диагноза при узловых образованиях щитовидной железы, поэтому наибольшая эффективность диагностических методов заключается в их комплексном применении.

Ключевые слова: узловой зоб, диагностика, щитовидная железа.

NODULAR GOITER: THE POSSIBILITIES OF MODERN DIAGNOSTIC METHODS (LITERATURE REVIEW)

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Abstract. There are many methods for investigating the thyroid gland pathology. None of them guarantee mistakes or false results at nodular goiter, especially before surgery. Thus, in 4-6% of patients malignant changes in nodes are diagnosed only after surgery.

The aim of the work was to systematize the modern methods of nodal goiter investigation, to analyse the indications to their application and informative.

All methods of nodal goiter diagnosis were conditionally divided into three groups: methods for determining the functional state of the thyroid gland, visualization methods and methods of morphological diagnosis. However, the primary and obligatory research method remains the clinical examination of the patient with palpation of the thyroid gland and neck. Auscultation of the trachea at the level of the thyroid gland has practical significance only in cases of tracheal stenosis with dense goiter.

Among the laboratory methods of determining the thyroid gland functional state, the determination of the basal secretion level of the thyroid stimulating hormone is extremely sensitive. Determination of thyroxine and triiodothyronine levels is performed as for general fraction, and free fraction. For the diagnosis of the thyroid gland functional changes, a thyroliberin test is used, which is positive for hypothyroidism and negative for hyperthyroidism.

In diffuse toxic goiter (DTG) and chronic autoimmune thyroiditis (Hashimoto, CATH) in the blood serum specific antibodies to the thyroid gland are specified. At CATH elevated levels of antibodies to the thyroglobulin and microsomal fraction are observed, at DTG – to receptors of thyroid stimulating hormone.

Among the methods of visualization, sonography is widely used. In addition to determination of the shape, size, location of nodes during the study structural changes in tissues, especially their blood supply, can be determined. The informativeness of the study is increased when conducting a pulsed spectral and energy doppler study. A spiral computer or magnetic resonance imaging is also used.

Morphological studies hold a leading position in the diagnosis of nodal goiter. Thus, thin-needle aspiration puncture biopsy under sonographic control with subsequent cytological examination of punctulus is obligatory. The use of malignancy markers and wedge-shaped dehydration markers increases the informative nature of the method.

Histological examination is carried out both in the traditional classical way and in the frozen sections of tissues. It can be complemented by immunohistochemical and morphometric methods of diagnosis.

Intraoperative laser autofluorescence spectroscopy also allows to establish the morphological structure of the thyroid gland nodal formations.

Methods of nodular goiter diagnosis have a large variety. Each of them has certain disadvantages. This does not allow to be guided by the results of only one of them in most cases. The most informative diagnostics is achieved with their complex carrying out and interpretation of the results.

Key words: nodal goiter, diagnosis, thyroid gland.

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MALE INFERTILITY AS A RESULT OF GENETIC DISORDERS (REVIEW)

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Introduction. Infertility is a very complex international problem that involves 15% of family couples having unprotected sexual intercourse. Admittedly, a number of factors can influence the birth rate. Approximately one third of infertility cases are associated with male reproductive failure. Another third includes female reproductive problems, and the last one – both male and female factor and other unknown factors of infertility [1]. In spite of numerous evidences of general statistics from all over the world they do not reflect examples and specificities of separate countries and regions. In the whole world there is no sufficiently accurate information indicating the rate of male infertility [2].

An accurate definition of the whole volume of male infertility is a kind of challenge. First of all, population surveys focus on family couples in general and women, in particular. It is indicative of a very specific population. Specific information concerning the number of infertile families is insufficient, and it can result in misrepresentation of real data. Second, male infertility is not fairly highlighted compared to the female one, especially in countries with cultural differences and patriarchal structure, which can prevent obtaining accurate statistical data and their processing. The third point is that male infertility has never been defined as a disease resulting in inadequate statistics. Demographic and clinical studies differ by their epidemiological definition of infertility.

Certain clinical studies investigated infertility for many years, while other clinical researches examined infertility within the period of five years [1].

