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The importance of BRCA1 gene 5382insC mutation detection in an asymptomatic patient: a case report

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We report a case of a patient with the BRCA1 5382insC mutation in the location 17q21. The patient was referred for genetic counseling because of infertility. While consulting the patient for infertility and collecting the family tree, the patient told that her mother, grandmother and aunt had or still have ovarian cancer. So the patient received a genetic test for six most often BRCA1 and BRCA2 gene mutations. The test showed that the patient had the mutation of BRCA1 5382insC gene. The BRCA1 5382insC mutation increases the risk of getting breast cancer 10 times and ovarian cancer 20 times, compared with the general population. To reduce the risk of breast and ovarian cancer the patient received advices on healthy life style, screening tests for ovarian cancer and was offered to consult an oncologist about prophylactic oophorectomy.

Key words: breast and ovarian cancer, BRCA1/A2 mutations, genetic screening

INTRODUCTION

Breast cancer (BC) is one of the most common cancer types in the world. There are many risk factors: estrogen exposure, alcohol consumption, radiation exposure, obesity, chronic stress (Karami, 2014). Also the risk of cancer increases with patient's age: 80% of cancer cases occur in patients who are over 50 years old.

There are also genetic reasons for cancer. Certain genes mutations like BRCA1 and BRCA2 increase the risk of the disease (Valachis, 2014; Smith, 2011). BRCA1 and BRCA2 are human genes that produce tumor suppressor proteins. Like many other tumor suppressors, the proteins produced from the BRCA1 and BRCA2 genes help prevent cells from growing and dividing too rapidly or in an uncontrolled way. In women who have a BRCA1 or BRCA2 gene mutation there is an increased risk of getting breast cancer and ovarian cancer (Cecener, 2014). It is important to ask patients about their family history of breast cancer so as to find it in earlier stages (Saito, 2014). Among women, breast cancer is the most commonly diagnosed cancer after nonmelanoma skin cancer, and it is the second leading cause of cancer deaths after lung cancer. In 2012, there were 1,692,000 breast cancer report cases worldwide.

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The most common genes mutations associated with BC are four:

- BRCA1,
- BRCA2,
- TP53,
- PTEN.

But researchers have found other common genes that can slightly increase women's risk of developing breast cancer.

Unfortunately, no tests are available for these genes yet but they include

- CASP8,
- FGFR2,
- TNRCP,
- MAP3K1,
- rs4973768,
- LSP1.

BRCA1 gene cytogenetic location is 17q21. In addition to female breast cancer, mutations in the BRCA1 gene increase the risk of several types of cancer: fallopian tube cancer, male breast cancer, and pancreatic cancer. Many of these mutations change one of the amino acids used to make the BRCA1 protein, resulting in a protein that cannot perform its normal DNA repair function, and cells become to proliferate in an uncontrolled way. BRCA1 gene mutation increases the risk of BC from 60% to 85%, and the risk of fallopian tube cancer from 40% to 60% (Foulkes, 2014). BRCA2 gene cytogenetic location is 13q12.3. Mutations in one copy of the BRCA2 gene can lead to an increased risk of ovarian cancer, prostate cancer, pancreatic cancer, fallopian tube cancer, male breast cancer, and an aggressive form of skin cancer called melanoma.

METHODS

In this case report, the patient was sent for genetic molecular testing to detect BRCA1 and BRCA2 genes mutations. The test is done by extracting DNR from the leukocytes according to standard methods. Molecular testing is based on the PCR reaction and DNA analysis by scanning BRCA1 and BRCA2 genes and looking for structure mutations. Usually a BRCA1 and BRCA2 mutation analysis is targeted only for coding exons and implicates protein-truncating mutations in BRCA1 and BRCA2 inactivation. Also mutations can be attributed to other exonic mutation, mutations in introns and untranslatable regions (Ozcelikemail, 2012). Usually searching is performed for the six most common BRCA1 and BRCA2 genes mutations: BRCA1 185delAG, BRCA1 300>G(C61G), BRCA1 2080delA, BRCA1 415delA, BRCA1 5382insC, BRCA2 6174delT.

