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HISTORICAL REVIEW AND CLASSIFICATION OF RARE DISEASE EPIDEMIOLOGICAL REGISTRIES

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ИСТОРИЯ И КЛАСИФИКАЦИЯ НА ЕПИДЕМИОЛОГИЧНИТЕ РЕГИСТРИ ЗА РЕДКИ БОЛЕСТИ

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РЕЗЮМЕ

Редките болести се характеризират с ниско разпространение на отделното заболяване, но взети заедно, редките заболявания засягат около 13.5 милиона хора в Европейския съюз. Това определя редките заболявания като предизвикателство за общественото здравеопазване. Липсата на база данни за пациенти и научни изследвания в областта на редките болести е ясно осъзната от изследователите. Пациентските епидемиологични регистри може да са основа за разрешаване на проблемите, свързани с диагностицирането, лечението и планирането в здравеопазването. Това се осъществява чрез събирането както на ретроспективни, така и проспективни данни и интегриране на центровете на национално и международно ниво. Настоящата публикация има за цел чрез проучване на достъпната научна литература да проследи историческото развитие на епидемиологичните регистри за редки болести и да представи съществуващи класификации за тези регистри.

ABSTRACT

Basic characteristic of rare diseases is low prevalence of each particular disease but all together rare diseases affect about 13.5 million people in the European Union. This fact determined rare diseases as a public health challenge. The absence of a patients' database and research in the field of rare diseases is clearly understood by the researchers. Patients' epidemiological registries could be the basis for solving problems related to the diagnosis, treatment and public health planning. It could be done through the collection of both retrospective and prospective data and integrating the clinical centers on national and international level. This publication aims to trace the historical development of epidemiological registries for rare diseases and to submit existing classifications for these registers by exploring the available scientific literature.

Keywords: epidemiological registries, rare diseases, patient registry, history, classification

Ключови думи: епидемиолични регистри, редки болести, пациентски регистър, история, класификация

INTRODUCTION

Most rare diseases are life-threatening, chronic or debilitating conditions and the majority of them are genetically determined. Since their distribution is low joint efforts of all stakeholders are required to improve diagnosis, care and prevention of patients. [8, 34] A disease is considered to be rare if it affects less than 5 in 10.000 persons in the European Union. In USA diseases or conditions that affect fewer than 200.000 people are considered as rare diseases. [28] The impact of each rare disease is limited, but rare diseases taken together seem to be a real challenge for public health authorities. [1, 4]

Often there is a lack of knowledge regarding rare diseases. The reason is that a clinic or a small group of clinics do not have enough cases to achieve effective follow-up of the pathophysiology of a disease. [1, 31, 35]

There is a need for a central registry in which the diagnostic information of primary and outpatient care to be collected systematically. In this way it is possible to use data from the registry for planning and evaluation in health care. [25, 39, 40] Patient registry can provide a basis for solving many problems by collecting both retrospective and prospective data over a long period of time and integration of centers at national and international level. [34]

HISTORY OF EPIDEMIOLOGICAL REGISTRIES

Historically, medical records were always kept in accordance with the tradition of the careful methodical research. They were often used for creation of a disease registry that was helpful for observing the incidence, the disease course and the health services. [30] There is available data for registration of the population of the Roman Empire in the 3rd century A.D. in connection with acceptance of new soldiers in the army. [19] Some authors seek early records back in 1086 when was created the so called „Domesday Book“ – a historical book compiled in 1086 on the orders of William the Conqueror. All possessions of England were carefully written in it. [29] There is an evidence of 1538 for the regular collection of short entries on the orders of Thomas Cromwell, according to which the spiritual person of each parish should keep records of church baptisms, weddings and funerals. After more than 200 years the people came to the conclusion that the collection of statistics should not be done by the church and in 1837 the civil registration system was based. Also as a starting point for the registries birth can be accepted the list of dead people in London. From 1603 to 1836 the information was gathered by officials of the parish and published once a week. The aim was to provide early warning in case of a cholera epidemic in order timely measures to be taken. Initially this list contained both the number of deaths from cholera and other diseases, but later in 1629 started to record the death cause and in the early 18th century the age to which the person died was also noted. [13] Up to 1850 a large amount of information was collected on separate towns, communities, regions or countries which was available for detailed study and analysis. This dataset was categorized as demographic statistics, including births, marriages and deaths, morbidity and migration. These sources of information are the basis of William Farr's achievements (1807–1883) who worked at the General Registry Office in London. [13] Registries have been used in cancer studies in 1940 as a tool to measure the incidence of can-

cer and to support research related to the etiology of cancer by recording clinical cases reported in a given period of time or a particular place. [6, 18, 26, 28]

Many countries had organized their national registries as a result of a good example of the Canadian patient registry, created in the mid 60s of last century. [7, 23]

Some records have been presented in the literature once, starting with the injuries registry sustained in 1970 at Cook County Hospital and joints plastics registry at Mayo Hospital in England. From that moment projects creating registries had increased significantly. In Sweden there was a doubling of the number of national registries for four years between 2001 and 2005, increased from 40 to 70 registries. [11] A number of records were created in the 20th century in the context of changing social, political, professional and technological factors. But thanks to the maintenance cost, limited information (provided by clinicians out of their work responsibilities), the difficulties in controlling the quality of data and limited sponsorship, many records were closed in the late 80s of the last century and only a few international registries are still functioning. [5, 8, 29, 38]

In its simplest form, many years ago, the registry consisted of a collection of questionnaires on paper, stored in the „shoebox" by doctors. Today registries are a set of computerized data. [22] Rapid technological progress and other discoveries in recent years had led to new opportunities for the development of patient records. [34] Most of the modern databases for storing information are online databases that provide easy access to the users from all points of the globe. European Society for Immunodeficiencies had initiated the creation of an online database of clinical and laboratory data in 2004. This project, supported by the European Commission and the pharmaceutical industry (www.pptaglobal.org), was one of the most comprehensive records maintained by physicians in Europe, receiving information from 64 centers in 29 countries. [21]

Thanks to the electronic clinical records which are increasingly complementing the recordings made by hand, a large amount of clinical information was stored in electronic format. The possibility of collecting data on patient records to become a part of the routine medical care, started to look real. This allowed the existence of national patient registries worldwide, covering a large part of the population.

Patient registries have both prospective and retrospective possibility for follow-up. They are the most appropriate tool for studying the characteristics of health care providing invaluable information for evaluation / audit and planning of health services and monitoring their use. [30]

REGISTRY DEFINITIONS AND TERMINOLOGY

Though the history of registries is long and electronic records had developed basing on handwritten records, the terminology used in the field of registries did not changed significantly. [2, 3, 15, 17] The term „registry" stems from several Latin words – the Latin word „registrum", from Latin word „regesta" („list, recorded items") and from the Latin word „regerere" („recording back to the past"). The meaning of the term „registry", applied to public health systems, is both variable and uncertain. As a result of the lack of specific terminology, values or disadvantages of the registries are subject to broad interpretation. Therefore, any discussion of the use of patient registries should be preceded by an agreement on the meaning of the term itself. [21]

In many cases, researchers wishing to evaluate a group of patients needed a registry of these patients. [11] A study in PubMed, made in September 2011 showed a total of over 98.000 titles related to both terms used in English language designating registry – for „registry" – 70.604 titles and for „registry" – 27.461 titles. The term „registry" is commonly used to describe health-oriented databases. The difference between registries and other databases is that the collected information is linked to specific identifiable persons.

Study in the literature shows that there is no universal agreement on what is „registry". Registry is a database of a group of people, containing a clearly defined set of health and demographic data collected for specific purposes related to public health. [29]

Bellows determined the registry as a system of records, often used in the field of public health. This system serves as a tool for administering programs related to long-term care, tracking or monitoring of individual cases.

„Registered population" is a group of individuals who are selected for continuous monitoring, treatment or observation due to stay in one and the same clinic or were diagnosed alike. The most important element of the registry is the continuous updating of records for each individual in a population group. [5]

Another researcher, Brooke, determined the registry as a file of documents containing information about individuals collected in a systematic and comprehensive manner to serve a predetermined purpose. [8]

According to Tucker, the registries are designed to collect information on a specific topic and are usually limited in scope. He distinguishes between monitoring systems and registries, but considered that the data from the registries can be useful in follow-up systems. [33]

The definition of a registry of Arts is based on research articles dating from 1949 to 1991: „A systematic collection of clearly defined set of health and demographic data for patients with specific health characteristics maintained in a central database for a predetermined purpose." Although this definition indicates the important characteristics of the registries there are several reasons to look for a better definition. For example, data collection approaches and data models vary widely between different databases. Registry is a repository of data, allowing their current collection, their change or deletion. Registry is defined as operating system for research or patient management, including standardized and complete set of data, based on prospective and systematic follow-up of patients with the same disease or therapeutic intervention. This definition is based on the definition of Arts and emphasizes the important difference that the registries are functional subset of the databases (i.e., all registries are databases, but not all databases are registries. [11]

According Richesson registries of diseases are controlled lists of persons with a certain clinical status and associated data. These lists are used to support public health and clinical research activities. Such records are tools to evaluate the incidence of diseases and to support the specification of etiology by recording cases reported within a certain time or place. [28] Solomon describes the registry as a database for the identification of people, containing a specific set of health and demographic data collected for a specific purpose in the field of public health. [29]

The WHO definition of „patient registry" is: a file of documents containing uniform information of individuals which is collected systematically in order to serve a predetermined scientific, clinical purposes or purposes related to health policy." This definition does not predetermine the amount of collected data, which may be minimal or extensive, but implies duration, in contrast to slice studies.

