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Contemporary insight into the diagnostic and therapeutic strategy in secondary malignant diseases of the spine and spinal cord – who and how to treat?

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Съвременен поглед към диагностичната и терапевтичната стратегия при вторични злокачествени заболявания на гръбначния стълб и гръбначния мозък – кой и как да се лекува?

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РЕЗЮМЕ

През последното десетилетие се наблюдава засилен научен интерес към възможностите за лечение на пациенти с онкологични заболявания. Това се дължи както на нарастващата честота на тази патология, така и на значително по-високата преживяемост на болните, която съпътства бързото развитие на медицинската технология. Повишената преживяемост на пациентите води до по-честата диагностика на гръбначни метастази и необходимостта от развитие на унифициран алгоритъм за поведение при тях. Вторичните злокачествени заболявания на гръбначния стълб и мозък са усложнение свързано с висок риск от тежка инвалидизация

ABSTRACT

There is an increased scientific interest in the treatment of oncological patients during the last decade. This is based on both the increasing incidence of the pathology and considerably prolonged survival of these patients resulting from the rapid development of the medical technology. Prolonged survival leads to higher rate of diagnosing of spinal metastases and necessitates the introduction of uniform treatment algorithm. Secondary malignant diseases of the spine and spinal cord present a devastating complication connected with high risk of severe disability and excruciating pain. Therefore, this is an important issue with both medical and social significance.

на болните и се съпътстват от силна болка. Това ги прави важен проблем както с медицинска, така и със социална значимост.

Бурното развитие на спиналната хирургия и въвеждането на надеждни системи за реконструкция и стабилизация на засегнатите от метастатичните лезии сегменти, при максимално възстановяване на анатомичната и биомеханична функционалност, дава възможност за възможно най-голям радикализъм в туморната резекция. Повишената преживяемост на пациентите с вторични злокачествени гръбначни заболявания извежда на преден план стремежа към съхраняване и повишаване на качеството на живот и максимална им самостоятелност при осъществяване на ежедневните нужди.

Следователно, целта на този обзор е да изясни съвременните аспекти в диагностиката и лечението на метастатичните заболявания на гръбначния стълб и мозък.

Ключови думи: *гръбначни метастази, оперативно лечение, качество на живот, реконструкция, стабилизация*

The rapid development of spinal surgery and the introduction of reliable systems for spinal reconstruction and stabilization of the involved segments resulting in optimal restoration of the anatomic and biomechanical properties of the spine create favorable conditions for more radical tumor resections. Prolonged patient survival brings out the aspiration for preserving and increasing the quality of life and maximal independence of daily living.

Therefore, the aim of this review is to cast a light on the contemporary aspects of the diagnostics and treatment of the spinal metastatic disease.

Key words: *spinal metastases, surgery, quality of life, reconstruction, stabilization*

INTRODUCTION

The aging of the population and the prolonged survival in oncological patients lead to higher rate of diagnosing secondary malignant spinal neoplasms. This is an advanced stage of the systemic disease which is associated with high risk of severe disability, excruciating pain, poor general condition and, therefore, is an important issue with both medical and social significance[3]. Treatment of spinal metastases is becoming more important with emphasis on patients' quality of life (QoL) [36]. The surgery plays a major role in the treatment complex due to the introduction of contemporary spinal systems and instrumentation which allow the neurosurgeon to perform maximal and safe tumor resections, decompression of the neural elements, reconstruction and stabilization of the involved spinal segment. The current review aims at summarizing and analyzing the contemporary directions in the diagnostics and treatment of the secondary malignant spinal diseases.

INCIDENCE AND HISTOLOGICAL ORIGIN

Metastatic spinal tumors are more common than the primary spinal tumors and share the same histological features with the primary source tumors from which they derive. More than 65–70% of cancer patients develop bone metastases. The greater percentage is located in the spine and only 10–15% of patients are symptomatic. Over 90% of spinal tumors are metastatic [31]. Spinal metastases are the third most common tumors after those affecting the lungs and liver. In 10% of cases the primary source remains unknown. 75% of spinal metastases derive from prostate, breast, renal, lung and thyroid cancer [5,8,23,28].

Extradural spinal metastases present 95–98% of cases and in 80% they affect the verte-

bral body and pedicles [5,21]. Intramedullary metastases are reported in 0.9–4% of cases and characterized by rapid progression of focal neurological deficit which requires urgent surgery [14,19]. 10–15% of spinal metastases develop pathological fractures [9].

The secondary malignant spinal tumors most commonly affect the vertebral body and pedicles and their epidural extension is usually circumferential. This leads to severe damage of the three-column system of spinal stability [33].

The incidence of segmental distribution demonstrates that the thoracic spine is affected in 60–80% of cases, the lumbar spine – in 15–30%, and the cervical spine – in 10%. 10–38% of spinal metastases are multiple and located in more than one spinal segment [5,12]. The stability of the thoracic spine is greater compared to the lumbar and cervical spine. This is due to the stabilizing and immobilizing role of the thoracic cage and the sternum [37]. The incidence of spinal metastases in men older than 60 is four fold higher in comparison with men below 60 and three fold higher in women over 60 [2].

The spine is also often affected by multiple myeloma, especially, the malignant B-cell non-Hodgkin's lymphoma which causes osteolysis resulting from the activation of the osteoclasts. Only in 2–10% of cases the lesions are solitary. The incidence of this disease increases with age and is most common over 65–70 years [11,35]. Over 80% of multiple myeloma patients develop symptomatic spinal metastases [10].

CLINICAL PRESENTATION AND DIAGNOSTICS

The clinical presentation may follow acute or insidious evolution. The classical triad of symptoms of spine metastases includes pain, spinal instability and neurological deficit [13]. The clinical presentation includes the following symptoms of different incidence and intensity:

1. Pain and localized vertebral syndrome
   Pain is the most common symptom seen in 90–100% of cases [9,36]. It is a result of bone destruction, injury to the ligamentous apparatus, compression and infiltration of the dura mater [2]. The pain may be: localized (resulting from the periosteal stretching and reaction); radicular (in cases of radicular compression); axial/mechanical (due to instability of the involved segment) [21]. Bone metastases are the most common cause for pain in cancer patients [23].
2. Focal neurological deficit
   Neurological deficit is registered in 60–70% of cases by the time of diagnosis [9]. Patients with complete loss of neurological function below the level of injury usually do not recover and the prognosis is grim [30]. Usually, the neurological deficit occurs within weeks to 2 months after the onset of pain syndrome [2]. The type of focal neurological deficit depends on the level of the lesion and its localization.
3. Spinal deformity leading to the development of kyphosis, scoliosis or kyphoscoliosis and localized gibbus [2].
4. Pathological fracture of the vertebral body as a result of collapse caused by the metastatic lesion. The vertebral body and pedicles are affected in over 85% of cases and in more than 10% it causes pathological fracture with subsequent development of neurological deficit [25].
5. Segmental instability leads to increased radicular and axial pain as well as high risk of acute neurological deterioration.

The diagnostics of the metastatic spinal diseases includes thorough clinical examination in conjunction with imaging studies. Plain X-rays, myelography, computed tomography and magnetic-resonance imaging (MRI) can be applied either separately or in combination. The MRI usually shows hypointensity on T1-weghted images and hyperintensity on T2-weighted images [6,31]. This is the diagnostic modality of choice which is becoming increasingly popular in recent years. Moreover, MRI is routinely used as an examination for preoperative planning of the contemporary therapy by means of stereotactic radiosurgery [15,16]. Rarely, are the intervertebral discs affected by the neoplastic process for their avascular nature [2]. The vertebral body and the pedicles are 20 times more

commonly affected compared to the vertebral laminae and the posterior elements of the extradural space [4].

Another useful examination with high diagnostic sensitivity is the bone scintigraphy with Tc^{99m}. This isotope is captured by the neoplastic cells, thus, the study can detect lesions measuring 2 mm and is able to diagnose metastatic disease between 2 and 18 months prior to their roentgenological debut [31].

TREATMENT OPTIONS

The contemporary therapeutic trend in the treatment of metastatic spine lesions requires interdisciplinary approach. This is important because the final goal is to provide better QoL, despite that the treatment is generally palliative in such patients.

1.Operative treatment

Indications for surgery [5, 18, 25, 31]:

- Severe pain unrelieved by conservative measures
- Progression of the focal neurological deficit
- Presence of pathological fracture
- Compression of the neural elements by the growing tumor
- Segmental spinal instability
- Progressive spinal deformity with formation of kyphosis, scoliosis, kyphoscoliosis or regional gibbus
- Radio-resistant tumors
- Neurological deterioration after reaching the maximal radiotherapeutic dose
- Life expectancy more than 3 months
- Absence of metastases in other vital organs
- Satisfactory general status allowing more aggressive treatment
- Histological verification of the tumor type and specifying of unknown primary source

Aims of surgery [18, 28, 31]:

- Decompression of neural structures
- Maximal tumor resection, if possible – total resection
- Achieving histological verification of the tumor type
- Reconstruction and stabilization of the involved segment or the accompanying pathological fracture
- Improving patient's QoL and daily independence as much as possible

The choice of the appropriate surgical approach and technique should be individual and depending on the localization of the tumor tissue in relation to the neural structures, the involved spinal segment and the absence of paravertebral spread [38]. Posterior, posterolateral and anterior surgical approaches are commonly used. Anterior approaches are suitable and widely used for the cervical spine. Anterior approaches in the thoracic and lumbar spine require thoracotomy and laparotomy, respectively. Therefore, these approaches necessitate the participation of visceral and thoracic surgeons, require longer operative time and are associated with higher rate of complications[3, 20] . The anterior thoracic approaches may lead to pulmonary (atelectasis, pneumonia, respiratory failure), technical (hemo-pneumothorax, wound infections) and somatic complications (embolism, stroke, ileus, urinary infection, acute renal failure) [20].

In the lumbar segment the complications can be vascular (arterial or venous trauma and/or thrombosis), neurogenic (bladder and bowel disturbances, hyperpathic pain in the lower extremities), wound problems (infection, herniation, dehiscence), ureter injury and somatic (embolism, stroke, urinary infections, acute renal failure). The complication rate can reach 40% [20]. Posterior decompression, posterolateral resection of the vertebral body, reconstruction and stabilization of the involved segment are commonly used in the thoracic and lumbar spine [2].

