are compelled to supply ATP from anaerobic ways. In other words, required ATP is supplied by the glycolytic pathway. ATP yield of anaerobic/glycolytic way is very low compared with aerobic way. High ATP requirements are increase the affinity of glucose to the tumor tissue.

Usage of glucose derivatives for drug targeting to tumor tissue is very useful method, despite being an old idea. 2-deoxy-D-glucose (2-DG) is also a glucose analogue and an inhibitor for

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glucose transport and glycolytic ATP production [3]

Positron emitter radioactive ^{18}F complexed Deoxy-D-glucose (^{18}F-deoxy-D-glucose: ^{18}FDG) is routinely used for the detection and staging of tumors with positron emission tomography (PET). Radioactive positron emitter ^{18}F successfully targeted to tumor tissue by the Deoxy-D-glucose.

Boric acid $B(OH)_3$ and its anion borate $B(OH)_4^-$ have solution chemistry that is quite different from most other oxyanions. Borate forms by the addition of a hydroxyl group to the trigonal planar boric acid molecule, forming a tetrahedral anion. The pK of this reaction is 9.2 [4]

$B(OH)_3 + OH^- \leftrightarrow B(OH)_4^-$ pKa 9.2

Boric acid and borate both typically exist as monomers in solution at low concentrations (below 25 mM) but at higher concentrations many poly-borate polymers are known to form [5, 6].

Due to simple complexation properties of borate anions and easy intracellular uptake properties of 2-DG, the synthesis and complexation yield of Boric acid with Deoxy-D-Glucose (^{10}B-DG) were examined.

Material and Methods

Complexation reaction of $B(OH)_3$ and 2-DG and FT-IR/ATR measurements

The complexation reaction of boric acid with polyhydroxyl compounds, such as tiron, has been studied, and the reaction has been well defined in previous studies [6]. In same reaction conditions were applied for $B(OH)_3$ and 2-DG complexation.

A Perkin Elmer PE100 Infrared Spectrophotometer with Universal ATR Sampling Accessory was used for spectroscopic studies. All spectra were measured in the range between 1600 and 750 cm^{-1}, at resolution of 4 cm^{-1} [7]. Distilled water was used as background and to clean the diamond probe between each sample. All measurements were realized at room temperature. Deionized water prepared with a Milli-Q SP system (Millipore).

0.1 M **Boric acid** ($B(OH)_3$; Sigma-Aldrich, B6768) and 0.5 M **Tiron** (4,5-Dihydroxy-1,3-benzenedisulfonic acid disodium salt, Sigma-Aldrich, D7389) solutions were prepared with the same volume of deionised water and incubated for 1 hour at pH:3 and 50°C.

0.1 M **Boric acid** ($B(OH)_3$; Sigma-Aldrich, B6768) and 0.5 M **Deoxy-D-glucose** (2-DG: Sigma-Aldrich, D8375) solutions were prepared with the same volumes of deionized water and incubated for 1 hour at pH:3 and 50°C.

Both solutions were then mixed in the same tube and incubated for 1 hour at pH:3. The pH was gradually increased from pH:3 to pH:7 and stabilized at physiologic pH:7.4. FTIR-ATR analysis were done for only $B(OH)_3$, only Tiron, only DG and complexed B-Tiron and B-DG. Complexation between boric acid and the 2-DG may be expressed as eqn.

$B(OH)_3 + H_2O \leftrightarrow B(OH)_4^- + H^+$ Ka= $[B(OH)_4^-][H^+] / [B(OH)_3]$
$B(OH)_4^- + DG \leftrightarrow B\text{-}DG + H^+$ Ka= $[B(OH)_4^-][DG] / [B\text{-}DG]$

HPLC studies

The following quality control studies were done to confirm Boric acid, 2-Deoxy-D-glucose and Borono-2-Deoxy-D-glucose. Table 1 shows chromatographic conditions used analytical experiments in HPLC. A low- pressure gradient HPLC system (LC-10ATvp quaternary pump and SPD-10A/V UV detector and a syringe injector equipped with a 1 ml loop and 7-µm RP-C-18 column 250 x 4.6 mm I.D. (inner diameter), Macherey–Nagel), was used for analytical experiments.

Table 1. Chromatographic conditions used analytical experiments in HPLC

Column in analytical exp.:	RP-C18(250x4.6mm)
Flow speed in analytical exp.:	0.7 mL/min
Wave length:	240 nm
Temperature:	30 °C
Pressure:	76 bar
Mobile phase in analytical exp.:	18 mM NaOH

LC-MS

Liquid chromatography mass spectrometry (LC-MS) chromatograms were taken using a HCTultra LC-MS instrument. Chromatographic conditions used in this study were given in Table 2. The parameters were optimized and set as followed. Ion source Type ESI pos and ESI neg, Mass Range Mode Ultra Scan (26000 m/z/s), Column No column, direct infussion, Capillary pos -4000 V and neg +4000 V, Drying gas tempreture 300 °C, Drying gas pressure 5 psi, Nebulizing gas pressure 10 psi .

Table 2. Chromatographic conditions for LC-MS experiments

Ion source type:	ESI pos and ESI neg
Mass range mode:	Ultra Scan (26000 m/z/s)
Column:	No column direct infussion
Capillary:	pos -4000V and neg +4000V
Drying gas tempreture:	300 °C
Drying gas pressure:	5 psi
Nebulizing gas pressure:	10 psi

Results

Complexation reaction of $B(OH)_3$ and 2-DG

FT-IR/ATR results of ^{10}B-Tiron and ^{10}B-DG (Fig. 1) have similar peak shifts which indicate complexation due to literature results (Fig. 2, 3), [7]. The IR spectra of these solutions of $B(OH)_3$, 2-deoxy glucose (2-DG) and ^{10}B-DG showed that formation bonding between ^{10}B and 2-DG by the disappearance of asymmetric stretching of $B(OH)_3$ at 1413 cm^{-1} and decreasing peaks intensity of 2-DG solution at 1264 cm^{-1} (O-H blending of deoxyglucose) and 1067 cm^{-1}, 1029 cm^{-1} and 1015cm^{-1} (C-O stretching of deoxyglucose).

Figure 1. Chemical synthesis of Borono-Deoxy-D-glucose

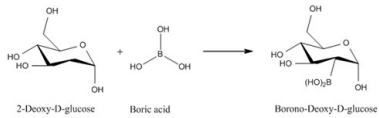


Table 3. LC–MS/MS Spectrum (m/z) Values for Borono-2-Deoxy-D-glucose Compounds and Some Different Fragments and Proposed Structures of Selected Fragments

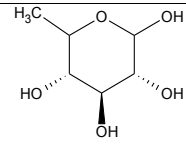
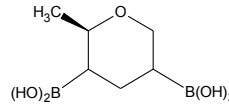
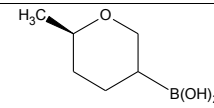
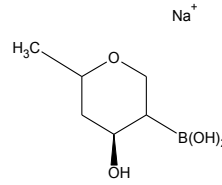
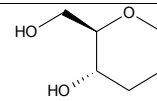
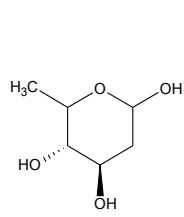
Frag.	Structure	m/z
1		164,1
2		187,7
3		143,9
4		182,9
5		132,1
6		171,1