US National Committee for Health Statistics defines registries as „an organized system for collection, storage, retrieval, analysis and dissemination of information about individuals who are with a particular disease or condition or already were exposed to substances (or circumstances), which are known or suspected to cause health damage." [28]

According to Gutierrez registry is an approved methodology for providing medical information in addition to that produced by placebo – controlled, randomized clinical trials. It is a valuable tool for long-term monitoring of effectiveness and safety. It is designed without limitations on the duration of the study or the involvement of stakeholders and is particularly suitable for capturing rare events and atypical reactions to treatment. [16, 28]

Knerr believes that registries are essential components of public health programs and provide data necessary for planning of health ser-

vices, public health monitoring, research and care of individuals. [21]

CLASSIFICATION OF EPIDEMIOLOGICAL REGISTRIES

Due to different defining factors the registries could be classified in several ways:

CLASSIFICATION ACCORDING TO TYPE OF DATA

Patients who participate in a registry were selected on the basis of a specific disease, presence of a condition (e.g. risk factor) or were subjected to particularly impact exposure. According to Pryor data registries are two basic types: 1) linked to a disease or oriented to the population or 2) relating to the results of the use of a procedure, treatment or equipment. [27]

CLASSIFICATION ACCORDING TO THE SCOPE

It is normal to distinguish between a population-based registries relating to a population group that is geographically fixed and clinical registries that are based on clinical centers in which the coverage of the population could not be precise. Clinical registries could vary from a standard one (intended for a research in one hospital department) to a registry that was a result of the combined efforts of medical staff to registry all clinical cases diagnosed in one hospital institution. These two types of registries are used for different purposes. It is important to make a difference between a full, comprehensive registry (which seeks to include all clinical cases meeting the criteria for inclusion in the registry) and partial registry. Partial records may be helpful for finding voluntary participants for clinical trials. [22, 32] Interest in patient registries is global. There are many registries that store information supplied by several countries. This is especially valuable in rare diseases where the pooling of information and the access to it lead to improvement of the diagnostic process and the quality of the medical care. [9, 10, 14, 20]

CLASSIFICATION ACCORDING TO THE DISEASE OUTCOME

The registries that are associated with determining the output of the patient health could be divided into two main broad categories and each of them may have a subcategories plurality.

- Product registry

  The included patients are exposed to a specific medicinal product as a medicine or equipment. The exposure may be transient, such as a single dose of medicament, implantation of an apparatus or a continuous intake of a drug. This type of registries may include all known patients or only some of them depending on the purpose of the study.

  Registries of pregnant women represent a separate subcategory of biopharmaceutical product registries, which are aimed to define the possible effects during pregnancy and the effects on the fetus.

- Registries for health services

  In the context of the assessment of patient's condition and disease outcome there are registries related to the evaluation of health services that are provided to the patients. Health services that can be registrated are those provided by random office visits during the course of a procedure or during longer hospitalization periods. In these registries one of the objectives is the evaluation of health services due to the disease outcome. Registries of health services are sometimes used to measure the quality health service by evaluating the health care delivery and outcome.

- classification according to the number of diseases

  Registries of a disease or condition are using specific health as a criterion for the registry inclusion. The duration of the observation period also can be used as a classifier. In these registries, the disease can be permanently present (e.g. a rare disease such as cystic fibrosis or Pompe disease), or the patient may have a disease or condition available for a limited time. The period of observation and the follow-up depend on the researcher's interest. The patients could be registrated during routine examinations or they may be included

through voluntary patient's registration regardless of health services (e.g. voluntary registration via the Internet). [10, 14, 20, 37]

There are two models to registry for a disease – one disease registry and registry for several diseases. Examples of the first type are separate registries for rare diseases such as pleuropulmonary blastoma, Hodgkin's disease, congenital central hypoventilation syndrome and others. An example of a registry for several related diseases is the British registry of rare pulmonary diseases, founded in 2001. It stores data for 11 rare lung diseases in adults. [1] The Spanish Rare Diseases Registries Research Network is an example for a registry identifying patients with 12 (initially) nonrelated rare diseases.

The disease registries can be differentiated depending on their purpose. For example, the administrative registries are used for the identification of a certain disease state patients who later could participate in an epidemiological study. Population-based registries store data related to a specific disease that is later used for analysis, generating of hypotheses and secondary research questions. Genetic records (those that identify individuals with a genetic mutation or profile) are increasingly used for tracking or relatives detecting. [24, 28]

CLASSIFICATION ACCORDING TO THE LEVEL OF ANONYMITY

Patient registries could be classified due to the level of anonymity of the contained data. There are several levels of anonymity:

1. Anonymous data are collected without an ID and can not be linked to their sources. This type of data is suitable for studies of morbidity, but it could not be used for clinical study. It provides the maximum level of patients' personal information protection and facilitates the cooperation among researchers.
2. The data rendered anonymous initially was possible to be identified and linked to its source, but after the deletion of all identifiers, it is no longer possible.
3. In the indirectly identifiable information data is used for research purposes and may be connected with its source only through the use of a code. This type of data is most commonly used in clinical trials.
4. When directly identifiable data is available identifiers such as name, number of patient or clear pedigree. The hospital files of patients are an example for this type of data. The use of such data is under strict rules in most countries. [22, 36]

COMBINED REGISTRIES

Reality shows that many of the registries could be assigned to several of those categories, which definitely hinders their classification. Most of them should be defined as combined, i.e. they are meeting several criteria for classification. [22, 32] That is why it should be pointed out that those registry classifications are not optimal, since many of the registries could fall into several categories simultaneously.

The registries are a specific type of collected database. There are other databases that have their place in the group of repositories of information, but for them it is questionable whether they could be classified as registries. Such databases are:

- Health system databases – these are electronic hospital files in which the patient's diagnosis was encoded typically using the International Classification of Diseases (ICD) of the WHO. These databases are clinical tool for reporting the number of patients using a specific type of medical services. They are not provided for research purposes. In the field of rare diseases their use is limited due to the fact that there is no ICD code for more than 240 rare diseases.
- Special (Ad hoc) studies – this type of database is aiming the opportunity to respond to one or more specific research questions. This is a single collection of data which could be repeated over time. The collected information has a specific format in accordance with the analysis made in advance. The study protocol was designed to ensure a clear answer to the questions posed by researchers. In this type of database population sample was fully representative of

the population and the costs associated with the study were smaller than those required for the maintenance of a database for a long period of time. Special Ad hoc surveys are flexible instrument containing protocols adapted to the latest findings regarding a disease.

◊ Cohorts

Registry can be regarded as a prospective method for epidemiological investigation which in many ways is similar to the cohort. A cohort is defined group of individuals and these people are followed up to observe what happens with their condition. In a registry the group of people was determined by the criteria that were set out for the study purposes. [22] Unlike conventional epidemiological cohort studies that focus primarily on morbidity manifested within unaffected populations, an advantage of cohort studies using patient registry is finding the outcome (for example no change in health status or recovery) in people with specific health problem. In the context of the registries the data may be transverse (all selected patients were recorded once) or longitudinal (data was collected at different periods of time for the same patients). In the field of rare diseases presence of cohort is very desirable as this is usually the only way to gather enough information to have a possibility for a proper analysis because of the small number of clinical cases. [12, 22]

CONCLUSIONS

Scientific literature provides data on long-term historical development of epidemiological registries for rare diseases. There are many attempts to classify these registries and yet there isn't available classification providing their proper distribution. There is strong awareness for the necessity of such classification existence. It will support the basis for the establishment, functioning and administration of the registries for rare diseases. Thus the basic needs of all stakeholders (patients, public health authorities, researchers, pharmacy industry and the registries administrators) would be answered.

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Hepcidin and anemia in rheumatoid arthritis – is there a diagnostic tool?

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Хепсидин и анемия при ревматоиден артрит – има ли клинично приложение?

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РЕЗЮМЕ

ВЪВЕДЕНИЕ:

Хепсидинът е ключов регулатор на системната хомеостаза на желязото. Патогенезата на анемията на хронично заболяване (АХЗ) се свързва със стимулиран хепсидинов синтез поради възпалението. Високите хепсидинови нива са причина за намалена чревна абсорбция на желязото и потиснато освобождаване от макрофагите, които водят до последваща хипоферемия и нарушена еритропоеза.

МЕТОДИ:

за периода 2013–2014 г. е изследван серумен хепсидин с верифициран ELISA метод при 40 здрави доброволци и 40 пациенти с ревматои-

ABSTRACT

AIM:

Hepcidin is a key regulator of iron homeostasis. The pathogenesis of anemia of chronic disease (ACD) is associated with stimulated hepcidin synthesis caused by inflammation. High hepcidin levels are due to reduced intestinal iron absorption and inhibited release from macrophage, leading to subsequent hypoferremia and abnormal erythropoesis.

DATA:

For a period of 2013–2014 we studied serum hepcidin levels using verified ELISA method in 40 healthy volunteers and 40 patients with rheumatoid arthritis (RA). Patients were divided into two groups – with iron-deficiency anemia (IDA) and ACD.

ден артрит (РА). Пациентите бяха разделени на две групи – с желязо-дефицитнаа анемия (ЖДА) и с АХЗ.

РЕЗУЛТАТИ:

Установено е статистически значимо повишение на серумния хепсидин при пациенти с АХЗ 90.4 ± 5.1 μg/L спрямо контролната група 3.052 – 37.75 μg/L (P < 0.001). Пациентите с ЖДА имаха значително по-ниски стойности на хепсидин в серума спрямо тези с АХЗ 0.78 ± 0.07 μg/L (P < 0.001).