RESULTS

We want to present a rare case report, share patient's clinical data and discuss the latest published results about BRCA1/A2 genes mutation from 2009 to 2014, important to breast and ovarian cancer. A 40-year-old female patient (born August 15, 1973) was consulted by a physician because of infertility. The physician sent the patient to a geneticist to make the frequent test because of infertility. The karyotype test was done and it did not show any changes (46XX). During the collection of the family tree the patient mentioned that her grandmother and mother died of ovarian cancer. Then the patient was tested for the 6 most frequent BRCA gene mutations:

- BRCA1 185delAG,
- BRCA1 300>G(C61G),
- BRCA1 2080delA,
- BRCA1 415delA,
- BRCA1 5382insC,
- BRCA2 6174delT.

The test confirmed our suspicions. The genetic test showed that the patient had a germinal mutation of BRCA1: 5382insC gene. BRCA1 5382insC mutation increases the risk of getting breast cancer 10 times and ovarian cancer 20 times, compared with the general population.

Family history

The Figure shows family members who had or have ovarian cancer. It is seen that a proband had a tendency to have the BRCA1 gene mutation because her mother, grandmother and her aunt had ovarian cancer.

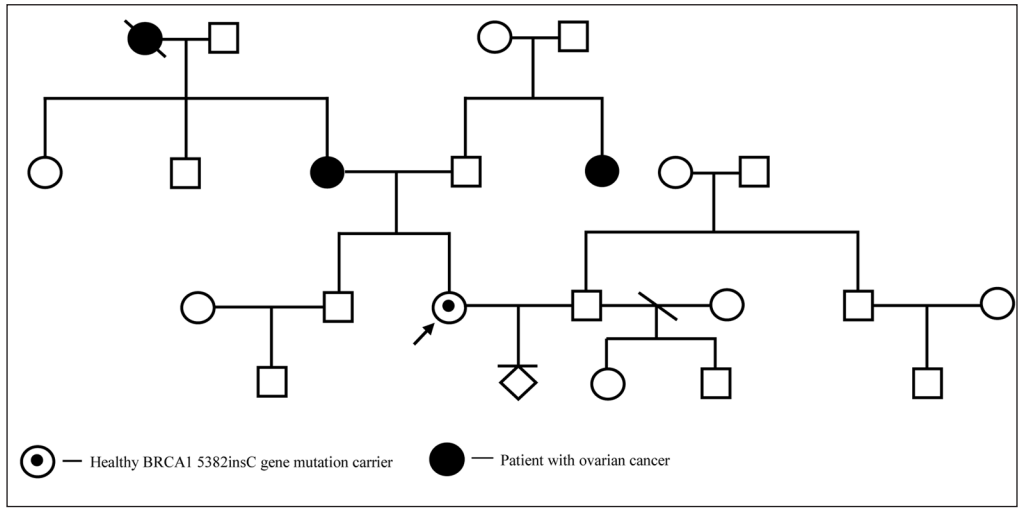

Figure. Patient family tree

DISCUSSION

BRCA1 and BRCA2 genes mutation typically increases the risk of breast and ovarian cancer about 90%. The BRCA1 and BRCA2 genes provide instructions for making a protein that is directly involved in repairing damaged DNA. In the nucleus of many types of normal cells, the BRCA1 and BRCA2 proteins interact with several other proteins, including the proteins produced from the BRAC51 and BARC1 genes, to mend breaks in DNA. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer. The inheritance way of this cancer, that is regulated by BRCA1 and BRCA2 genes mutation, is an autosomal dominant (Paradiso, 2011). The research suggests that the BRCA1 protein also regulates the activity of other genes and plays a critical role in embryonic development (Oktay, 2010). As we can see, it might be a reason why our patient with BRCA1 gene mutation has fertility problems. The findings of a large international prospective study suggest for the first time that women with BRCA1 mutations should have preventive ovarian surgery (prophylactic oophorectomy) by age 35, as waiting until later age appears to increase the risk of ovarian cancer before or at the time of the preventive surgery (Finch, 2014). Women with BRCA2, however, do not appear to be at an increased risk of cancer by 35 years, so the prophylactic oophorectomy may be delayed to later age (Mac Bride, 2013). Moreover, women with BRCA1 and BRCA2 mutations who had this surgery experienced a 77 percent reduction in their overall risk of death by age 70. Also patients with BRCA1 or BRCA2 mutations must have routine screening for breast cancer (self-exams, mammograms, doctor visits) like all women who are older than 50 years old (Synowiec, 2014). Men who test positive for BRCA1 and BRCA2 gene mutations are considered to be at higher-than-average risk for prostate cancer. They should talk to their doctors about beginning screenings, including an annual digital rectal examination and a prostate-specific antigen (PSA) blood test between ages 40 and 50. Men's risk for breast cancer stays very low, but it is still higher than it is for men who do not have the mutations of BRCA1 or BRCA2 genes. So if a man notes any unusual breast changes or lumps he has to visit his doctor immediately.