Satisfactory general status and presence of solitary metastasis may impose more aggressive surgery such as the one-stage „en-block" vertebrectomy. This method can provide radical resection of the spine lesion. The use of this approach is justifiable because it may offer prolonged survival of patients with solitary metastasis up

to 30 months [34]. The indications are: solitary spinal metastasis, absence of other organ metastases and considerable paravertebral extension [1,28,32]. Surgery should be performed prior to radiotherapy because, otherwise, wound complications increases three fold [2,16].

2. Contemporary mini-invasive procedures – percutaneous vertebroplasty (PVP) and kyphoplasty (PKP).

These procedures offer considerably lower rate of postoperative pain in 80–82% of the cases [29]. They are used when the life expectancy is less than 3 months and surgery is not indicated [3]. In neoplastic lesions the complication rate reaches 5–10%, whereas in osteoporotic fractures it is only 1–3% [7]. Kyphoplasty may considerably reduce the risk of cement leakage [11,22]. Indications for PVP and PKP are the presence of painful pathological fracture or medically intractable pain resulting from an osteolytic focus.

Contraindications are: the presence of symptom-free compression fracture; medically curable pain; local or generalized infection; coagulopathy; allergy to bone cement; presence tumor mass compressing the spinal cord. Relative contraindications are: loss of vertebral body height with more than 70%; multiple metastases (more than 5); fracture affecting the posterior column causing radicular pain and less severe axial pain [21].

In recent years, the PVP and PKP are combined with percutaneous radiofrequency ablation. This procedure provides the formation of a cavity in the anterior 2/3 of the vertebral body and offers better cement distribution which reduces the risk of clinically evident extravasation [17].

3. Radiotherapy (RT)

RT reduces pain in 80% of the cases but the rate of patient recovery and independence is considerably lower – less than 30% of the cases [18]. Usually, the reduction of pain intensity is registered after two weeks post-irradiation [21]. The total irradiation dose is limited by the tolerance of the spinal cord [15].

4. Radiosurgery (RS)

RS is a contemporary method used mainly for solitary metastases where surgery is inappropriate. The maximal intratumoral irradiation dose that is applied by means of CyberKnife® or GammaKnife® varies between 12.5–25 Gy (20 Gy on average). This method reduces pain in 86% of the cases and neurological deficit – in up to 84% [15]. Stereotactic RS provides maximal target coverage with optimal fractionated dose and at the same time it considerably reduces the irradiation of the surrounding „risk organs“ [27]. RS aims at pain reduction, prevention from pathological vertebral fracturing and delay of neurological deterioration [15].

5. Chemotherapy (CT)

CT is of limited use in spinal metastasis treatment. The major indications for CT are the malignant hematologic spinal diseases and some cases where the tumor from the primary source is chemosensitive.

6. Hormonotherapy

In general, it may be used in the treatment of metastases from breast cancer.

7. Physical therapy and rehabilitation

It plays an important role in the palliative care of these patients.

The average age of patients suffering from metastatic tumors to the spine and spinal cord is 52–58.3 years [36]. Surgery is indicated if the expected improvement of QoL exceeds the direct operative risks [36]. The aim of surgery is to prolong survival as well as to increase patient's daily independence [12]. This sometimes can justify a „redo“ surgery in cases with local recurrence and good general status of the patient. Apart from surgery, the adjuvant therapy usually includes RT and CT. Preoperative endovascular embolization of the feeding vessels is sometimes indicated in order to reduce the perioperative blood loss and risk [24].

The preoperative RT and CT increase both wound complications and immunosuppression.

Therefore, careful patient selection for surgical treatment is of great importance. On the contrary, postoperative RT leads to prolonged survival, adequate pain control and improved QoL.

CONCLUSION

The current literature review and analysis demonstrates that the adequate selection of appropriate surgical candidates suffering from spinal metastatic disease in accordance with the established indications leads to improved QoL. Thus, the surgical treatment should be considered to be the first step in the complex therapeutic algorithm. Apart from surgery, it should also include RT and CT whenever indicated. If open surgery is contraindicated, one should bear in mind the contemporary percutaneous techniques and radio-surgical methods.

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Wilson's disease – a diagnostic and therapeutic approach

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Болест на Wilson – диагностичен и терапевтичен подход

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РЕЗЮМЕ

Болестта на Wilson е наследствено автозомно рецесивно нарушение на билиарния меден транспорт. В резултат на това медта се натрупва и оказва токсично въздействие в черния дроб, мозъка, корнеята и бъбреците. Протича главно с чернодробни и нервно-психични прояви. Диагнозата се основава на комплексната оценка на клиничната картина, лабораторните данни за отклонения в медната обмяна и резултатите от морфологичните, генетични и образни изследвания. Болестта на Wilson да бъде лекувано. Лечението е насочено към намаляване на токсичното отлагане на мед в тялото и постигане на негативен меден баланс. е необикновено генетично заболяване поради това, че може ефективно Терапията с хелатори и цинкови соли е опора на лечението до живот. Чернодробната транспантация осигурява корекция на подлежащия метаболитен дефект.

Ключови думи: Болест на Wilson, биохимични тестове, генетично изследване, точкова система, хелатори, чернодробна трансплантация

ABSTRACT

Wilson's disease is a hereditary autosome recessive disorder of biliary copper transport. This results in copper accumulation and its toxic influence on liver, brain, cornea and kidneys. It presents mainly with hepatic and neuropsychiatric disturbances. The diagnosis of Wilson's disease is based on the complex evaluation of the clinical symptoms, laboratory data about abnormalities of copper metabolism as well as of the results from the morphological, genetic and image examinations. Wilson's disease is an unusual genetic disorder because of the fact that it can effectively be treated. The management of the disease is focused on the reduction of the toxic copper accumulation in the organism and the achievement of a negative copper balance. The therapy with chelating agents and zinc salts supports life-long treatment. Liver transplantation warrants the correction of the underlying metabolic defect.

Key words: Wilson's disease, biochemical tests, genetic examinations, diagnostic scores, chelators, liver transplantation

INTRODUCTION

Wilson's disease is an autosome recessive disorder characterized by pathological copper accumulation initially in the liver and, subsequently, in the nervous system and other tissues as well. It presents with a broad scope of hepatic and neuropsychiatric abnormalities. If a specific treatment is absent, copper accumulation advances and leads to a fatal outcome.

DIAGNOSIS OF WILSON'S DISEASE

The diagnosis of Wilson's disease is based on a broad combination of laboratory tests and clinical manifestations. Examinations are justified in any case of isolated elevation of aminotransferases, chronic hepatitis of undefined reason, haemolytic anaemia, neurological symptoms, and unexplained psychiatric disease including sudden behavioural changes as well (9,20,22,36).

BIOCHEMICAL LIVER TESTS

Serum aminotransferase activity is, usually, abnormal in Wilson's disease except for the very young age. In numerous individuals, however, the degree of the elevation of the aminotransferases can be slight and thus not reflect the severity of the liver disease (28,39).

Ceruloplasmin

Ceruloplasmin is a copper-binding protein that is related to approximately 90 per cent of circulating copper in healthy individuals. The normal ceruloplasmin concentration is of 0,2–0,4 g/L and serum ceruloplasmin below 0,2 g/L suggests Wilson's disease (22,28). Approximately 90 per cent of the patients with neurological symptoms, 75 per cent of those with hepatic manifestations and about 90 per cent of the presymptomatic patients present with a low or intermediately low ceruloplasmin level. However, it should be remembered that between 10 and 20 per cent of the patients present with low-bordeline or normal ceruloplasmin values (4,9,22,28,33,39). Besides the clinical benefit of this measurement is limited by the fact that ceruloplasmin concentrations below 0,2 g/L can be established in one per cent of the control subjects, in 10–20 per cent of the heterozygotic carriers, in patients with copper deficiency, in Menkes disease, in pathology related to hypoproteinaemia such as nephrotic syndrome, protein-losing enteropathy, malabsorption, including gluten enteropathy, malnutrition, severe hepatic failure as well as to a terminal stage of every liver disease (9,28,33,39). Besides ceruloplasmin represents an acute-phase reactant and it increases in response to inflammation, infection, and trauma. It is elevated in pregnancy, intake of estrogens and contraceptive means as well (8,9,28). The method of estimation is of importance, too. The immunologic method used in clinical practice renders an account of the whole amount of ceruloplasmin, i. e. bound to copper, active or holoceruloplasmin and not bound to copper or apoceruloplasmin and that is why its levels are higher. The enzymatic method measures the oxidase activity of the active protein only, however, it is not routinely applied in practice. Because of these peculiarities, serum ceruloplasmin should not be used alone as a definitive test for the diagnosis of Wilson's disease and for its rejection (11,13,22,23).

Uric acid

Serum uric acid can be reduced at the manifestation of the disease because of renal tubular dysfunction, i. e., Fanconi's syndrome (28).

Urinary copper excretion

Urinary copper excretion is increased in most untreated patients. The 24-hour cupriuria over 1,6 μmol/24 hours is a reliable diagnostic test in a clinically manifested disease (22,28,29). Copper values over 0,64 μmol/24 hours are strongly indicative of Wilson's disease and require further examinations. The levels between 0,6 and 1,6 μmol/24 hours do not allow the exclusion of Wilson's disease in asymptomatic patients (22). The heterozygotic subjects can present with intermediate levels, too. The ben-

efit of this measurement is restricted by the fact that the higher urinary copper levels can be observed in other liver diseases presenting with a hepatocellular necrosis such as autoimmune hepatitis, acute liver failure and cholestatic diseases as well (22,28,33,39).

D-penicillamine challenge cupriuria is an important and useful additional diagnostic test (1,2,8,22,28). It has been standardized in children only and possesses a high diagnostic value if the urinary excretion exceeds 25 μmol/24 hours after stimulation by D-penicillamine in a dose of 1000 mg. The predictive value of this test in adults remains not specified yet (14,25,28). Clinical experience and our own observations demonstrate that the test is of a diagnostic importance when the provoked cupriuria surpasses by five times the basal one as well as when this elevation is by five times over the normal value in combination with clinical, laboratory, or genetic criteria (1,22).

Serum copper

Although Wilson's disease is a disorder of copper accumulation, total serum copper consisting of free and cerulopasmin-bound copper is, usually, reduced proportionally to the diminished ceruloplasmin in circulation.