ЗАКЛЮЧЕНИЕ:

Надеждното изследване на серумен хепсидин би улеснило правилния избор на терапевтичен подход при третиране на анемията при РА. Степента на повишение може да отдиференцира пациенти с функционален дефицит на желязо от тези с ретикулоендотелиална блокада. Хепсидинът е потенциален индикатор за дефицит на желязо при пациенти с РА с анемия и активно възпаление.

Ключови думи: анемия, ревматоиден артрит, хепсидин, хронично възпаление

RESULTS:

A statistically significant increase hepcidin levels were found in patients with ACD 90.4 ± 5.1 μg/L compared to the control group 3.052 – 37.75 μg / L (P < 0.001). Patients with IDA had significantly lower levels of serum hepcidin compared to those with ACD 0.78 ± 0.07 μg/L (P < 0.001).

CONCLUSIONS:

Reliable serum hepcidin would facilitate the correct choice of a therapeutic approach in the treatment of anemia in RA. The rate of increase may differentiate patients with a functional iron deficiency from those with reticuloendothelial blockade. Hepcidin is a potential indicator of iron deficiency in patients with RA with active inflammation and anemia.
Key words: anemia, rheumatoid arthritis, hepcidin, chronic inflammation

INTRODUCTION

Maintaining a balance of iron in the body is critical to the state of health. Identifying hepcidin as a key hormone of iron dramatically improves our understanding of the molecular control mechanisms of iron homeostasis and allows more detailed understanding of the pathophysiology in clinical disorders. Recent studies highlight the role of hepcidin as a useful diagnostic tool and therapeutic target in various diseases with impaired exchange of iron.

Hepcidin regulates systemic iron homeostasis – absorption in the duodenum, recycling from erythrocytes and control release from hepatocytes. It is a peptide which is synthesized by the liver in response to a series of signals according to the iron needs of the body. The biological action of hepcidin is mediated by its binding to the receptor ferroportin, which is the only known iron exporter that presents in the duodenum, macrophages, hepatocytes, placenta. The hormone binds to the receptor in general complex is internalized and unlocks lysosomal ferroportin structure [1–4].

AIM

This study describes significant differences in serum hepcidin quantification between control group with no evidence of iron metabolism disorders and patients with rheumatoid arthritis with iron-deficiency anemia and anemia in chronic diseases.

MATERIALS AND METHODS

SUBJECTS

The clinical study was conducted during the period of 2013–2014 and includes the following groups: a control of 40 healthy volunteers with no laboratory evidence of impaired iron metabolism and 40 patients with RA diagnosed at the Clinic of Rheumatology at the University Hospital „St. Ivan Rilski „. RA activity was determined by Disease Activity Score calculator for RA.

All enrolled subjects completed the informed consent according to the Declaration of Helsinki (Directive 2001/20 / EC).

Age distribution in the different groups is shown in Table 1.

Iron status was characterized in all groups based on a biochemical (performed on automatic biochemical analyzer Cobas Integra 400, Roche Diagnostics) and haematological parameters (automatic hematology analyzer Advia 2120, Siemens Healthcare Diagnostics). (Table 2).

Table 1. Age distribution of the groups

group	control	RA
n	40	40
mean	35.1	47.7
SD	5.6	8.4

n – number of included persons, mean – mean value

DATA ANALYSIS

Statistical evaluation of the data was made by Student t-test (unpaired, two-tailed) with statistically significant differences at $P < 0.05$ and Pearson correlation.

RESULTS

On the basis of the following criteria – CRP, transferrin saturation percentage (TSAT%), the level of ferritin and index of soluble transferrin receptors (sTfr(i)), patients with anemia in RA were divided into two groups: **a)** as IDA if there was no active inflammation (defined by the level of CRP > 10 mg/L) and at least one of the following conditions 1) transferrin saturation < 20% and the level of ferritin < 30 ng/mL; 2) index of sTfR > 1 mg/ng and **b)** as ACD if there was active inflammation, and at least one of the following two conditions 1) the transferrin saturation < 20% and ferritin > 100 ng/mL; 2) index of sTfR < 1 mg/ng and ferritin > 30 ng/mL. There is a statistically significant increase in serum hepcidin in patients with RA with ACD 90.4 ± 5.1 μg/L ($P < 0.001$) and lower levels in RA with IDA 0.78 ± 0.07 μg/L ($P < 0.001$) compared to healthy individuals. Reference ranges for serum hepcidin in the Bulgarian population is 3.053 – 37.75 μg/L [5].

We looked for a correlation between serum ferritin and hepcidin in patients with RA. The results obtained are shown in Figures 1 and 2.

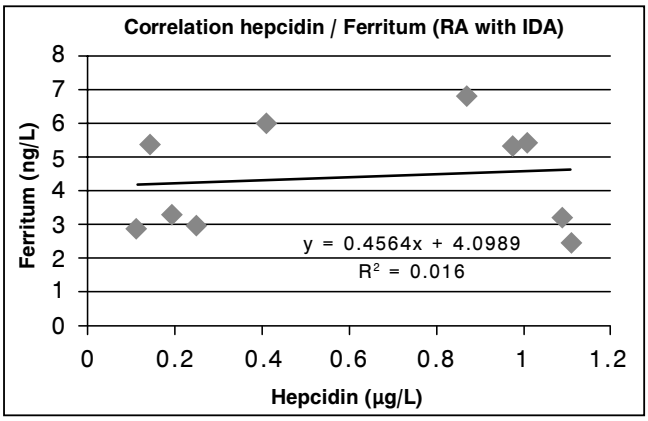
Table 2. Laboratory parameters of iron metabolism in different groups – control, RA with IDA, RA with ACD

parameter	control group	RA with IDA	RA with ACD
Hgb (g/L)	142.7 ± 13.3	93.0 ± 8.5	115.5 ± 2.6
CRP (mg/L)	2.24 ± 0.5	9.0 ± 0.3	88.3 ± 14.8
sTfr(i) (mg/ng)	0.06 ± 0.02	0.03 ± 0.01	0.03 ± 0.01
SolTfr (mg/L)	2.8 ± 0.7	6.6 ± 0.3	2.7 ± 0.4
Ferritin (ng/mL)	115.16 ± 2.9	4.2 ± 1.3	100.1 ± 53.4

Results are given as mean value ± SD.

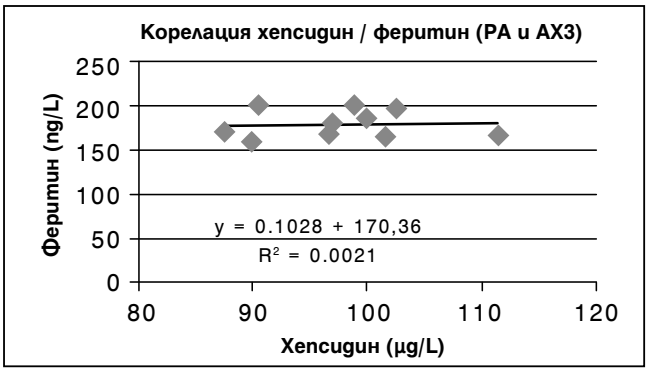
Hgb – hemoglobin; CRP – C reactive protein; sTfr(i) – index of soluble transferrin receptors; SolTfr – soluble transferrin receptors

Figure 1. Correlation between hepcidin and ferritin in patients with RA and IDA



A correlation of $r^2 = 0.016$ was established.

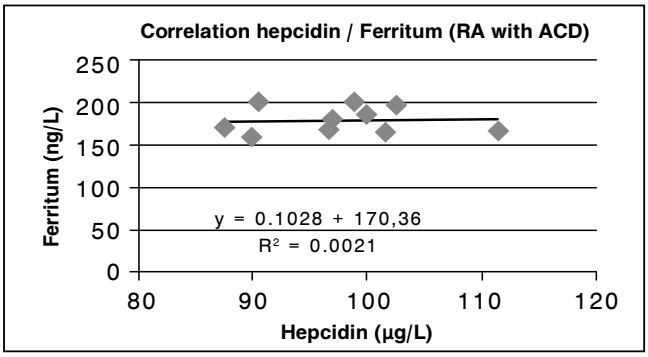
Figure 2. Correlation between hepcidin and ferritin in patients with RA and ACD



A correlation of $r^2 = 0.0021$ was established.

The results for serum hepcidin obtained of the groups are shown in Figure 3.

Figure 3. Serum hepcidin levels in different groups – control and RA



RA – rheumatoid arthritis, IDA – iron-deficiency anemia, ACD – anemia in chronic disease

Serum hepcidin levels are – in RA patients with ACD 90.4 ± 5.1 µg/L, in RA with IDA 0.78 ± 0.07 µg/L, in control group 18.4 ± 1.9 µg/L.

DISCUSSION

Quantification of serum hepcidin in this study was done by verified ELISA. Obtained analytical limit of detection (LoD) established as the mean ± SD of three tenfold certain zero standard is 0.022 µg/L. Measuring range is 0.0625 µg/L – 8 µg/L [5].

The results show an expected significant increase in serum hepcidin in patients with ACD compared with the control group. Also, a decrease in the hepcidin levels is shown in patients with IDA.

Rheumatoid arthritis is a multifactorial condition that is associated with ACD. It may also include iron deficiency due to a) bleeding in the gastrointestinal tract caused by applied therapy or b) redistribution in inflamed tissues. Establishment of iron deficiency in patients with ACD is clinically relevant because: 1) IDA is treatable, 2) diagnosis can precede further investigation of the cause of anemia, and 3) can prevent unnecessary supplementation with iron.