Global evidence is indicative of the fact that the distrubution of infertility due to male factor ranges within 20-70% and that the percentage of infertile men ranges from 2-5% to 12% [3]. In 30% - 40% of cases there was no factor found associated with male infertility, the phenomenon being named idiopathic male infertility. A said group includes men without anamnesis of fertility and any negative consequences of endocrine, genetic and biochemical laboratory examinations [4,5]. Most of these idiopathic cases are likely to be of genetic origin because, as we know, the number of genes that are involved in human spermatogenesis is over 1 thousand. At present, only a few genes which are implicated in the process of testis formation, testis descent and spermatogenesis have acquired routine clinical application [6,7].

Genetic disorders in case of infertility. Matzuk and Lamb proposed to unite genetic disorders of male reproductive system into 4 groups **(table):** chromosomal (numeric/structural) anomalies and microdeletions of Y chromosome, disorders of determination of sex/sexual differentiation, disorders of hypothalamic-pituitary-gonadal regulation, disorders of producing and functioning of sperm [8].

Men with a low number of spermatozoa can be provided with a possibility of fatherhood by means of in vitro fertilization (IVF), intracytoplasmic spermatozoon injection (ICSI) and selection of spermatozoa directly from the testicles in case of azoospermia. Spermatozoa of infertile men possess a higher risk of aneuploidy, structural chormosome abnormalities, DNA disorders and the risk of transmission of genetic defects to offsprings [9].

Chromosomal pathology is the leading reason of spermatogenic failure. Microdeletions of the azoospermia factor (AZF) regions of the Y chromosome are on the second place of genetic disorders that lead to male infertility. These two pathologies are the only commonly known genetic causes of spermatogenic failure, whose frequency increases with the severity of the spermatogenic defect, reaching up to an overall 30.0% (15.0% karyotype abnormalities and 15.0% of AZF microdeletions) in azoospermic men [10]. There is a great number of monogenic disorders that lead to male infertility, most of them being a part of group of disorders of hypothalamic-pituitary-gonadal system. However the most numerous group of pathologies concerns various syndromes of pleiotropic gene action, that are related to different disorders defining sex/sexual differentiation, disorders of hypothalamic-pituitary-gonadal regulation, and also disorders of producing and functioning of sperm [11].

The review of 11 publications including 9766 infertile men shows that frequency of chromosome abnormalities is 5,8%, including 4,2% gonosome abnormalities and 1,5% autosomal abnormalities. The frequency of abnormalities from the data obtained from three sets of newborn boys was 0,38% out from the general number 94 465, including 131 (0,14%) cases of gonosome abnormalities and 232 (0,25%) autosomal abnormalities [12]. Frequency of chromosome abnormalities increases with aggravation of testicular failure severity. A patient with a number of spermatozoa in ejaculate less then 5 millions per ml is characterized by ten times as much frequency (4%) of autosomal abnormalities as comapred to the whole population. Men with non-obstructive azoospermia possess a higher degree of the risk of gonosome abnormalities [13].

Gonosome abnormalities (Klienfelter's syndrome (KS) and variant (47, XXY; 46, XY/47, XXY mosaicism). KS is the most spread abnormality of the sex chromosome abnormalities and associated with hypergonadotropic hypogonadism and infertility [14]. An adult man with KS is characterized by testicular hypoplasia and lack of spermatozoa in seminal fluid. Testosterone level may be normal or low, estradiol index is normal or high. Increase in estradiol results from over-expression of aromatase CYP19 [15]. Early hormonal therapy is recommended for patients with KS to assure normal puberty and prevent long-term consequences of hypogonadism. Cryopreservation of ejaculated spermatozoa or testicular tissue should be offered to all young, postpubescent KS men who are starting androgen replacement therapy or being considered for it [14,16].

Microdeletions of Y chromosome. Male-related genes including sex-determining region of Y-chromosome (SRY) and several spermatogenesis-related genes are accumulated in Y chromosome. Every 5-10-th of males presenting without sperm in the ejaculate carry a deletion of the Y chromosome [17]. This deleted region includes the Azoospermia Factor (AZF) locus, located in the Yq11, which is divided into four recurrently deleted non-overlapping subregions - AZFa, AZFb, AZFc and AZFd. Each of these regions contains one or a few genes-candidates, mutations in which lead to disorders of process of spermatogenesis. These regions have several candidates for the factor. Thus, AZFa contains USP9Y and DBY that encode an ubiquitin specific protease and a RNA-helicase, respectively; AZFb comprises several candidate genes such as RBMY encoding an RAN-binding protein; and AZFc contains genes of DAZ and CDY family [11].

