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Сравнителен анализ на герминативни и соматични генетични варианти при овариален карцином

*Молекулярна характеристика,
клинична значимост и
терапевтични приложения*

Плевен 2026

**Сравнителен анализ на герминативни и соматични генетични варианти
при овариален карцином**

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монография

Първо издание, 2026

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ISBN 978-954-756-375-9

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ПРЕДГОВОР

Овариалният карцином е едно от най-сериозните предизвикателства в съвременната онкогинекология поради късната диагностика, агресивния клиничен ход и сложната му биологична хетерогенност. През последното десетилетие молекулярната онкология трансформира разбирането за това заболяване, като разкри, че зад общата клинична диагноза се крие спектър от генетично и функционално различни подтипове, определяни от специфични герминативни и соматични изменения.

Настоящата монография е посветена на сравнителния анализ на герминативни и тумор-специфични генетични варианти при овариален карцином, базиран на клинично-молекулярно изследване на 33 пациентки чрез масивно паралелно секвениране (NGS). Основната цел е да се интегрират данните от наследствената предиспозиция и туморната геномна еволюция в единна аналитична рамка, която да подпомогне персонализирания диагностичен и терапевтичен подход.

Особено внимание е отделено на ролята на хомоложната рекомбинация, HR-дефицита и TP53-доминантните механизми на геномна нестабилност, както и на подтип-специфичните мутационни профили при високостепенни серозни и несерозни карциноми. Чрез съпоставянето на герминативни и соматични варианти се демонстрира моделът на взаимодействие между наследствената предиспозиция и клоналната туморна еволюция, който има пряко отражение върху терапевтичните решения и фамилното консултиране.

Монографията има за цел не само да представи резултати, но и да предложи приложима рамка за интерпретация на NGS данни в клиничната практика. В условията на бързо развиваща се геномна медицина става все по-осезаема необходимостта от стандартизирани подходи към молекулярната диагностика, правилна вариантна класификация и мултидисциплинарна интерпретация.

Трудът е предназначен за лекари по медицинска генетика, онколози, патолози, гинеколози, специализанти и студенти по медицина, както и за всички специалисти, ангажирани в областта на персонализираната онкогенетика.

В контекста на съвременната молекулярна онкология овариалният карцином се очертава като моделно заболяване, при което интеграцията на герминативната и соматичната геномика открива нови възможности за диагностика, лечение и превенция.

1. Увод

1.1. Актуалност на проблема

Овариалният карцином заема особено място сред злокачествените заболявания при жените поради диспропорцията между честотата му и високата смъртност, която го характеризира. Макар да се диагностицира по-рядко в сравнение с други онкологични заболявания на женската репродуктивна система, той остава водеща причина за летален изход в рамките на онкогинекологията (1). Този факт отразява не толкова агресивността на всички форми на заболяването, колкото съвкупността от биологични и клинични особености, които затрудняват ранното му разпознаване.

Клиничната изява на овариалния карцином често е неспецифична и се развива постепенно, което води до късно диагностициране и ограничени възможности за радикално лечение. В този контекст заболяването се превръща не само в медицински, но и в значим социален проблем, свързан с продължително лечение, високи разходи за здравната система и сериозно отражение върху качеството на живот на пациентките и техните семейства (2). Хетерогенността на заболяването допълнително усложнява терапевтичния подход и налага интеграция на клинични, хистологични и молекулярно-генетични данни в процеса на вземане на решения (3).

1.2. Историческо развитие на познанията за овариалния карцином

Развитието на научните представи за овариалния карцином преминава през няколко основни етапа, отразяващи напредъка на медицинската наука като цяло. В продължение на десетилетия заболяването е било възприемано като хомогенна нозологична единица, дефинирана основно чрез морфологични характеристики и клинично протичане. Този подход е ограничавал възможностите за диференцирана диагностика и индивидуализирано лечение (4).

Постепенното въвеждане на хистопатологични и имунхистохимични методи позволява разграничаването на различни хистологични подтипове и поставя началото на по-прецизна класификация. Паралелно с това епидемиологичните наблюдения водят до формулиране на ключови хипотези относно ролята на репродуктивните фактори,

включително идеята, че кумулативният ефект от повтарящите се овулационни цикли може да допринася за канцерогенезата (5).

С навлизането на молекулярната генетика се осъществява фундаментална промяна в разбирането за заболяването. Идентифицирането на наследствени форми и на специфични генетични пътища в патогенезата трансформира овариалния карцином от морфологично дефинирано заболяване в молекулярно стратифицирана група неоплазми (6)

1.3. Съвременни концепции за произхода и биологията на заболяването

Съвременният научен консенсус разглежда овариалния карцином като сбор от биологично различни заболявания, които споделят анатомична локализация, но се различават по произход, молекулярен профил и клинично поведение. Натрупаните данни показват, че за част от най-агресивните подтипове първичният туморен процес възниква извън самия яйчник, като фалопиевата тръба се утвърждава като ключов източник на високостепенния серозен карцином (7).

За други хистологични форми се предполага връзка с хронични възпалителни състояния и патологични процеси като ендометриозата, което подчертава значението на тъканната микросреда и локалния имунен отговор. От биологична гледна точка овариалният карцином се характеризира с динамична геномна архитектура, изразена клонална хетерогенност и способност за адаптация под селективен натиск, включително в условията на системна терапия (8)

Тези характеристики определят заболяването като еволюираща система, при която генетичните изменения не са статични маркери, а активни участници в процесите на прогресия и терапевтична резистентност (9).

1.4. Цел и задачи на монографията

Целта на настоящата монография е да предложи интегративен и задълбочен анализ на овариалния карцином, който обединява клинични, хистологични и молекулярно-генетични аспекти в единна концептуална рамка. Чрез критично осмисляне на съвременните научни данни трудът цели да допринесе за по-доброто разбиране на биологичната хетерогенност на заболяването и за усъвършенстване на диагностичните, прогностичните и терапевтичните подходи.

Наред с обзорния и аналитичен характер, монографията има и изразен **изследователски фокус**, като в нея се представят и анализират **резултати от собствено проучване**, насочено към **сравнителен анализ на герминативни и соматични генетични варианти при пациенти с овариален карцином**. Генетичните изследвания са проведени чрез **масивно паралелно секвениране (next-generation sequencing, NGS)**, което позволява детайлна молекулярна характеристика както на туморната, така и на герминативната ДНК и осигурява основа за прецизна интерпретация на генетичните находки в клиничен контекст.

Основните задачи на монографията включват:

- систематизиране на съвременните епидемиологични и етиологични данни за овариалния карцином;
- представяне и критичен анализ на хистологичните и молекулярните класификации;
- изследване на ролята на герминативните и соматичните генетични изменения в патогенезата и туморната еволюция;
- анализ и интерпретация на резултатите от собственото NGS-базирано проучване;
- оценка на клиничните и терапевтичните приложения на молекулярно-генетичните находки;
- обсъждане на възможностите за персонализирана медицина, генетично консултиране и превенция.

1.5. Методологичен подход и структура на изложението

Монографията е разработена чрез аналитичен и синтетичен подход, базиран на критичен преглед на международната научна литература и актуалните клинични препоръки. Използваният интердисциплинарен модел съчетава данни от клиничната практика, патологичната диагностика и медицинската генетика.

Структурата на труда следва логиката на постепенно задълбочаване – от общите епидемиологични и етиологични аспекти към молекулярните механизми и клиничните приложения. Този подход позволява разглеждането на овариалния карцином като комплексно, динамично и биологично хетерогенно заболяване, чието разбиране изисква интеграция на знания от различни области (3,9).

МОРФОЛОГИЧНО И ИМУНОХИСТОХИМИЧНО БАЗИРАНИ СКРИНИРАЩИ КРИТЕРИИ ЗА СЕЛЕКЦИЯ НА ПАЦИЕНТИ С ВЕРОЯТНИ МУТАЦИИ НА BRCA1 ГЕНА ПРИ ПЪРВИЧЕН КАРЦИНОМ НА ЯЙЧНИК

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Резюме и цел: Карциномът на гърдата (КГ) и овариалният карцином (ОК) са едни от най-честите злокачествени заболявания, засягащи жените. В етиологията и на двата карцинома участват фактори на средата и генетични изменения. Сред основните гени, определящи предиспозиция за КГ и ОК, най-чести са BRCA1 (BReast CAncer 1) и BRCA 2 (BReast CAncer 2). Случаите на КГ или ОК, при които се открива герминативна мутация в BRCA1/2 се определят като наследствени. Тъй като определянето на генетичните изменения в BRCA1/2 е скъпо изследване ние си поставихме за цел да селектираме, на базата на определени морфологични и имунохистохимични критерии, пациентки с доказан карцином на яйчника, за генетично изследване на изменения в BRCA1.

Материал и методи: Обект на ретроспективен анализ бяха 29 случая със серозен папиларен ОК от архива на отделението по Клинична Патология на УМБАЛ „Д-р Г. Странски“ Плевен. Извърши се морфологична оценка и последващо имунохистохимично изследване с антитела срещу p53, anti BRCA 1 и против пролиферативния маркер Ki-67

Резултати: От изследваните 29 серозни папиларни карциноми на яйчника 19 (65,52%) се установиха с данни за загуба на имунохистохимичната експресия за BRCA1 и подходящи за последващо генетично изследване за изменения в BRCA1.

Заключение: Наборът от морфологични и имунохистохимични критерии позволява отсяване на жените, подлагани на генетично тестване, тъй като то е скъпо, а честотата на BRCA1 мутациите в общата популация е изключително ниска.

Ключови думи: карцином на яйчник, скрининг, морфологични и имунохистохимични критерии, генетично тестване

MORPHOLOGICALLY AND IMMUNOHISTOCHEMICALLY BASED SCREENING CRITERIA FOR SELECTION OF PATIENTS WITH POSSIBLE MUTATION OF BRCA1 GENE IN PRIMARY OVARIAN CANCER

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Summary and aim: Breast cancer (BC) and Ovarian cancer (OC) are some of the most common cancers affecting women. Environmental factors and genetic alterations are involved in the etiology of both cancers. The main susceptibility genes that predisposed to BC and OC are BRCA1 (BReast CAncer 1) and BRCA 2 (BReast CAncer 2). Those of BC and OC which are due to germline mutation in BRCA1 / 2 are defined as hereditary. Because of the expensiveness of genetic testing for mutations in BRCA1 we aimed to select patients with ovarian cancer, suitable for genetic testing, on the base of certain morphological and

immunohistochemical criteria.