Figure 2. Complexation of $B(OH)_3$ -Tiron FTIR-ATR

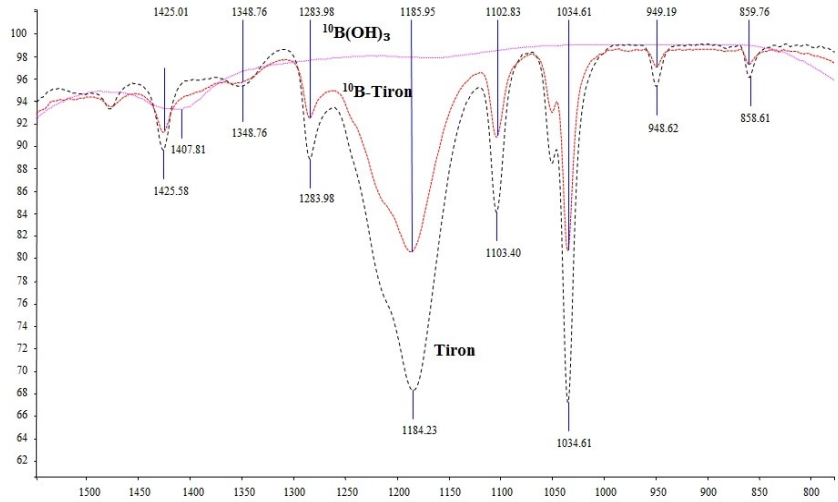
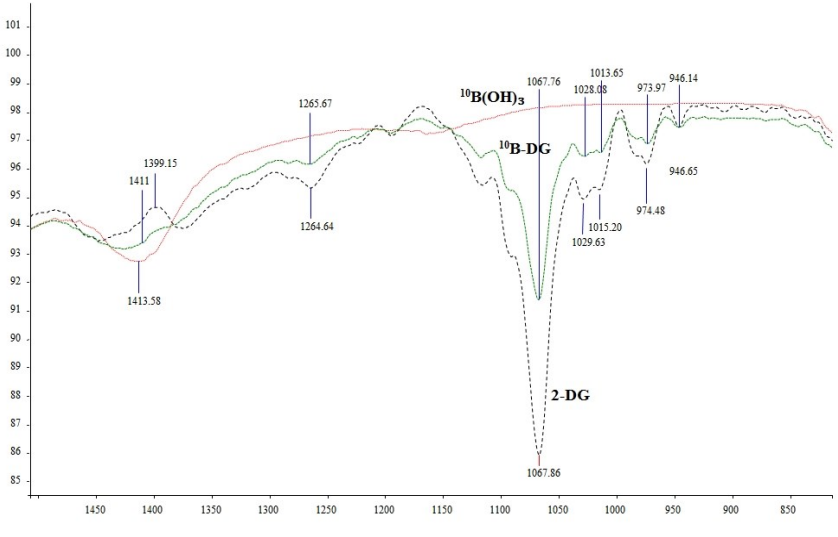


Figure 3. Complexation of $B(OH)_3$ -2DG FTIR-ATR



Shao and coworkers have shown that Boric acid - Tiron (1,2-dihydroxybenzene-3,5-disulfonic acid disodium salt monohydrate) complex characterization by ^{11}B NMR spectra and proved forming complex between Boric acid and Tiron [6] In this work Boric acid-Tiron complex were investigated by IR Spectra. The IR spectra of solutions Tiron, B, B-Tiron were taken. The IR spectra (Figure 2) showed that the disappearance of asymmetric stretching of $B(OH)_3$ at 1407 cm^{-1} like in Figure 3. This indicates that boric acid form complex with deoxyglucose like Tiron.

Results of HPLC and LC-MS studies

HPLC chromatograms confirmed that Borono-2-Deoxy-D-glucose synthesized with 80% yield. Three peaks were detected for Borono-2-Deoxy-D-glucose HPLC analyses, the retention times of related compounds were different from each other as is seen in Figure 4 and Figure 5. Retention times are 3.68, 4.18 and 4.87 min for Boric acid, 2-Deoxy-D-glucose and Borono-2-Deoxy-D-glucose, respectively.

LC–MS spectrum (m/z) values for Borono-2-Deoxy-D-glucose compounds and some different fragments and proposed structures of selected fragments (m/z) values are 162,1 : 187 : 143,9 : 182,9 : 132,1 : 169,1.

Discussion

Most cancer cells exhibit increased glycolysis and use this metabolic pathway (anaerobic pathway) for generation of ATP as a main source of their energy supply because of delayed angiogenesis. This phenomenon is known as the Warburg effect and is considered as one of the most fundamental metabolic alterations during malignant transformation. Although delayed angiogenesis seen as a chance to delay for metastases, makes malignancies chemotherapy-resistant. Beside of chemotherapeutic resistant, oxygen-free environment due to malignant transformation makes cancer cells resistant to radiotherapy too [8] Importantly, the increased dependence of cancer cells on glycolytic pathway for ATP generation provides a biochemical basis for the design of therapeutic strategies to preferentially kill cancer cells by pharmacological inhibition of glycolysis. Several small molecules have emerged that exhibit promising anticancer activity *in vitro* and *in vivo*, as single agent or in combination with other therapeutic modalities [9].

2-Deoxy-D-glucose is a glucose molecule which has the 2-hydroxyl group replaced by hydrogen, so that it cannot undergo further glycolysis. As such, it acts to competitively inhibit the production of glucose-6-PO_4 from glucose at the phosphoglucoisomerase level [10].

2-DG is easily uptaken by the glucose transporters of the cell. Therefore, cells with higher glucose uptake, for example tumor cells, have also a higher uptake of 2-DG.

Inhibition of glycolysis by the small glycolysis inhibitors (GI) brought up to the use of combine usage of glycolysis inhibitors with chemotherapeutics in the treatment of malignant tumors therefore affectivity research of 2-DG - Chemotherapeutic combine treatments were recently started in clinical trials [11].

Due to higher glucose uptake of tumor cells, radiolabelled 2-DG (^{18}F-DG) is also routinely using for tumor imaging and staging with positron emitting tomography since 1990's (PET) [12].

Even if alternative reactions can be used for 2-DG and boric acid complexation which enrolled in the study as alternative boron carrier; 2-DG and Boric Acid thought to be complexed rapidly and easily via low-high pH reactions due to poly-hydroxyl components of two molecules. Low-high pH reactions have been recommended in the literature for similar boric acid reactions [6].

If compare with low-high pH complexation reaction results, yield is very low for other reactions and reaction time is not reasonable. For example, nucleophilic substitution reaction is more widely used for 18F, 2-DG complexation reaction and electrophilic fluorination reaction has an important place in the synthesis of 18F-FDG. Synthesis of 18F-FDG in radio-fluorination reactions, triflates produces a moderate consistent yield at about 50 to 60% [13].

Boric acid reacts with polyhydroxyl compounds as a Lewis acid to form complex in aqueous solution. 2-Deoxy-D-glucose has the 2-hydroxyl group therefore simple pH complexation reaction was designed as defined in previous studies [6].

Figure 4. HPLC chromatograms of 2-Deoxy-D-glucose and Borono-2-Deoxy-D-glucose (first pink peak belongs to 2-Deoxy-D-glucose, Rt (Retention time):4.18 min and the second black peak is Borono-2-Deoxy-D-glucose, Rt (Retention time): 4.87 min)

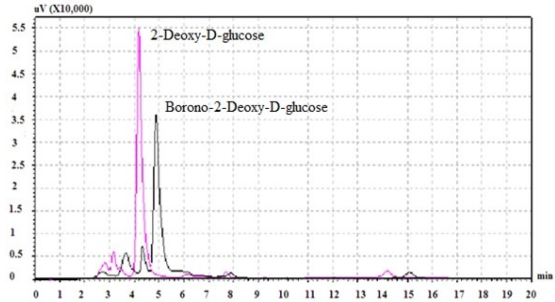
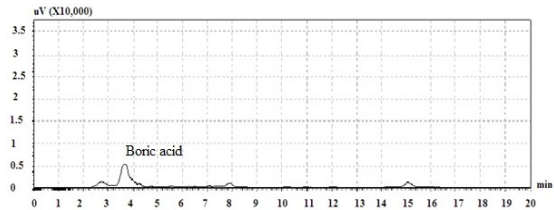


Figure 5. HPLC chromatograms of Boric acid $B(OH)_3$, Rt (Retention time): 3,68 min



We have accomplished the effective and simple synthesis of ((2*R*)-4,5,6-trihydroxy-2-(hydroxymethyl)tetrahydro-2*H*-pyran-3-yl)boronic acid by the low-high pH reaction in high yields and short time. This method also could be applied to synthesis of (6-fluoro-2,4,5-trihidroxyoxan-3-yl) boronic acid. Complexation of $B(OH)_3$ with 2-DG was observed with FT-IR/ATR also proved with LC–MS and yield of complexation was measured by the HPLC. Peak areas of HPLC chromatograms confirmed that Borono-2-Deoxy-D-glucose synthesized with a higher consistent yield at about 80%.