In a research of 25 patients - 20% of all patients had at least one microdeletion in more than one region of AZF loci. Totally 17 microdeletions were observed with one case showing up deletions in three AZF regions, and 4 cases having deletions in two AZF regions. The rate of deletions was 42% for AZFc, 35% for AZFa and 23% for AZFb [10].

Autosomal abnormalities. Genetic consulting should be available for all family couples requiring treatment of infertility due to autosomal disorder of karyotype in either or both sexual partners. The most frequent autosomal karyotype abnormalities are: Robertson's translocation, reciprocal translocation, paracentric inversion [18]. These structural chromosomal abnormalities are associated with a higher risk of occurance of aneuploidy or unbalanced chromosomal complements of the fetus [8,12].

Chromosomal abnormalities of spermatozoa. Examination of spermatozoa is needed to determine chromosomal abnormalities in men with normal or pathological karyotype. Severe lesions of spermatogenesis and also translocations lead to aneuploidy, and first of all aneuploidy of the sex chromosome [12,19].

One more problem of genetic disorders is *DNA fragmentation in spermatozoa*. Men with oligozoospermia

Table.

Classification of genetic disorders associated with male infertility

Chromosomal (numeric/structural) anomalies and microdeletions of Y chromosome: *Gonosome abnormalities* • (Klienfelter's syndrome (KS) and variant (47, XXY; 46, XY/47, XXY mosaicism) • Mixed gonadal dysgenesis (45, X/46, XY) • Structural anomalies of Y chromosome • Translocations between Y chromosome and X/autosomes • Man with karyotype 46, XX *Autosomal abnormalities* • Robertsonian translocations and reciprocal translocations Inversions • Partial duplications • Mosaicism for trisomy of 21-st chromosome • Marker chromosomes *Microdeletions of Y chromosome*	**Disorders of determination of sex/sexual differentiation:** • Pseudohermaphroditism (NR5A1) • Sex reversal (50X9, SRY, NR0B1) • Syndrome of Denys-Drash WT1) • Pseudovaginal perineoscrotal hypospadias (SRD5A, SRD5A2) • Cryptorchidism (HOXA10, INSL3, GREAT) • Congenital bilateral absence of the vas deferens (CFTR) • Syndrome of persistence of mullerian ducts (AMN, AMNR)
Disorders of hypothalamic-pituitary-gonadal regulation: • Hypogonadotrophic hypogonadism (GNRH, KAL, PC1, GNRHR, LEP, PCSK1) • Defects of pituitary gland or gonadotropins (LHB, HESX1, LHX3, PROP1) • Disorders of biosynthesis of steroid hormones (StAR, CYP21, TDD, CYP17) • Disorders of metabolism of steroid hormones (SRD5, SRD5A) • Disorders of action of steroid hormones (AR, E5R)	**Disorders of producing and functioning of sperm:** • Myotonic dystrophy (DMPK) • Noonan szndrome (PTPN11) • Sickle cell anemia (HBB) • Kartagener syndrome (DNAIl, DNAH5) • Primary ciliary dyskinesia (DNAIl, DNAH5) • Fanconi anemia (FANCA) • Ataxia-teleangiectasia (ATM)

have a higher risk of DNA lesion in spermatozoa. This tendency is directly connected with a lower ability to natural fertilization and chance increase to preterm interruption of pregnancy [8,20]. DNA fragmentation is underevaluated in male infertility, but represents an extremely important parameter indicative of infertility and potential outcome of assisted reproduction treatment. Oxidative stress is the major cause of DNA fragmentation in male infertility but may be modifiable in many cases [21,22,23]. Varicocele is one of frequent causes of high levels of DNA damage in spermatozoa [22].

It is known, that the decreased activities of some enzymes of the oxidoreductase system, e.g. superoxide dismutase, are implicated in sperm DNA fragmentation process [24,25,26].