Material and Methods: *We have conducted a retrospective analysis of 29 cases with serous papillary OC, taken from the archives of the Department of Clinical Pathology, University Hospital "Dr. G. Stranski" Pleven. We performed morphological assessment and subsequent immunohistochemical study with antibodies against p53, anti BRCA 1 and anti proliferative marker Ki-67.*

Results: *Nineteen (65.52%) of all 29 cases were found with loss of immunohistochemical expression of BRCA 1 and we defined them as suitable for genetic testing of BRCA1 mutations.*

Conclusion: *A set of morphological and immunohistochemical criteria allows screening of women that should be referred for genetic testing, as it is expensive, and the incidence of BRCA1 mutations in the general population is very low.*

Key words: *Ovarian cancer, screening, morphological and immunohistochemical criteria, genetic testing*

Карциномът на гърдата (КГ) и овариалният карцином (ОК) са една от най-честите злокачествени неоплазми, засягащи женското население. Двете заболявания са мултифакторни, като в етиологията им участват както фактори на средата, така и генетични алтерации. Редица проучвания доказват сходната генетична етиопатогенеза при наследствените форми на КГ и ОК. Обща характеристика и при двата типа карцином е възможността за по-голяма честота на неоплазмите в определени фамилии, като тогава се говори за фамилен - КГ или ОК. Натрупването в едно семейство, на повече случаи с такива заболявания се дължи на налична генетична предразположеност.

Сред основните гени, определящи генетична predisposition за карцином на гърда и яйчник, най-често са BRCA1 (**BR**east **C**Ancer **1**) и BRCA2 (**BR**east **C**Ancer **2**). Измененията в тези гени са отговорни за около 40 % от случаите на фамилен рак, като унаследяването е по автозомно-доминантен тип [1] и носителството им е свързано с 65-80 % кумулативен риск за развитие на заболяване в здрави родственици.

Локализацията на BRCA1 на хромозома 17q21 е уточнена през 1990 г. [2]. BRCA1 заема 81 Kb от ДНК, съдържа 22 кодиращи участъци (екзони) и е отговорен за синтеза на белтък, съдържащ 1863 аминокиселини, които кодират протеини, участващи основно в клетъчната ДНК репарация. От своя страна, BRCA1 белтъчният продукт участва и в регулацията на процеси като транскрипция, убиквитинация и контрол на клетъчния цикъл. Поради участието на гена в поддържането на геномната стабилност на клетката, загубата на функцията му води до геномна нестабилност. Точният механизъм на действие е комплексен и недостатъчно изяснен. При носителите на мутация в BRCA1, туморите в гърдата най-често се характеризират с липса на естрогенови, прогестеронови и HER2 рецептори (тройно-негативен фенотип), докато при носителите на BRCA2 мутации, туморите експресират

естрогенови рецептори [3].

Случаите на КГ или ОК, при които се открива герминативна мутация в BRCA1/2 се определят, като наследствени. Скринингът за BRCA1/2 дефекти е ключов момент, както с оглед последващия терапевтичен подход при пациентки с диагностициран тумор, така и с оглед поведението спрямо здравите родственици, които е възможно да са унаследили мутации, свързани с по-висок риск за развитие на КГ, ОК или злокачествена неоплазма с друга локализация

Изследването за носителство на патологични мутации в тези тумор-супресорни гени, които не се срещат често, е скъпо и отнема много технологично време до получаване на резултата. Въз основа на определени морфологични критерии и категории опитния патолог, може да има активна позиция в селекцията на пациенти, с развил се вече злокачествен тумор и да разпознае или да заподозре коя от изследваните неоплазми е с вероятна мутация на BRCA1 гена.

Процесът на откриване на носители на мутации в BRCA 1 гена е важен с оглед клиничното поведение при тези пациенти. Пациенти, носители на герминативни мутации на тези гени, са склонни към развитие на първични тумори с друга локализация, като стомах, панкреас, гърда и аднекси. Тези пациенти се нуждаят и от детайлно проследяване, от оптимизирано и навременно адювантно лечение, което да е ефективно при този тип генетични дефекти, независимо от органното разположение на тумора. Родствениците на такива пациенти би следвало да бъдат изследвани с оглед на повишения риск за развитие на неоплазми.

Определянето на възможната връзка на туморите на яйчниците с вероятен модел на канцерогенеза, включващ наличие на BRCA1 мутации или дефект в BRCA пътя се основава на пет морфологични характеристики. Първият морфологичен критерий е ниска степен на диференциация на тумора. Серозни овариални карциноми, с ниска степен на диференциация (G3) е много по-вероятно да са свързани с

virtual environment (TV, computers, mobile phones) and their impact on health. We examined a total of 881 students from various cities and towns throughout the country. Survey results showed: adolescents often abuse the time spent with computers, TV, mobile conversations; a large percentage of students prefer the virtual world to other types of entertainment; there is a high percentage of students who formed a certain degree of dependence on working with the Internet, calling on GSM and watching TV; a significant percentage of students and their parents do not know about the harmful effects of modern technology (TV, GSM, computers) on human health; some of the surveyed children have not only one, but several health complaints when watching TV, using GSM and computing; thus, largest percentage of all children surveyed have complained of headache, visual disturbances and fatigue. Recommendations have been made.

Key words: risk factors, virtual environment, students

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Infantile form of GM1 Gangliosidosis - Case Report

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GM1 gangliosidosis is an autosomal recessive lysosomal storage disease caused by deficiency of the enzyme acid beta-galactosidase. This deficiency results in accumulation of GM1 gangliosides in the lysosomes leading to lysosomal swelling, cellular damage, and organ dysfunction. There are three types of GM1 gangliosidosis based on the age of onset. The infantile form (type 1) is characterized by progressive organomegaly, dysostosis multiplex, facial coarsening, and progressive neurologic deterioration within the first year of life. We present a 7-month-old girl with classical clinical features of this rare lysosomal storage disorder.

Key words: beta-galactosidase, GM1 gangliosidosis

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Prader-Willi Phenotype in a Patient with Fragile X Syndrome

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The Fragile X syndrome (FXS) is the most frequent cause of inherited intellectual disability, that occurs in approximately 1/4000 males and 1/8000 females. This X-linked disorder is caused by an expansion of a trinucleotide CCG repeat (>200)

on the promotor region of the FMR1 gene. Epilepsy, autism and obesity are common problems in the FXS. The majority of male fragile X patients show the typical phenotype consisting of long face, large, prominent ears, and post-pubertal macroorchidism. A special subphenotype of the FXS is reported which is characterised by extreme obesity, small, broad hands and feet, and hypogenitalism or delayed puberty. It resembles the Prader-Willi syndrome. We describe a patient with Prader-Willi phenotype and the typical full mutation in FMR1 gene.

Key words: autism, epilepsy, Fragile X syndrome, Prader-Willi phenotype

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Microdeletion Form of Wolf-Hirschhorn Syndrome - Case Report

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Wolf-Hirschhorn syndrome (WHS) is a well known condition caused by the loss of genomic material from the short arm of chromosome 4 (4p16.3) with an estimated prevalence of about 1/20,000-50,000 births. The variability in the extent of the 4p deletion leads to a wide spectrum of clinical manifestations. The classical phenotype includes typical facial appearance, microcephaly, growth retardation, developmental delay, hypotonia, seizures and congenital visceral malformations. Widespread clinical use of novel molecular techniques has increased the detection rate of submicroscopic chromosomal aberrations associated with WHS. We present a patient with mild dysmorphic features, developmental delay, apparently „normal“ karyotype, and a microdeletion encompassing WHSC1 and LETM1 genes.

Key words: 4p16.3 microdeletion, Wolf-Hirschhorn syndrome

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Clinical and Genetic Data of Down Syndrome - a Survey on Cases in the Section of Medical Genetics - Pleven

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Down syndrome (DS) is the most common chromosome disorder among live born babies and the most common genetic cause of mental retardation. Aim of the study was to summarize the clinical and genetic information of Down syndrome (DS)

cases, established in the Section of Medical Genetics, Medical University of Plevan for the period (January 2006 - May 2014). A total of 55 children with DS were diagnosed by routine cytogenetic analysis. The clinical and passport data were taken from medical and genetic records.

Most (90%) of the patients were diagnosed before 1 year age (53% in the first week after birth), because of dysmorphic features for DS. The distribution of DS cases, according to cytogenetic variant was as follows: 91% standard trisomy 21, 5.4% mosaic and 3.6% translocation DS. About 29% (16/55) of DS individuals have disease-associated congenital anomalies (mainly heart malformations 25%). Maternal age ≥ 36 ys at the time of birth had 40% of the women. Maternal serum screening test was not offered during pregnancy in the majority 85% (47/55) of mothers. About 73% (40/55) of children with DS are grown of their biological parents.

Down syndrome is usually diagnosed early after birth, mainly in the early neonatal period. Most 60% of DS children have young mothers (under 36 years old). About 1/3 of DS individuals have associated anomalies (mainly heart defects). There is an insufficiency in offering the screening test to pregnant women that restrict their opportunity for early prenatal diagnosis of this condition and informed reproductive decision.

Key words: Down syndrome, chromosome abnormalities, cytogenetic variants, prevention

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PRELIMINARY DATA FROM A STUDY ON POLYMORPHISM RS4244285 OF P4502C19 CYTOCHROME GENE IN PATIENTS WITH ACUTE CORONARY SYNDROME, UNDERGOING TREATMENT WITH DUAL ANTIPLATELET THERAPY WITH CLOPIDOGREL AND ASPIRIN

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Received: May 17, 2016

Revision received: June 08, 2016

Accepted: September 15, 2016

Summary

Administration of antiplatelet therapy Aspirin and Clopidogrel (CLP) is a corner stone in patients with Acute Coronary Syndrome (ACS) undergoing Percutaneous Coronary Intervention (PCI) with/without stent implantation. The CYP2C19*2 allele is the most important genetic variant determining response to CLP. We aim to investigate frequency of CYP2C19*2 polymorphism in patients with ACS and significance for the individual response to CLP therapy. The preliminary data of a study including a total of 120 patients with ACS undergoing PCI with stent placement and treated with dual antiplatelet therapy (CLP and Aspirin) are presented. So far 18 patients (41-81 year age) are tested for CYP2C19*1/*2 polymorphisms. The genotype CYP2C19*1/*1; CYP2C19*1/*2 and CYP2C19*2/*2 is demonstrated in 50%, 33%, 17% respectively, of the patients. The established frequency of CYP2C19*2 allele (33%) is significantly higher ($\chi^2=5.220$; $p=0.022$) than in healthy Bulgarian individuals (16%). In-stent thrombosis have developed 3 (17%) of patients: 2 are CYP2C19*1/*2 carriers, and 1 – homozygous CYP2C19*2/*2. The preliminary data demonstrate high prevalence of CYP2C19*2 polymorphism in patients with ACS and point to significance of the variant for CLP therapy. Further extension of the study with larger samples and monitoring of the patients are required to determine the effects of the polymorphism on the prognosis for major adverse cardiovascular events.

Key words: CYP2C19 polymorphism, Clopidogrel, Acute Coronary Syndrome, in-stent thrombosis

Introduction

Acute coronary syndrome (ACS) is the most severe manifestation of ischemic heart disease, which remains among the leading causes of death worldwide, despite the use of modern treatment. ACS is a life threatening condition and includes the following categories of patients: diagnosed with STEMI (myocardial infarction with ST-segment elevation), NSTEMI (myocardial infarction without ST-segment elevation) and UA (unstable angina pectoris).