In this work, due to successfully carrier properties, 2-DG thought to be alternative Boron carriers for BNCT application and boron (^{10}B) successfully complexed with 2-DG.

Acknowledgments

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1984A/G adrenomedullin (rs3814700) gene polymorphism: can it be responsible for unexplained recurrent early pregnancy loss?

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Abstract

Objective: The etiology of recurrent miscarriage (RM) is heterogeneous and the current data cannot be able to cover all the aspects of RM. Adrenomedulline (ADM) has been very popular with the discovery of vital functions in maintaining an uneventful pregnancy. Idiopathic RM may result due to defective placentation and implantation process associated with altered ADM function and levels. So, we hypothesized that increased ADM gene polymorphism could play a role in idiopathic RM cases

Methods: This prospective case-control study consisted of 60 women; 30 of whom had three consecutive pregnancy losses, who admitted to the outpatient clinic of department of obstetrics and gynecology or department of genetic at our tertiary center. Genomic DNA was extracted from peripheral blood and the frequency of genotypes and alleles of –1984A>G ADM (rs3814700) gene polymorphism was examined by polymerase chain reaction and restriction fragment length polymorphism (PCR/RFLP) method

Results: The mean ages were 29.36±6.22 and 32.15±5.43 in RM and control group, respectively (p=0.314). For -1984A>G polymorphism, the frequency of A allele was 91.7% and 93.3% in RM and control group, respectively (p=0.72). The frequency of G allele was 8.3% and 6.7% in RM and control group, respectively (p=0.72). Regarding the incidence of genotype; AA genotype was 83.3% and 86.7% in RM and control group, respectively (p=0.71). AG genotype was 16.7% and 13.3% in RM and control group, respectively (p=0.71).

Conclusions: -1984A>G ADM gene polymorphism does not seem to be associated with idiopathic RM

Keywords: Recurrent pregnancy loss, Adrenomedullin, gene polymorphism, -1984A>G polymorphism

Introduction

Recurrent miscarriage (RM) is three or more consecutive pregnancy losses before 22 gestational weeks [1]. The prevalence is approximately 0.8-1.4%, if only clinical RM (evidence of pregnancy with ultrasonographic and histologic findings) is taken into account; the prevalence is 2-3%, if also biochemical losses (urinary HCG positivity with no evidence of sonographic or histologic endometrial findings) are taken into consideration (2). In fact, there is a "rule of 30%'s" regarding the outcome of conceptions: 30% of them are lost before they implant into the endometrium. Further 30% of them are lost after the implantation; however, before the next menstrual period begins. So, only 30% of them end up in live birth (3). The etiology of RM is heterogeneous and the current data cannot be able to cover all the aspects of RM. Still approximately 50% of RM is unexplained. The well-known factors are classified as genetic, immunologic factors, thrombophilia, endocrinological causes, uterine malformations and obesity (2-5). Due to exaggerated oxidative stress, uterine natural killer cells via increased angiogenesis during the implantation period have been thought as a cause for idiopathic RM (6). Recent studies have showed that adrenomedullin (ADM) was important in angiogenesis, extracellular cytotrophoblast migration and placentation (7, 8). The normal physiological maternal adaptation to the pregnancy occurs with the increased serum ADM levels (8). In compromised pregnancies such as preeclampsia –a result of defective placentation-, the increase in ADM levels does not occur (8).

It is showed that GG genotype for ADM gene causes a decrease in ADM production, whereas AA genotype is associated with increased ADM levels. -1984A>G variant in the promoter region of the ADM gene, which probably decreases adrenomedullin transcription and, in consequence, decreases ADM concentration (9). From that point of view, idiopathic RM may result due to defective placentation and implantation process associated with altered ADM function and levels. So, we

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hypothesized that ADM gene polymorphism could play a role in idiopathic RM cases and we aimed to investigate the frequency of ADM -1984A>G polymorphism in idiopathic RM cases.

Material and Methods

This prospective case-control study consisted of 60 women; 30 of whom had three consecutive pregnancy losses, who admitted to the outpatient clinic of department of obstetrics and gynecology or department of genetic at our tertiary center. The other 30 women were age-matched healthy multiparous women admitted to the outpatient clinic at our department during the study period. Women with congenital uterine anomalies, large uterine myomas, cervical insufficiency, hereditary thrombophilia or genetic abnormalities were excluded from the study. Institutional Ethic Commitee approved the study. All participants signed informed consent.

Genomic DNA was extracted from peripheral blood by commercial İnvitrogen Genomic DNA extraction kit following the manufacturer's instructions and stored at -20^{0}C. The frequency of genotypes and alleles of –1984A>G ADM (rs3814700) gene polymorphism was examined by polymerase chain reaction and restriction fragment length polymorphism (PCR/RFLP) method.

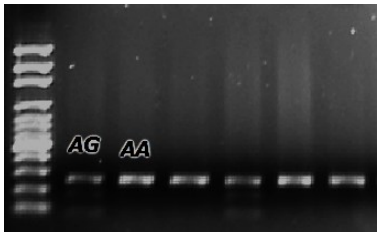
PCR was performed in a 25 µl reaction containing 150 ng DNA, 10x PCR buffer, 2.5 mM $MgCl_2$, 20 µM dNTPs, Primer Forward (10 pmol/ µl), Primer Reverse (10 pmol/ µl), 5U/µL Hot Start Taq polimerase. Amplification conditions were set like as; an initial activation step of 94°C for 15 min followed by 35 cycles of denaturation at 94°C for 45 s, annealing at 60°C for 45 s, extension at 72°C for 1 min and 45 s and a final extension step at 72°C for 10 min. PCR products (250 bp) were digested with restriction enzyme HpyCH4III at 37^{0}C for two hours and digested fragments were analyzed by agarose gel electrophoresis.

The AA genotype was identified at the presence of 250 bp, heterozygous AG genotype in presence of 250,166 ve 84 bp and homozygous GG genotype in presence of 166,84 bp (Figure-1).

Results

The mean ages were 29.36±6.22 and 32.15±5.43 in RM and control group, respectively (p=0.314). Regarding the -1984A>G polymorphism, the frequency of A allele was 91.7% and 93.3% in RM and control group, respectively (p=0.72). The frequency of G allele was 8.3% and 6.7% in RM and control group, respectively (p=0.72). Regarding the incidence of genotype; AA genotype was 83.3% and 86.7% in RM and control group, respectively (p=0.71). AG genotype was 16.7% and 13.3% in RM and control group, respectively (p=0.71).

Figure 1: The band appearance of ADM gene –1984A>G polymorphism in agarose gel. There was no GG genotype in study group.



Discussion

In the present study, we examined -1984A>G ADM (rs3814700) gene polymorphism in the RM group and compared it with the healthy multiparous Turkish women. Adrenomedullin (ADM) is a 52 amino acid peptide, which was firstly discovered in pheochromocytoma in 1993 (6). It was shown that ADM had role in vasodilatation and angiogenesis (7,8). It is also well-known that an uneventful pregnancy depends on adequate blood supply between feto-maternal interfaces. The alterations in uterine vasculature – especially around the implantation side- is one of the main physiologic adaptations in pregnancy (8). Recent studies pointed that ADM has important role in placentation and also in maintaining a successful pregnancy.

To the best of our knowledge, our study is first by evaluating ADM gene polymorphism in idiopathic recurrent pregnancy losses. Recent studies regarding ADM and pregnancy losses focused mainly on ADM levels in plasma. Nakatsuka et al evaluated plasma ADM levels and pulsed Doppler ultrasonography measurements in RM with positive antiphospholipid and anti-nuclear antibodies and in control groups. They found increased plasma ADM levels in RM group (10). The study of El-Mashad et al consisted of 40 idiopathic RM and 43 control cases. They showed that plasma ADM levels were also increased in idiopathic RM group (11).

Both studies agreed with that plasma ADM levels were correlated with the uterine artery pulsatility index (10,11). These findings may be regarded as the evidence of that oxidative stress caused ADM levels to increase.