To avoid breast cancer for all the women, they should try to change the lifestyle and make it healthy that means:

- Limit alcohol,
- Do not smoke,
- Control your weight,
- Be physically active,
- Breast-feed,
- Limit the dose and duration of hormone therapy,

• Avoid oral contraceptive,

• Avoid exposure to radiation and environmental pollution.

After the genetic testing patients should be referred to genetic counseling so as to be informed about prophylactics. A geneticist should recommend the following for a woman who has the mutation on BRCA1 or BRCA2 genes:

• As it is already mentioned in the discussion, consider possible prophylactics (including preventive (prophylactic) surgical removal of your ovaries, breast, or even both before cancer has an opportunity to form (Nestle-Krämling, 2012)). Talking about breast removing (mastectomy) many women try to avoid it because of bad looking. But after all, there is a reconstruction possibility after mastectomy. Current breast reconstruction techniques are diverse and may involve the use of an autologous tissue flap, a prosthetic implant, or both. So patient's appearance would be normal (Pilgrim, 2014; Lokich, 2014; Pinel-Giroux, 2013). Also women can choose breast-conserving therapy which is alternative to mastectomy for the treatment of invasive breast cancer, but it is not applicable to all patients (Tung, 2011; Garcia-Etienne, 2009).

• Discuss with your physician about taking hormonal therapy medicines such as tamoxifen, raloxifen, or exemestane. These drugs could reduce the risk of developing breast cancer. To low the risk of ovarian cancer, doctors should offer to take ten oral contraceptives. While data is not clear on the safety of oral contraceptives in people at high risk for breast cancer, some doctors do recommend them for carriers of BRCA1 and BRCA2 mutations. This recommendation depends on factors, including which mutation you carry and how much breast or ovarian cancer is in your family.

• Also there is chemotherapy treatment which is effective because research shows that the 5-year local recurrence-free survival rate with multimodality therapy was 95% (Ho, 2012).

CONCLUSIONS

In conclusion, if there are cases of breast or ovarian cancer in a family, it is necessary to perform a genetic test of BRCA1 or BRCA2 genes mutation, even in healthy subjects, at least the 1st degree relatives, in order to know if a patient is in high risk group. If the test is positive, the patient is followed by self-exams, ultrasound examination, mammograms, MRI and specific blood tests. After discussing with the physician the patient also should consider preventive (prophylactic) surgical removal of ovaries or breasts.

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References

1. Finch AP, Lubinski J, Møller P, Singer SF, Karlan B, Senter L, Rosen B, Maehle L, Ghadirian P, Cybulski C, Huzarski T, Eisen A, Foulkes WD, Kim-Sing C, Ainsworth P, Tung N, Lynch HT, Neuhausen S, Metcalfe KA, Thompson I, Murphy J, Sun P, Narod SA. Impact of ophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014; 15: 1547–54.

2. Cecener G, Egeli U, Tunca B, Erturk E, Ak S, Gokgoz S, Tasdelen I, Tezcan G, Demirdogen E, Bayram N, Avci N, Evrensel T. BRCA1/2 germline mutations and their clinical importance in Turkish breast cancer patients. Cancer Invest. 2014 Oct; 32(8): 375–87. doi: 10.3109/07357907.2014.919302. Epub 2014 Jun 2.

3. Foulkes WD. BRCA1 and BRCA2 – update and implications on the genetics of breast cancer: a clinical perspective. Clin Genet. 2014; 85: 1–4.

4. Garcia-Etienne CA, Barile M, Gentilini OD, Botteri E, Rotmensz N, Sagona A, Farante G, Galimberti V, Luini A, Veronesi P, Bonanni B. Breast-conserving surgery in BRCA1/2 mutation carriers: are we approaching an answer? Ann Surg Oncol. 2009; 16: 3380–7.

5. Ozcelik H, Shi X, Chang MC, Tram E. Long-range PCR and next-generation sequencing of BRCA1 and BRCA2 in breast cancer. J Mol Diagn. 2012 Sep; 14(5): 467–75. doi: 10.1016/j.jmoldx.2012.03.006. Epub 2012 Aug 6.