According to the recommendations of the European Society of Cardiology, in patients with

Results: In the multivariable models, CES-D score was a significant ($P \leq 0.05$) predictor for the General Facet and the Physical and Psychological Health, and Environment domains of the WHOQOL-BREF, the Eastern Cooperative Oncology Group (ECOG) performance score for the General Facet and the Physical Health and Social Relationships domains, and the NEO-FFI conscientiousness scale score for the Physical Health, Psychological Health and Environment domains. For the EORTC QLQ-C30 scale scores, CES-D score, was a significant ($P \leq 0.05$) predictor for all five functioning scale scores and the Global Health Status/QoL score, the ECOG performance score for the Physical, Role, and Social Functioning scale scores, and employment for the Global Health Status/QoL and Physical Functioning scale scores.

Conclusions: Depressive symptoms, performance score, and conscientiousness are important predictors of (HR)QoL in patients with advanced stage NSCLC. Supportive care interventions should be directed against depressive symptoms and aimed at improving performance score to stimulate an increase in (HR)QoL during oncologic treatment.

Legal entity responsible for the study: Erasmus University Medical Center

Funding: ZonMw

Disclosure: All authors have declared no conflicts of interest.

161P

Metabolic factors were associated with the outcome of gemcitabine-treated patients with advanced NSCLC identified by high through-put liquid-chip

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Background: Gemcitabine is one of the most frequently prescribed chemotherapy regimen for patients with advanced NSCLC. There is an urgent but un-met need to develop the prognostic biomarkers for the regimen. We reasoned the metabolic factors might be associated with the prognosis of this regimen.

Methods: This study was a prospective, exploratory, registered trial (ChiCTR-POC-15007228). Newly-diagnosed, chemotherapy-naïve patients with advanced NSCLC who were prescribed with gemcitabine chemotherapy (cisplatin or carboplatin) were enrolled. Blood was sampling before the initiation of the chemotherapy. The metabolic factors were determined by liquid-chip (FLEXMAP 3D). The ERCC1 and RRM1 were detected by commercially available real-time PCR kits. The sera gemcitabine concentration was measured with HPLC. The primary end-point was OS.

Results: From March 2012, to December 2013, 59 patients were enrolled. 13 metabolic factors (C-peptide, Ghrelin, GIP, GLP-1, Glucagon, IL-6, Insulin, Leptin, MCP-1, PP, PYY, TNF- α , Amylin) were measured and most of them could be detected in the peripheral blood. C-peptide (25.8 and 15.7 months, $p=0.04$) and Insulin (25.8 and 14.9 months, $p=0.01$) were found to be related to poor prognosis. The prognostic value remained in multi-variate COX regression model (HR = 2.20 and 2.37 respectively). However, neither ERCC1 ($p=0.56$), or RRM1 ($p=0.70$), nor gemcitabine concentration ($p=0.17$) was related to the survival.

Conclusions: C-peptide and insulin are novel and promising biomarkers for gemcitabine treatment and warrant further validation.

Legal entity responsible for the study: N/A

Funding: N/A

Disclosure: All authors have declared no conflicts of interest.

162P

Molecular markers in advanced non small cell lung cancer patients receiving gemcitabine & cisplatin

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Background: Despite improvement in the standard treatment of advanced Non Small Cell Lung Cancer (NSCLC), the overall prognosis is very poor. Using molecular markers as a predictor for chemotherapy response is a hot area of research.

Methods: This is a prospective study conducted in National Cancer Institute (NCI), Cairo University, including eligible patients with advanced NSCLC who received first line chemotherapy (Gemcitabine and Cisplatin). ERCC1, BRCA1 and RRM1 proteins level in blood samples by ELISA and their genes expression by PCR were detected. The primary objective was the correlation between molecular markers and clinical response (CR), while the secondary objectives were assessment of correlation between expression of these markers and Time To Progression (TTP) and Overall Survival (OS).

Results: 71 patients included and followed up during the period from Jan 2011 to Jan 2014 with median follow up 5.6 months. There was no significant correlation between ERCC1, RRM1 and BRCA1 expression and clinical response (p values = 0.14, 0.65, 0.67 respectively). Patients with high ERCC1 expression had shorter TTP (3.5 vs 6.1 months; $P=0.001$) and OS (6.6 vs 10.9 months; $P=0.022$). Patients with low RRM1 expression had almost the same TTP of patients with high RRM1 (4.2 vs 4.7 months; p value = 0.91); but they had longer OS (10.8 vs 7.0 months; $P=0.052$). No significant correlation between the BRCA1 expression and survival were found (TTP was 4.8 months in patients with high expression versus 4.7 months in low expression; P value = 0.7) (OS was 10.5 months in patients with high expression versus 7.8 months in low expression; P value = 0.46).

Conclusions: High expression of ERCC1 and RRM1 are associated with poor outcome in patients with advanced NSCLC treated with Gemcitabine and Cisplatin, ERCC1 and RRM1 may considered as predictive and prognostic markers for patients receiving Gemcitabine and Cisplatin.

Legal entity responsible for the study: National Cancer Institute

Funding: National Cancer Institute, Cairo, Egypt

Disclosure: All authors have declared no conflicts of interest.

163P

Prevalence of epidermal growth factor receptor (EGFR) gene mutations in non small cell lung cancer (NSCLC) in Bulgarian population

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Background: In the last couple of years genetic tests have become a significant part of the diagnosis of NSCLC. Mutational analysis and genomics profiling have advanced the field of lung cancer pointing out the critical role of some mutations in the treatment of the disease. The aim of this study is to determine and evaluate the EGFR mutation in Bulgarian patients with NSCLC.

Methods: In this prospective study we included 440 patients (320 male, 120 female, age 45 to 70 years) stage IIIB (10.8%)-IV (81.1%) with histology for NSCLC. Tumor samples amole

were collected between July 2013 and November 2015. DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor tissue, using the Cobas[®] DNA Sample Preparation Kit. For the mutational screening we used the Cobas[®] EGFR Mutation Test v2, performed on the Cobas[®] 4800 System. All mutations were detected at 5% sensitivity with the exception of the 2240_2257del18 exon 19 deletion mutation, detected at a sensitivity of >10%. Presence of more than 50% adequate tumor tissue was confirmed by a pathologist.

Results: Histological evaluation found 380 (86.4%) cases with adenocarcinoma, 40 (10%) with squamous-cell carcinoma and 20 (4.6%) with NSCLC- NST. From all 440 tested samples in 58 (13.2%) we found mutation in the EGFR gene. By 37 (63.8%) of them (15 male, 22 female) it was an activating mutation in EGFR gene and by 21 (36.2%) mutations were linked to insensitivity to TKIs. The prevalent type of activating EGFR mutation was deletion in exon 19 (in 24 cases – 64.9%), in 11 (29.7%) cases – L858R in exon 21, in 1 (2.7%) case – S768I in exon 20 and by one patient we found double heterozygosity – S768I in exon 20 and G719X in exon 18. Half of the patients were non-smokers. 97.3% of the tumor samples with activating mutations were adenocarcinomas, the rest with histology for squamous-cell carcinoma. 81.1% of the samples were from the primary tumor and the rest from the secondary metastasis. All patients with activating mutations were treated with first line TKIs according to guidelines.

Conclusions: This study successfully provided insights into the prevalence and type of the EGFR gene mutation, which was detected in 13.2% of the studied Bulgarian population and corresponds to the publicly available data.

Legal entity responsible for the study: Medical University Pleven, Department of Pathology

Funding: Roche national program for patient support and EGFR testing

Disclosure: All authors have declared no conflicts of interest.

164P

A review of prognostic factors for patients with epidermal growth factor receptor mutation positive advanced non small cell lung cancer (EGFR+NSCLC)

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Background: It is important for patients with EGFR+NSCLC to receive both EGFR tyrosine kinase inhibitor (EGFR-TKI) and platinum doublet chemotherapy to achieve longer overall survival (OS). Up to the present, either treatment as first line setting is reasonable. However some previous prospective studies showed that patients with exon 21 L858R status EGFR+NSCLC may survive longer if they take platinum doublet chemotherapy as first line setting before EGFR-TKI. We examined which factors have an impact on OS most among patients with EGFR+NSCLC on a real-life setting.

Methods: A retrospective chart review was performed on 74 patients who had advanced stage or recurrent EGFR+NSCLC and received one or more regimen cytotoxic chemotherapy or EGFR-TKI at The Tazuke Kofukai Medical Research Institute Kitano Hospital between Jun 2007 and Jun 2015. We assessed the relationship for the status of EGFR mutation, the order of treatment steps, exist of brain metastasis, patient's characters and OS. Then the contributing factors for OS were analysed using Cox proportional hazards model.

Results: The characteristics of 74 patients with EGFR+NSCLC were as follows; EGFR mutation status exon 19 deletion/exon

21 L858R/minor mutation: number of patients (male) 37 (16)/32 (16)/5 (3), age 67.4 years-old, clinical or pathological stage of NSCLC: IIB/IIIA/IIIB/IV 1/7/4/62, ECOG-performance status(ECOG-PS): 0-1/2-4/unknown 65/6/3, existence of brain metastasis at the first time: 19, first line treatment: cytotoxic chemotherapy/EGFR-TKI 31/43, patients received both chemotherapy and EGFR-TKI/chemotherapy or EGFR-TKI only: 58/16. Median OS was 908 days for all patients. Most significant factor impacted on OS was ECOG-PS (p=0.01), and there were no relations between OS and any other factors.

Conclusions: ECOG-PS is a most important prognostic factor for patients with EGFR+NSCLC on a real-life setting. Contrary to previous study, types of EGFR mutation and the order of treatment steps didn't impacted on OS.

Legal entity responsible for the study: The Tazuke Kohukai Medical Research Institute Kitano Hospital

Funding: The Tazuke Kohukai Medical Research Institute Kitano Hospital

Disclosure: All authors have declared no conflicts of interest.

165P

Long noncoding RNA LUCAT1 is associated with poor prognosis in human non-small cell lung cancer and affects cell proliferation via regulating p21 and p57 expression

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Background: Recently, long non-coding RNAs (lncRNAs) is identified to play a key role in regulating cellular process, such as proliferation, invasion and metastasis. These lncRNAs are shown to be ectopic expressed in tumorigenic processes. However, the role and clinical relevance of LUCAT1 in non-small cell lung cancer (NSCLC) remain unclear.

Methods: Polymerase chain reaction (qPCR) assays was used to analyse the expression of LUCAT1 in non-small cell lung cancer (NSCLC) tissues and cell lines. MTT and colony formation assays were performed to evaluate the effect of LUCAT1 on proliferation, and flow cytometry was performed to evaluate cell apoptosis. The NSCLC cell lines were transfected with si-LUCAT1 and injected into nude mice to investigate the effect of LUCAT1 on oncogenesis in vivo. The connection between LUCAT1 and EZH2 was verified by RIP. The related protein levels of LUCAT1 targets were studied by ChIP.