Kato and co-workers showed that ADM was produced mainly by the vascular tissue, especially endothelium and vascular smooth muscle (12). ADM has a complex interactive relation with various molecules such as prostaglandins (PG's), nitric oxide (NO), atrial natriuretic peptide (ANP),

renin aldosterone system (RAS), norepinephrine, arginine vasopressin, endothelin-1 and adrenocorticotropic hormone (ACTH) (13). There are a few studies in the literature regarding the possible gene polymorphisms and RM. The data about the association of the polymorphisms of the eNOS gene and methylenetetrahydrofolate reductase (MTHFR) and RM is conflicting: Tempfer et al conducted a prospective study with 105 RM cases and evaluated the endothelial nitric oxide synthase (eNOS) gene polymorphisms. They found that eNOS gene polymorphisms could be a genetic determinant for the developing idiopathic RM (14). Similarly, Suryanarayana et al. showed that eNOS gene polymorphisms were associated with an increased risk of RM (15). Makino et al. found that only NO concentration but not the polymorphism of MTHFR and eNOS gene are associated with RM (16). In accordance with that, Zammiti et al. pointed that there was no association between the eNOS gene polymorphisms and the risk of RM (17).

Kato and co-workers suggested that ADM increased during the pregnancy as a result of the physiologic adaptations which in turn increases the utero-placental blood supply (12). Recent studies provided further data that ADM had a key role for placentation (18-20). The placentas of murine fetuses which lack the ADM gene showed typical pathological features of preeclampsia which is a result of improper placentation (21).

We hypothesized that patients with idiopathic RM may have had problems regarding the early period of pregnancy including the implantation and placentation window. With this aim, we evaluated these RM patients with the frequency of genotypes and alleles of –1984A>G ADM (rs3814700) gene polymorphism. Compared with parous control group, we could not show any significant difference. The main limitation of our study was the sample size. The second limitation was that we could not investigate the tissue expression of ADM. And also we had no data about the smoking status of the study population.

Our preliminary results showed no difference between the RM and parous women in terms of –1984A>G ADM (rs3814700) gene polymorphism. Further prospective studies with greater sample size may be conducted to investigate any other relations

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Conflict of Interest: The authors declared that they had no conflicts of interest.

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Histopathological Review of Male Breast Cancer Cases

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Abstract

Objective: Male breast cancer (MBC) accounts for less than 1% of all breast cancer diagnoses and all cancer cases in men.

Methods: We included 33 MBC cases and analyzed histopathological features and survival data.

Results: The mean age was 63.5, mean tumor diameter was 3 cm. Central quadrants (69.2%) was most common localization, invasive ductal carcinoma (75.8%) was most common histological subtype. Most of the cases (78.6%) were grade 2. Nipple involvement was noted in 9, tumor necrosis in 9, perineural invasion in 15, dermal lymphatic emboli in 10 cases. Nearly half of the cases (45.5%) showed lymph node metastasis. There was statistically significant relation between lymph node metastasis and stromal lymphocyte response, tumor necrosis (p=0.008, p=0.013) also between grade and dermal lymphatic emboli (p=0.04). Non-tumoral parenchymal findings were columnar cell lesions (CCL), (n: 5) and gynaecomastia (n: 3). Majority of the cases showed estrogen receptor (90.9%) and progesterone receptor (77.2%) positivity. Overall survival analysis showed significant results between grade (p=0.008), lymph node metastasis (p=0.03), dermal lymphatic tumor emboli (p=0.02), nipple involvement (p=0.02) and survival.

Conclusions: Our results showed good correlation with literature data in terms of histopathological features and prognostic factors. Confidential data about etiological and prognostic factors will be collected through these reports showing institutional experiences. The significance of CCL in MBC etiology, the impact of intratumoral stromal lymphocyte response, hormone receptor-HER2 status on survival should be clarified in larger series.

Keywords: Male breast cancer, Prognosis, Histopathology

Introduction

Male breast cancer (MBC) accounts for less than 1% of all breast cancers diagnoses and all cancer cases in men [1]. Incidence rate is higher in North America, Europe and Africa [2]. The mean age at diagnosis is 67 which is higher than the mean age reported in woman [3]. Etiopathological factors of MBC are genetic predisposition (BRCA2 mutation), estrogen-testosterone ratio alterations (Klinefelter syndrome, obesity, liver cirrhosis, exogenous estrogen therapy), radiation exposure and occupational risks [1,4,5].

Most common histopathological subtype is invasive ductal carcinoma (85-90%) [4,6]. The vast majority (65-90%) of MBC are estrogen and progesterone receptor positive [4,6]. Axillary lymph node metastasis is observed in nearly half of MBC cases [7].

The current approaches in MBC treatment are surgery (simple-modified radical mastectomy, sentinel node biopsy), hormonotherapy, radiotherapy, chemotherapy [6].

Our aim was to analyze the demographic and clinical characteristics of MBC patients and predictive factors impact on overall survival.

Material and Methods

We included 33 MBC cases diagnosed between 2000-2014 in Tepecik Training and Research Hospital. We reviewed hematoxylin-eosin stained sections in terms of histological tumor type, grade, necrosis, perineural invasion, dermal lymphatic invasion, DCIS component, nipple involvement, lymph node metastasis, stromal lymphocyte response, non-tumoral parenchymal features. We also searched pathology reports for tumor diameter, localization, hormone receptor, HER2 status and archive records for survival data.

Statistical Analysis

Statistical analyses were performed by using SPSS software version 16. Overall survival rates were

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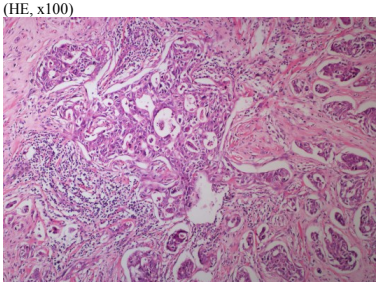
estimated by Kaplan-Meier. Pearson's chi-square test and Mann Whitney U test were used to analyze the data, as appropriate. The results were considered to be statistically significant when $p < 0.05$

Results

The mean age was 63.5 (min:48, max:90), mean diameter was 3cm (min:1, max:5 cm). We could achieve follow up/survival data of 22 cases of which 14 alive and 8 died. Mean follow up period was 55.8 months (min:3, max:155). Central quadrant (69.2%) was the most common localization. Histopathological subtype was invasive ductal carcinoma (IDC) in 25 cases (75.8%), papillary carcinoma in 3 cases (9%), ductal carcinoma in situ (DCIS) in 5 cases (15.2%). Of the 25 IDC cases, 5 exhibited in situ component. Twenty two cases were grade 2 (78.6%), six cases were grade 3 (21.4%). Lymph node excision was performed in 22 cases and 10 cases (45.5%) showed lymph node metastasis. Six cases had distant metastasis. Nipple involvement was noted in 9 cases, of which 7 located in central quadrant, 8 were IDC, 1 was pure DCIS and 1 had in situ component in addition to invasive component. Tumor necrosis was seen in 9 cases (27.3%), perineural invasion in 15 cases (45,5%), tumor emboli in dermal lymphatics in 10 cases (30.3%). There was a statistically significant relation between presence of tumor emboli in dermal lymphatic and central quadrant localization (p= 0.03). We noted stromal lymphocyte response in tumoral areas in six cases of which five showed lymph node metastasis (Figure 1). Correlation between the presence of stromal lymphocyte and lymph node metastasis was statistically significant (p=0.008). There was also statistically significant relation between lymph node metastasis and tumor necrosis (p=0.013) also between grade and dermal lymphatic tumor emboli (p=0.04).

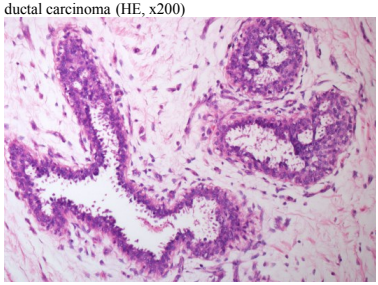
Non-tumoral parenchymal findings were columnar cell hyperplasia (n:5) (Figure 2) and gynaecomastia (n:3).

Figure 1: Stromal lymphocyte response in tumoral areas (HE, x100)



Hormone receptor and HER2 status were documented in 22 cases. Estrogen receptor was positive in 20 (90.9%), progesterone receptor in 17 (77.2%) and HER2 in 3 (13.6%) cases.