The estimation of total serum copper level is a routine laboratory test of a low diagnostic value. Its levels are, usually, low in asymptomatic patients or in cirrhosis. Serum copper could be within normal values in spite of the low ceruloplasmin ones in severe liver insufficiency. Serum copper could substantially be elevated in case of haemolysis with or without fulminant manifestations as well as in acute liver failure because of Wilson's disease (39).

On the background of a low ceruloplasmin, the normal or increased copper levels testify to an enhanced concentration of free copper not bound to ceruloplasmin (28,39). The serum concentration of free toxic copper has been suggested as a diagnostic test for Wilson's disease (9,28). Its testing validity depends on the methods for ceruloplasmin measurement, i. e. the widely used immunologic method or the enzymatic one. The latter is more sensitive and more recommended as it determines copper-containing active ceruloplasmin only; however, it has not become any routine assay yet. There exists a method for direct free copper estimation that is not accessible for routine application yet, too. Free copper determination is of higher value when monitoring the response to treatment than as an independent diagnostic test (5,11,13,22,28).

Copper content in liver parenchyma

Quantitative copper determination in the liver is the best and most definitive test for the evaluation of Wilson's disease. This has been described in the literature available as a gold standard for the diagnosis of the disease (4,13,22,28). Copper concentration exceeds 250 μg/g (over 0,4 μmol/g) in dry tissue in 80 per cent of the patients (9,13,22). However, its distribution in the liver is not regular, especially during the late stages of the disease. The quantitative variability can be due either to a sample error, or to an unreliable single estimation. The quantitative determination is accomplished by means of mass spectroscopy or atomic absorption spectroscopy. This modern method is, however, not accessible in the routine clinical practice yet. It is not applied in Bulgaria yet, too.

Copper in hepatocytes as established by routine histochemical examination varies considerably. In the early stages of the disease, copper is located mainly in cytoplasm and bound to metallothionein; thus it can be proved by means of very sensitive staining only. Later on, copper can be predominantly found in lysosomes. It can be established by means of a less sensitive staining with rhodamine and rubeanic acid or, as lysosome copper-bound protein – with orcein stain (1,27,28,30). The histochemical examination with rhodamine can prove both copper and copper-bound protein and, therefore, represents a pathognomonic feature of Wilson's disease; however, it occurs in 10 per cent of the examined patients only (13). That is why the

absence of a positive result does not exclude the diagnosis of Wilson's disease (9,30).

Kayser-Fleischer rings

Kayser-Fleischer rings represent a distinctive pathognomonic sign of this disease. They are built-up by copper sedimentations on the posterior surface of Descemet corneal membrane. When visible under direct inspection, they look usually like a golden-brown or grayish band near the iris. The reliable precise identification of the rings requires an examination under biomiscroscope by an experienced ophthalmologist (28,33,35). These rings are present in 95–99 per cent of the patients with neurological or psychic symptoms and only in 50–60 per cent of the patients with a predominant liver damage when making the diagnosis (22,28,39). However, the absence of a Kayser-Fleischer ring does not exclude the diagnosis of Wilson's disease even in the patients with a neurological form.

The presence of a 'sunflower' cataract is another finding. It can be revealed under biomicroscope, too. It represents a greenish or brownish pigmentation of copper sedimentations on the anterior or posterior lens capsule. It does not cause any significant reduction of vision (3,7,10,15,28).

Both ocular alterations can disappear during the effective drug treatment or following liver transplantation although the extent of their diminution and disappearance does not correlate with coping (22,28).

Genetic investigations

Up-to-date, more than 600 mutations of ATP7B gene have been identified. That is why the creation of a simple screening diagnostic test is a difficult task (7,27). If one establishes a given mutation responsible for Wilson's disease, the pathology is confirmed; however, the negative result is not capable of excluding this disease (22). Large-scale trials fail to establish any mutations in 13–15 per cent of the patients.

Mutation analysis is useful in certain populations demonstrating a limited number of ATP7B mutations like in Eastern Europe (H1069Q), Sardinia (c-441_427del115), China (Arg778Leu), etc. Data interpretation is additionally hampered by the fact that most patients are compound heterozygotes and present with various mutations of each allele (28,35).

Haplotype analysis is based on the polymorphisms surrounding ATP7B gene and is used for patients' familial screening. After determination of proband's mutation or haplotype, the same specific region in DNA of first-degree relatives can be studied. This technique is valuable when defining the genetic status of asymptomatic siblings, i. e. if they are either homozygotes or hererozygotes, or are no mutation carriers in case of impossible identification of proband's mutations (11,22,28).

When Wilson's disease is diagnosed, any first-degree relatives should undergo screening for this disease. Familial screening based on haplotype or mutation analysis is necessary in order to detect the asymptomatic mutation carriers with a view to administer the therapeutic regime prior to the emergence of the clinical symptoms (2,9). When the molecular analysis can't be performed, the standard examination should include a set of functional liver tests, serum ceruloplasmin, 24-hour cupriuria and examination of the presence of Kayser-Fleischer rings (29).

Neuroimaging methods of examination

Computer tomography, magnet resonance imaging and magnetic resonance spectroscopy of the brain can establish alterations in basal ganglia, white matter, thalamus, and brainstem. The patients with neurological symptoms should undergo a brain examination at the onset when diagnosing the disease (28,29,38).

Diagnostic scoring system

In 2001, during the 8th international conference on Wilson's disease and Menkes disease in Leipzig, Germany, a scoring system for diagnosis of Wilson's disease was proposed. Its purpose was to ensure objective criteria of high sensitivity and specificity for the disease. This

Table 1.
Scoring system for diagnosis of Wilson's disease (Leipzig, Germany, 2001)

Typical clinical symptoms and signs		Other tests	
Kayser-Fleischer rings		Liver copper (in the absence of cholestasis)	
Present	2	>5x ULN** (>4 µmol/g)	2
Absent	0	0,8 – 4 µmol/g	1
		Normal (<0,8 µmol/g)	-1
		Rhodamine-positive granules***	1
Neurologic symptoms*		Urinary copper (in the absence of acute hepatitis)	
Severe	2	Normal	0
Mild	1	1–2x ULN	1
Absent	0	>2 ULN	2
		Normal, but >5x ULN after D-penicillamine	2
Serum ceruloplasmin	0	Mutation analysis	4
Normal (>0,2 g/L)	1	On both chromosomes detected	1
0,1 – 0,2 g/L	2	On one chromosome detected	0
<0,1 g/L		No mutations detected	
Coombs-negative hemolytic anemia	1		
Present	0		
Absent			

* or typical abnormalities at brain MRI
** ULN, upper limit of normal
*** If no quantitative liver copper available

Total score evaluation:
4 or more – Diagnosis established
3 – Diagnosis possible, more tests needed
2 or less – Diagnosis very unlikely

system underlies the guidelines for approach in Wilson's disease accepted by от EASL in 2011 (11) (Table 1).

It becomes, therefore, obvious, that there is no single parameter and gold standard for diagnosis of Wilson's disease. Only the complex evaluation of the clinical and laboratory data and the results from the morphological, genetic and image examinations contributes to the correct diagnosis. In some cases, both clinical observation and therapeutic test with penicillamine help the definite determination of the diagnosis (21).

TREATMENT OF WILSON'S DISEASE

Wilson's disease is a severe but treatable disorder necessitating timely and adequate management. Treatment options include mainly drug therapy and liver transplantation.

DRUG THERAPY

The objective of drug therapy is to reduce toxic copper sedimentation in the organism, to result in a negative copper balance and to prevent its accumulation. This can be achieved either by increasing the urinary copper excretion, or by reducing the intestinal copper resorption. Both chelating agents D-penicillamine and trientine are the first-line drugs (20,36).

D-PENICILLAMINE

D-penicillamine mobilizes copper by inducing the synthesis of metallothionein that forms a non-toxic compound with copper and/or forms with it a soluble complex to be excreted with urine. In most patients with a predominant hepatic form of the diseases, a clinical improvement can be observed after 6–8 weeks of treatment; however, sometimes one needs 12–24 months prior to reading the favourable effect.

Treatment starts in a dose of 750–1500 mg daily as the maximal dosage is of 2 g daily, i.e. 15–20 mg/kg daily divided into four or two intakes. The drug is best taken one hour before or two hours after meal. Tolerability of penicillamine improves when starting the treatment with increasing dosages, from 125 or 250 mg daily up to and increasing by 125–250 mg every 4–7 days and reaching up to the therapeutic dosage (5,8,19,28,29).

D-penicillamine can induce pyridoxine deficiency and that is why one recommends the supplementation of vit. B6 in a dose of 25–50 mg daily. Some authors prefer a weekly dosage of 50 mg that ensures an adequate prevention (11,22,29,39).

D-penicillamine usage is associated with numerous side effects which are observed in 20–30

per cent of the patients. Early hypersensitivity reactions are established during the first month of treatment and present with nausea, fever, exanthema, lymphadenopathy, and proteinuria. They are usually transient; however, they require a temporary reduction or even cessation of the drug and application of antihistamine means or corticosteroids. The significant bone marrow toxicity includes a severe thrombocytopenia, neutropenia, or total aplasia. In such cases, the treatment should immediately be ceased. Late unwanted reactions occur in about two per cent of the patients and consist of nephrotoxicity, lupus-like syndrome, immune complex nephritis or Goodpasture syndrome, skin toxicity such as *elastosis perforans serpiginosa*, pemphigus or pemphigoid lesions, lichen planus, aphthous stomatitis, and *cutis laxa*. Very late side effects occur seldom and include nephrotoxicity, myasthenia gravis, polymyositis, ageusia, suppressed immunoglobulin A secretion, risk of infection, and serous retinitis. After over-dosage treatment, hepatotoxicity, reversible sideroblastic anaemia and haemosiderosis have been reported (9,11,22,28).

The improvement of the patients presenting with neurological manifestations is more delayed, sometimes after 3 years of treatment. Deterioration of these symptoms has been described in 30–50 per cent of the patients and that is why the treatment should either be carried out carefully, or the application of another drug should be started (22,27–29).