Results: The expression of LUCAT1 was obviously up-regulated in NSCLC cancer tissues compared to non-tumor tissues, and its expression was bound up with tumor size, tumor TNM stage, lymphatic metastasis and overall survival. Univariate and multivariate analyses revealed that LUCAT1 expression acted as an independent predictor for overall survival. Animal experiments significantly showed that the proliferation was inhibited by LUCAT1 knockdown both in vitro and in vivo. Furthermore, we also displayed that LUCAT1 played a crucial role in G1 arrest. What's more, we further affirmed that LUCAT1 was correlated with enhancer of zeste homolog 2 (EZH2) by repressing the expression of p21 and p57. Here, we first report the role and molecular mechanism of LUCAT1 in the NSCLC cellular processes.

Conclusions: Our results show that LUCAT1 could be a poor prognostic biomarker in NSCLC and regulate cancer biology.

Legal entity responsible for the study: Jiangsu Provincial People's Hospital, Nanjing Medical University

Funding: The National Natural Science Foundation of China, The National Scientific Foundation of Jiangsu Provincial of China

Disclosure: All authors have declared no conflicts of interest.

Pfeiffer syndrome type 2 – two cases from the Pleven Registry of Congenital Anomalies

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Pfeiffer syndrome is a rare autosomal dominant congenital disorder with the main features of acrocephalic skull, midfacial hypoplasia, syndactyly of hands and feet, broad thumbs and big toes. Three clinical subtypes (with different diagnostic and prognostic implications) have been identified. We report on two cases of Pfeiffer syndrome type 2 (one of them diagnosed prenatally and the other detected in the newborn), identified through screening for congenital defects as an activity of the Pleven Registry of Congenital Anomalies (member of EUROCAT). Case 1 was a male foetus from terminated pregnancy following prenatal diagnosis. Foetal morphology ultrasound in the 28th week of gestation revealed craniosynostosis, cloverleaf skull, flat face, exophthalmos, macroglossia, short ribs, deformed spine, and abnormally shortened limbs (micromelia). Clinical examination after birth confirmed the diagnosis of Pfeiffer syndrome type 2. Case 2 was a boy (born at term, 40th week of gestation) diagnosed with Pfeiffer syndrome type 2 at birth. Multiple malformations were presented including cloverleaf skull, craniosynostosis of coronal suture, midfacial hypoplasia, depressed nasal bridge, high palate, exophthalmos, down-slanted palpebral fissures, hypertelorism, low-set ears, short neck, broad and medially deviated thumbs and hallux, clinodactyly V, skin syndactyly of II-III toe, short thorax with sternal depression, and anal atresia. The patient died from respiratory distress syndrome on the ninth day after birth. Severe malformations, high mortality and problems in clinical management determine poor prognosis in most cases of Pfeiffer syndrome type 2. Early prenatal diagnosis in pregnancies with severe foetal malformations and poor prognosis gives parents more time and opportunities for reproductive choices.

Key words: Pfeiffer syndrome type 2; cloverleaf skull; registry of congenital anomalies; prenatal diagnosis

INTRODUCTION

In 1964, Pfeiffer (1) was the first to describe acrocephalosyndactyly syndrome, characterized by bicoronal craniosynostosis, midface hypoplasia, broad thumbs and great toes, and partial and variable soft tissue syndactyly. The type of inheritance is autosomal dominant with complete penetrance and variable expressivity related to the presence or absence of syndactyly and the degree of severity. Pfeiffer syndrome (PS) (OMIM 101600) was classified into three clinical subtypes by Cohen in 1993. Type 1 is a 'mild' form of the syndrome, with brachycephaly, midfacial hypoplasia, finger and toe deformities, and autosomal dominant pattern of inheritance. Type 2 main features are cloverleaf skull, elbow ankylosis, poor prognosis and early demise (usually sporad-

ic cases). Type 3 has the same features as type 2, but without cloverleaf skull (2).

Molecular genetics has provided better understanding of the molecular basis of PS, which is due to mutations in fibroblast growth factor receptor 1 (*FGFR1*- 8p11.2-p11) or *FGFR2* (10q26) (3).

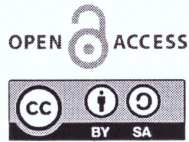
We report on two cases of PS type 2 (one of them prenatally diagnosed and the other one detected in the new-

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Primljeno/Received: 8. 11. 2017., Prihvaćeno/Accepted: 14. 5. 2018.



CHROMOSOMAL ABNORMALITIES AND Y CHROMOSOME MICRODELETIONS IN BULGARIAN MALE WITH AZOOSPERMIA OR SEVERE OLIGOSPERMIA

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SUMMARY

Male infertility is a complex disease, and genetic abnormalities are among the main causal factors for the disorder. Aim: In order to evaluate the proportion of the most common genetic factors in etiology of male infertility, examination for chromosomal abnormalities and microdeletions of Yq chromosome (delYq) was carried out in Bulgarian males with severe infertility.

Materials and methods: The study was retrospective and involved a total of 142 infertile Bulgarian males (63 patients with azoospermia and 79 patients with severe oligozoospermia /sperm count < 5×10⁶/ml), referred (2007-2016) for genetic testing, after preliminary examinations to exclude some more frequent causes for male infertility. Cytogenetic analysis by GTG-banding was carried out in 137 men, and molecular testing for AZF region microdeletions of Y chromosome by multiplex PCR was carried out in 109 men.

Results: Chromosomal abnormalities were found in 16.8% of all investigated infertile men and the frequencies in patient subgroups with azoospermia and oligozoospermia were 20.7% (12/58) and 13.9% (11/79) respectively. The established frequency of delYq was 5.5% (6/109) in the overall group of infertile male and higher - 9.5% (6/63) in a subgroup of patients with azoospermia. The overall proportion of the two genetic factors was 30.2% in patients with azoospermia and 14% in men with oligozoospermia. In conclusion, chromosomal abnormalities and delYq account for about 22% of cases with severe infertility in Bulgarian men. Genetic testing should be a routine part of examinations in infertile males and along with genetic counseling; they provide an opportunity for the best choice of an appropriate technique for assisted reproduction of the couples.

Keywords: male infertility, genetic causes, chromosomal abnormalities, Y chromosome microdeletions

INTRODUCTION

Infertility is a global health problem affecting 10–15% of couples at reproductive age and in half of these cases, a male causal factor can be identified [1-5]. It is estimated that about 7% of all men have problems with their fertility [6]. Male infertility is a complex disease, and several factors have been involved in etiology of the disorder: endocrine abnormalities, infections, environmental exposure, genetic defects and others. However, in 30-40% of these cases, no specific cause could be found [1,4].

Genetic abnormalities are thought to play an important role in multifactorial etiology of the disorder, accounting for 10-15% of severe male infertility, including chromosomal aberrations and single gene mutations [3,6]. Among genetic disorders are hypogonadotropic hypogonadism, mutations in the androgen receptor, cystic fibrosis gene mutations, genetic polymorphisms and Y chromosome linked infertility. Chromosomal anomalies are the most common genetic causes of male infertility found about 10 times more frequently in infertile men (4-16%) than in the general population (0.4%) [4,6]. The microdeletions of azoospermia factor (AZF) region in the Y chromosome are considered as the most frequent known molecular-genetic cause of severe impairment of spermatogenesis, detected in about 10% of men with non-obstructive azoospermia and 3-5% of men with idiopathic severe oligozoospermia [6].

Aim: In order to evaluate the proportion of the most common genetic defects in etiology of severe male infertility we investigated the frequency of chromosomal abnormalities and Y chromosome microdeletions in Bulgarian males with azoospermia or severe oligozoospermia.

MATERIAL AND METHODS

Patients

The current study was retrospective, based on the data of the Section of Medical Genetic, Medical University of Pleven (for the period 2007-2016) and included men with infertility, candidates for ART, referred for genetic counseling and genetic testing after preliminary examina-



A Clinical Case of Patient Carrying Rare Pathological PSEN1 Gene Mutation (L424V) Demonstrates the Phenotypic Heterogeneity of Early Onset Familial AD

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OPEN ACCESS

Edited by:

Paolo Brambilla,
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Reviewed by:

Hubertus Axer,
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Cukurova University, Turkey

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Specialty section:

This article was submitted to
Neuroimaging and Stimulation,
a section of the journal
Frontiers in Psychiatry

Received: 02 August 2019

Accepted: 31 October 2019

Published: 11 December 2019

Citation:

Stoychev KR, Stoimenova-Popova M,
Chumpalova P, Ilieva L, Swamad M
and Kamburova-Martinova Z (2019)
A Clinical Case of Patient Carrying
Rare Pathological PSEN1 Gene
Mutation (L424V) Demonstrates the
Phenotypic Heterogeneity of Early
Onset Familial AD.
Front. Psychiatry 10:857.
doi: 10.3389/fpsy.2019.00857

Dementia comprises several neurodegenerative disorders with similar neuropsychiatric features and Alzheimer's disease (AD) is the most common of them. Genetic factors are strongly implicated into its etiology especially for early-onset cases (EOAD) occurring before the age of 65. About 10% of these are inherited in autosomal dominant fashion via pathogenic polymorphisms in three genes—APP, PSEN-1, and PSEN-2. Despite genotypic clarity, however, phenotypic variability exists with different symptom constellations observed in patients with identical mutations. Below, we present a case of a 39-year-old male with a family history for early onset dementia who was referred to our department with anamnesis for abrupt behavioral change 7 months prior to hospitalization—noticeable slowing of speech and reactivity, impaired occupational functioning and irritability, followed by aphasic symptoms and transient episodes of disorientation. He was followed up for 2 years and manifested rapidly progressing cognitive decline with further deterioration of speech, apraxia, acalculia, ataxia, and subsequently bradykinesia and tremor. Based on the clinical and neuroimaging findings (severe cortical atrophy), familial EOAD was suspected and a whole exome sequence (WES) analysis was performed. It identified a heterozygous missense variant Leu424Val (g.71074C > G) in PSEN-1 gene considered to be pathogenic, and only reported once until now in a Spanish patient in 2009. Despite genotype identity however, distinct phenotypic presentations were observed in the two affected subjects, with different neuroimaging findings, and the presence and absence of seizures in the Spanish and Bulgarian case, respectively. Besides, myoclonus and spastic paraparesis considered “typical” EOAD clinical features were absent. Age of symptom onset was consistent with two of the reported mutations affecting 424 codon of PSEN-1 gene and significantly earlier than the other two implying that factors influencing activity of PSEN-1 pathological forms are yet to be clarified. Furthermore, our patient had co-occurring lupus erythematosus (LE) and we suggest that this condition might be etiologically linked to the PSEN-1 mutation. In addition to illustrating the symptomatic heterogeneity of PSEN-1 caused EOAD, our study confirms that in patients presenting

with early cognitive deterioration and family history for dementia, WES can be especially informative and should be considered as a first-line examination.