6. Ho AY, Gupta G, King TA, Perez CA, Patil SM, Rogers KH, Wen YH, Brogi E, Morrow M, Hudis CA, Traina T, McCormick B, Powell SN, Robson ME. Favorable prognosis in patients with T1a/T1bN0 triple-negative breast cancers treated with multimodality therapy. Cancer. 2012; 118: 4944–52.

7. Karami F, Mehdipour P. A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int. 2013; 2013: 928562. doi: 10.1155/2013/928562. Epub 2013 Nov 7.

8. Lokich E, Stuckey A, Raker C, Wilbur JS, Laprise J, Gass J. Preoperative genetic testing affects surgical decision making in breast cancer patients. Gynecol Oncol. 2014 Aug; 134(2): 326–30. doi: 10.1016/j.ygyno.2014.05.028. Epub 2014 Jun 5.

9. Mac Bride MB, Neal L, Dilaveri CA, Sandhu NP, Hieken TJ, Ghosh K, Wahner-Roedler DL. Factors associated with surgical decision making in women with early-stage breast cancer: a literature review. J Womens Health (Larchmt). 2013; 22: 236–42.

10. Nestle-Krämling C, Kühn T. Role of breast surgery in BRCA mutation carriers. Breast Care (Basel). 2012; 7: 378–82.

11. Oktay K, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast / ovarian cancer risks. J Clin Oncol. 2010; 28: 240–4.

12. Paradiso A, Formenti S. Hereditary breast cancer: clinical features and risk reduction strategies. Ann Oncol. 2011; 22: 31–6.

13. Pilgrim S, Pain S. Bilateral risk-reducing mastectomy is the safest strategy in BRCA1 carriers. Eur J Surg Oncol. 2014; 40: 670–2.

14. Pinel-Giroux FM, El Khoury MM, Trop I, Bernier C, David J, Lalonde L. Breast reconstruction: review of surgical methods and spectrum of imaging findings. Radiographics. 2013; 33: 435–53.

15. Saito M, Matsuzaki M, Sakuma T, Katagata N, Watanabe F, Yamaguchi Y, Schetter AJ, Takenoshita S, Nomizu T. Clinicopathological study of non-palpable familial breast cancer detected by screening mammography and diagnosed as DCIS. Breast Cancer. 2014; 21: 140–5.

16. Smith KL, Isaacs C. BRCA mutation testing in determining breast cancer therapy. Cancer J. 2011; 17: 492–9.

17. Synowiec A, Wcisło G, Bodnar L, Gasowska-Bodnar A, Szczylik C. Screening for ovarian cancer in BRCA1/BRCA2 mutations carriers. Ginekol Pol. 2014; 85: 377–81.

18. Tung N. Management of women with BRCA mutations: a 41-year-old woman with a BRCA mutation and a recent history of breast cancer. JAMA. 2011; 305: 2211–20.

19. Valachis A, Nearchou AD, Lind P. Surgical management of breast cancer in BRCA-mutation carriers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014; 144: 443–55.

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BRCA1 GENO 5328INSC MUTACIJOS BESIMPTOMINIO PACIENTO ORGANIZME APTIKIMO SVARBA: KLINIKINIS ATVEJIS

Santrauka

Pateikiame atvejį, kai pacientei pasireiškė BRCA1 5328insC mutacija (17q21 lokacijos forma). Pacientė dėl nevaisingumo buvo nukreipta konsultuotis pas gydytoją genetiką. Paaiškėjo, kad moters senelė sirgo, o mama ir teta serga kiaušidžių vėžiu. Pacientei buvo skirtas genetinis tyrimas, ieškota šešių dažniausių BRCA1 ir BRCA2 genų mutacijų. Tiriant aptikta BRCA1 5328insC geno mutacija, kuri 10 kartų padidina tikimybę susirgti krūties ir 20 kartų kiaušidžių vėžiu, palyginti su bendrąja populiacija. Siekiant sumažinti krūties ir kiaušidžių vėžio pasireiškimo riziką pacientei buvo patarta laikytis sveikos gyvensenos, atlikti kiaušidžių vėžio patikros tyrimus, pasiūlyta kreiptis į ginekologą dėl profilaktinio kiaušidžių pašalinimo.

Raktažodžiai: krūties ir kiaušidžių vėžys, BRCA1/A2 genų mutacijos, genetiniai tyrimai