Future of hepcidin is related to the possibility of its agonists and antagonists as a therapeutic agent in the treatment of ACD and IDA. Reducing of hepcidin levels or countering biological effects of hepcidin could overcome the negative effects of inflammation on erythropoesis by enhancing the mobilization of stored iron and increase intestinal absorption of element. These new therapeutic approaches could reduce or eliminate all toxic effects of parenteral iron and Co-reduction of erythropoetin stimulating agents (ESAs) needs. In these cases, serum hepcidin would be therapeutic target in the management of therapy in RA.

CONCLUSIONS

Determination of serum hepcidin is still a novelty in Bulgarian medical practice. The introduction of a reliable routine method for the measurement of hepcidin in biological fluids

is a step forward in the treatment of diseases with impaired iron homeostasis. This study in patients with RA and IDA or ACD confirms the ability of verified immunochemical method to differentiate the cause of anemia. It provides a basis for choosing the correct therapeutic approach in the treatment of anemia.

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CLINICAL CHARACTERISTICS OF CHRONIC LYMPHOCYTIC LEUKEMIA IN YOUNG PATIENTS

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КЛИНИЧНА ХАРАКТЕРИСТИКА НА ХРОНИЧНА ЛИМФОЦИТНА ЛЕВКЕМИЯ ПРИ МЛАДИ ПАЦИЕНТИ

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РЕЗЮМЕ

Хроничната лимфоцитна левкемия (ХЛЛ) е хетерогенно заболяване. Има противоречия относно прогнозата на т.н. „млади“ пациенти. Характерна за тях е толерантността към терапия, което би трябвало да предопредели добра прогноза. От друга страна някои изследователи акцентуират върху по-агресивния ход на болестта в тази възрастова група. **Цел** на проучването е да се изследва клиничната характеристика и хода на ХЛЛ при пациенти под 55 годишна възраст. **Пациенти и методи**: Пациентите с ХЛЛ (общ брой 160) бяха диагностицирани и лекувани в УМБАЛ „Св. Георги“, Пловдив за периода 1991–2013 година. От тях 28.7% бяха пациенти под 55 годишна възраст – „наблюдавана група“. Останалите пациенти характеризират „контролната“ група. **Резултати:** Липсва сигнификантна разлика между двете групи по клиничен стадий (Rai), честота на екстранодално ангажиране и на автоимунни феномени, p >0.05. В контролната група преобладаваха болни с по-лош performance status 4, (p=0.001). Общата преживяемост в наблюдаваната група бе 85.35 ±

ABSTRACT

Chronic lymphocytic leukemia (CLL) is a heterogeneous disease. There are contradiction in prognosis of „young“patients .The increased tolerance to therapy is typical for them and also defines a better prognosis.On the other hand, some investigations put ascent on a more aggressive course of the disease in the younger patients'group. **The purpose** of the study is to investigate clinical characteristics and evolution of CLL patients who are younger than 55 years. **Methods and Patients**: Patients with CLL (total number 160) were diagnosed and treated in University Hospital „Sv. Georgy“ , Plovdiv in the period 1991–2013. The overall proportion of young patients below 55 years of age was 28.7% – „observed group“. The other patients are the „control“ group. **Results:** There is not statistically significant difference between both groups in distribution in clinical stages (Ray), and the frequency of extranodal involvement and autoimmune phenomena, p >0.05. Patients with a bad performance status 4 predominate in the control group (p=0.001). The overall median survival in observed group is 85.35

7 месеца, а при контролната група – 47.08 ± 7 месеца (p=0.001). **Заключение:** В проведеното проучване „младите“ и по-възрастни пациенти бяха със сходна клинична характеристика и ход на болестта за периода на проследяване. По-добрата преживяемост на „младите“ пациенти свързваме с техния по-добър общ зравен статус. Данните за преживяемостта не подкрепят идеята за по-агресивен ход на хроничната лимфоцитна левкемия при млади пациенти.

Ключови думи: хронична лимфоцитна левкемия, прогноза, млади пациенти, общ преживяемост

± 7 months, and in the control group is 47.08 ± 7 months, with significant difference, p=0.001. **Conclusion:** In our study younger and older patients display a similar distribution of clinical features and disease progress for follow-up period. Better performance status of these patients is in association with longer survival. Data about survival do not suggest an idea of more aggressive evolution of CLL in young people.

Key words: chronic lymphocytic leukemia, prognosis, young patients, overall survival

INTRODUCTION:

Chronic lymphocytic leukemia (CLL) is a heterogeneous disease . The average age at the diagnosis is 65–70 years. About 7–20% of the cases in Europe are below 55 years of age (1). The increased tolerance to therapy is typical for younger patients and also defines a better prognosis. The younger patients have a chance of a full/complete and prolonged remission by use of intensive methods of treatment. On the other hand, some investigations put ascent on a more aggressive course of the disease in the younger patients'group. (2) Their purpose is to identify young patients with high-risk features, who are candidates for intensive curative methods. In the view of the fact that the appropriate age for allogeneic and autologous transplantation is below 55years, most authors define „young“ patients as less than 55-year-old. (1.3,4.5)

THE PURPOSE of the study is to investigate clinical characteristics and evolution of CLL patients who are younger than 55 years.

METHODS AND PATIENTS

Patients with CLL were diagnosed and treated in University Hospital „Sv. Georgy“ , Plovdiv in the period 1991–2013. The total number of registered cases in this period was 160 patients. The diagnosis was defined in accordance to the recommendations of the *International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines.* (6)

Baseline demographics, clinical characteristics and survival are derived from the clinical records of all patients and maintained on a prospective basis. The age was defined at the time of diagnosis.

Survival curves were calculated according to Kaplan-Meier and compared with the log-rank test. Statistical analysis was carried out using the SPSS v.7.5 statistical programs.(7)

RESULTS

The overall proportion of young patients below 55 years of age in our series of 160 cases was 28.7%. The clinical characteristic of compared patients groups is presented at table 1.

1. Clinical stage distribution : There is not a significant clinical stage (Ray) difference between both group of patients. Clinical stages II and III predominate in the observed group.
2. Most patients of the observed group have good ECOG (Eastern Cooperative Oncology Group) Performance status (PS) 1+2 (54.3%). There is a significant difference in the proportion of patients with a bad PS 4 between the observed and control group (p=0.001). They predominate in the control group.
3. The frequency of extranodal involvement. There is a trend of more frequent extranodal involvement in the observed group without statistically significant difference, p>0.05

Tabl 1. Clinical characteristics of both group patients

Characteristics	Observed group, n=46 n	%	Control group, n=46 n	%	p
– Sex:					
male	34	73.9	40	67.7	p>0.05
female	12	26.1	19	32.3	
– Clinical stage (Rai)					
0	1	2.17	1	2.22	p>0.05
I	7	15.2	7	15.55	p>0.05
II	14	30.43	17	37.77	p>0.05
III	19	41.30	16	27.11	p>0.05
IV	7	15.2	8	17.77	p>0.05
Missing data	5		10		
– ECOG PS:					
0	4	8.69	4	6.77	p>0.05
1–2	29	63.04	21	35.59	p>0.05
3–4	3	6.52	23	38.98	p=0.001
Missing data	10		11		
– Autoimmune disorders	5	10.86	5	8.47	p>0.05
– Extranodal involvement	9	19.56	11	18.64	p>0.05

Tabl. 2. Registered genetic abnormalities

Genetic abnormality	Observed group n=6	%	Control group n=17	%
Del (13)(q14)	5	83.3	5	29.4
Del(11)(q22)	–			
Trisomy 12q	–		4	23.5
Del(11)(q22) + Del (13)(q14)	–		2	11.7
Del(11)(q22) + Del (13)(q14)+ trisomy 12q	–		1	5.8
Normal cariotype	1	16.6	5	29.4

4. There is not statistically significant difference between both groups in the frequency of autoimmune phenomena, p >0.05.The most frequent autoimmune disorders, associated with CLL are Hashimoto's thyreoiditis, bronchial asthma, systemic lupus erythematosus. A patient has had a combination of rheumatoid arthritis, Hashimoto's thyreoiditis and Guillain-Barre polyradiculoneuritis.

5. There are 14 cases (8.7%) of registered second primary malignant tumor (cancer) among 160 CLL patients. Only one patient of those 14 cases is in the category" young" .

6. Pre-treatment molecular-genetic survey with FISH method has been applied to 6 patients of the observed group and 17 of the control group. The most frequently proven genetic abnormalities in both groups are del (13)(q14) or monosomy 13 (in the observed group up to 83.3%). Multiple genetic abnormalities were registered in 3 patients of the control group.

7. There is positive family history of malignancy in 8 out of 160 CLL registered patients. They have first degree relatives with malignant disorders. Only 2 of them are „young" CLL. Gastric cancer is particularly frequently diagnosed in families with individuals affected by CLL.

8. The overall median survival in observed group is 85.35 ± 7 months, and in the control group is 47.08 ± 7 months, with significant difference, p=0.001. Fig 1.