Keywords: phenotypic heterogeneity, whole exome sequencing, PSEN1 mutation, genetic inheritance, early onset Alzheimer's disease (EOAD)

BACKGROUND

Several neurodegenerative disorders are grouped under the umbrella term dementia (1) and these include Alzheimer's disease (AD) comprising more than 60% of cases, vascular dementia (VD), dementia with Lewy bodies (DLB), and frontotemporal dementias group (FTD) (2). Their symptoms often overlap (3) and precise diagnosis is difficult but may be boosted by several approaches, including genetic testing. (4).

Genetic background of dementia syndrome is widely recognized (5). It may present as a complex condition with many genes of small effect contributing to illness risk or, more rarely, as an autosomal dominant disease running in families (6). Such forms are almost exclusively found among early onset dementia (EOD) patients, i.e., diagnosed under the age of 65. With prevalence exceeding 40.0% of patients for some dementia subtypes (7), EOD is evidently not sporadic (8), and the genetic underpinnings of AD and FTD have been most extensively studied (9).

Early-onset AD (EOAD) represents 5.5% all AD cases (10) and in 10% of the affected, a familial model of inheritance is seen (11). Its clinical course is markedly accelerated (12) and myoclonus in the early stages may be common (13). To date, three major EOAD causative genes are recognized (14): mutations in Presenilin-1 (*PSEN-1*, 14q24.2) are identified in up to 50% of patients (15), abnormal forms of Amyloid Precursor Protein gene (*APP*, 21q21.3) are found in 15-22% (16), and Presenilin-2 (*PSEN-2*, 1q42.13) pathological variants account for less than 2.5% (17). So far, 51 pathological forms have been reported for *APP*, 220 for *PSEN-1*, and 16 for *PSEN-2* (18). All but a few of them are involved in the pathogenesis of AD through the process of formation of amyloid- β protein built plaques, which are a histopathologic hallmark of the disease and a central component of the "amyloid cascade hypothesis" for AD (19).

Several phenotypic clues point to the involvement of a particular gene. While spastic paraparesis and "cotton wool plaques" (20) are associated with a *PSEN-1* mutations, cerebral amyloid angiopathy with cerebral haemorrhages is typical for *APP* ones (21) and families with *PSEN-2* caused AD are primarily of Volga-German origin and with later onset of symptoms (22). However, recent studies show that clinical phenotype is not rigidly linked to aetiological genotype and may be modified by a number of factors such as previous experience, cognitive activity and epigenetic mechanisms (23). *PSEN-1* mutations are a good example of that given the remarkable heterogeneity in neuropsychiatric features among affected individuals whose symptoms are often nearly identical to those seen in FTD or DLB (24).

Below, we describe a clinical case of an EOAD patient carrying a rare form of *PSEN-1* mutation who was followed-up for

2 years after disease onset. His clinical presentation exemplifies the large symptomatic variability of EOAD dementia even in its aetiologically clarified monogenic forms.

CASE PRESENTATION

The subject first presented for consultation in October 2016 (aged 39) at the Department of Psychiatry of Plevin University Hospital with a history of abrupt behavioral change 7 months prior to hospitalization. Slowing of speech and responsivity as well as impaired occupational functioning were noticed first (the patient was working as a croupier in a small casino at that time). Several months after that, mild dysarthria and difficulties finding the right words (i.e., dysnomic manifestations) occurred, followed by emotional lability with frequent and brief episodes of sadness (crying) or irritability with verbal outbursts. Transient episodes of disorientation and perplexity appeared after that. Relevant medical history included head trauma without loss of consciousness in 2014 and a skin form of lupus erythematoses since 2007, currently in remission. These conditions were not considered as causally related to presenting symptoms. Premorbid functioning was appropriate to social background and academic level (high school) and what attracted attention was family history showing that the patient's father had been diagnosed with dementia syndrome started at about 44 years of age and lead to death in a psychiatric institution 4 years after that. Unfortunately, available medical records were limited, with CT data for cortical atrophy described as an instrumental finding and rapidly progressing severe memory disturbance and dyspraxia followed by avolitional-apathy syndrome pointed out as clinical features.

During a short hospital stay, CT scan and a battery of cognitive tests were performed showing moderate cortical atrophy in par with a moderately severe dementia syndrome (MMSE score of 14) presenting with significant short-term memory impairment, problems with concentration, and sustained attention during cognitive tasks, substantially damaged abstract thinking with reduced ability to form and understand concepts, difficulties with verbalization of his own mental experiences. Constructional dyspraxia was prominent together with writing problems (dysgraphia) while biographical memory was relatively spared. Laboratory check-up including CBT, renal and liver biochemistry, serum glucose, lipid profile, vitamin B12, folate and TSH levels, urine test as well as immunological examination for luetic and HIV infections did not reveal deviations. EEG examination was not judged to be indicated since patient did not show epileptic activity. Cerebrospinal fluid (CSF) biomarkers test and PET were not done because these diagnostic approaches are still with

CARRIER SCREENING FOR SINGLE-GENE DISORDERS – A BRIEF REVIEW

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Summary

Carrier screening (CS) is an approach to pre-reproductive identification of couples at risk of having offspring with a single-gene disorder (SGD). The goal of CS is to facilitate reproductive autonomy and informed decision-making of the revealed risk couples. Initially, CS was introduced in the 1970s among the Ashkenazi Jewish population in the USA with a high incidence of Tay-Sachs disease. Until recently, CS had a limited application, mainly among individuals of a particular ethnicity or family history of SGD, and a limited number of conditions are included. Implementing the revolutionary technology of next-generation sequencing revealed a much more comprehensive range of possibilities for CS. The expanded alternative variant introduced a new concept that allows screening for hundreds to thousands of SGDs without pre-selection of individuals based on their ancestry or family history. Furthermore, the number of detected pathogenic variants is much higher compared to the traditional CS. Currently, there is insufficient experience with the application of expanded CS, and the lack of uniform guidelines is a major problem when it comes to massive implementation. Nevertheless, the significant potential of the expanded CS has given rise to a growing interest in it and provoked in-depth discussions about the opportunities of widespread application in practice.

Keywords: carrier screening, recessive disorders, ethnic-based, universal, expanded

Introduction

Genetic disorders are gradually gaining more attention during the last decades, primarily due to the remarkable advances in molecular technologies allowing a better understanding of genetic mechanisms and the achievement of more adequate diagnoses. Single-gene disorders comprise approximately 39% of all rare conditions [1, 2]. It is estimated that they collectively account for 10% of infant mortality and between 10% and 34% of pediatric hospitalizations [3]. Recessive single-gene disorders (autosomal and X-linked) constitute a rather significant proportion of all mendelian diseases. Even though their true prevalence is still unknown, it is considered that there are more than 1700 recessively inherited conditions

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Received: September 30, 2021

Revision received: October 10, 2021

Accepted: November 25, 2021

Review

Genetic Basis of Dual Diagnosis: A Review of Genome-Wide Association Studies (GWAS) Focusing on Patients with Mood or Anxiety Disorders and Co-Occurring Alcohol-Use Disorders

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Citation: Stoychev, K.; Dilkov, D.; Naghavi, E.; Kamburova, Z. Genetic Basis of Dual Diagnosis: A Review of Genome-Wide Association Studies (GWAS) Focusing on Patients with Mood or Anxiety Disorders and Co-Occurring Alcohol-Use Disorders. *Diagnostics* **2021**, *11*, 1055. <https://doi.org/10.3390/diagnostics11061055>

Academic Editor: Drozdtoi Stoyanov

Received: 10 May 2021

Accepted: 3 June 2021

Published: 8 June 2021

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Abstract: (1) Background: Comorbidity between Alcohol Use Disorders (AUD), mood, and anxiety disorders represents a significant health burden, yet its neurobiological underpinnings are elusive. The current paper reviews all genome-wide association studies conducted in the past ten years, sampling patients with AUD and co-occurring mood or anxiety disorder(s). (2) Methods: In keeping with PRISMA guidelines, we searched EMBASE, Medline/PUBMED, and PsycINFO databases (January 2010 to December 2020), including references of enrolled studies. Study selection was based on predefined criteria and data underwent a multistep revision process. (3) Results: 15 studies were included. Some of them explored dual diagnoses phenotypes directly while others employed correlational analysis based on polygenic risk score approach. Their results support the significant overlap of genetic factors involved in AUDs and mood and anxiety disorders. Comorbidity risk seems to be conveyed by genes engaged in neuronal development, connectivity, and signaling although the precise neuronal pathways and mechanisms remain unclear. (4) Conclusion: given that genes associated with complex traits including comorbid clinical presentations are of small effect, and individually responsible for a very low proportion of the total variance, larger samples consisting of multiple refined comorbid combinations and confirmed by re-sequencing approaches will be necessary to disentangle the genetic architecture of dual diagnosis.

Keywords: mood disorders; anxiety disorders; alcohol use disorders; comorbidity; genetics; GWAS

1. Introduction

Alcohol use disorders (AUDs) affected >100 million people in 2016 [1], whereas, a year earlier, 322 million lived with depression and 264 million suffered from anxiety disorders [2]. In addition to being globally significant health problems in their own right, these disorders occur together much more frequently than expected by chance, confirming a phenomenon known as *comorbidity* or *dual diagnosis* which has been verified by a number of population- [3–9] and clinically [10–14] based studies over the past three decades. Generally estimated, odds ratios (OR) for the association are 1.64 and 1.53 for the combination anxiety disorder–AUD and depression–AUD respectively [15].

Co-occurring mood and anxiety disorders increase the severity of AUD and associated disability [16] whereas AUD negatively impacts anxiety and mood disorder by worsening symptoms [17], magnifying suicide risk [18], and compromising treatment efficacy [17,19]. Thus, advances in understanding the mechanisms underlying comorbidity will ultimately result in better treatment outcomes. The variety of explanation hypotheses of comorbidity [20] may be broken down to two groups [21]. According to the causal or illness-mediated theories [22], a primary alcohol, mood, or anxiety disorder directly or indirectly causes the

Familial Lynch syndrome with early age of onset and confirmed splice site mutation in MSH2: A case report

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Received October 19, 2021; Accepted February 9, 2022

DOI: 10.3892br.2022.1522

Abstract. Lynch syndrome (LS) is an autosomal dominant cancer syndrome. It can be caused by mutations of several genes, including MLH1, MSH2, MSH6, PMS2, MLH3 and MSH3, which are responsible for DNA mismatch repair, and LS affects 3-5% of patients with colorectal cancer (CRC). LS is associated with a high risk of cancer in several different locations, although the most commonly affected regions are the colon (20-70% risk), endometrium (15-70% risk), stomach (6-13% risk) and ovaries (4-12% risk). In the present report, the familial case of LS with a detected pathogenic variant in the MSH2 gene is described. The proband was a male who was diagnosed with CRC at the age of 25 years. Genealogy analysis revealed a total of seven affected relatives (including the proband), one of whom (I degree relative, mother) had synchronous cancers (endometrial and ovarian) and five others (of II and III degree relation) had ovarian cancer. Genetic analysis using next generation sequencing detected a heterozygous germline mutation in the MSH2 gene (c.1386 + 1G > A) in the proband and his mother, confirming the diagnosis of LS. The results of the recommended genetic test in an asymptomatic relative of the proband (II degree relative, uncle), found the same familial mutation. Subsequent prophylactic colonoscopy of this relative revealed early stage CRC. The presented case confirms the need for specific genetic analysis, alongside genetic counseling, in hereditary cancer

syndromes. Active genetic prophylaxis in patients with LS allows early detection of primary cancers in other locations, and pre-symptomatic genetic analysis of relatives is an option for early diagnosis.