Conclusions. All the professionals involved in the field of andrology should be well familiar with the issues of genetic abnormalities associated with infertility to ensure correct medical tactics provided to family couples requiring it.

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ЧОЛОВІЧЕ НЕПЛІДДЯ ЯК РЕЗУЛЬТАТ ГЕНЕТИЧНИХ ПОРУШЕНЬ

Николайчук Р. П.

Резюме. Робота присвячена аналізу доступних авторам досліджень генетичних порушень, що ведуть до чоловічого неплідддя. Вказується, що за міжнародними даними фактор чоловічого неплідддя сягає близько половини пар, що звертаються за допомогою в центри допоміжних репродуктивних технологій. Третину випадків чоловічого неплідддя складає ідіопатичне неплідддя. Відомо, що в більшості випадків даного безпліддя причиною можуть бути генетичні порушення, адже людський сперматогенез контролюється більш ніж тисячею генів. На даний момент тільки декілька з них визначаються при рутинному обстеженні пацієнтів.

Розглянуто питання розподілу на групи основних причин безпліддя та вказано основні патології, що відносяться до кожної із них. Вказується на той факт, що найбільш поширеними патологіями є аномалії статевих хромосом, а саме, синдром Клайнфельтера та мікроделеції У хромосоми. Другою найпоширенішою генетичною патологією прийнято вважати аутосомні аномалії (Робертсоновські та реципрокні транслокації, парацентричні інверсії).

На підставі проведеного аналізу можна сказати, що генетичні механізми займають досить високий відсоток серед чоловіків і є необхідність більш детального їх дослідження та приділення уваги андрологами та генетиками, а особливо, у випадках ідіопатичного чоловічого неплідддя.

Ключові слова: чоловіче неплідддя, генетичні порушення, хромосомні аномалії, причини безпліддя.

МУЖСКОЕ БЕСПЛОДИЕ КАК РЕЗУЛЬТАТ ГЕНЕТИЧЕСКИХ НАРУШЕНИЙ

Николайчук Р. П.

Резюме. Работа посвящена анализу, доступных авторам, исследований генетических нарушений, ведущих к мужскому бесплодию. Указывается, что по международным данным фактор мужского бесплодия составляет около половины пар, обращающихся за помощью в центры вспомогательных репродуктивных технологий. Треть случаев мужского бесплодия составляет идиопатическое бесплодие. Известно, что в большинстве случаев причиной идиопатического бесплодия могут быть генетические нарушения, ведь человеческий сперматогенез контролируется более чем тысячей генов. Сейчас только несколько из них определяются при обычном обследовании пациентов.

Рассмотрены вопросы распределения на группы основных причин бесплодия и основные патологии, относящиеся к каждой из них. Указывается тот факт, что наиболее распространенными патологиями являются аномалии половых хромосом, а именно, синдром Клайнфельтера и микроделеции У-хромосомы. Второй распространенной генетической патологией принято считать аутосомные аномалии (Робертсоновские и реципрокные транслокации, парацентричные инверсии).

На основании проведенного анализа можем сделать вывод, что генетические механизмы бесплодия занимают достаточно высокий процент среди мужчин и назревает необходимость более глубокого исследования андрологами и генетиками, особенно, в случаях идиопатического мужского бесплодия.

Ключевые слова: мужское бесплодие, генетические нарушения, хромосомные аномалии, причины бесплодия.

MALE INFERTILITY AS A RESULT OF GENETIC DISORDERS (REVIEW)

Nykolaichuk R. P.

Abstract. Infertility is a very complex international problem that involves 15% of family couples and approximately one third of cases are associated with male reproductive failure. The percentage of infertile men ranges from 2-5% to 12%. In 30% – 40% of cases there was no factor found associated with male infertility, the phenomenon

being named idiopathic male infertility. A said group includes men without anamnesis of fertility and any negative consequences of endocrine, genetic and biochemical laboratory examinations. Most of these idiopathic cases are likely to be of genetic origin because, as we know, the number of genes that are involved in human spermatogenesis is over 1 thousand.