DISCUSSION

There are problems of „young" patients with new diagnosed CLL: significant psychosocial

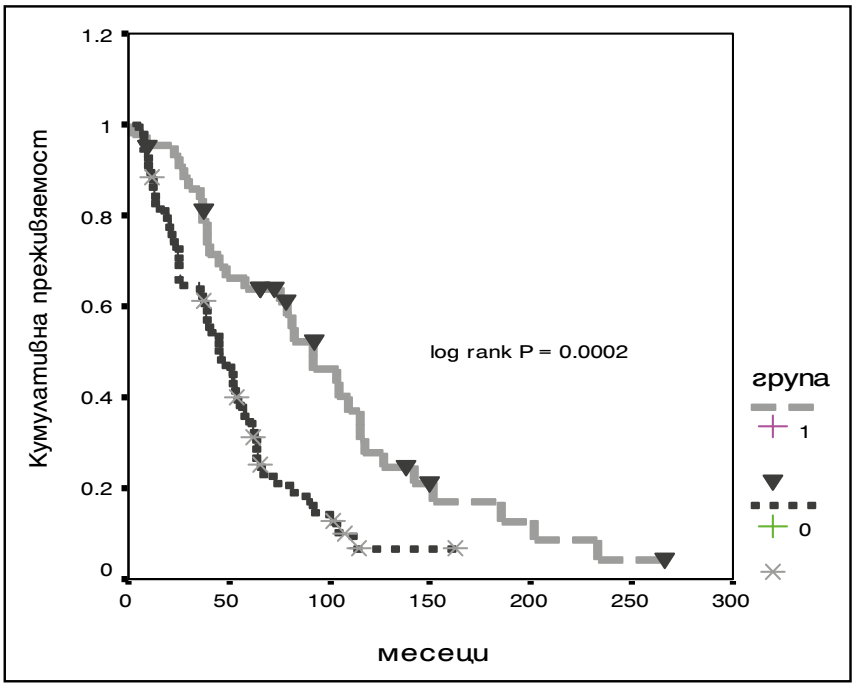

Figure 1.
Kaplan-Meier survival curve of observed (1) and control (2) group

stress, related to the diagnosis; unemployment risk; negative impact on doing household chores; early disability.

Two new trends of treatment are offered to this age group for reasons that include better tolerance to therapy: allogeneic and autologous stem-cell transplantation.(8.9) The second one is consolidation therapy aiming to eliminate minimal residual disease.Patients with high prognostic risk, deletion 17p, recurrent disease and resistance to treatment, should be included in the transplantation programs . Consolidation regimen includes Alemtuzumab, which can be associated with complications risky to older patients. (10.11)

Comparison of clinical characteristics between both groups in our study reveals that there is no difference in the distribution of sex, clinical stages, incidence of extranodal envolvement. A trend of higher rate of autoimmune disorders and complications is registered in the observed group. Better PS of young patients is associated with lower comorbidity (12.13).

In the control group we register higher incidence of second primary malignancies, which is typical in general for elderly. There is an opinion in the literature that CLL-related immunodeficiency predisposes to the development of second cancers more likely than age.(2)

Multiple genetic aberrations do not occur in our „young" patient group but the small number of observed patients does not allow us to do deduction. Five categories of genetic aberrations in CLL patients are defined in the literature: 17p deletion, 11q deletion, 12q trisomy, normal karyotype, and 13q deletion as the sole abnormality. According to Doner et al. the median survival times for patients in these groups are different – 32, 79, 114, 111, and 133 months, respectively. The same author (14) registers negative impact of 11q deletion in young patients, the prognosis of 13q deletion is better for all age groups.

The overall survival of young CLL patients was longer than that of older ones (7.1 versus 4.1 years) according to Molica et al. Observed group survival in our study is in line with the range of survival values in other series in the literature. (15) According to Ferrajoli et al. (1) as soon as the disease evaluates and requires treatment, CLL young patients' life expectancy is significantly reduced, which directs our attention to the more aggressive disease.

CONCLUSION

In our study younger and older patients display a similar distribution of clinical features and disease progress for follow-up period. We have found a trend of higher incidence of autoimmune disorders in young CLL group. Better performance status of these patients is in association with longer survival. Data about survival do not suggest an idea of more aggressive evolution of CLL in young people.

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STUDY OF AGGRESSION AMONG ADOLESCENTS (AGED 14–18) FROM THE CITY OF PLOVDIV

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ПРОУЧВАНЕ НА АГРЕСИВНОСТА СРЕД ПОДРАСТВАЩИ НА ВЪЗРАСТ ОТ 14 ДО 18 ГОДИНИ ОТ ГРАД ПЛОВДИВ

Б. Тилов, дм
Катедра по управление на здравните грижи, МУ Пловдив

РЕЗЮМЕ

ЦЕЛ

Да се изследва агресивността сред юноши между 14 и 18 години от град Пловдив. **Материал и методи:** От анкетираните лица 277 (45.9%) са момичета и 327 (54.1%) са момчета в приблизително съотношение 1:1, с малка разлика в полза на момчетата P<0.05. Най-многобройна е групата на 16 и 17 годишните – 28.81% и 30.63%. Две трети от учениците, участващи в проучването са с двама родители 75.7±1.71 %. За целта на изследването е използвана валидирана методики за измерване на агресивността на Бъс-Пери за български условия, която е предназначена за измерване на четири вида агресивност: физическа, вербална, гняв и враждебност.

РЕЗУЛТАТИ

Настоящото изследване се проведе на няколко етапа. Първият етап включи определяне на

ABSTRACT

INTRODUCTION

The number of minor and underage children, registered at the Juvenile Crime Prevention Center (JCPC) in 2009 was 2.7% higher than in 2008 and reached 4 158. In 2009, as well as in the years before, the share of boys was around 83%, and of girls – 17%. [13] **Aim:** Study of aggressiveness among adolescents between 14 and 18 years of age from the city of Plovdiv. **Material and method:** Out of the total number of investigates persons, 277 (45.9%) are girls and 327 (54.1%) are boys in an approximate ratio of 1:1, with a small difference in favor of boys, P<0.05. The group with the largest number of subjects is the group of 16 and 17-year-olds – 28.81% and 30.63%. Two thirds of the students participating in the study have two parents, 75.7±1.71%. For the purpose of this study, the Buss-Perry validated method for measuring aggression has been used in Bulgarian conditions, which is intended for meas-

вътрешната съгласуваност на отделните скали на въпросника за измерване на агресивността. Анализът на данните е свързан с три основни характеристики: пол, възраст и учебно заведение. Съществува статистически значима разлика по пол на скала Физическа, „Вербална агресивност“, гняв, враждебност и обща агресивност P<0.001 /U=11.0/. **Заключение:** От направеното проучване установяваме добра вътрешна съгласуваност на използваната методика върху изследваната група от юноши (14–18 години) и статистически значими разлики на методиката по полов признак и училище.

Ключови думи: агресивност, юноши, Бъс-Пери;

urement of four types of aggression: physical, verbal, anger and hostility.

RESULTS

This study has been conducted in several stages. The first stage includes determining the internal consistency of individual scales of the questionnaire for aggression measurement. Data analysis is related to three basic features: gender, age and educational institution. There exists statistically significant gender difference in reference to the scale of Physical, „Verbal aggression“, anger, hostility and general aggressiveness P<0.001 /U=11.0/. **Conclusion:** The conducted study has revealed good internal consistency of the methodology used on the investigated group of adolescents (aged 14–18) and statistically significant methodology differences in reference to the gender and school features.

Key words: aggression, adolescents, Buss-Perry;

INTRODUCTION

The number of minor and underage children, registered at the Juvenile Crime Prevention Center (JCPC) in 2009 was 2.7% higher than in 2008 and reached 4 158. The children registered at JCPC are mostly boys. In 2009, as well as in the years before, their share was around 83%, and of girls – 17%. More than 2/3 (79.1%) of the children registered at JCPC come from the 16 and 17 year age groups, ant those at the age of 14 and 15 make up 20.9% of the total number of children. A main factor for the occurrence of antisocial behavior is considered the unfavorable environment (conflict family, criminal family and criminal peer environment). 2 590 (19.7%) minor and underage children come from socially disadvantaged families, and in 2008 their number was 2 499 (18.4%). The year 2009 marked an increase in the number of minor and underage children who committed crimes against the person – murders (attempted and committed) by 57.1% (11 persons), of bodily injuries by 32.0% (351 persons) and of rapes by 28.6% (18 persons), compared to previous years. An increase by 32.9% is also observed in the number of minor and underage children who committed robbery, respectively 315 persons.[13]

Aggression can be defined through the following characteristics: interpersonality; intentionality; potential to harm in a specific state; aversion – for the object of aggression.[3] Another reason for aggressive behavior is the risk for the personal self-esteem, which may cause a defensive aggressive response.[2] Buss and Perry describe aggression by means of the following components: behavioral component (instrumental) – inflicting physical or emotional harm; affective component (anger), which can vary from irritation to rage, and cognitive component, hostility, bitterness, convictions demonstrating negativism. [4]

AIM

The aim of this research is the study of aggressiveness among adolescents between 14 and 18 years of age from the city of Plovdiv.

MATERIALS AND METHODS

The examined group consists of 604 school students of eight secondary schools of general education and vocational secondary schools in the city of Plovdiv. The age of the students participating in the study is between 14 and 18 years. From the initial number of 641 participants in the study were excluded 37 persons, for reasons of incorrect or incomplete filling out of questionnaires. The students included in the study make up 2.3% of the students in the city, which makes the extract representative for the purpose of the current study. Out of the total number of studied adolescents, 41 (6.8 %) are at the age of 14, and 119 (19.7%) at the age of 15. 17-year-olds make up the largest number – 185 (30.6%), whereas students at the age of 16 are 174 (28.8%), and 18-year-olds are 85 from the studied subjects (14.1%). Out of the total number of persons answering the questionnaire, 277 (45.9%) are girls, and 327 (54.1%) are boys, in an approximate ratio of 1:1, with a small difference in favour of boys, $P<0.05$.