Introduction

Lynch syndrome (LS) is the most common hereditary cause of colorectal cancer (CRC), accounting for 3-5% of all CRC cases (1). LS was previously termed hereditary nonpolyposis CRC (HNPCC) to emphasize the absence of colon polyps and to distinguish it from the other types of hereditary CRC, which are characterized by the presence of polyps, such as Adenomatous Polyposis Coli and Hamartomatous Polyposis syndrome (1). It is estimated that LS is possibly the most common hereditary cancer syndrome, with an overall prevalence of 1/100-1/180 in the general population (1). LS is associated with a high lifetime risk of developing several types of cancer, primarily CRC (20-70% risk with an average age of diagnosis of 44-61 years), endometrial cancer (15-70% risk with an average age of diagnosis of 44-61 years), ovarian cancer (risk 4-12% with an average age of diagnosis of 42.5 years), gastric cancer (risk 6-13% with an average age of diagnosis of 56 years) and for other cancers (small intestine, brain, skin, hepatobiliary and urinary tract, overall risk 15%) (2). The etiology of LS is an inherited germline mutation in one of the Mismatch Repair (MMR) genes-MLH1 (3p22), MSH2 (2p21), MSH6 (2p16), PMS2 (7p22), MLH3 (14q24), MSH3 (5q14), MSH5 (6p21) or MLH2 (2q32) (3). The MMR system is responsible for repairing single base mismatches and small insertions and deletions that occur predominantly during replication (4). According to Knudson's 'two-hit' hypothesis, failure of the MMR repair system is a consequence of bi-allelic inactivation of MMR genes (classical tumor suppressor genes) (3). Therefore, individuals who are carriers of one germline mutation in these genes are simply predisposed to cancer. If the somatic mutation in the second wild-type allele occurs during the carrier's lifetime, a cancer will develop. The somatic mutation in the corresponding wild-type allele is typically a point mutation (3).

A deficiency in the MMR complex leads to a high mutation rate, especially in repetitive DNA sequences (dispersed

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Key words: Lynch syndrome, mismatch repair deficiency, pathogenic variant, splice site, genetic counseling, colorectal cancer, ovarian cancer, endometrial cancer

Genetic predisposition in female patients with triple-negative breast cancer

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Received July 27, 2023; Accepted November 23, 2023

DOI: 10.3892/wasj.2023.217

Abstract. Triple-negative breast cancer (TNBC) is an immunohistochemical tumor type characterized by the absence of estrogen, progesterone and human epidermal growth factor receptors. Its complexity renders it difficult to select an effective therapy. TNBC accounts for ~15% of all breast cancer cases in the Caucasian population and 35% among African American women; it is most common in women <40 years of age. The present study examined the spectrum and frequency of germline mutations in genes with a high and moderate penetrance in a cohort of women with TNBC. Molecular analysis was performed with a multigene panel of 94 genes for cancer predisposition using next-generation sequencing. The mean age of the TNBC cohort at the time of diagnosis was 44 years, 14 years younger than the mean age of the non-TNBC cohort (58 years). The results revealed a high frequency (41.2%) of pathogenic/likely pathogenic variants in susceptible genes in women with TNBC. Pathogenic germline variants in BRCA1/2 were found in 32% of the women (70% of pathogenic variants detected), and alterations in other predisposing genes (FANCM, CDKN2A and BLM) were found in 9% of the women. The data of all the patients with TNBC studied revealed a family history of cancer in 30% of the cases; most frequently, this involved relatives with breast cancer (11.8%). In the present study, the most frequent variant detected (in 11.8% of patients with TNBC) was a pathogenic variant in the BRCA1 gene (c.5266dup). The recommendations of genetic

counselors for patients with a pathogenic BRCA1/2 germline variant followed accepted prevention and risk reduction guidelines. By contrast, in the case of a detected pathogenic germline variant in genes with a moderate or low penetrance, the recommendations depended on the assessment of genetic counselors based on age at diagnosis, family history, the gene affected and the pathogenic variant.

Introduction

Breast cancer remains the most frequently diagnosed type of cancer among women worldwide, accounting for 31% of all cancer cases (1). The situation is similar in Bulgaria, with 26.8% of all cancer cases (<https://www.sbaloncology.bg/index.php/bg/>). Despite the improvement in diagnostic techniques and treatment, breast cancer is still the most common cause of cancer death in women (2). Breast cancer is genetically and clinically heterogeneous and has several subtypes. The most widely used classification is from an immunohistochemical perspective and is based on the expression of the following hormone receptors: Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). According to the latter, four subtypes of BC are widely recognized: i) Luminal A (presence of ER and/or PR and absence of HER2, and a low expression of the proliferation marker, Ki-67, <20%); ii) luminal B (presence of ER and sometimes PR, and the absence of HER2 and a high expression of Ki-67, >20%); iii) HER2 subtype (high expression of HER2, and the absence of ER and PR); iv) triple-negative breast cancer (TNBC) (absence of ER, PR and HER2) (3).

TNBC accounts for ~15% of all BC cases among Caucasian women and 35% in African American women (4); it is most common in women <40 years of age (3). This breast cancer subtype is more likely associated with a larger tumor size, a poorly differentiated histology and a higher incidence of lymph node metastases, leading to more aggressive behavior and poor outcomes (4). As with other breast cancer types, TNBC exhibits heterogeneity in histology, patterns of dissemination, response to therapy and outcomes. The majority of cases of TNBC have been shown to be invasive ductal carcinomas, although other histologies are possible, with the 5-year survival rates ranging

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Key words: triple-negative breast cancer, genetic predisposition, pathogenic variant, genetic risk

Single Case

Netherton Syndrome with a Novel Likely Pathogenic Variant c.420del (p.Ser141ProfsTer5) in SPINK5 Gene: A Case Report

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Keywords

Netherton syndrome · *SPINK5* gene mutation · Trichorrhexis invaginata · Acitretin · Case report

Abstract

Introduction: Netherton syndrome (NS) is a rare autosomal recessive genodermatosis in the group of congenital ichthyosis. The clinical manifestations of the syndrome vary from a very mild clinical manifestation occurring with the picture of ichthyosis linearis circumflexa to exfoliative erythroderma. It can be fatal in the first days of a newborn's life due to dehydration, hypothermia, weight loss, respiratory infections, and sepsis. A specific anomaly of the hair trichorrhexis invaginata is considered pathognomonic for the syndrome. Genetic testing of *SPINK5* gene is key to confirming the diagnosis and starting early treatment. **Case Presentation:** We present a case report of NS in a 6-year-old boy who suffered from generalized erythroderma and desquamation of the skin from birth. The patient has atopic diathesis, recurrent skin infections, increased levels of IgE, and delayed physical development. Two genetic variants in *SPINK5* gene with clinical significance were identified. The first detected variant is a nonsense mutation, predicted to cause loss of normal protein function either by protein truncation or by nonsense-mediated mRNA decay. The second variant is a likely pathogenic frameshift mutation that truncates the protein in 5 amino acids. The child was treated with acitretin, without satisfactory effect. **Conclusion:** The genetic variant we have described correlates with a severe clinical phenotype of NS. The second genetic variant of the *SPINK5* gene, inherited from the father in our case, is novel and has never been published in the literature.

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Published by S. Karger AG, Basel

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Article

Colorectal Cancer: A Brief and Simplified Analysis of a Complex Disease

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Abstract: *Background and Objectives:* This study examined factors influencing the onset and progression of colorectal tumors, including patients’ epidemiological data, tumor location (right-sided, left-sided, and rectal), histomorphology, perineural or intraneural invasion, lymph node status, immune reactions, mismatch repair (MMR) status, and commonly observed mutations. Our primary goal was to evaluate their predictive and prognostic value and interactions. *Materials and Methods:* We analyzed a retrospective cohort of 100 patients with colorectal adenocarcinoma diagnosed between 2020 and 2023, using formalin-fixed paraffin-embedded (FFPE) tumor blocks. The methods included routine H&E microscopy, immunohistochemistry, Next-Generation Sequencing (NGS), and subsequent statistical analysis. *Results:* The findings showed a median diagnosis age of 70 years, with no gender-specific tumor localization. Right-sided tumors were prevalent, especially among patients with a defective MMR (dMMR), which represented 89% of dMMR cases. MMR status significantly correlated with tumor localization. We observed significant relationships between tumor grade, lymphovascular invasion, and overall tumor stage. Higher tumor grades and stages correlated with increased lymphovascular invasion and lymph node involvement. Interestingly, tumor budding did not correlate with lymph node metastasis but was significantly associated with higher tumor grades. Most BRAF mutations were found in right-sided tumors, indicating a significant correlation with this localization. *Conclusions:* This study focuses on the diversity of colorectal cancer (CRC) by examining how genetic and histological characteristics vary based on tumor location or other tumor variables.

Keywords: colorectal adenocarcinoma; left and right-sided; histologic type; peritumoral budding; lymphovascular and perineural invasion; lymph node metastasis; MMR status; mutations; NGS



Citation: Petrov, K.; Ivanov, I.; Popovska, S.; Betova, T.; Kamburova, Z. Colorectal Cancer: A Brief and Simplified Analysis of a Complex Disease. *Medicina* **2024**, *60*, 2034. <https://doi.org/10.3390/medicina60122034>

Academic Editor: Claudio Gambardella

Received: 22 October 2024

Revised: 20 November 2024

Accepted: 6 December 2024

Published: 10 December 2024



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1. Introduction

Cancers of the colon and rectum are among the leading causes of illness and death worldwide, contributing significantly to the global disease burden, with rising incidence rates in many regions.

According to data from 2022, globally, for both sexes, colon carcinomas rank fourth in incidence, with approximately 1,150,000 cases annually, and fifth in mortality, with approximately 540,000 cases. Rectal carcinomas, on the other hand, are eighth in incidence, with approximately 740,000 cases, and tenth in mortality, with approximately 340,000 deaths per year for the same period [1].

In the United States, it is estimated that there will be 152,810 new cases of colon and rectal cancers combined for both sexes. Additionally, the estimated number of deaths from these cancers in both sexes will be 53,010 in 2024. Colorectal cancer has now become a leading cause of death in men and the second leading cause in women under the age of 50 [2].