Trientine

Trientine or triethylenetetramine dihydrochloride is copper-chelating agent. It has been introduced as an alternative therapy for the patients without any tolerability of penicillamine. Trientine increases urinary copper excretion. Its usual initial dose is of 750–1500 mg daily divided into two or three intakes and its maintenance dose is of 750–1000 mg daily.

Trientine possesses a few side effects only. The early toxicity includes bone marrow suppression and proteinuria. The most common side effect is a reversible sideroblastic anaemia resulting from a copper deficiency. Some autoimmune disturbances such as lupus-like reactions can represent potential late side effects; however, they usually occur in patients on initial penicillamine therapy (11,19,22,28,39).

Trientine is an effective management option for Wilson's disease. It is indicated in the patients with penicillamine intolerability. It is effective as a first-line therapy even in the patients with decompensated liver disease. Some authors recommend trientine as a first-line therapy because of the lower incidence rate of the neurological deterioration and side effects as well (6,11,39).

Zinc

Zinc induces the synthesis of an enterocytic metallothionein which is an endogenous chelator of metals. This protein possesses a higher affinity to copper than to zinc. The firm bond to copper hinders its further resorption. Then it is lost with feces by exchanging the enterocytes by their normal turnover (2,11,16,22,28,31). Besides zinc can enhance the level of the hepatocellular metallothionein. In this way, copper binding to metallothionein forms non-toxic complexes in liver. It has been established that zinc is extraordinarily active when reducing the oxidative damage and increasing gluthatione in hepatocytes as well (12).

Zinc is used as a first-line therapy in asymptomatic patients, as a maintenance treatment and in the patients with predominant neurological manifestations because it very seldom deteriorates neurological signs (4,11,18,22,28,32,37,39). Its dose amounts to milligrams of elementary zinc. In children and adults, the dose is of 150 mg daily divided in three intakes.

Zinc salts such as sulphate, acetate, and gluconate are characterized by very few side effects.

Gastric irritation is a primary trouble in 10–15 per cent of the patients. It is more outlined with zinc sulphate. Zinc acetate causes least gastrointestinal disorders. A deteriorated liver function with one patient's lethal outcome has been reported. Zinc can exert an immunosup-

pressive effect and diminish leukocyte haemotaxis. One can observe an elevated serum lipase and/or amylase without any clinical and x-ray evidence of pancreatitis (11,22,28).

Tetrathiomolybdate

Ammonium tetrathiomolybdate (TM) is a powerful experimental chelating agent. There are two mechanisms of action. With the first mechanism, the drug taken with food binds the endogenously secreted copper to the present protein in the intestinal lumen and thus this complex can't be resorbed. With the second mechanism, TM absorbs if taken between meals and forms a complex with free copper and albumin in blood. This copper can't enter the cells anymore and becomes metabolically inactive. In this way, free toxic copper decreases rapidly (5,8,11,22,28).

TM has been suggested for the initial treatment of the patients with neurological manifestations because of the fact that it hardly leads to deterioration of the symptoms. It still persists as an experimental therapy and is not offered to the market yet. Nowadays the clinical experience with TM remains limited. Its profile of safety is good. Insignificant side effects such as bone marrow suppression and weak elevation of aminotransferases have been observed in 10–15 per cent of the patients treated with TM (6,11,28).

Antioxidants

Toxic copper effect in Wilson's disease leads to free-radical liberation. It has been found out such patients present with reduced serum and hepatic vit. E levels. That is why antioxidants and, mainly, vit. E play a role as an additional management option. Sometimes an improvement of the symptoms has been established following vit. E supplementation; however, no careful investigations have been carried out yet (2,11,28,29).

Treatment of the fulminant hepatic failure

The patients with commonly fatal fulminant hepatic failure due to Wilson's disease require life-saving liver transplantation. Prior to accomplishing the transplantation, plasmapheresis (plasma exchange), haemosorbtion, or haemodialysis can be performed. These procedures can protect kidneys from copper tubular damage and thus avoid renal failure. Albumin dialysis stabilizes the patients with fulminant hepatic failure because of Wilson's disease and delays the need of transplantation without abolishing it. In such cases, molecular adsorbent recirculating system ultrafiltration (MARS) can prove effective (24,28).

Liver transplantation

The indications for liver transplantation include the fulminant form of Wilson's disease, young cirrhosis patients with severe hepatic failure who do not respond to 2–3-month long treatment, or patients with acute liver insufficiency after therapy cessation (3,11,19,22,26,28,29,32). Orthotopic liver transplantation corrects the metabolic defects of the disease and favours the normalization of extrahepatic copper accumulations. The prognosis after this intervention is good. It is not recommended as an initial treatment for the neurological form of the disease as these patients usually respond well to drug therapy. There are scientific communications about hepatocyte transplantation in LEC rats as an animal model of Wilson's disease. There are encouraging results demonstrating the normalization of the histological patterns and biliary copper excretion (17,29, 39), especially in patients with liver insufficiency (34).

Other methods of treatment

Amitriptyline reduses copper-induced apoptosis of hepatocytes as proved in an animal model (11). *In-vitro,* treatment with pharmacological chaperones 4-phenylbutirate and curcumin, partially restored protein expression of most ATP7B mutations (11,29). Gene therapy within selected populations with a dominant mutation promises to be an effective option in the future (29,32).

Treatment during pregnancy

The treatment should go on during pregnancy as the cessation of medication could lead to acute hepatic failure. A dose reduction of penicillamine during the first trimester down to and even below the maintenance dosage of ~10 mg/kg daily has been recommended. During the last trimester, the dose should be of 25–50 per cent of that prior to pregnancy in order to avoid fetal copper deficit and warrant better wound healing following Caesarean section (19,28,29).

Prognosis

The prognosis of the patients with Wilson's disease on continuous treatment is excellent even if at the time of the diagnosis of this disease liver cirrhosis has been found out. With treatment, the neurological, psychic and hepatic abnormalities gradually improve and liver tests usually normalize. The prognosis remains unfavourable in the patients with advanced disease, rapidly progressive hepatic insufficiency, and severe haemolysis (19,22,28,29).

CONCLUSION

Wilson's disease is a rare hereditary but treatable disorder of copper metabolism. The diagnosis is easy in the patients presenting with the classical manifestations of liver damage, Kayser-Fleischer ring, neurological symptoms, low ceruloplasmin levels and high urinary copper excretion. However, it is difficult in the patients with either fulminant hepatitis, or chronic liver disease only. It is noteworthy that there is no gold standard for the diagnosis. It is based on the combination of clinical, laboratory, morphological and instrumental examinations. Advances of genetic technologies and opportunities for hepatocyte transplantation represent a challenge of contemporary diagnosis and offer new promising options for future treatment. Despite this progress, however, clinicians stand in need of full consideration of Wilson's disease in the differential diagnosis and of search for appropriate diagnostic methods for early detection and timely adequate therapeutic approach. If initialized sufficiently early, therapy usually leads to complete control of the symptoms and warrants normal patient's survival and individual quality of life.

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Operative treatment of metastatic spinal disease: review and retrospective analysis of our experience for 10-year period (2000–2009)

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Оперативно лечение при метастатични гръбначни заболявания: обзор и ретроспективен анализ на нашия опит за десет-годишен период (2000–2009)

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РЕЗЮМЕ

Съвременната литература обръща все по-голямо внимание на поведението при пациенти с вторичните злокачествени гръбначни заболявания, поради нарастващата социална значимост на тази патология.

Цел: Да се анализитат ретроспективно резултатите от проведеното лечение при болни със спинални метастази и да се проведе анализ на литературата с оглед прецезиране на поведението.

Материал и методи: В настоящата статия представяме данни за 130 пациенти лекувани в Клиниката по Неврохирургия при УМБАЛ"Св. Георги"-Пловдив по повод на вторични злокачествени гръбначни заболявания между 2000 и 2009 година. При подбора на подходящите за оперативно лечение пациенти са използвани скалата на Karnofsky и модифицираната скала Tokuhashi score. Тежестта на клиничната изява

ABSTRACT

The world literature pays greater attention on the treatment of the secondary malignant spinal diseases due to the increasing social significance of this pathology.

Aim: To retrospectively analyze the results from the treatment of patients with metastatic spinal disease and to perform review of literature in order to clarify the optimal treatment strategy.

Material and methods: The current study includes 130 patients treated for metastatic spinal disease between 2000 and 2009 at the Clinic of Neurosurgery of St George University Hospital in Plovdiv. The Karnofsky Performance Scale (KPS) and the Modified Tokuhashi Score Scale (MTSS) were used to select appropriate patients for operative treatment. The severity of the clinical symptoms was assessed by the Frankel Scale (FS).

Results: Operative treatment was performed in 95 patients (73.1%) and 35 patients were not

е определяна според скалата на Frankel за степента на неврологична увреда.

Резултати: Оперативно лечение е проведено при 95 болни (73,1%), а неоперирани са 35 (26,9%). От оперираните 95 пациенти при 8 е извършена корпоректомия, при 20 хемиламинектомия, при 31 ламинектомия на едно ниво, при 25 ламинектомия на две нива, а при 11 ламинектомия на повече от две нива. При осемте случая с корпоректомия е приложена предна шийна инструментация с титаниевава плака и автотрансплантат. При един случай е приложена задна шийна инструментация. При четиринадесет от случаите с локализация в торакален или лумбален сегмент е приложена транспедикулна стабилизация.

Заключение: Оперативното лечение на вторичните злокачествени гръбначни заболявания при правилен подбор на пациентите води до повишаване на качеството им на живот и самостоятелността в ежедневието.

Ключови думи: *гръбначна метастаза, оперативно лечение, качество на живот*

operated (26.9%). The surgical treatment included corpectomy in 8 cases, hemaleminectomy in 20 cases, one-level laminectomy in 31 cases, two-level laminectomy in 25 cases, multiple-level laminectomy in 11 cases. Bone graft and titanium plate was used in 8 cases with corpectomy to achieve fusion and stabilization the spine. Posterior cervical instrumentation was applied in 1 case. Posterior transpedicular screw fixation was performed in 14 cases.

Conclusion: The appropriate patient selection for operative treatment of metastatic spinal disease leads to better quality of life and improved daily independence.