Figure 2: Columnar cell like changes in a case of invasive ductal carcinoma (HE, x200)



Overall survival analysis showed significant results between grade (p=0.008) (Figure 3), lymph node metastasis (p=0.03), dermal lymphatic tumor emboli (p=0.02), nipple involvement (p=0.02) and survival.

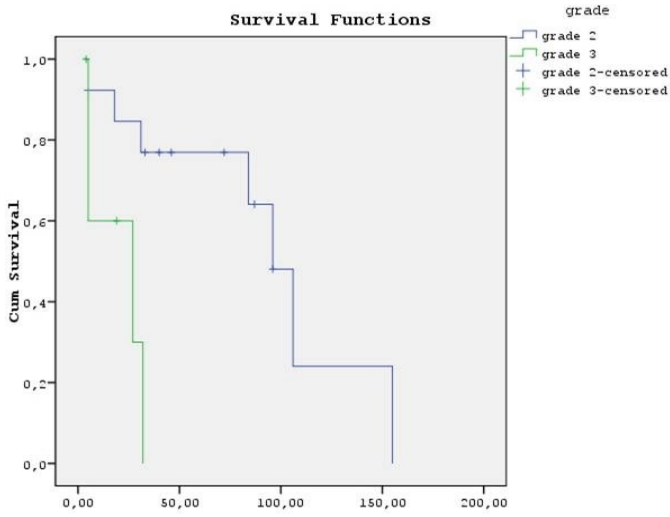
Discussion

Grujicic et al and Bruce et al reported IDC as most common subtype because male breast normally consist of only ducts [8,9]. Lobular tissue is present only in case of increased estrogen exposure [4]. Papillary carcinoma is more frequent in male (2–4%) than women [4]. In our study two most common subtypes were IDC (75.8%) and papillary carcinoma (9%).

DCIS accounts nearly 10% of MBCs [10]. In our study pure DCIS was seen in 15.1% of the cases. Lanitis et al reported accompanying in situ component in 78.6% of invasive cancer cases though it was 20% in our serial.

Etiology of MBC is still not clear. Defined risk factors are family history and increased estrogen levels. We could not achieve family history in our cases. But we search for proliferative lesions around tumoral areas. Columnar cell lesions (CCL) are well known precursors of low grade breast neoplasia in female though their role in MBC has not been established. Also the association between gynaecomastia and male breast cancer risk is not clear [1]. Ni et al investigated columnar cell lesions in 71 male patients who underwent breast surgery for benign and malignant lesions. They noted columnar cell like changes in 39 patients. The incidence of CCL was similar in malignant and benign lesions [11]. Another recent study found no CCL around invasive cancer, gynaecomastia and normal breast tissue [12].

Figure 3: Relation between grade and survival (Kaplan-Meier, p=0.008)



In our serial three breasts carcinoma cases had accompanying gynaecomastia, five had CCL without atypia. The incidence and the role of CCL in MBC carcinogenesis should further analyzed in larger series.

As the majority of MBC cases are hormone receptor positive, hormone treatment is indicated in the vast majority of the patients. But the impact of hormone therapy on survival is still controversial. No strong evidence was reported between ER status and prognosis of MBC [13,14]. We could not find significant relation between ER positivity and overall survival (p=0.52). Besides mean survival time for ER (+) (62.8±10.6) cases was lower than ER (-) (90±4.2) cases. But we have no data if hormone receptor positive cases achieve hormonotherapy or not.

There are conflicting data about tumor-infiltrating lymphocytes and breast cancer prognosis. Loi et al found that extensive lymphocytic infiltration in node positive, ER/HER2 negative breast cancer is associated with excellent prognosis [15]. Rathore et al reported stromal CD3 positive TILs were significantly associated with positive lymph node status [16]. In our study we examined stromal lymphocyte infiltration in tumoral areas and half of the cases exhibiting extensive stromal lymphocyte showed lymph node metastasis. Clinical stage is identified as important prognostic factor in MBC in many studies. The prognosis depends on tumor size, grade, lymph node status [13,17,18]. The overall 5- year survival in case of lymph node metastasis is 57%, whereas it is 85% in non-metastatic cases [18]. Age, size, grade, lymph node metastasis and steroid receptor status are defined as independent prognostic factors for MBC survival [8]. Bergmann et al found that metastasis at diagnosis, older age, higher tumor stage and smoking status are independent factors associated with risk of death [8]. Grujicic et al showed 100% overall survival for tumors ≤2cm, 38% for tumors >5cm [8]. According to our study the relation between tumor diameter, grade, nipple involvement, lymph node metastasis, dermal lymphatic emboli and survival were statistically significant.

Conclusion

Our results showed good correlation with literature data in terms of histopathological features and prognostic factors. Confidential data about etiological and prognostic factors will be collected through these reports showing institutional experiences. The significance of CCL in MBC etiology, the impact of intratumoral stromal lymphocyte response on prognosis, also hormone receptor and HER2 status on survival should be clarified in larger series.

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The analysis of doppler flow alterations in intrauterine growth restricted pregnancies

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Abstract

Objective: Intrauterine growth restriction (IUGR) is a common clinical condition. For some clinicians, it is still not clear which patients should be referred to a tertiary center. In this study, we aimed to analyse the sonographic parameters of IUGR suspected pregnancies and find out which finding is the most sensitive in the diagnosis of IUGR.

Methods: Doppler flow findings and biometric measurements of 50 IUGR suspected pregnancies admitted to our perinatology outpatient clinic between March 2013 and March 2014 were evaluated. 60 healthy singleton pregnancies were assigned as the control group. The same measurement were performed and compared. The diagnosis of IUGR was made on one of the followings: AC measurement < 10 p, uterine artery RI >0.58, the fetal growth rate < 10 p, fetal weight < 10 p. Gestational week was calculated regarding the last menstrual period and confirmed with the first trimester ultrasonographic findings.

Results: In IUGR and control group, maternal age was 26.63 ± 5.19 and 29.48 ± 5.79, respectively (p=0.327); gravida was 1.74 ± 0.99 and 2.13 ± 1.51 (p=0.290); parity was 0.63 ± 0.89 and 0.98 ± 0.49, (p=0.703); gestational week was 34.82 ± 3.27 and 34.21 ± 4.07 (p=0.70), respectively. Umbilical artery PI was 1.51 ± 0.96 in IUGR group and 1.00 ± 0.22 in control group (p<0.001). Fetal MCA PI was significantly lower in IUGR group (1.61 ± 1.57 vs 1.98 ± 0.74; p=0.005). AUC values obtained by ROC analysis were as following: 0.590 for HC/AC; 0.655 for UA/MCA ratio; 0.622 for Oligohydramnios; 0.559 for UA PI.

Conclusions: HC/AC ratio >1 and umbilical artery PI >0.95 have the highest sensitivity for IUGR (Sensitivity 82% and 80%; specificity 56% and 44%, respectively). Oligohydramnios and UA/MCA PI ratio were shown to have the highest specificity (specificity 70%).

Keywords: IUGR, HC/AC, Oligohydramnios, umbilical artery PI, cerebral artery PI.

Introduction

Intrauterine growth restriction (IUGR) is the clinical condition which is characterized by the decrease in fetal growth and failure of the fetus to reach its growth potential (1). The incidence of IUGR is approximately 5-7% (2).

Fetal growth occurs in 3 phases: fetal cell hyperplasia in early pregnancy; fetal cell hyperplasia and hypertrophy followed by fetal cell hypertrophy in the third trimester. Fetal growth is 5 g/day for the first trimester, 10 g/day for the mid-trimester and 30-35 g/day in the third trimester (especially after 32-34 gestational weeks) (3).

The lack of appropriate fetal growth is classified in two main groups: asymmetric IUGR with decreased subcutaneous fat tissue and symmetric IUGR with decreased growth in all body parts of the fetus. Chromosomal abnormalities, structural anomalies, intrauterine infection and toxic agents may be the cause of symmetric IUGR by affecting the fetal growth. However, most cases with IUGR occur due to uteroplacental insufficiency with significant risk for fetal hypoxia (1).