КЛИНИЧЕН СЛУЧАЙ НА NEUROFIBROMATOSIS-NOONAN SYNDROME

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Въведение

Неврофиброматоза тип I (NF1), известна още като Болест на Von Recklinghausen, представлява едно от честите моногенни заболявания с честота около 1 на 3000 и автозомно доминантен тип на унаследяване. Главните критерии за диагноза включват: ≥ 6 пигментни петна тип „café-au-lait“; ≥ 2 нодули на Lisch; лентигиноза аксиларно и ингвинално; ≥ 2 неврофиброми; оптични глиоми; костни лезии (псевдоартроза, хипоплазия на крилата на сфеноидната); фамилна история за NF1 [5]. Причинява се от мутации в NF1 - супресорен ген разположен в хромозомен регион 17q11.2 [6, 8].

Синдромът на Noonan (NS) е автозомно доминантно заболяване, с честота 1 на 1000-2500 и представлява едно от най-честите генетични състояния, засягащи нервната система [8]. Клиничните прояви включват: типично лице (с триъгълна форма, хипертелоризъм, епикант, птоза, ниско разположени ротирани уши), широк врат, ниска линия на окосмяване, нисък ръст, аномалии на гръден кош, сърдечни дефекти (най-вече пулмонална стеноза), крипторхизъм, умерено умствено изоставане, хеморагична диатеза и др. [4]. NS е генетично хетерогенен, като най-често (50% от случаите) се установяват мутации в PTPN11 гена (хромозомен регион 12q24) и по-рядко мутации в гените SOS1, RAF1, KRAS [6, 8].

Neurofibromatosis-Noonan синдромът (NFNS) се описва като състояние, обединяващо белези на NF1 и NS, като генетичната му природа е неуточнена. [8] Проучвания напоследък определят NFNS, по-скоро като вариант на NF1, основавайки се на факта, че при тези пациенти мутациите в NF1 гена са най-чести, докато мутации в PTPN11 гена не се намират [3].

Клиничен случай

Пациентка се за 10 годишно момиче, насочено за генетична консултация и цитогенетично изследване, по повод: нисък ръст, птериgium коли, множествени пигментни невуси по тялото - съмнение за синдром на Търнер.

Из анамнезата: Момиче от II-ра бременност патологично протекла (болки и кървене), родено с нормален механизъм, при раждане с тегло 3600 гр и ръст – 49 см. Растеж и развитие: нормална изкуствено (поради агалактия), данни за лежестепенно изоставане в нервнотелесическото развитие - проговорила на 3 год. възраст; с говорни нарушения. Родителите са клинично здрави, с възраст при раждане на майката-28 г. и бащата-31 г. **Фамилни данни** - нормални на 17 год. с епилепсия и метаболитен синдром.

Семнословно дърво (изградено, по данни на майката) – отсъства информация за други родственици с белези на неврофиброматоза тип 1 (пигментации по кожата, фибромни образувания, нарушения в зрението и слуха) или с нарушения в умственото развитие.

Вншни фенотипни белези:

Ръст – 134 см (-1SDS), тегло – 36 кг (+15%); лицев дисморфизъм – макроцефален череп, епикант, нисък корен на носа, високо натиеско небце, ниско разположени уши, къс врат с ниска линия на окосмяване, птериgium коли, деформиран щитовиден гръден кош (хлътнал стернум); раздалечени мамили; нормални външни гениталии - начално пубархе, фиброзно образуване на дясната голяма лабия. По цялото тяло (труп и крайници) - множествени (повече от 6 броя), с различни размери пигментни петна (с начало изява от раждането, без ясна динамика по отношение увеличаването им).

Клиничен случай на новородено момиче с Ichthyosis congenita, резултат от мутация в ALOX12B гена

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Резюме

Понятието Автозомно рецесивна вродена ихтиоза (АРВИ) се отнася за група от редки заболявания на кератинизацията, класифицирани като несиндромна форма на ихтиоза. Тази група е изключително хетерогенна, както клинично, така и генетично (открити са девет гена, асоциирани с АРВИ). Най-често АРВИ се изяснява клинично при раждане под формата на Collodion baby, с честота 1:50000 до 1:100000 раждания за Европа. Постнатални усложнения и смърт се описват съответно в 40% и 11% от случаите на тази форма. За българската популация липсват публикувани данни относно честотата и мутационния спектър на АРВИ.

Представяме случай на новородено момиче с Collodion baby. Бебето е родено преждевременно (в 36-37 г.с.) с опъната, лъскава кожа и малкоформативни стигми: ектропион, малки лошо моделирани уши, къса шия, брахидактилия с недоразвити нокти. Кожният статус показва типична за вродената ихтиоза еволюция: десквамация на повърхностния слой на едри ламели с подлежаща ранима кожа, образуване на дълбоки, сълящи разгади, с лимфна течност. В следващите дни, във връзка с развит стафилококов сепсис, състоянието на новороденото се влошава и то експира на 5-ия ден след раждане.

Поради бързия ход на усложненията, завършили с летален изход при детето, не е взет биологичен материал за генетична диагностика. Молекулярно-генетичният анализ при майката, започнал с директно секвениране на TGM1 гена (с най-голям дял по литературни данни в етиологията на АРВИ), не установи генетични дефекти. Изследването на следващия по честота ген - ALOX12B, показва наличие на мутация c.1562A>G (в хетерозиготно състояние). Същият молекулен дефект се потвърди и при бащата. Поставянето на точна клинична и генетична диагноза при случаи на вродена ихтиоза дава възможност за навременна и адекватна генетична консултация и ефективна профилактика (пренатална диагностика) на заболяването в засегнатите семейства.

Представеният от нас случай ще допринесе за обогатяване на знанията относно честота и генетичния спектър на вродената ихтиоза в българската популация.

Ключови думи: Вродена ихтиоза, Ichthyosis congenita, Collodion baby, ALOX12B

Clinical case of a newborn girl with Ichthyosis congenita – result of a mutation in ALOX12B gene

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Abstract

Autosomal recessive congenital ichthyosis (ARCI) is a group of non-syndromic disorders of keratinization that is characterized with clinical and genetic heterogeneity. The main skin phenotypes are Lamellar Ichthyosis, Congenital Ichthyosiform Erythroderma and Harlequin Ichthyosis. Genetic analysis has implicated nine genes involved in the etiology. Most of the patients with ARCI are born enveloped in a collodion membrane (Collodion baby) and the incidence of this phenotype is between 1:50000 to 1:100000 for the European population. Collodion baby is usually associated with a premature delivery, increased perinatal morbidity (40%) and mortality (10%). Concerning Bulgarian population, there is no published data about the incidence of this disorder and the common mutations.

We report a case of a female baby with the phenotype of Collodion baby. The neonate (born in 36-37 g.w.) was covered by a translucent parchment like membrane. She also had dysmorphic features: ectropion, small wrinkled ears, short neck, brachydactyly with hypoplastic nails. The skin status showed typical for the disorder evolution: desquamation of the surface that revealed erythroderma. In the next few days the baby was getting worse and died at the 5-th day after birth due to Staphylococcal sepsis.

The genetic material from neonate had not been obtained, because of the complications and early death. The parents had been genetically tested. The analysis of mother started with the sequencing of TGM1 gene (the most common gene involved in the etiology of ARCI) did not reveal genetic defects. The following analysis of ALOX12B gene detected c.1562A>G (in heterozygous state) and the same mutation was confirmed in the father.

The achievement of a precise clinical and genetic diagnosis in cases with ARCI gives better opportunity for adequate genetic counseling of the affected families and effective prevention (prenatal diagnosis) of the disease.

The reported case of Collodion baby will contribute to enrichment of the knowledge about incidence and genetic spectrum of congenital ichthyosis in Bulgarian population.

Keywords: Ichthyosis congenita, Collodion baby, ALOX12B

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СИНДРОМ НА NETHERTON ПРИ 6-ГОДИШНО МОМЧЕ

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Синдромът на Netherton е рядко заболяване, което често създава сериозни усложнения в неонаталната възраст. То може да завърши с летален изход в първите дни от живота на новороденото, дължащ се на дехидратация, хипотермия, загуба на телло, респираторни инфекции и сепсис. Заболяването се среща при 1:200 000 новородени и засяга предимно женския пол. Клиничните прояви на синдрома варират от съвсем лека клинична изява, протичаща с картината на ichthyosis linearis circumflexa, до ексфолиативна еритродермия. Други усложнения, свързани със синдрома, са умствено и физическо изоставане [1].

КЛИНИЧЕН СЛУЧАЙ

Представяме 6-годишно момче, което постъпва за първи път в Клиниката по кожни венерически заболявания, УМБАЛ – Плевен. Родено е в 37 гестационна седмица чрез Цезарово сечение от втора, нормално протекла бременност, с телло 3350 г и ръст 53 см. От раждането боледува с генерализиран еритем и едроламелозна десквамация по кожата. На 5-дневна възраст, с неонатална инфекция и в увредено общо състояние детето постъпва за лечение в Неонатологичното отделение на СБАЛДБ „Проф. д-р Иван Митев“, София, откъдето е изписано след 3-месечно лечение, без промяна в състоянието – с телло 2900 г и диагноза Erythrodermia ichthyosiformis congenita. Препоръчана е ежедневна локална терапия с емолиенти и

проследяване. Поради периодично обостряне на състоянието, изразяващо се в силен еритем, оток и изтичане на серозен ексудат от кожата, детето неколкратно е хоспитализирано и лекувано чрез интравенозно приложение на антибиотици и Humanalbumin 20%, прилагани са локални кортикостероиди и емолиенти. По данни на майката детето има силно изразен денонощен сърбеж. На фона на непрекъснато провежданото амбулаторно лечение със системни антихистамини, системни и локални антибиотици и емолиенти, майката съобщава, че кожата остава зачервена и много суха, покрита с повърхностни ерозии и жълтеникави люспи с неприятна миризма, вкл. в областта на капилициума и външните слухови канали. Детето има крехка и чуплива коса. По повод тези оплаквания на 5-годишна възраст то е консултирано по данни от медицинската документация в Gay's and St. John's Institute of Dermatology, Лондон, където е потвърдена диагнозата аутозомно рецесивна вродена ихтиоза и е препоръчана терапия с Acitretin в доза 0.25-0.5 мг/дневно. Детето е фамилно необременено.

Соматичен статус: Дете от мъжки пол, на възраст 6 год. и 2 месеца, с телло 19 кг и ръст 109.5 см, BMI – 17. Момчето е в добро общо състояние, афебрилно, с невропсихическо развитие съответно на възрастта и леко забавено физическо развитие. Сърдечносъдова и дихателна системи – везикуларно дишане, ритмична сърдечна дейност. Корем над нивото на гръдния кош, палпаторно мек

и неболезнен, черен дроб и слезка не се палпират увеличени. Succusio renalis – двустранно отр. Генерализирана микрополиаденопатия, ангажираща субмандибуларни, аксиларни и ингвинални периферни лимфни възли двустранно.