Key words: *spine metastasis, surgery, quality of life*

INTRODUCTION

The treatment of metastatic spinal disease is an interdisciplinary problem with increasing social impact during the last decade due to the aging of the population and the prolonged survival in cancer patients [2,9,10]. The social significance and early diagnosis in metastatic spine patients is a result of its growing incidence. Metastatic spinal tumors are reported to be 75–90% of all cases with spinal neoplasms [2,4,5,9]. Almost 40–50% of bone metastases are located in the spine and 30–70% of cancer patients show evidence of spinal metastases on autopsy [1,5,9,15].

Clinical presentation consists of early onset of localized and/or radicular pain with constant intensity. It results either from the growing tumor mass which compresses the surrounding neural elements or from the pathological vertebral fracture. Other signs include localized spinal deformity and progressing focal neurological deficit [2,5,9,14,15,16].

The greater percentage of spinal metastases origin from lung, breast, prostate and renal cancer [1,4,9,10]. Magnetic-resonance imaging (MRI) should be the diagnostic modality of choice for its superior informative resolution and detailed anatomy which play a major role in the preoperative planning and the postoperative follow-up. Bone scintigraphy (BS) should also be used because it may provide the earliest diagnosis [5,6,9].

The major indications for surgical treatment are the persistent severe pain and the progressive focal neurological deficit resulting from neural compression, vertebral pathological fracture, spinal instability, radio-resistant primary tumor and the necessity for obtaining histological diagnosis [5,6,9,13,15,16]. Surgery is usually combined with adjuvant radiotherapy and/or chemotherapy. In general, operative treatment following prior radiotherapy is associated with greater risk of complications and, therefore, one should bear in mind when choosing the optimal treatment regimen [10]. Aggressive treatment should aim at prolonging

survival and improving patient's quality of life (QoL) which can be achieved after thorough and careful patient selection [1,2,4,9,10,13,15,16].

The object of the current study is to present the results from the treatment of secondary malignant spinal neoplasms and to retrospectively analyse the material in order to draw conclusions based on our experience and the review of literatiure.

MATERIAL AND METHODS

The current study includes 130 patients treated for metastatic spinal disease between 2000 and 2009 at the Clinic of Neurosurgery of St George University Hospital in Plovdiv. 87 (66.9%) were male and 43 were female (33.1%). The segmental distribution of the spinal metastases is presented in Table 1.

Table 1.
Segmental distribution of the spinal metastases

Spinal segment	Number of cases	%
Cervical	9	6,92 %
Thoracic	72	55,39 %
Lumbar	34	26,15 %
Multiple	15	11,54 %
Total	130	100 %

The Karnofsky Performance Scale (KPS) and the Modified Tokuhashi Score Scale (MTSS) were used to select appropriate patients for operative treatment (Table 2) [15]. The severity of the clinical symptoms was assessed by the Frankel Scale (FS) (Table 3).

Table 2.
Modified Tokuhashi Score Scale

Parameters	Score (points)
1. Global status	0 – Poor 1 – Stable 2 – Good
2. Evidence of extra-spinal bone metastases	0 – >/= 3 metastases 1 – 1–2 metastases 2 – 0 metastases
3. Number of vertebral metastases	0 – >/= 3 metastases 1 – 2 metastases 2 – 1 metastases
4. Visceral metastases	0 – inoperable 1 – operable 2 – no metastases
5. Primary source	0 – pancreas, esophagus, stomach, bladder, osteosarcoma, lungs 1 – liver, unknown primary source 2 – others 3 – uterus, kidneys 4 – rectum 5 – thyroid gland, prostate gland, breast
6. Neurological deficit	0 – plegia 1 – paralysis 2 – no motor deficit

Table 3.
Severity of the neurological deficit and the clinical presentation based on the FS

Grade	Clinical symptoms	% of cases
A	Complete loss of sensory and motor functions	34,7 %
B	Complete motor and incomplete sensory loss	18,1 %
C	Severe but not complete motor and partial sensory loss	13,1 %
D	Partial motor and sensory loss – able to walk unassisted	19,3 %
E	Absent motor and sensory impairments	15,6 %

RESULTS

The major part of the metastatic spinal tumors in our series affects the bone structures and the spinal epidural space. 5 cases had intradural localization and only 1 case was with intramedullary localization of the metastasis from colorectal cancer. In 12 cases there was considerable paravertebral spread of the tumor formation. The histological type of the spinal metastases is presented in Table 4.

Table 4.
Histological distribution of spinal metastases based on the primary source

Primary source	Number of cases (%)
Lung cancer	16 (16,8 %)
Prostate cancer	13 (13,7 %)
Breast cancer	12 (12,6 %)
Renal cancer	8 (8,4 %)
Lymphoma	7 (7,4 %)
Thyroid cancer	3 (3,2%)
Stomach cancer	3 (3,2 %)
Bladder cancer	1 (1,1 %)
Melanoma	1 (1,1 %)

Primary source	Number of cases (%)
Colorectal cancer	1 (1,1 %)
Plexus chorioideus carcinoma	1 (1,1 %)
Endometrial cancer	1 (1,1 %)
Sarcoma	2 (2,1 %)
Non-differentiated carcinoma	26 (27,3 %)
Total	95 (100 %)

The clinical presentation includes early onset of radicular and/or localized pain in 98% of cases. The progression of the focal neurological deficit is also common. Sensory deficit is established in 83% of the cases, motor deficit – in 80% of the cases and urinary and bowel disturbances – in 52% of the cases.

The imaging diagnosis was obtained by X-ray, contrasted myelography, computed tomography (CT) and magnetic-resonance imaging (MRI), separately or in combination. Based on the data from the clinical presentation, the imaging studies and the physical state, surgery was performed in 95 patients (73.1%). 35 patients were not operated.

Table 5.
Operative techniques and surgical approach

Operative technique	Number of cases
Corpectomy (cervical segment)	8
Hemilaminectomy	20
Laminectomy (1 level)	31
Laminectomy (2 levels)	25
Laminectomy (more than 2 levels)	11
Total	95

Bone graft and titanium plate was used in 8 cases with anterior cervical corpectomy to achieve fusion and stabilization the spine. Posterior cervical instrumentation was applied in 1 case. Posterior transpedicular screw fixation was performed in 14 cases. The surgical treatment aimed at maximally radical and safe resection of the spine lesions (Table 6).

Table 6.
Extent of tumor resection

Extent of resection	Number of cases (%)
Total	26 (27,4 %)
Subtotal and partial	62 (65,3 %)
Biopsy	7 (7,4 %)
Total	95 (100 %)

Two cases of patients operated for lumbar and cervical metastases are presented in Figures 1 and 2.

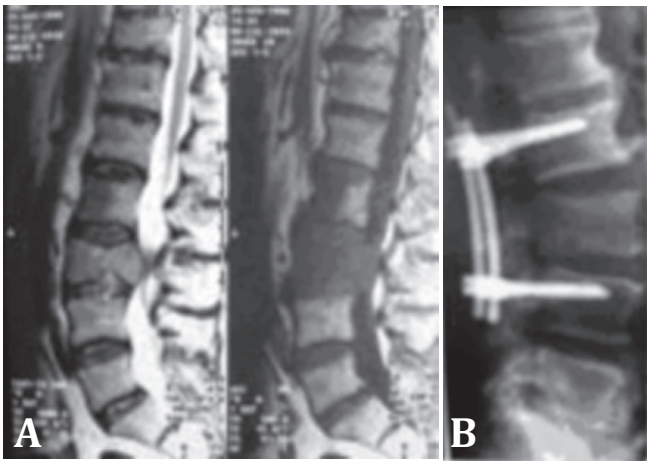

Figure 1. A – *Sagittal MRI image of the lumbar spine showing pathological fracture of L3 vertebra due to metastatic prostate cancer.* ***B –*** *Lateral postoperative X-ray after laminectomy, partial tumor resection and posterior pedicle screw fixation of the L2–4 segment.*

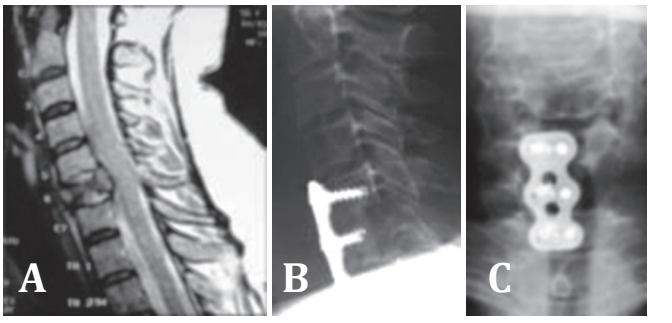

Figure 2. A – *Sagittal MRI image of the cervical spine demonstrating pathological fracture of C6 vertebral body due to metastatic fibrosarcoma with primary source in the right hip joint.* ***B and C –*** *Lateral and AP postoperative X-rays after C6 corpectomy, subtotal tumor resection and anterior cervical fusion and stabilization by means of iliac bone graft and titanium plate C5-C6 segment.*

Contraindications for operative treatment were multiple metastatic spinal disease, evidence of visceral metastases and advanced systemic cancer, poor global status, expected life expectancy less than 3 months and/or refusal to sign informed consent.

Early postoperative improvement was observed in 75.8% of the cases, without any

change were 14.7% of the cases, clinical deterioration – 2.1% of the cases and death in 7.4% of the cases (Table 7).

Table 7.
Number and cause of death

Cause of death	Number of cases
Pulmonary thromboembolism	2
Acute myocardial infarction	1
Ischemic stroke	1
Acute respiratory failure	1
Acute renal failure	1
Ascending spinal cord edema	1

The pain syndrome demonstrated the fastest and most significant improvement. Pain was of milder intensity and the need for analgesics was considerably reduced after surgery. Postoperative improvement of the focal neurological deficit was also observed and more than 60% of the cases increased their Frankel score to a more favorable grade.

DISCUSSION

The data presented in the current study and the number of hospitalized patients is similar to those published in the literature. There is no significant difference in the segmental distribution of the spinal metastases. As we also noted, the most commonly affected segment is the thoracic spine. The origin of the spinal metastases operated in our institution is most commonly from lung cancer, prostate cancer, breast cancer and renal cancer which is in accordance with the data from other large series [1,4,9,10,16]. It was noted that the larger percentage of cases were directed to consult with neurosurgeon with great delay. Most of them were admitted to the hospital as an emergency and 52% of patients were in higher Frankel grade – A or B.