The clinicians were used to evaluate the fetal growth according the population-based growth charts and fetal measurements below 10 percentile (p) were regarded as a pathological condition. However, the current trend is to construct the individual growth charts for every fetus, because poor perinatal outcomes are rare in fetuses below 10 p who has reached its genetic growth potential (called as “small gestational age-SGA”); in the other hand, a fetus between 10-20 p without reaching its growth potential (called IUGR) is prone for adverse perinatal outcomes (2). The differential diagnosis between SGA and IUGR fetuses is important to predict perinatal outcomes. Determination of fetal growth rate and fetal functions evaluated with amniotic fluid index (AFI) and umbilical artery Doppler is corner stone in differentiation of both conditions (3,4).

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Material and Methods

Doppler flow and biometric measurements of 50 IUGR suspected pregnancies who admitted to perinatology outpatient clinic between March 2013 and March 2014 are analyzed in this study. 60 healthy singleton pregnancies are randomly selected as control group.

The diagnosis of IUGR is based on the lack of the fetal growth on subsequent measurements repeated in 2 weeks. Gestational week is calculated according to the last menstrual date and early first trimester sonographic findings. The measurements are performed with Voluson 730 (GE Medical Systems, Milwaukee, WI) 3,5-MHz abdominal probe. All measurements are performed by two operators (BAU and HGP).

Bi-parietal diameter (BPD) is measured "in to out" at the level of inter-hemispheric fissure and thalamic nuclei. Head circumference (HC) is measured at the same level. Abdominal circumference (AC) is measured when liver, the horizontal part of portal vein, stomach and fetal vertebra are seen at the same circumferential level.

AFI is calculated with the sum of the four vertical pocket measurements. Oligohydramnios is AFI <5 cm. Umbilical artery Doppler evaluation is performed in free loop. Fetal middle cerebral artery Doppler evaluation (MCA) is performed at the proximal one third of Willis polygon. Three consecutive wave forms are needed for the calculations.

Statistical analysis is made with SPSS v.20. T-test is used for the comparison of the groups. The results are expressed in mean±standard deviation (SD). The significance of the markers for the IUGR diagnosis is defined with ROC analysis. AUC (area under the curve) is calculated. The sensitivity and specificity is determined according the ROC analysis.

Results

The mean maternal age was 26.63 ± 5.19 in IUGR and 29.48 ± 5.79 in control group, respectively (p=0.327). The mean gravida was 1.74 ± 0.99 and 2.13 ± 1.51 (p=0.29), the mean parity was 0.63 ± 0.89 and 0.98 ± 0.49 (p=0.703), the mean gestational week was 34.82 ± 3.27 and 34.21 ± 4.07 (p=0.70) in IUGR and control groups, respectively. Umbilical artery (UA) pulsatility index (PI) was 1.51 ± 0.96 in IUGR and 1.00 ± 0.22 in control group (p<0.001).

Fetal middle cerebral artery (MCA) PI was 1.61 ± 1.57 in IUGR group and 1.98 ± 0.74 in control group (p=0.005). UA PI was significantly higher and MCA PI is significantly lower in IUGR group (Table 1-2). In ROC analysis, AUC of ultrasonographic results for IUGR diagnosis was as following: HC/AC 0.590; Umbilical/cerebral PI 0.655, Oligohydramnios 0.622, UA PI 0.559. HC/AC ratio (>1) and UA PI (>0.95) had the highest sensitivity (sensitivity 82% and 80%; respectively.

Specificity 56% and 44%, respectively). Oligohydramnios and umbilical/cerebral PI ratio was the most specific findings with 70% specificity (Figure 1-2; Table-3).

Table 1: The comparison of demographic features of IUGR and control groups (Mean±**SD**)

	IUGR (n:50)	Control (n:60)	p
Maternal age	26.63±5.19	29.48±5.79	0.327
Gravida	1.74±0.99	2.13±1.51	0.290
Parity	0.63±0.89	0.98±0.49	0.703
Gest. week	34.82±3.27	34.21±4.07	0.700

Table 2: The comparison of clinical features of IUGR and control groups (Mean±**SD**)

	IUGR (n:50)	Control (n:60)	p
U.A. PI	1.51±0.96	1.00±0.22	0.001
MCA PI	1.61±1.57	1.98±0.74	0.005
AFI	7.44±4.78	14.23±5.02	0.001
EFW	2080.21±692.35	2405.33±972.70	0.005

U.A. PI: Umbilical Artery MCA: mid-cerebral artery; PI: pulsatility index; AFI: amniotic fluid indekx; EFW: estimated fetal weight

Table 3: The sensitivity and specificity of ultrasonographic findings

	Cut-off value	Sensitivity	Specificity
HC/AC	1.02	% 82	% 56
Oligohydramnios	≤5 cm	% 45	% 70
U.A. PI	0.95	% 80	% 45
UA/MCA PI	0.63	% 65	% 70

Discussion

In this study, we aimed to define the sensitivity of the sonographic findings in the diagnosis and management of IUGR suspected pregnancies. The first task in evaluating IUGR suspected pregnancy is to specify the gestational week accurately. The first trimester ultrasonographic scans with CRL measurements are most helpful with specifying the gestational week ±3 days (7).

The sonographic scans between 16-21 weeks may be mistaken for 10 days. The second task should be subsequent measurements of fetal growth with documentation of the lack of the fetal growth. Regarding IUGR cases with ongoing utero-placental insufficiency, accurate timing of the delivery is very important due to fetal hypoxia and

Figure 1: ROC analysis of HC/AC ratio and oligohydramnios for IUGR diagnosis. AUC (HC/AC)= 0.590 AUC (Oligohydramnios)= 0.622

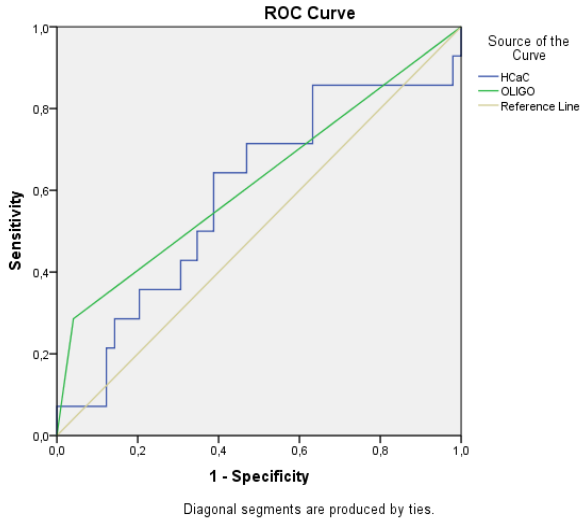
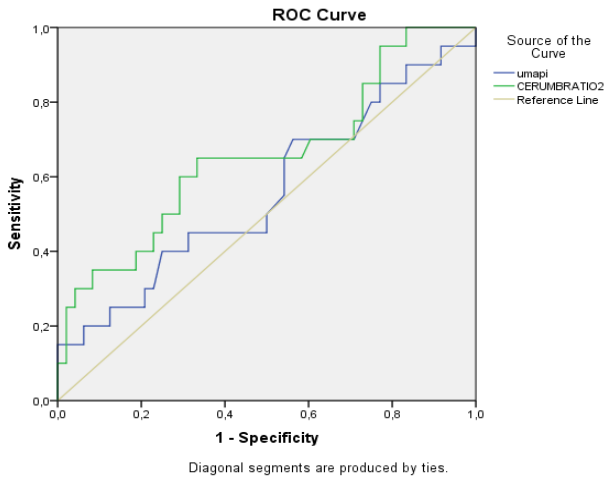


Figure 2: ROC analysis of umbilical artery PI and UA/MCA PI ratio for IUGR diagnosis. AUC (umbilical artery PI)= 0.559 AUC (UA PI/MCA PI)= 0.655



adverse perinatal outcome risks. The timing of delivery should be defined according to the gestational week, fetal presentation, and fetal Doppler flow findings (8).

Doppler evaluation is one of the most useful tools for fetal wellfare. UA Doppler study evaluates the resistance against the perfusion in feto-placental unit. Most commonly used clinical markers are pulsatility index (PI) and systolic/diastolic flow ratio (S/D).

PI is more useful, as S/D ratio could not be measured when absent end-diastolic flow occurs in

umbilical artery (9). Normal UA flow pattern is characterized by the low resistance and high end-diastolic flow (10). UA Doppler measurement may be performed in any segment; however, of clinical importance in interpreting the results: near the placental end, the end-diastolic flow increases; near the abdominal insertion of the cord, the resistance increases and end-diastolic flow decreases (11).