The collection of input information was conducted by school psychologists performing the function of monitoring authorities. For the purpose of this study, the Buss-Perry validated methodology for measuring aggression in Bulgarian conditions has been used. The Buss-Perry personality questionnaire (Aggression Questionnaire (AQ) for measuring aggression (Buss-Perry, 1992) is intended for measurement of four types of aggression: physical, verbal, anger and hostility. The questionnaire includes 29 items, rated by using a 5-point Likert-type scale. The scales include the four main factors: physical aggression, verbal aggression, anger and hostility, and general aggressiveness – an aggregate of the individual scales.

STATISTICAL METHODS

Alternative analysis, Non-parameter analysis and Variation analysis – for the comparison of mean values was used the normal distribution criterion, u criteria. Differences are regarded as statistically significant when the critical value of u is exceeded for $\alpha=0.05$. Correlation analysis – the analysis is used for the assessment of the strength of the relation between the studied indexes: Kendall's tau-b correlation coefficient and Spearman's rho correlation coefficient.

Statistical package SPSS version 17 and Microsoft Excel were used in the computer processing of gathered data base.

RESULTS

For the purpose of the study, an evaluation was made of the AQ internal consistency, the reliability and consistency coefficient Cronbach's alpha (α) and the t-criterion for normal distribution of examined subjects (see table 1). Mean values to individual scales have been calculated (see table 1).

The mean values in the individual scales found by us were compared to the results of analogous study on a group of Spanish adolescents (see table 2).

Assessment of aggression by gender

The mean value in the scale measuring the levels of physical aggression of the entire investigated group is 18.31±0.25. The comparison of the mean values of physical aggression by gender has revealed that higher levels of aggression are observed with boys, $P<0.001$ (see table 3). The comparison of the levels of verbal aggression and anger by gender makes obvious the fact that the indexes are higher with girls than boys within the group studied. $P<0.001$ (see table 3). From the results obtained we have concluded that the mean values of hostility among girls are considerably higher than those of boys within the group studied, $P<0.001$, and, as a whole, the levels of general aggressiveness with girls are significantly higher than those with boys, $P<0.01$, (see table 3).

Assessment of aggression by age

No statistically significant difference has been established in the assessment of physical aggression by age group $P>0.05$ ($F=0.71$), verbal aggression $P>0.05$ ($F=0.90$), anger $P<0.05$ ($F=1.51$), hostility $P>0.05$ ($F=0.54$) and general aggressiveness $P>0.05$ ($F=0.69$).

Table 1.
Mean values and reliability of AQ scales

Scale	Number	Mean ± SEM	SD	α	t	P
Physical aggression	604	18.31 ± 0.25	6.1	0.75	73.62	<0.001
Verbal aggression	604	16.36±0.16	4.0	0.51	99.81	<0.001
Anger	604	18.16 ± 0.23	5.6	0.70	78.35	<0.001
Hostility	604	17.52 ±0.21	5.3	0.65	81.17	<0.001
General aggressiveness	604	70.35 ± 0.66	16.38	0.85	105.53	<0.001

Table 2.
Comparison of mean values of AQ scales between Bulgarian and Spanish adolescents

Scale	Number	Mean ± SEM Bulgaria	Number	Mean ± SEM Spain	t	P
Physical aggression	604	18.31 ± 0.25	623	18.9±0.26	1.66	>0.05
Verbal aggression	604	16.36±0.16	623	10.8±0.14	26.15	<0.001
Anger	604	18.16 ± 0.23	623	17.8±0.21	1.15	>0.05
Hostility	604	17.52 ±0.21	623	19.8±0.23	7.32	<0.001

Table 3.
Comparison of mean values by gender for the individual aggression scales.

Scale	Gender	Number	Mean ± SEM	SD	U	P
Physical aggression	Men	327	19.13 ± 0.32	5.8	3.56	<0.001
	Women	277	17.35 ± 0.38	6.3		
Verbal aggression	Men	327	15.80 ±0.20	3.6	11.00	<0.001
	Women	277	17.01± 0.26	4.4		
Anger	Men	327	17.17 ± 0.30	5.4	4.67	<0.001
	Women	277	19.32 ± 0.35	5.8		
Hostility	Men	327	16.65 ± 0.29	5.3	4.55	<0.001
	Women	277	18.56 ± 0.30	5.1		
General aggressiveness	Men	327	68.74 ± 0.85	15.38	2.87	<0.01
	Women	277	72.25 ± 1.04	17.32		

ASSESSMENT OF AGGRESSION BY SCHOOL

The comparison thus made has served as basis for establishing the existence of statistically significant relations between the type of aggression and the type of school. We have found that schools differ in the levels of verbal aggression, P<0.01 (F=3.77), anger P<0.01 (F=2.79), hostility P<0.001 (F=4.11) and general aggressiveness P<0.01 (F=2.58).

DISCUSSION

The results have confirmed the validity of the set of instruments used for the investigated group of adolescents in Bulgaria. The internal consistency has demonstrated good rates, where the verbal aggression scale has lower values than the anticipated. The mean values by individual scales as established by us are close to the results from an comparable study conducted on a group of Spanish adolescents. [11], [12] Our study has higher rates of mean values in the verbal aggression scale, and lower values in the hostility scale in comparison with the Spanish group, (see table 2). Based on the results obtained, we could make the conclusion that regarding the physical aggression and hostility scales adolescents have lower values than the values of a similar study. [11], [12] We are draw attention to the significantly higher values with the verbal aggression scale and the compa-

rable values for the anger and general aggressiveness scales, as shown in table 2 [11], [12], 9

The results obtained for the scale of physical aggression confirm the data from research performed by Crick, Casas & Ku 3.6, in whose opinion, from early school age till secondary school age, physical aggression is a popular method of accomplishing desired aims and obtaining wanted items both for boys and girls. During that period, boys demonstrate more prominently explicit physical aggression behavior towards their male peers. This fact can also be accounted for by the clear relation established by Caspi and Moffitt between the behavior of girls and their early development. 5

Another research in the same area shows that girls use a lot more concealed hostile aggression compared to boys (7), which is also in confirmation of our findings. Such understanding presupposes the use of such forms of aggression against the opposite sex. In these cases, girls use explicit hostility against boys and concealed hostility against girls (8). Pulkkinen has found that aggressive behavior with boys and girls is equally steady and comparable (10).

A significantly high correlation dependence has been established between the results of the total aggregate scale for measuring aggression with the results of the other scales, with correlation coefficient for physical aggression $r=0.796$ ($p<0.001$), verbal aggression $r=0.722$ ($p<0.001$), anger $r=0.842$ ($p<0.001$) and hostility $r=0.672$ ($p<0.001$). The next highest correlating result is with the anger scale, with correlation coefficient for physical aggression $r=0.591$ ($p<0.001$), verbal aggression $r=0.555$ ($p<0.001$) and hostility $r=0.467$ ($p<0.001$). Lower levels of correlation are shown by the results of the scales for physical aggression and verbal aggression, with correlation coefficient $r=0.486$ ($p<0.001$), and verbal aggression and hostility $r=0.338$ ($p<0.001$). On the basis of the comparison this made, we think that the methodology used has good correlation dependence between the results of individual scales for the purposes of the study. In comparison with the results from another investigation in the same area on Egyptian adolescents, our results are more reliable, except for the hostility scale, which has lower values in reference to the individual scales. [1]

The kind of school also influences the levels of aggression $P<0.01$ ($F=2.58$). With general aggressiveness, the highest rates are found in reference to a school with predominating training of girls (98%). Second and third in the level aggression come vocational secondary schools with high percentage ration of boys. It is only the scale of physical aggression which is not influenced by the type of school, $P>0.05$ ($F=1.94$).

CONCLUSION

1. This study confirms the good internal consistency and stability of the scales used in the AQ.
2. The comparison of the studied subjects has revealed the presence of a significant difference in aggression between the two sexes to all AQ scales. Girls have higher results than boys to more of the investigated scales, verbal aggression, anger, hostility and general aggressiveness.
3. The comparison between individual schools has proved a statistically significant difference by this feature in all of the studied scales.
4. The correlation dependence between individual scales proves the existence of good internal consistency of the set of instruments used for measuring the levels of aggression. The highest level of correlation dependence with other scales is demonstrated by the general aggressiveness and anger scales.

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Inflammatory myofibroblastic tumor of the lung in 1 year and 9 month old child

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ВЪЗПАЛИТЕЛЕН МИОФИБРОБЛАСТЕН ТУМОР НА БЕЛИЯ ДРОБ У ДЕТЕ НА 1 г. и 9 м.

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РЕЗЮМЕ

Инфламаторните миофибробластни тумори /ИМТ/ са редки неопластични лезии с относително голяма честота при децата и младите хора. ИМТ се откриват в белите дробове, меките тъкани или вътрешните органи. Те са индолентни мезенхимни гранични неоплазми свързани с малък риск от агресивно поведение и метастази. Хирургичното лечение е основен метод на избор.

Ние представяме случай на момиченце на една година и девет месеца с оплаквания от треска, непродуктивна кашлица с продължителност един месец и анамнеза за рекурентни респираторни инфекции. Симптомите ѝ са прогресирали на фона на антибиотично лечение. Ro –gr и при CT се открива окръглена сянка заемаща целия горен дял вдясно с размери 45/60мм., която повишава плътността си при прилагане на к.м.; десен горнодялов бронх не се проследява, ателектаза на средния дял, групирани вкалцявания в паренхима. Оперативно е отстранена голяма туморна формация заемаща целия горен лоб, плътно прирастнала към гръдната стена,

ABSTRACT

The inflammatory myofibroblastic tumors (IMTs) are rare neoplastic lesions with a relatively high incidence in children and young people. IMTs may arise in lungs, soft tissue, or viscera. They are indolent mesenchymal borderline neoplasms associated with a small risk of aggressive behavior and metastasis. Surgery is the mainstay of treatment.