The surgical treatment of the cervical metastases which are located in the vertebral body offers maximally radical resection of the lesion by means of corpectomy followed by fusion and stabilization of the spine. The widely-spread usage of posterior transpedicular screw fixation determines the increasing number of surgically treated patients with thoracic and lumbar spinal metastases. As previously published data, our series demonstrates that vertebral bodies are six fold more often affected than the bone elements of the posterior column [3,4,5,6,11,16]. Based on this fact, we would recommend more radical resections such as the total en-block spondylectomy performed by Tomita et al. and Hasegawa et al. [3,11].

CONCLUSIONS

The increasing number of patients who suffer from metastatic spinal disease along with the considerable progress in spinal surgery lead to a greater interest in this pathology. The need for early diagnosis based on modern and accessible imaging studies is apparent. Spinal metastatic disease is an interdisciplinary problem which requires mutual efforts and team approach which should include surgery followed by radiotherapy and/or chemotherapy. Thus, patients will receive optimal disease control for a longer period. The prolonged survival of these patients brings forward the need for preservation of QoL and daily independence. Therefore, the surgery aiming at radical resection, neural decompression and stabilization of the spine will play a vital role in the near future.

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Follow-up of Esnault test following special exercises at home in chronic lumbalgies

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Проследяване на резултатите от теста на Esnault, след прилагане на специални упражнения в домашни условия при хронични лумбалгии

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РЕЗЮМЕ

Дизайн: Проспективно, проучване с тест в начало и ретест след 12 месеца.

Цел: Да отчетем ефекта на програма от домашни упражнения за подобряване подвижността на лумбо-пелвисната мускулатура.

Методи: След подписване на информирано съгласие 110 пациента с хронична болка в кръста бяха включени в контролирано проучване.

Всички бяха оценени чрез тест за екстензионни възможности – „**Biering тест" ,** тест за флексионни възможности – „**Itto тест" ,** тест за подвижност – **„Esnault тест"** и тест за издържливост – „**Pile тест"** , след това разделени в 2 групи: експерименталната група от 55 пациента с препоръчани специфични упражнения, и контролна група от 55 пациента, която не изпълнява специфичните упражнения, но следва насоките на лекуващия лекар.

Резултати: Пациентите от експерименталната група са със значителна редукция на болковия интензитет и функционалния дефицит след провеждане на специфичните упражнения,

ABSTRACT

Design: Prospective, study, test and retest at home after 12 months.

Objective: To report the effect of a program of home exercises to improve mobility of the pelvis-lumbar muscles.

Methods: After signing the informed consent 110 patients with chronic low back pain were included in the controlled study.

All were evaluated by test extensional features – **„Biering test"** , a test for flexional opportunities – **„Itto test**", an agility test – **„Esnault"** and a test and endurance test – **„Pile test"**, then divided into 2 groups: experimental group of 55 patients with recommended specific exercises and a control group of 55 patients who did not perform specific exercises, but follow the therapist's guidelines.

Results: Patients in the experimental group experience a significant reduction during the 12-month follow-up in pain intensity and functional deficits following a specific exercise. In the control group there was reported a worsening of these parameters.

която се задържа по време на 12-месечното проследяване. При контролната група се отчита влошаване на тези параметри.

Експерименталната група показа задоволително подобрение в повлияването на подвижността на лумбо-пелвисната мускулатура в резултат на прилаганите специфични упражнения.

При контролната група липсват подобрения, налице е аггравация на болковата симптоматика. И при 2-те групи нивото на участие в програмите беше сходно.

Заключение: Лечението със специфични упражнения се оказва по-ефективно от обичайно предписваното медикаментозно лечение при пациенти с хронична болка в кръста.

Ключови думи: Esnault, специални упражнения, хронични лумбалгии.

The experimental group showed a satisfactory improvement in response to mobility resulting from the application of specific exercises. In the control group no improvements in mobility of the pelvis-lumbar muscles was observed and there was an aggravation of painful symptoms. In both groups the level of participation in programs was similar.

Conclusion: Treatment with specific exercises is more effective than commonly prescribed medication in patients with chronic low back pain.

Keywords: *Esnault, special exercises, chronic lumbalgies*

INTRODUCTION

Chronic lumbalgies are a heterogeneous group of disorders occurring with recurrent low back pain with limitation of 3 months. In many countries, chronic low back pain (CBP) is a major cause of disability. It is believed that it affects 60 to 80% of middle-aged people at some point in their lives.

DESCRIPTION OF ESNAULT TEST.

The test requires a patient to lift an object from the ground and was first described by the French physiotherapist Michèle Esnault in 1991. It examines the mobility of the pelvic joints in lifting an object from the floor (3). Depending on the way of lifting the object, a score is given ranging from 0 to 3.

Protocol:

The patient lifts paper placed on the floor.

0 – lifts the paper with ease and in different ways.
1 – manages to carry out the test with minimal effort and slight stiffness.
2 – manages to carry out the test with difficulty, shows inflexibility or props hands on the knee.
3 – fails to realize the test or needs support.

Tracking the results of Esnault test.

The Esnault test results for participants from the experimental group are shown at testing baseline in Fig. 1 and at the end of the observation – Fig. 2.

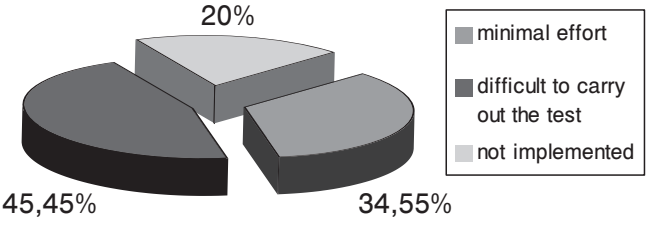

Fig .1. Esnault test results of patients in the experimental group at baseline.

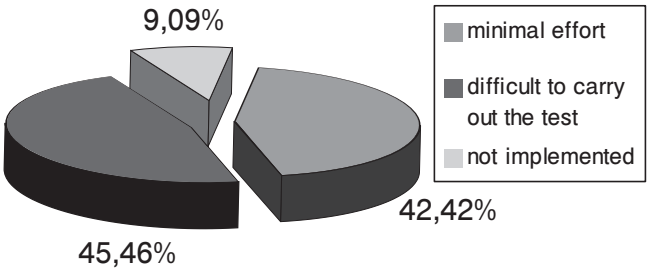

Fig. 2. Esnault test results of patients in the experimental group at the end of the observation.

At baseline, it is performed with minimum effort by 19 (34.55%) patients, 25 (45.45%) found it difficult to perform and 11 (20%) did not realize it.

At the end of the observation, the test is performed with minimal effort by 14 (42.42%) patients, 16 (45.46%) found it hard and 3 persons (9.09%) did not realize it – Table. 2.

We haven't found a statistically significant difference when comparing the initial and final results of the Esnault test of the experimental group at P> 0,05 (Z = 0,28).

However, the results of test in question show a positive effect which is evidenced by the reduction in complaints. Of all participants who initially performed the test with minimal effort, only 21.4% passed into the group of hard-testers. Of those who had difficulties at first, a majority (21.4%) passed into a less severe group and the same percentage of test participants passed into the group of „did not realize the test." The most sensitive change occurred in the third group, which at baseline could not do the test. After 12 months, 80% of it realized it, although with difficulty, and only 20% remained in the same group.

When comparing the test results from the Esnault test, we have established a deterioration of the participants in the control group at the end of observation P <0,001 (Z = 2,92) – Tab. 1. About half of the patients have remained on the initial level, while the rest passed into the negative.

When comparing the Esnault test results in experimental and control groups at the end of the observation, no statistically significant difference P <0,01 χ^2 = 10.72) has been observed – Fig 3. From the survey, 46% of controls could not realize the test, while in the experimental group this percentage was much lower (9.09%).

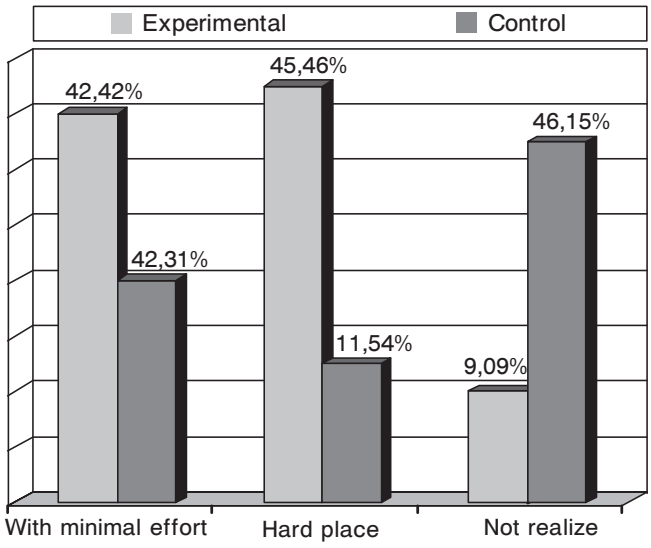

Fig. 3. Comparison of Esnault test results of patients in the experimental and control groups at the end of the observation.

Tab. 1.
Comparison between initial and final Esnault test results of patients in the control group.