We performed all measurements at the free loop and we obtained at least three consecutive wave forms. UA PI was significantly higher in IUGR group ($p<0.001$). If cut-off value for UA PI was regarded as 0.95, sensitivity was 80% and specificity was 45%. In an another study, UA PI sensitivity was found 46.7% (12). Our results are in agreement that UA PI is clinical useful to differentiate IUGR and SGA fetus.

Cerebral circulation has high resistance and characterized with continuous forward flow during a complete heart cycle (13). MCA provides 80% of the cerebral circulation. Besides, the measurements are obtained most easily among other fetal cerebral vasculature (14). That is why MCA is used for evaluation of IUGR fetuses. The measurement is performed ideally at the one third proximal segments near to Willis polygon (15). In case of fetal hypoxia, due to central redistribution, blood supply increases to adrenal gland and heart, whereas blood supply decreases to peripheric pathways.

This condition is defined as “brain sparing effect” and characterized with low PI (so, increased end-diastolic flow) (16). Brain sparing effect (BSE) can be also evaluated with cerebra-placental ratio (MCA/UA PI). BSE occurs if this ratio is below 5p according to the gestational week (17, 18). Gramellini et al. showed that MCA/UA PI remained stable during the last 10 gestational weeks (19). MCA PI was significantly lower in our IUGR group ($p=0.005$). However, MCA PI alone was not useful. If cut-off value for UA/MCA PI was regarded as 0.63, sensitivity was 65% and specificity was 70%.

The main limitations of our study were the retrospective design and the lack of the perinatal outcomes. Doppler studies are controversial in evaluating the low-risk pregnancies. The current trend suggests that routine Doppler evaluation does not add anything, so routine screening is not recommended (9, 20). Regarding the IUGR cases, the frequency of UA Doppler measurements is also controversial, because there are not enough randomized controlled studies (21). UA Doppler measurements can be repeated in every 2 weeks with non-stress test (NST) and AFI 2 times a week in IUGR with utero-placental insufficiency (21-23). If any abnormality is detected in Doppler studies, it can be repeated every week, unless end-diastolic flow gets lost (8). However, if there is Oligohydramnios or if there is absent end-diastolic flow in UA, then Doppler evaluation should be repeated 2-3 times in a week (25). If the pregnancy is below 34 weeks with absent end-diastolic flow in UA, daily ductus venosus (DV) Doppler and biophysical profile analysis is recommended.

Absent or reverse a-wave in DV Doppler, biophysical profile <6 or spontaneous persistent decelerations in NST are the findings for delivery. If the pregnancy is below 34 weeks with reverse flow in UA, the fetus should be delivered. If the pregnancy is beyond 34 weeks with absent end-diastolic flow, the fetus should be again delivered.

As a result, umbilical artery Doppler studies are the most important tool for defining the IUGR pregnancies. UA Doppler is easy to perform. Clinicians in peripheric health care centers may use of UA Doppler in deciding to refer the high risk pregnancies to a tertiary perinatology unit.

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Conflict of Interest: The authors declared that they had no conflicts of interest.

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Familial Recurrent Hydatidiform Moles: A rare case report

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Abstract
Recurrent hydatidiform moles (RHM) are described as the being of at least two molar pregnancies in the same patient. It is very rare. NLPR7 mutations are found high rate in patients with RHM. KHDC3L is the second responsible gene for RHM. In this paper, we present an interesting case of a familial RHM. Here, we have discussed the genetic counseling to be given to a patient who had been diagnosed as hydatidiform mole in her two previous pregnancies and whose sister had a history of four consecutive molar pregnancies. Because rate of NLPR7 mutation is high in individuals with recurrent molar pregnancy, patients should be recommended to have NLRP7 gene sequence analysis in the first place. If no mutation is detected in this gene, KHDC3l gene sequence analysis should be carried out.

Keywords: Recurrent hydatidiform moles, NLPR7, KHDC3L, Mutation

Introduction

Gestational trophoblastic disease is a tumor characterized by proliferation of trophoblast and originating from the placenta. It has a wide spectrum compose of partial (PHM) and complete hydatidiform mole (CHM), invasive mole, choriocarcinoma and placental site trophoblastic tumor. Hydatidiform mole (HM) appears once in every 600 pregnancies in Western countries but at higher rates in the Middle East, Latin America, Africa, and the Far East [1]. HM in next gestation is rare; its probability of occurrence is approximately 1% in sporadic PHM or CHM [2]. Recurrent hydatidiform moles (RHM) are described as the being of at least two molar pregnancies in the same patient [1]. In this study, we discussed the genetic counseling to be given to a patient who had been diagnosed as HM in her two previous pregnancies and whose sister had a history of four consecutive molar pregnancies.

Case

Twenty seven-year-old patient was admitted with a desire to conceive. Her obstetric history revealed 2 pregnancy losses at 8th week due to missed abortion. The pathologic examination of both curettage materials in those pregnancies were reported as PHM.

No pathologic finding was detected during gynecologic examination. Chromosome analysis of peripheral blood was normal. Family history revealed that patient's sister experienced 4 consecutive molar pregnancies. Patient, who wanted to know whether same condition would recur during her subsequent pregnancies, was recommended to have a NLRP7 gene sequence analysis, and KHDC3L gene sequence, if no mutation is found in this gene.

Discussion

Familial recurrent hydatidiform mole is an exceedingly rare clinical condition. Recurrent CHM in two Lebanese family members and recurrent PHM in one Lebanese family has been defined by Moglabey et al. [3]. They demonstrated that these molar pregnancies were diploid and genomes were bi-parental. Based on their data and previously reported FRHM cases, they presumed that the women with RHM pregnancy were homozygote for an autosomal recessive mutation. It was claimed that paternal genome did not contribute to development of molar pregnancy in autosomal recessive condition [4]. An extensive genomic screening was performed by the Moglabey et al. on the Lebanese family. Responsibility of FRHM gene

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had been demonstrated in order to map of these genes and a maternal gene [3]. After obtaining DNA from blood samples of the family members, a wide genomic screening was carried out with 250 microsatellite marker panel at 10-15cM interval. It was shown that defective gene was located in a 15,2 cM interval flanked by D19S924 and D19S890 loci in 19q13.3-13.4

NLRP7 (nucleotide oligomerization domain (NOD)-like receptor, pyrin containing 7) is the first identified gene that causes RHM localized in 19q13.4 region. NLRP7 is seen as a major gene as to screening studies conducted on various groups and populations. Mutation in this gene was detected in 48-80% of the patients who had at least two molar pregnancies. These mutations contain stop codon, minor deletion or insertions (less than 20 bp), splice mutations, major deletion or insertions and complex rearrangements. In addition to these mutations, two protein truncating mutations, L 823X stop codon mutation and a deletion from intron 8 through intron 11 and about 17 missense mutation were detected in patients with RHM or sporadic mole as single heterozygote mutation or variant. Pathologic significance of these single mutations and variants is still controversial and further data are needed to reach a conclusion [1]. According to Williams et al [4], homozygote or compound mutations exist in NLRP7 gene in most of the women with familial bi-parental HM, and these results confirm that this gene is a major cause of bi-parental HM.

NLRP7 transcripts were identified in liver, lung, spleen, thymus, placenta, endometrium, hematopoietic cells, testis, and in all oocyte stages and pre-implantation embryos [1. 5]. Knockdown of expression of NLRP7 gene in human embryonic stem cells causes earlier expression of two trophoblastic differentiation marker, GCM1 and INSL4, therefore it is suggested that lack of NLRP7 function alters trophoblastic differentiation. Knockdown of NLRP7 increases the level of HCG. This role of NLRP7 is very important in hydatidiform mole which is characterized by trophoblastic hyper proliferation and increased HCG production [1].

