Fanconi Anaemia with Biallelic *BRCA2* Variants Presented As Paediatric Cancer: Two Case Reports

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Introduction and Aim

Fanconi anemia (FA, MIM 227650) is a rare autosomal recessive condition affecting ~1 in 300 000 children. Aetiology of FA is genetically heterogenous and biallelic mutations in *BRCA2* gene are detected in ~3% of cases (FA group D1). FA is characterized by variable congenital abnormalities, short stature, bone marrow failure, hypersensitivity to DNA crosslinking agents, and a predisposition to malignancies. We report two paediatric Fanconi anaemia cases where biallelic mutations in *BRCA2* gene were detected.

Case Report

- The first patient is a girl who was diagnosed with grade IV meduloblastoma at 8 years old. Initially the surgery was performed and then the patient treatment was continued with radiation therapy (54 Gy) and chemotherapy. Family history - maternal grandmother died due to breast cancer before 50 years old (fig. 1). For patient testing "Onco-GeneSG®" gene panel analysis was performed and homozygous *BRCA2* pathogenic variant NM_000059.3:c.658_659delGT, p.(Val220IlefsTer4) was detected. Patient inherited these variants from both parents.

- The second patient is a boy who was diagnosed with nephroblastoma (Wilms tumor) at 5 years of age. Skin pigmentation abnormality was noticed: several café au lait spots and one melanocytic nevus on the truncus. The patient was treated with four courses of chemotherapy by UMBRELLA (2016 y.) protocol, which was followed by surgery. The treatment was continued with postoperative chemotherapy. Family history - maternal grandmother was diagnosed with breast cancer at 50 years old and paternal grandmother died due to ovary cancer (Fig. 2). "Onco-GeneSG®" gene panel testing was performed and compound heterozygous *BRCA2* variant was found: NM_000059.3:c.658_659delGT, p.(Val220IlefsTer4) and NM_000059.3:c.3847_3848del, p.(Val1283fs). The genetic testing showed that both parents are heterozygous for BRCA2 pathogenic variant..

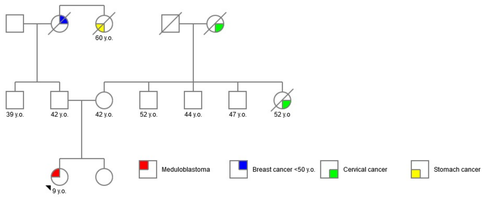

Fig. 1 Pedigree chart of the first clinical case

Discussion

Biallelic pathogenic variants in BRCA2 are associated with early-onset acute leukemia and solid tumors The cumulative probability of any malignancy is 97% by age six, including acute myeloid leukaemia, medulloblastoma, and Wilms tumor. The 1st patient is slightly older than the average reported. Experience with chemotherapy regimens for malignancy in FA patients is quite limited. Severe toxicity, including bone marrow aplasia without hematologic recovery, severe mucositis, and severe pulmonary and renal toxicities have been reported. Use of radiation therapy has been reported in patients with FA without immediate toxicity, however, this needs careful consideration due to baseline increased risk of other malignancies. Patients with biallelic pathogenic variants in BRCA2 should be carefully monitored for the other malignacies (hemathological and solid tumors).

It is known that heterozygous pathogenic variants in BRCA2 confer an increased risk of breast and ovarian cancer (84% and 27%, respectively by age 70) in women, as well as breast and prostate cancer in men. Genetic counselling and genetic testing should be provided for parents and siblings of the patient.

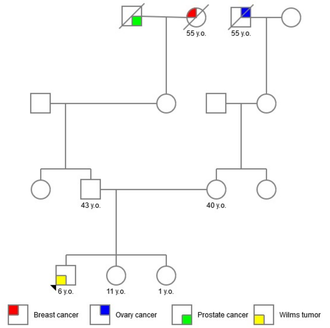

Fig. 2. Pedigree chart of the second clinical case

Conclusions

Genetic testing is especially important in the cases of paediatric cancer. If biallelic pathogenic variants in BRCA2 gene is detected there should be considerations regarding the treatment and follow up regimens. Moreover, it is importatn to provide proper genetic counselling for the family of the patient.

Key words

Fanconi anemia, *BRCA2*, meduloblastoma, Wilms tumor