We report the case of 1 year and 9 month old girl with complaints of fever, unproductive cough for one month and history of recurrent respiratory infections. The complaints progressed on the background of antibiotic treatment. Chest radiograph and CT scan showed round mass range over whole upper right lobe with measurement 45/ 60 mm., which increased its density when contrast was applied. Right upper lobe bronchus was not traced. Atelectasis of middle lobe and grouped calcifications in the parenchyma were found. A big tumor mass spread all over upper right lobe intimate adhered to the chest wall, subclavicular vessels, upper empty venue and most closely to the trachea, main bronchus and pulmonary artery was removed surgically. Atelctatic middle lobe was resected , histo-

подключичните съдове, горната празна вена и най-плътно към трахеята, главния бронх и пулмоналната артеря. Резецира се също и средния ателектатичен лоб. Диагнозата „ инфламаторен миофибробластен тумор“ се основава на хистологично и имунохистохимично изследване с прилагане на широк панел от антитела, предвид диференциално-диагностичните изисквания: vimentin (V 10 clone,DAKO),cytokeratin (AE1/AE3 clone,DAKO) , SMA (1A4 clone),S-100 protein (1:2000), desmin (DAKO 1:500),ALK, CD34,CD45,CD68 ,Tp53 и Ki 67 .

Ключови думи: инфламаторен миофибробластен тумор, педиатрична пулмопатология, имунохистохимия.

pathology revealed the diagnosis of an inflammatory myofibroblastic tumour of the lung. The latest is based on histology and immunohistochemical staining with broad antibody panel: vimentin (V 10 clone,DAKO),cytokeratin (AE1/AE3 clone,DAKO) , SMA (1A4 clone),S-100 protein (1:2000), desmin (DAKO 1:500),ALK, CD34,CD45,CD68 ,Tp53 и Ki 67 .

Key words: inflammatory myofibroblastic tumor, pediatric pulmopathology, immunochisochemstri.

INTRODUCTION

Inflammatory myofibroblastic tumor is defined by WHO as a myofibroblastic spindle cell soft tissue tumor with infiltrative plasma cells, lymphocytes, and eosinophils. It has been classified as an intermediate neoplasm in the current WHO histological typing of tumors of soft tissue and bone.[1.2] Although it has been reported to be the most common benign primary pulmonary tumor in childhood, accounting for more than 50%, these tumors are infrequently encountered in clinical practice. Moreover, these tumors are often a diagnostic dilemma for the surgeon and the pathologist since biopsy reveals only inflammatory cells.[3.4]

They have heterogeneous histlolological view, that's why a wide variety of names has been applied including plasma cell granuloma (created by Bahadori and Liebow in 1984), inflammatory pseudotumor, xanthogranuloma, fibrous histiocytoma, inflammatory fibrosarcoma.

IMTs were described in most organs and anatomic sites, but their usual localization is in the lungs. They consist above 1 % of lung tumors, but among benign children lung tumors they reach 50%. They were thought to be benign, but the recent data assigns them to borderline tumors since metastatic or progressive disease has been reported. Clinical, radiological and histological similarity with malignant tumors make the diagnosis difficult.

CASE REPORT

We report the case of 1 year and 9 month old girl, treated at the Division of Child surgery, Univercity Hospital Pirogov 7588 04.03. 2013.

Clinical data. A girl with complaints of fever, unproductive cough for one month and history of recurrent respiratory infections. The complaints progressed on the background of antibiotic treatment. Objectively the patient is in satisfactory state with pale skin and mucous membranes. Laboratory data are hypochromic anaemia, raised erythrocyte sedimentation rate /ESR/, leukocyte shifting. Elevated muscle tone of the extremities made walking impossible. Auscultation finding- reduced breathing upper right, without crepitations. Ultrasound diagnosis- atelectasis of the right lung, hepatosplenomegaly, no increased abdominal lymph nodes. Chest radiograph and CT scan showed round mass range over whole upper right lobe with measurement 45/ 60 mm., which increased its density when contrast was applied. Right upper lobe bronchus was not traced. Atelectasis of middle lobe and grouped calcifications in the parenchyma were found / fig. 1 /.

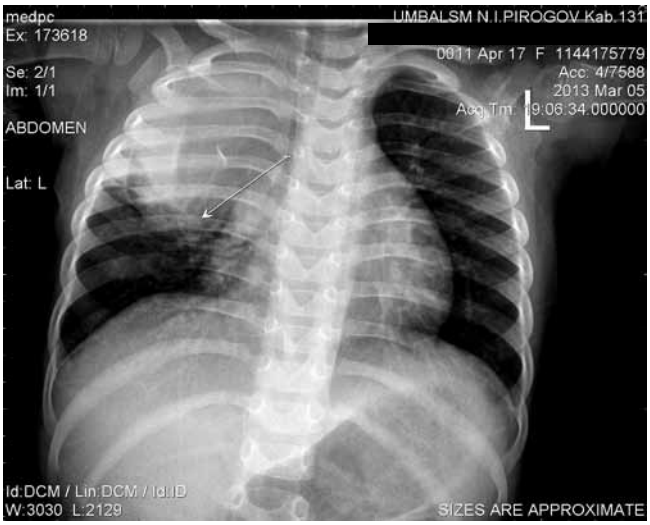

Fig 1.

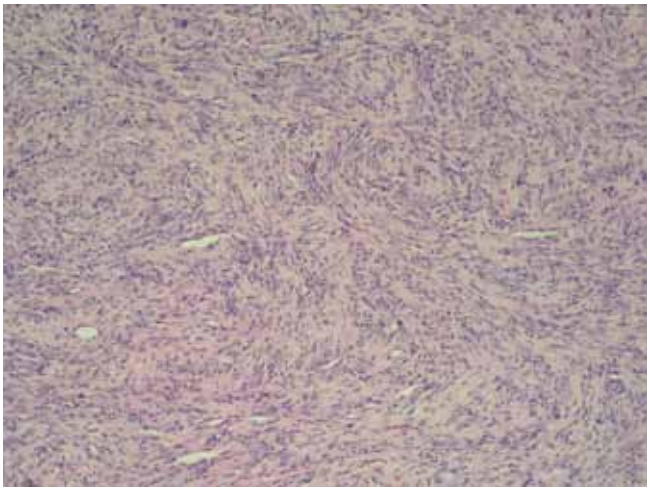

Fig. 2

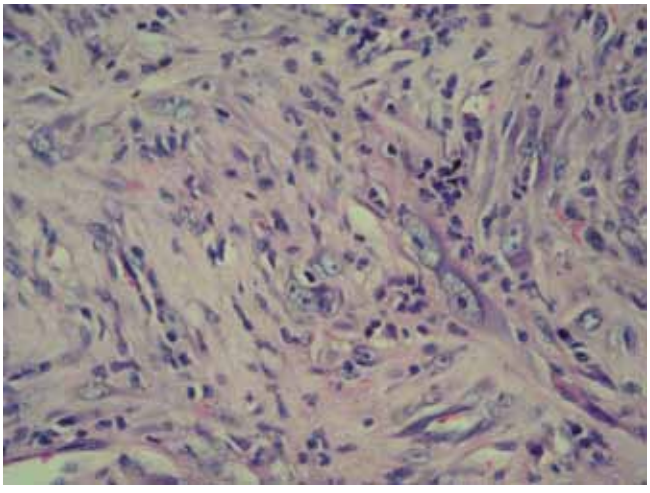

Fig.3

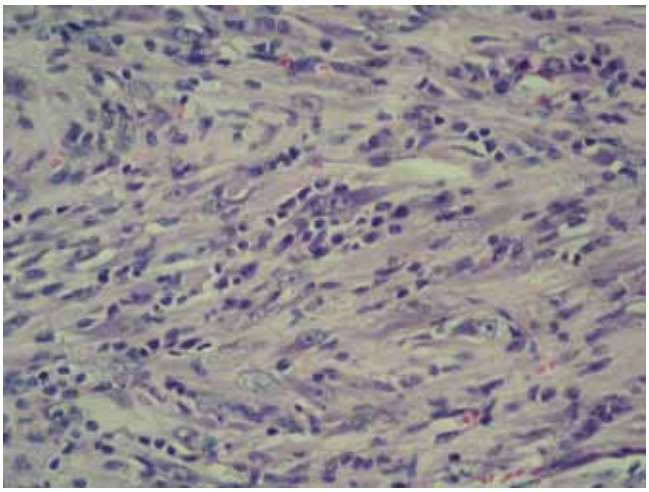

Fig. 4

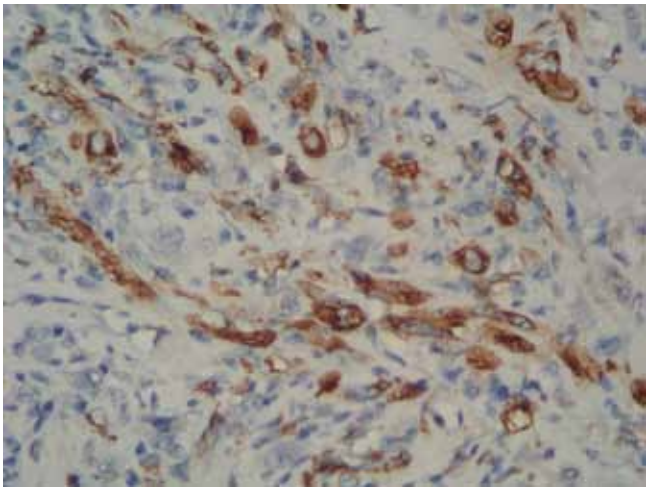

Fig. 5

The big tumor mass spread all over upper right lobe intimate adhered to the chest wall, subclavicular vessels, upper empty vein and most closely to the trachea, main bronchus and pulmonary artery was removed surgically. Atelectatic middle lobe was resected.