IL-1β secretion decreased in mononuclear cells in NLRP7 mutation or rare variants has been shown by the Messaed et al. [6]. Current data shows some linkages between IL-1β and ovulation and oocyte maturation. As levels of IL-1β increase, related with ovulation rate increases, oocyte and subsequent normal embryonic growth rate decrease. However, this role of IL-1β on oocytes contradicts with data in cells of the patients with NLRP7 mutations. In addition, mice with deficiency of IL-1β were found to be fertile, and IL-1β signal deficiency does not affect fertility and embryo viability in mice. As a result, perhaps combination of these roles of NLRP7, some effects on oocytes, effects on embryonic and trophoblastic tissue proliferation and differentiation and other effects on hematopoietic inflammatory cells and down regulation in maternal immune response contribute to HM [1]. According to Nguyen et al. [1]role of NLRP7 in down regulation of maternal inflammation and insufficiency in spontaneous elimination of non-viable pregnancies is a basic aspect that enables differentiation of this disease from other forms of early pregnancy losses.

KHDC3L (KH domain containing 3-like) identified in 2011 is the second gene responsible for recurrent HM. KHDC3L is localized on chromosome 6. It is thought to be the responsible gene in 10-14% of RHM patients without a mutation in NLRP7. Four mutations have been reported so far. KHDC3L transcripts were identified in all oocyte stages, pre-implantation embryos and many tissues containing hematopoietic cells. Similar to expression profile of NLRP7, expression of KHD3CL is the highest during germinal vesicle phase in oocytes and it drops during pre-implantation process and it becomes undetectable during blastocyst phase [1].

Because the rate of NLPR7 mutation is high in individuals with recurrent molar pregnancy, NLRP7 gene sequence analysis should be recommended for in the first place. If no mutation is detected in this gene, KHDC3L gene sequence analysis should be carried out. For NLRP7 gene, 11 exon PCR products are examined with direct sequence analysis and a comparison is made with NM_001127255.1 sequence. For KHDC3L gene, 3 exon PCR products are examined with direct sequence analysis and comparison is made with NM_001017361 sequence [1].

The purpose of DNA test in these patients is to determine the chance for having a healthy baby or to detect the risks of recurrence of molar pregnancy and malign sequel. A woman who has two defective allele for NLRP7 gene has a rather low potential of delivering a normal alive baby. Nguyen et al. reported only 3 (7%) alive deliveries in 43 cases in their own study groups. No live birth was reported in other

RHM patients who have NLRP7 or KHDC3L mutation. No live birth was reported in few cases that had two defective alleles belonging to KHDC3L gene. NLRP7 and KHDC3L genes are necessary for oocyte. Therefore, in theory, oocyte donation should be suggested in order to improve reproductive outcomes in these patients [1].

In 2011, healthy live birth with oocyte donation in a patient with compound heterozygote mutations of p.E13GfsX7 and p.R693P in NLRP7 gene has been reported by the Fisher RA et al. [7]. This result establishes the major role of NLRP7 gene in pregnancy and oocyte development and provides a hope for normal pregnancy in other women.

If there are not any mutations in NLRP7 and KHDC3L genes in FRHM cases, currently undetected mutations in these genes or mutations in unidentified genes can be responsible [1].

Genomic screenings involving more cases in large groups will provide more data on genetic origin in HM cases.

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A mortal accident caused by a broken toilet seat cover

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Abstract
According to hospital records, a 36 years old, 1.75 m in length, average weight man was brought to Izmir Bozyaka Training and Research Hospital by 112 ambulance at 01/07/2011, 21:20 PM with an injury caused by fracture of toilet seat cover when he was sitting. In the examination, a 20 cm length oblique section with active bleeding was seen at the right gluteal region and superior gluteal artery and vein injury was detected. Department of orthopedics controlled bleeding, patient admitted to intensive care unit but he was accepted as dead at 06:35 AM.

Keywords: Superior Gluteal Artery, Vein Injury

Introduction

According to World Health Organization (WHO), an accident is an incident that occurs unwillingly and causes physical and mental damage by a sudden external force. Accidents are generally classified according to the locations where they occur [1, 2]. An accident that occurs in a home or around it are named as home accident and these are thought as a serious public health problem due to common related injuries [1]. Injuries can be categorized by intent: unintentional or 'accidental' and intentional. Unintentional are road traffic injuries, poisoning, drowning, falls and burns. Injuries can also be classified by place and activity e.g. home or leisure accidents, occupational [3, 4]. Accidents are a major cause of death, injury, and lost productivity, and they impose a heavy financial burden [5]. Injuries impose one of the greatest health risks in terms of mortality and morbidity among adolescents and young adults [6]. Worldwide, injuries are leading causes of death in all age groups [7].

In this study, case ended with death by a broken toilet seat cover is presented and it is aimed to review preventive measures to avoid these accidents.

Case

According to hospital records, a 36 years old, 1.75 m in length, average weight man was brought to Izmir Bozyaka Training and Research Hospital by 112 ambulance at 01/07/2011, 21:20 PM with an injury caused by fracture of toilet seat cover when he was sitting. In the examination, a 20 cm length oblique section with active bleeding was seen at the right gluteal region and superior gluteal artery and vein injury was detected. Department of orthopedics controlled bleeding, patient admitted to intensive care unit but he was accepted as dead at 06:35 AM.

Autopsy was performed by Division of Council of Forensic Medicine in Izmir. At the external examination; it is seen that there are surgical sutures in the right gluteal region (Picture 1). Autopsy showed bleeding from right superior gluteal artery and vein injury as the cause of death (Picture 2).

Specimens were taken for toxicological analysis. On toxicological analyze, there is no toxic substance at blood and urine.

Discussion

Home accidents are an important and under-estimated public health issue and an important and under-estimated housing issue. Unintentional injuries within the home environment have not been recognized to the same extent as road traffic or occupational injuries [8, 9]. The majority of injuries of children under five and people aged 75 and over occur in the home [10, 11].

According to Kaz'ar G et al [12], home accidents constitute approximately the half of all accidents and show an increasing tendency. 35% of all injuries occurred within home environments in Sweden [12] and therapeutic measures for a home

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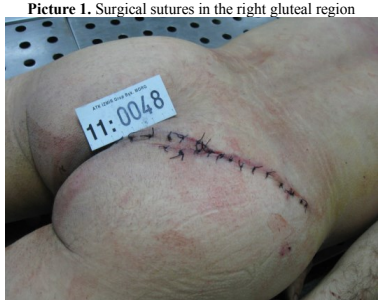
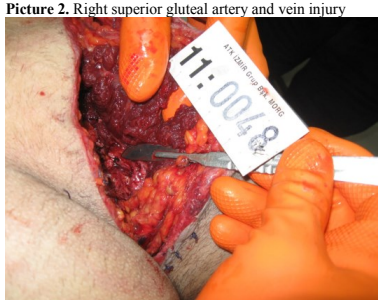
accident victim costs approximately 1,300 USD annually in Norway [13] and, in France, 10 % of all public health costs is caused by home accidents [2].

Picture 1. Surgical sutures in the right gluteal region



The home environment is an important setting for unintentional injuries. About one fifth of all fatal unintentional injuries take place in a home [14]. In the Netherlands each year, approximately 17 injuries per 100 inhabitants are medically treated; three-quarters of these are home and leisure accidents [7].

Picture 2. Right superior gluteal artery and vein injury



In the New Zealand it was estimated that there was an associated increase in the odds ratio of a home injury occurrence of 22% (16). In Turkey, various studies show that home accidents account for 18–25% of all accidents [1]. The proportion of fatal home accidents among all fatal accidents in the UK in 1990 was 2.5%, while in Turkey this was 5.7% [1].

Falls were most common followed by burns, electrocutions and poisonings [2, 15]. The toilet was the most common site of home accident followed by the sitting room, the kitchen, the bedroom and the dining room [15]. In our case, accident was occurred in the toilet.

The literature on the prevention of home accidents mention various measures, mainly defining sources of potential danger according to the psychological and motor development of children appreciating that all children, regardless of the age, are at enhanced risk for home accidents, education of parents and attending personal, home-safety measures on the basis of legal regulations, home-designing and production of safe household articles, special safety regulations for household equipment's and environmental conditions, labeling of chemical agent containers, supervision of home-safety measures by inspectors and financial support for families to safety-improving measures [2].

Fatal home accidents have increased seriously in recent years. To prevent home accidents, with some behavioral changes, home equipment's and products must be produced appropriately for home security.

Preventing home accidents with essential measures will not only avoid lots of many injuries and deaths but will also avoid unnecessary economic losses in health expenditures.

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