Genetic disorders of male reproductive system can be divided into 4 groups: chromosomal (numeric/structural) anomalies and microdeletions of Y chromosome, disorders of determination of sex/sexual differentiation, disorders of hypothalamic-pituitary-gonadal regulation, disorders of producing and functioning of sperm.

Spermatozoa of infertile men possess a higher risk of aneuploidy, structural chromosome abnormalities, DNA disorders and the risk of transmission of genetic defects to off springs.

Chromosomal pathology is the leading reason of spermatogenic failure. Frequency of chromosome abnormalities increases with aggravation of testicular failure severity. A patient with a number of spermatozoa in ejaculate less then 5 millions per ml is characterized by ten times as much frequency (4%) of autosomal abnormalities as compared to the whole population. Men with non-obstructive azoospermia possess a higher degree of the risk of gonosome abnormalities.

One more problem of genetic disorders is DNA fragmentation in spermatozoa. Men with oligozoospermia have a higher risk of DNA lesion in spermatozoa. This tendency is directly connected with a lower ability to natural fertilization and chance increase to preterm interruption of pregnancy. Oxidative stress is the major cause of DNA fragmentation in male infertility but may be modifiable in many cases.

Considering the above mentioned, it can be noted that genetic disorders play a great role in male reproductive failures. All the professionals involved in the field of andrology should be well familiar with the issues of genetic abnormalities associated with infertility to ensure correct medical tactics provided to family couples requiring it.

Key words: male infertility, genetic disorders, chromosome anomalies.

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БИОЛОГИЧЕСКИЕ АСПЕКТЫ СВЯЗИ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ И ТКАНЕЙ ПАРАДОНТА

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Связь публикации с плановыми научно-исследовательскими работами. Данная работа является фрагментом научной темы кафедры «Развитие и морфофункциональное состояние органов и тканей экспериментальных животных и людей в норме, в онтогенезе под влиянием внешних факторов», № государственной регистрации 0111U009598.

Всё больше появляется данных о том, что пародонтит (ПД) связан с повышенным риском развития сердечно-сосудистых заболеваний (ССЗ) как этиопатогенный фактор. Пациенты с ПД подвергаются воздействию бактерий и их продуктов, которые имеют доступ к кровообращению непосредственно через воспаленные ткани полости рта и косвенно через слюну и желудочно-кишечный тракт, что приводит к системным воспалительным и иммунологическим ответам со стороны организма [1]. С ПД связана также стойкая эндотоксемия, которая идентифицируется как важный кардиометаболический фактор риска [2].

Начало и распространение ПД происходит в результате нарушения баланса (дисбактериоза) комменсальной оральной микробиоты (зубной бляшки), которая затем взаимодействует с иммунной системой хозяина, что является причиной развития низкосортного системного воспаления [3], при этом взаимодействие с иммунной системой хозяина включает в себя пути, которые признаны проатерогенными и наиболее частой причиной ССЗ [4]. Как ПД, так и ССЗ являются хроническими заболеваниями, которые развиваются медленно и могут начинаться уже в подростковый период, хотя временная последовательность не известна. По данным эколого-эпидемиологических исследований риск заболеваний коронарных артерий и ишемического инсульта значительно увеличиваются при наличии ПД и потери зубов [5].

Сравнительно мало данных о прямом вкладе пероральной микробиоты в ССЗ, хотя периодонтальные бактерии неоднократно были обнаружены в атеросклеротических бляшках, но механизм их вовлечения в атерогенез пока не ясен [6]. Количество бактериальной ДНК в атеросклеротической бляшке коррелирует с количеством присутствующих лейкоцитов, что указывает на то, что бактерии могут участвовать в локальном иммунном ответе [7].

Важным фактором вирулентности грамотрицательных бактерий, доминирующих в оральной микробиоте при ПД, являются липополисахариды (ЛПС), которые входят в состав их клеточных мембран и являются эндотоксинами. В организме человека ЛПС играют центральную роль в иммунных ответах хозяина, характеризуется синтезом цитокинов и активацией иммунной системы. При этом воспаление является обычной реакцией на синтез цитокинов, что провоцируют риск развития атеросклероза (АС) и тромбоэмболических процессов [8]. Поступление ЛПС в кровообращение называется эндотоксемией,