Начало на проучването At baseline	Показатели Indicators	Край на проучването End of study			Общо Total
		С минимални усилия With minimal effort	Трудно осъществява Hard placed	Не реализират Failed	
Без проблеми No problems	Абс. Abs. бр No.	1 A	– –	– –	1 A
	p± Sp Dr. ± Sp	100,00± – 100,00 ± –	– –	– –	100,00 100.00
С минимални усилия With minimal effort	Абс. Abs. бр No.	7 7	1 A	3 3	11 11
	p± Sp Dr. ± Sp	63,64±14,50 63,64 ± 14,50	9,09± 1,00 9,09 ± 1,00	27,27± 1,73 27,27 ± 1,73	100,00 100.00
Трудно осъществява Hard placed	Абс. Abs. бр No.	– –	4 4	5 5	9 9
	p± Sp Dr. ± Sp	– –	44,44± 2,00 44,44 ± 2,00	55,56± 16,5655,56 ± 16,56	100,00 100.00
Failed Не реализират	Абс. Abs. бр No.	– –	– –	5 5	5 5
	p± Sp Dr. ± Sp	– –	– –	100,00± 2,23100,00 ± 2,23	100,00 100.00

The mobility of participants over 50 years is weaker and they found it more difficult to perform the test at baseline (fig .4 and at the end of monitoring – fig.5). A large percentage of them (41.2%) failed to realize it early in the study P <0,01 (t = 11,48)

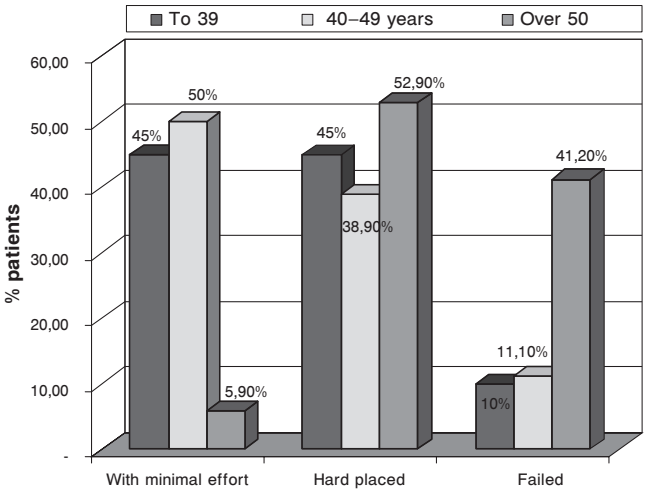

Fig. 4. Test results of Esnault tests of patients in the experimental group at baseline according to their age.

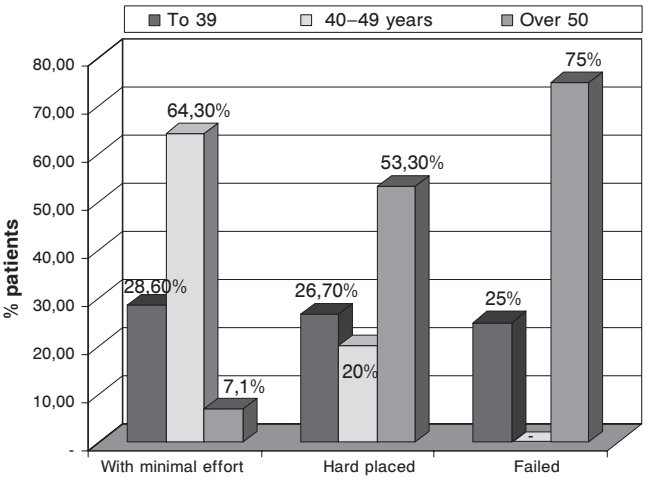

Fig.5. Esnault test results of patients in the experimental group according to their age at the end of the observation.

At the end of the study the proportion of patients over 50 years performing the test with minimal effort was very small (7.1%). The largest share of hard-testers in this age range (53.3%) and those for which realization was not possible are (75%) – Fig 5.

Table 2.
Coefficient of correlation between Esnault test results of patients from the experimental group and the main parameters tested at the beginning and end of the observation.

Показатели Indicators	В началото на наблюдението At the beginning of the observation		В края на наблюдението At the end of the observation	
	r_{xy} r_{xy}	P P	r_{xy} r_{xy}	P P
Интензитет на болката Intensity of pain	+0,88 0.88	<0,001 <0.001	+0,86 0.86	<0,001 <0.001
Възраст Age	+0,36 0.36	<0,01 <0.01	+0,36 0.36	<0,05 <0.05
Пол Sex	+0,01 0.01	>0,05 > 0.05	-0,12–0.12	>0,05 > 0.05
Рискови фактори Risk Factors	+0,40 0.40	<0,01 <0.01	+0,56 0.56	<0,001 <0.001

Table 3.
Esnault test results of patients
in the experimental group at the beginning and end of the observation by presence of risk factors.

Esnault Резултати от теста на Esnault test results	Рискови фактори Risk Factors	Абс. Abs. брой number	x x ± ± S x S x	S x S x	U U	P P
В началото на наблюдението At baseline	Липсват No	22 22	1,50 ± 0,13 1,50 ± 0,13	0,60 0.60	2,93 2.93	<0,01 <0.01
	Има Yes	33 33	2,09 ± 0,13 2,09 ± 0,13	0,72 0.72		
В края на наблюдението At the end of the observation	ЛипсватNo No	17 17	1,35 ±0 ,1 5 1,35 ± 0, 1 5	0,61 0.61	59,50 59.50	<0,01 <0.01
	ИмаYes Yes	16 16	2,06 ±0,1 4 2,06 ± 0,1 4	0,57 0.57		

We have determined direct correlation (from moderate to high level) of the Esnault test results of participants in the experimental group and their age, presence of risk factors and pain intensity at the beginning and end of the observation – table 2.

We have not registered any relationship between gender and the results obtained in Esnault test P> 0.05.

Patients with no risk factors present score significantly higher on Esnault test both at the beginning and end of the study – Table 3.

The influence of pain intensity on the Esnault test results of patients from the experimental group is presented in Fig.6 . All patients with mild pain (up to 3 items at VAS test performed with minimal effort, 80% of participants with moderate pain (4–6 on section VAS) performed it with difficulty and 50% of those with severe pain (over 7 p. at VAS) failed to realize it, which supports the claim that the intense pain reduces the patients' flexibility.

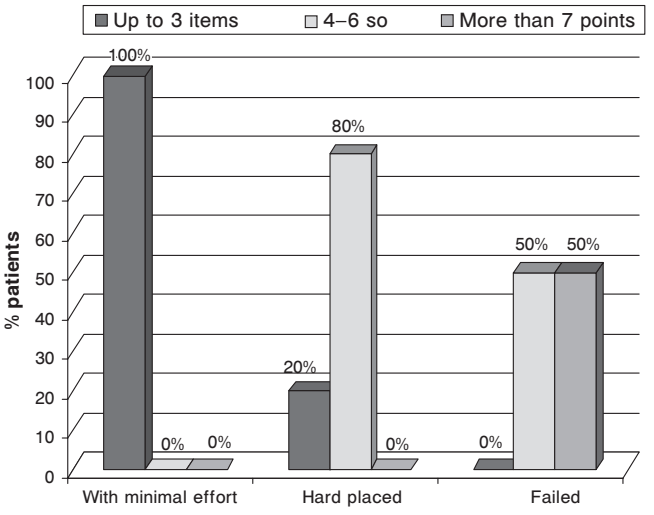

Fig .6. Esnault test results of patients in the experimental group at the end of the observation according to the severity of pain on VAS.

Using a stepwise multiple regression analysis we find that the factors mentioned at the beginning of the observation with the greatest weight on the results obtained are pain intensity and age of patients studied P <0,001 (F = 93,24). These two factors explain 78% of all values. At the end of the observation the same analysis demonstrates that the greatest weight on the results is exerted by the severity of pain P <0,001 (F = 82,78), as this factor explains 72% of values.

DISCUSSION

Analyzing the test results of participants in the Esnault test of the experimental group, we have found no statistically significant difference between the initial and final results. However, we have found a positive effect in the reduction of complaints. The above statement is supported by the fact that after administration of therapeutic gymnastics in the 12th month of observation, 80% of the patients have performed the test and only 20%found it still impossible. For participants in the control group there was no functional improvement compared with the initial deficit. Seeing a deterioration at the end of the survey, half of the patients remained on the primary level and the rest passed into the negative. χ No statistically significant difference was observed when comparing the two groups – 46% of the controls can not fulfill the test and far less of the participants in the experimental group (9, 09%) P <0,01 χ^2 = 10.72). The positive effect in the experimental group is due to the implementation of the training for mobility, which is facilitated by the mobility of the spine, pelvis and hips. It involves applying mobility exercises in the flexional and extensional position of the spine, spinal pullout and exercises for active stretching of adductor, abductor and hip muscles from ischio-crural muscle group. A Study by Kirkaldy et al. (2001) demonstrated that the rotation and mobility of erector spinae muscle are significantly improved by the application of flexional and extensional exercises for the spine, and the variants for mobility and rotation of *erector spinae* muscle increase considerably at the end of the study (7). Bandy et al. (1997) found that to achieve good results the stretching exercises should be performed every day by holding a position for 30 seconds (1). Khalil (1994) et Mayer (2004) demonstrated that, in chronic lumbalgies, the achievement of a good lumbar-pelvis mobility releases muscle

tension and helps increase the threshold of pain and articular amplitudes in treatment periods of 15 days (6). In a study Kraydzhikova (2011) et Gencheva found that autostretching after exercise reduces muscle imbalance and contributes to the prevention of disease in the spine and back muscles (8,4).

We have determined direct correlation of the Esnault test results of participants in the experimental group and their age, presence of risk factors and pain intensity at the beginning and end of the observation. In our study, gender does not affect these results.

Older patients (over 50) have greater functional disability both at baseline- 14.2% failed to realize it, and at the end of the study where the proportion of failure by test patients over 50 years grows to 75%. The lower mobility of these participants is connected with the changes that occur with age in the articular-ligament apparatus and the formation of muscle imbalance. The results of the study of Lindgren et al. (2004) confirm our claim. The authors found that the cohort of patients followed for 2 years, participants over 50 showed significantly lower mobility of the spine and hip compared with younger participants. According to the researchers, impaired mobility comes as the result of muscle imbalance and emerges due to less extensor force compared with that of the flexors of the body (9).

With the stepwise multiple regression analysis of tracer factors we have proved that the intensity of pain has the greatest weight on the results in the experimental group of patients both at the beginning and end of the observation. This factor explains the top 78% of the readings and 72% at the end of the observation. Although pain intensity remains significant in the experimental group, after testing, it attenuated at 80% of participants who have completed grade – „not implemented“ in a way – „hard placed“. Reduction of the pain symptomatics was due to the implementation of stabilization exercises and exercises for the extensor of the corpse. The most important component in an exercise program is to improve neuromuscular activation and control of the target muscle (2). In the literature we have found evidence supporting the theory that these exercises are an effective means for the reduction of pain and the degree of disability (2). A randomized clinical trial of George et al. (2005) demonstrates that the implementation of the stabilization exercises with activation of m. transversus abdominis reduces the recurrence of back pain within 3 years after the first pain episode. Patients with more than 30% discrepancy in the cross-area of mm. multifidi and been subjected to stabilizing exercises have 50% lower risk exposure of recurrent low back pain during the first year and 40% fewer relapses over the next 3 years after treatment, compared with individuals with standard medical care and treatment. The lack of stabilization exercises is defined as a potential predictor of individual risk and progress of low back pain (5).