PATHOLOGICAL EVALUATIONS

Biopsy № 3478–3481/ 2013: Microscopically spindle cell tumor consisted of interweaved fascicles. Cell composition included fibroblasts, histiocytes, myofibroblasts, without certain atypia, with large vesicular nuclei and prominent nucleoli. Some of the cells resembled myoblasts. The tumor was rich in vessels, mainly of capillary type. Among spindle cells was found

abundant inflammatory infiltrate of lymphocytes, plasma cells, occasional eosinophil leukocytes / fig. 2/.

The tumor fields showed variations: similarity to the fibrous histiocytoma with inflammatory reaction, proliferation of granulation tissue and zones, suspicious of rhabdomyoblast differentiation / fig.3 and fig. 4 /.

Immunohistochemical staining was made with panel of primary antibodies / Dako Corporation/ against various antigens : vimentin / V 10 clone, Dako/, cytokeratin / AE 1/ AE 3 clone, Dako/, SMA / 1A4 clone/, S- 100 protein / Dako 1: 2000/, desmin / Dako 1:500/, ALK , CD 34, CD 45, CD 68, p 53, Ki 67. The immunohistochemical investigations showed generally strong positive staining for vimentin , smooth muscle actin was positive in the blood vessels walls and in some spindle cells, / fig. 5/ , CD 45 was positive in inflammatory cells, CD 34 was positive in the blood vessels, CD 68 was positive in histiocites. Ki 67 proliferative index was about 2 %. The rest of immunohistochemical reactions was negative. The above mentioned immunophenotypic features were consistent with the myofibroblastic differentiation in this tumor. Histological and immunological phenotype validated the diagnosis inflammatory myofibroblastic tumor.

DISCUSSION

Similar to the others published cases, the described case presented nonspecific clinical findings with pulmonary symptoms and chest X- ray and CT scan which directed the diagnosis along the malignant neoplasm. The presence of hypo chromic anaemia has been reported in some of the publications, but obscure neurological disorder in this case indicates the presence of multifunctional genetically disturb ground.

The notion of IMT being a reactive lesion or a true neoplasm is controversial / 7 /. Recent data suggest the relationship between IMT and prior chronic pneumonias / 4 / and association with human herpes virus -8 and overproduction of IL- 6 and cycline D /2 /, circumstances that suggest primary inflammatory process. IgG4 related immunopathologic processes may be involved. The anamnesis 'data of repeated pneumonias, laboratory tests and hepatosplenomegaly give us a reason to accept the idea of inflammatory genesis in the reported case. The recent hypothesis of benign character of IMT is confuted by the reports of malignant course – metastatic or progressive disease outside the thoracic cage for the primary pulmonary IMT / 6 /. Contemporary cytogenetic studies present IMT like neoplasms. This standpoint is supported by described clonal chromosomal abnormalities, chromosomal rearrangements involving the ALK receptor tyrosine- kinase locus region (2p23) or DNA aneuploidy in IMT / 1, 7/. Chemotherapy treatment of some aggressive IMTs supports the hypothesis of their neoplastic nature / 6 /.

IMT with its variable cell composition makes the differential diagnosis with tumors and tumor like lesions in the lungs, including localized consolidated pneumonia, fibrous histiocytoma, plasmocytoma, hyalinizated granulomas, amyloid tumor, malignant fibrous histiocytoma, sarcomatoid carcinoma, pleuropulmonary blastoma, difficult. It is particularly difficult to distinguish it from other mesenhymal neoplasms attended by inflammatory infiltrate. Unique histologic examination cant solve the diagnostic problem and it requests application of immunohistochemical panel of antibodies to determine not only the histogenesis, but also the pathogenesis of the process. In this sense examination for the protein p 53 / positive in malignant neoplasms/ and ALK / positive in some IMT / may contribute helpful information.

IMTs represent interest with there rarity, uncertain etiology and pathogenesis as well as the problems they cause in clinic pathological, diagnostic and therapeutic aspect. According to the latest statements, surgery is the treatment of choice and its radicality and completeness are the most important prognostic factor. Until

recently there have been limited effective treatment options for unresectable disease. Identification of anaplastic lymphoma kinase (ALK) fusion genes in approximately 50% of IMTs and the role of ALK inhibition in the treatment of this disease represent interest . A recent phase I dose-escalation trial of the selective MET/ALK inhibitor crizotinib showed a long-term partial response in a patient with IMT carrying an ALK translocation. Multiple second-generation ALK inhibitors are currently being investigated in the preclinical and clinical trial setting.

To create a base for standard examinations and protocol for treatment, detail investigation on clinical course and pathomorfology of more IMT cases are necessary.

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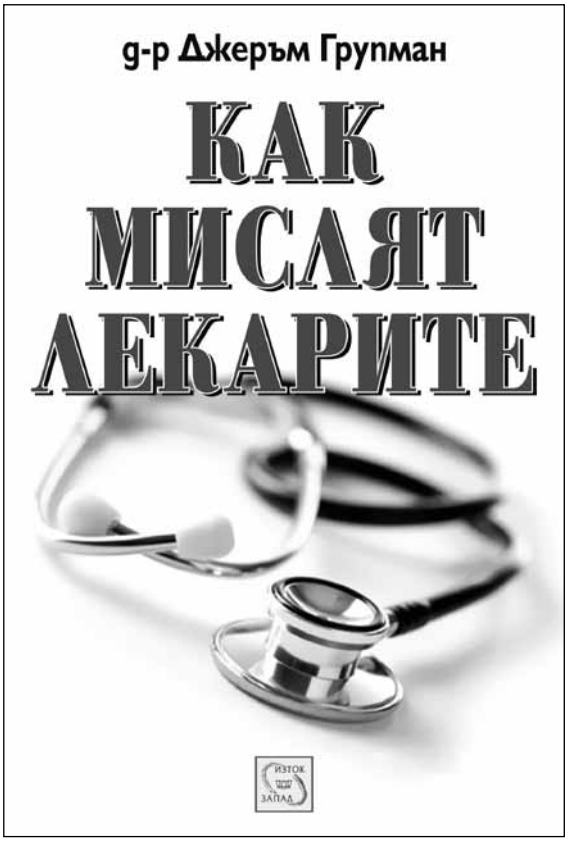
Търсете

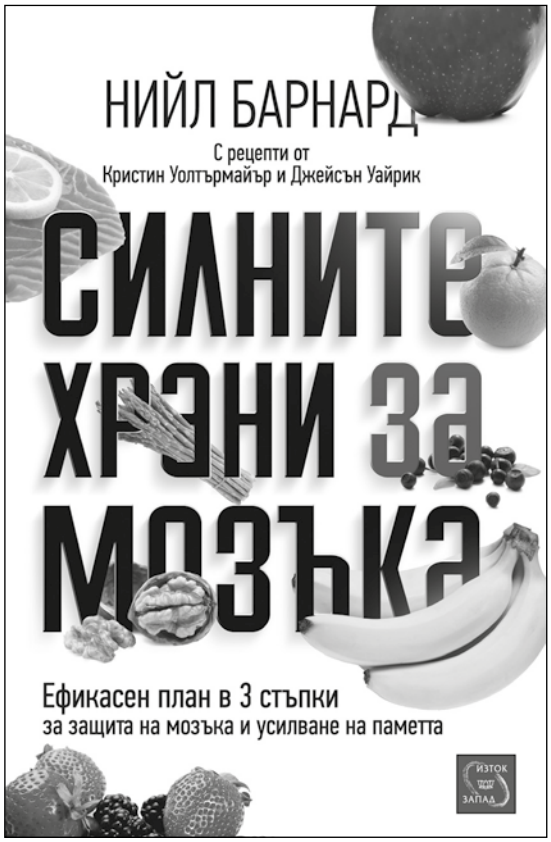

КЛАВДИЙ ГАЛЕН
ИЗКУСТВОТО за ЗАПАЗВАНЕ на ЗДРАВЕТО
ИЗТОК ЗАПАД
БИБЛИОТЕКА здраве


д-р Джеръм Групман
КАК МИСЛЯТ ЛЕКАРИТЕ
ИЗТОК ЗАПАД


МЕЛАНИ ТЪРНСТРОМ
ХРОНИКИ НА БОЛКАТА
Лечения, митове, мистерии, молитви, дневници, мозъчни скенери, изцеление и науката за страданието
ИЗТОК ЗАПАД

Търсете


д-р ПЕТЯ АРНАУДОВА
МАЛКА
МЕДИЦИНСКА
ЕНЦИКЛОПЕДИЯ
ЗА ВСЕКИ
ИЗТОК ЗАПАД


НИЙЛ БАРНАРД
С рецепти от
Кристин Уолтърмайър и Джейсън Уайрик
СИЛНИТЕ ХРАНИ ЗА МОЗЪКА
Ефикасен план в 3 стъпки
за защита на мозъка и усилване на паметта
ИЗТОК ЗАПАД


Шиам Сингха
БИБЛИОТЕКА здраве
ХРАНЕНЕТО като лечение
ИЗТОК ЗАПАД