Дерматологичен статус: Патологичните кожни промени ангажират капилициума, лицето, тялото и крайниците на фона на генерализирана кожна ксероза. В областта на лицето и тялото се представят от дифузен еритемодем и едроламелозна десквамация. По екстензорната повърхност на горните крайници, предната повърхност на бедрата и задната повърхност на подбедриците се наблюдават добре контурирани еритемосквамозни плаки, покрити от едри жълтеникави сквами, на фона на непроменена околна кожа. Установява се птоза на горните клепачи и ектропион на двете очи (фиг. 1, 2 и 3). В областта на външните слухови канали – запущалки от сквамокрусти. Нокти – б.о. Косми – липсват веждите и отчасти миглите. При дерматоскопия на скалпа с дерматоскоп 3Gen – DermLite DL4, с поляризирана светлина и работно увеличение 10x, се установяват полета с промени по хода на космените стъбла по типа на Trichorrhexis Invaginata (TI) (фиг. 4а и б).

ИЗСЛЕДВАНИЯ И КОНСУЛТАЦИИ

Параклинични изследвания: Пълната кръвна картина с диференциално броене на левкоцити и биохимич-

НАСЛЕДСТВЕН РАК НА ГЪРДАТА: ПРОФИЛ НА ГЕРМИНАТИВНИ МУТАЦИИ, СПОРЕД ВЪЗРАСТТА НА ДИАГНОСТИЦИРАНЕ HEREDITARY BREAST CANCER: PROFILE OF GERMLINE MUTATIONS BY AGE AT DIAGNOSIS

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ABSTRACT

The advent of new genomic technology - Next Generation Sequencing (NGS) - has led to an expansion of knowledge and the introduction of new tests related to the genetic spectrum of predisposition to oncologic diseases. Genomic studies have enabled the identification of both new predisposition genes and new pathogenic variants (mutations) in already known genes.

We present the results of a study on genetic predisposition in women with breast cancer in relation to age at diagnosis. The studies were conducted in the Laboratory of Genomic Medicine and Precision Pathology of the "Leonardo da Vinci" Competence Center within the European project BG05M2P001-1.002-0010.

A total of 203 women with breast cancer were analyzed using an NGS panel containing 94 cancer predisposition genes.

Patients were categorized into the following six age groups: under 29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, over 70 years. In the age groups under 29 years, between 30-39 years and 40-49 years, the most frequently affected genes are the highly penetrant BRCA1 and 2, while in the groups after 40 years, the moderately penetrant genes (most frequently CHEK2 variants) are more frequently affected.

The use of panels with a larger number of cancer predisposition genes in genomic testing expands the possibilities for discovering the genetic determinants associated with the disease, and the description of the newly discovered pathogenic variants enriches the scientific database related to this pathology.

Keywords: age, breast cancer, genetic predisposition

Въведение

Ракът на гърдата (РГ), в световен мащаб, е най-често диагностицираното онкологично заболяване и водеща причина за смърт сред жените. По данни за 2018 г., броят на новодиагностицираните случаи в света са 2,088,849, което представлява около една четвърт (24%) от всички онкологични заболявания, засягащи жените. Установява се нарастване на честотата на РГ с 3,1% годишно (от 641,000 за 1980 до > 1,6 милиона за 2010г.), като тази тенденция се запазва и след 2010г., което се обяснява с увеличаването и застаряването на населението. В световен мащаб изчисления среден риск на жена до 74 годишна възраст за развитие на рак на гърдата е 5,03%.

За Европа, РГ също е най-често диагностицираното заболяване сред жените (562 500 през 2018 г.). Средно 20% от случаите на РГ в Европа се установяват при жени под 50 годишна възраст; 36% се срещат при жени между 50–64 години, а останалите случаи - при жени над 65г. Смята се, че една от 8 жени в Европа ще развие рак на гърдата преди 85,3-годишна възраст. Жените в Европа, починали от тази диагноза през 2018 са 138 000 (Cancer today [Internet]).

За България, ново диагностицираните случаи с РГ през 2018 са 4 016 (25.7% от всички ново диагностицирани онкологични заболявания сред жените), а смъртните случаи за същата

МОЛЕКУЛНИ МЕХАНИЗМИ НА КАНЦЕРОГЕНЕЗА ПРИ ТУМОРИ НА ОКОТО

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Абстракт

Канцерогенезата, в частност и тази при туморите на окото, представлява неконтролируем растеж и развитие на клетките, избягвайки нормалните процеси на регулация. Тези заболявания, от генетична гледна точка се дължат на взаимодействието на генетични фактори и фактори на средата. В зависимост от ролята, която играят в процесите на туморогенеза, генетичните фактори се делят най-общо на две – прото-онкогени и тумор-супресорни гени. По отношение на туморите на окото все още се проучват различните молекулни механизми.

По тази причина си поставихме за цел да обобщим направените досега открития в областта на молекулярната генетика при тумори на окото.

Направена беше справка, включваща различни литературни източници, за влиянието на различни генетични фактори върху риска за развитие на тумори на окото, прогнозата и терапевтичните възможности. Анализирани бяха ключови гени, участващи в етиологията на туморите на окото, като Rb1 при ретинобластом, и беше обсъдено значението на генетичния тест като подход в диагностиката и лечението на този вид тумори. Натрупаните знания за молекулните механизми на тяхното възникване, както при деца така и при възрастни, дава възможност за развиване на потенциалните терапевтични подходи, свързани с генетичните дефекти, както и на перспективите за персонализирана медицина в онкологията на окото. Чрез комбинирането на генетични изследвания и клинична практика, може да се изгради ефективна стратегии за превенция и лечение на очните тумори.

Въведение

Ракът представлява група заболявания, характеризиращи се с неконтролируем растеж, пролиферация и разпространение на клетките. От генетична гледна точка е мултифакторно заболяване, резултат от взаимодействието на генетични фактори и фактори на средата. Нормалните клетки се превръщат в ракови, поради натрупването на дефекти (мутации) в ДНК, които могат да бъдат герминативни (унаследени от някой от родителите) или соматични (възникнали в хода на индивидуалния живот на човек, спонтанно или индуцирано под действието на фактор на средата)(1).

Неопластичният процес се развива, когато мутациите създават предимство на раковите клетки пред нормалните, като правят възможно преодоляването на естествените регулаторни механизми на клетъчния цикъл и имунната система на организма. В резултат на всичко това, изменените клетки започват да се делят неконтролируемо и да се разпространяват(1).

Гените участващи в канцерогенезата, в зависимост от ролята, която имат върху клетъчната пролиферация, могат да се разделят на две основни категории: тумор-супресорни гени (подтискащи пролиферацията) и прото-онкогени (активиращи пролиферацията) (1).

Прото-онкогени (ПОГ) са нормални гени, чиито белтъчни продукти активират клетъчната пролиферация. Белтъчните продукти на тези гени са: растежни фактори или рецептори

ГЛАВА 3

ГЕНЕТИКА НА ТРОЙНО НЕГАТИВЕН КАРЦИНОМ НА ГЪРДА (ТНКГ)

Автор: д-р Зорница Камбурова

Тройно-негативният рак на гърдата е с агресивен ход, засяга по-често млади жени (под 40 г.), често се диагностицира в късен стадий, тумора обикновено е с по-големи размери, ниско-диференциран и с по-често засягане на лимфните възли [1, 2]. Заболяването е с по-агресивен ход от другите хистологични типа на карцином на гърдата (КГ), като са установени по-висока честота на рецидивите и по-лоша прогноза, като тези характеристики в голяма степен се дължат на това, че по-голямата част от ТНКГ се диагностицират в късен (3-ти) стадий [3]. Установено е, че най-често рецидива се появява между 1-3 година след диагностицирането, а смъртността е най-висока в първите 5 години от лечението, сравнено с другите не-ТНКГ [4]. Този тип КГ се характеризира с по-добър отговор на неoadювантна химиотерапия (30-40%) и пациентите с такъв отговор имат по-добра преживяемост. За съжаление, пациенти с недобър отговор след химиотерапията имат много лоша прогноза [5]. Рецидивите след TNBC са свързани с висок риск от метастазиране в бял дроб или централна нервна система, и по-рядко кости, като средната преживяемост в тези случаи е около 1 година [4, 6-8].

Поради всички изброени характеристики на този хистологичен вариант на КГ, усилията на учените продължават да са насочени, както към изучаване на етиологията на ТНКГ, с цел профилактика и ранна диагностика, така и към определяне на точната молекулярната характеристика на тумора, с цел прогноза и ефективна персонализирана терапия.

Етиология на тройно-негативния рак на гърдата от генетична гледна точка

От генетична гледна точка етиологията на ТНКГ, както и на всички видове КГ е мултифакторна, резултат от взаимодействието на генетични фактори (мутации), унаследени или придобити, и негенетични фактори (рискови фактори). Негенетичните

Глава 5

РЕЗУЛТАТИ ОТ СОБСТВЕНИ ПРОУЧВАНИЯ

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Генетично предразположение при жени с ТНРГ

Нашият екип проведе обширно проучване върху генетичната предразположеност при РГ сред Български пациентки. Проучването обхваща 202 жени с хистологично доказан РГ, не селектирани по възраст, фамилна история и хистологичен тип. Установената от нас честотата на ТНРГ е 16,8% (34/202), което съвпада с литературните данни от проучвания правени сред други популации [1, 2, 3]. Намерената средна възраст на диагностициране сред пациентките с ТНРГ – 44 г. е с повече от 10 години по-малка в сравнение с останалите хистологични типа, където установената средна възраст на диагностициране е 58 г. Генетичният анализ беше проведен със секвениране от следващо поколение с платформа на Illumina® (MiSeq DX, NextSeq 550), като беше използван таргетен панел, включващ 94 гени за предиспозиция към онкологични заболявания. Установената честота на носителство на патогенни/вероятно патогенни варианти в гените за предразположение сред жените с ТНРГ е 41,2% (14/34), като носителството на патогенни варианти в BRCA1/2 засяга 32% от жените (70% от откритите патогенни варианти), а измененията в други предразполагащи гени – 9% от тях. Средната възраст на диагностициране при всички жени, носители на прединвазивни мутации е 40 г. (29 г. до 61 г.). Сред жените, диагностицирани над 40 г. възраст, не открихме носителство на мутации в BRCA1, както и в другите предразполагащи гени, но намерихме при една пациентка (2,9%) диагностицирана на 41 г. с патогенен вариант в BRCA2. Установеният от нас процент на носители е висок в сравнение с другите Европейски популации (докладвана честота 15%-19%) [3], като стойността е подобна на тази, която се открива при популацията на Афроамериканците (39%) [4-9]. Съществуват две възможни обяснения за това: първото е, че групата е относително малка (34 жени); второто е, че изследвана група се състои предимно-голямата си част (около 80%) от пациентки диагностицирани с ТНРГ на млада