The presence of risk factors influences outcomes in the experimental group at the beginning and end of the observation, as the mobility of patients with no risk factors present is significantly greater. This shows that socio-economic factors contribute to reduce functionality in patients suffering from backaches. In literature we have found no evidence to support this claim.

CONCLUSIONS:

1. The application in the experimental group kinesitherapeutic program with special exercises has a positive effect expressed in the reduction of complaints. The absence of such a program is linked to worsening the functional status of the participants in the control group.
2. The intensity of pain influences the Esnault test results, as the functionality of the muscles of the body are significantly reduced in subjects with more pronounced painful symptoms.
3. The age of the participants influences the results of the four tests, while in patients over 50 years, mobility, extensional, flexional and power capabilities of the torso were significantly reduced.
4. Risk factors influencing the Esnault test results, as patients exposed to risk factors, have lower scores on test applications.
5. Gender does not affect the Esnault test results.

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Main characteristics of the reproductive period of the Turkish ethnicity in Bulgaria

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Medical University – Plovdiv,

Основни характеристики на репродуктивния период при турския етнос в България

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Медицински Университет – Пловдив, ФОЗ

РЕЗЮМЕ

Цел на проучването е да се очертаят основните характеристики на репродуктивния период при турското население. При проследяване раждаемостта на изследваните четири генерации жени ясно се откроява тенденцията за намаляване на средния брой родени деца в турското семейство. Установи се скъсяване на средната продължителност на репродуктивния период, за който се формира семейството. Този факт е свързан основно с по-късното встъпване в брак на жените, тъй като не се установи разлика в средната възраст при раждане на последно дете.

Ключови думи: репродуктивен период, турски етнос, раждаемост, среден брой деца

ABSTRACT

The purpose of the research is to outline the main characteristics of the reproductive period of the Turkish population. Following the birth rate of the four generations of women the trend for decrease in the average number of born children in the Turkish family is clearly distinguished. There was founded a shortening of the average length of the reproductive period which is formed family. This fact is related mainly to the later marriage of women as no difference is found in the average age at birth of last child.

Keywords: reproductive period, Turkish ethnicity, birth rate, average number of children

INTRODUCTION

For many years some specific peculiarities of the reproductive process of the Turkish ethnicity were observed: early onset of first birth, higher birth rate, and prolonged reproductive activity of female [7]. Until 1900 the birth rate in the region of Kardzhali exceeds the average one for the country. In the year 2000 there has been some decline and in the past three years the data come close to the average for the country, but remain higher [1,2,3,4].

The purpose of the research is to outline the main characteristics of the reproductive period of the Turkish population.

MATERIAL AND METHODS:

Following the method of direct individual inquiry the opinion of females of Turkish ethnical origin was studied. Two identical studies were carried out in the region of the town of Kardzhali within a ten-year period and the first study was from the year 2000. In the questionnaire questions are set out for the mothers of the females questioned, which allows for comparison of baseline indicators of four generations of women. The date we obtained were analyzed by analysis of frequency distribution: descriptive statistic, non-parametric analysis (Pearson chi-square test) and Student's t-test. Level of significance was accepted at $p<0.05$. Data was analyzed using SPSS v.16.

RESULTS AND DISCUSSIONS

The duration of the reproductive period is highly dependant on the age of contracting the marriage, the size of the proto- and inter-genetic intervals and the age of last childbirth.

The age of contracting marriage, followed for the four groups of females shows typical growth trend. The first group of females, born in the period around 1920 has the lowest average age of contracting marriage 18,52±0,17 years, while for the last group, born around 1980 the age has increased by approximately four years – 22,36±0,57 years P<0,001 (u=6,46) (table.1.). In the last 20 years the rates have accelerated and this is grounds for an increase of this indicator by two years.

The changes observed are in line with the increase of the average age at marriage, registered in the country. The Turkish girls nowadays start their family life at older age. Relatively high percent are the once married after the age of 26 years, while 10 years ago only 3,4% of the questioned fell into this interval P<0,001 (χ^2=26,08). It is sticking that for this ethnicity the tradition to get married at younger age by 15years of age is kept. The younger women more often prefer to achieve a carrier, to get higher education. This in turn leads to shortening the period for reproduction, the birth of the first children is delayed, the next childbirths are becoming less common and gradually the model of the large Turkish families moves towards extinction.

Analogic to these, changes are observed also in the average age of the first childbirth. The comparison between the two groups of respondents shows that this age has increased by approximately two years from 21,87±0,24 to 23,82±0,57, P<0,01 (u=3,14), but despite the observed increase it is still lower than the average one for the country 26,2 years .

The duration of the protogenetic period also underwent modification. In the second study significant shortening of the period from the marrying until the birth of the first child was established P<0,05 (u=2,30), while from 1,71±0,15 years is became 1,31±0,09 years.

When studying the fertility the question of the so called exhausted fertility arises, i.e. what

Table 1.
Results from specific demographics indicators in both studies

Indicators	Study in 2000 г.		Study in 2011	
	Mother I	Respondents I	Mother II	Respondents II
Mean number of children	3,34±0,15	1,65±0,07	2,53±0,15	1,31±0,11
Mean age of marriage	18,52±0,17	20,42±0,24	20,24±0,37	22,36±0,57
Mean age of first birth	20,41±0,24	21,87±0,24	21,47±0,39	23,82±0,57
Mean age at last birth	28,24±0,53	25,65±0,36	26,92±0,60	27,75±1,16
Mean length of the reproductive period	9,69±0,58	–	6,90±0,65	–

is the duration of the period, for which the final formation of the size of the family ends. Studies show that the changes in the age of the first childbirth, the intervals between the births and the changes to the number of births lead to the ending of the reproductive functions of the female at younger age [6].

In this regard, in order to find the actual fertility of the Turkish ethnicity, only the data of the mothers of the respondents were used, since for them the reproductive period has ended.

Shortening is established of the average duration of the reproductive period, in which the family is formed from 9,69±0,58 for the women born around 1920 to 6,90±0,65 for the women born around 1960 P<0,01 (u=3,21). This fact is related mainly to the later marrying of the women, since there was no difference established in the average age of birth of the last child P>0,05 (u= 1,65) (Table 1).

The Turkish population and their reproduction are at a relatively young age, since over 88% end reproduction by the age of 30 (Fig.1).

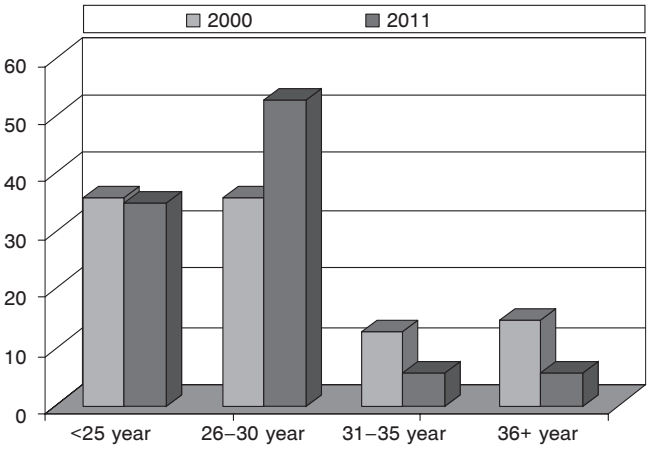

Figure 1. Age at birth of last child

In order to study the opinion of the women with respect to the rates of formation of the family the following question was asked: What is the age, which the woman shall not exceed for her last childbirth?

The average age, indicated by the women questioned is 36,98±0,52 years, which is by approximately 9 years more than the data received with respect to the actual age for the last childbirth P<0,001 (u=5,98).

In the study of the inter-genetic periods / the periods between two births/ a significant difference was established only between the first and second child. Practically by decreasing the number of born children in the study of 2011 these periods do not affect the duration of formation of the family.

By decreasing the duration of the reproductive period the average number of children in the Turkish families has decreased too, from 3,34±0,15 to 2,53±0,15 P<0,001 (u=3,83) [2,5,8]. Favorable is the fact that for this period also the number of deceased children has decreased P<0,01 (u=4,23), most probably because of the improved conditions of life, the higher health culture and higher quality of the medical care.

CONCLUSIONS:

1. With each succeeding generation increase of the average age at which marriage is contracted and the first child is born, is observed in the Turkish ethnicity studied.
2. The Turkish ethnicity and their reproduction are at relatively young age, but the duration of their reproductive period remains significantly long because of their early marriage and birth of first child.
3. Following the birth rate of the four generations of women the trend for decrease in the average number of born children in the Turkish family is clearly distinguished.
4. Significant difference is established between the actual age of ending the reproductive activity and the opinion of the respondents on the limit age for birth of the last child.

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„PERSONALITY, PSYCHOLOGICAL CLIMATE, AND BURN-OUT“

Edited by Drozdstoj Stoyanov

„ЛИЧНОСТ, ПСИХОКЛИМАТ И СИНДРОМ НА ПРОФЕСИОНАЛНО ИЗПЕПЕЛЯВАНЕ“

Под редакцията на доц. д-р Дроздстой Стоянов

Burn-out is a psychological disengagement from life characterized by both emotional exhaustion and social alienation. The phenomenon of burnout is an increasing source of personal demoralization and ineffectiveness in professional settings like medical centers. This growing problem in modern society leads to unprofessional and ineffective behaviors, such as anxiety, irritability, impatience, cynicism, and lack of empathy. This monograph is designed to begin the process of correcting the problem of burnout by understanding its causes in terms of those aspects of an individual's personality that make him or her vulnerable to the stresses of an institution's psychological climate. We need to understand people in their psychosocial context in order to be able to plan interventions that can help to prevent or relieve burn-out in the workplace.

Much work on burn-out has focused on characterizing its psychopathology and resulting exhaustion, cynicism, and inefficacy. This monograph emphasizes the need to characterize both the strengths and the weaknesses of individuals that influence their overall well-being, including physical, emotional, social, cognitive, and spiritual aspects of health [Cloninger and Zohar, 2011].

The authors are able to characterize the whole person by using the Temperament and Character Inventory (TCI), which distinguishes between a person's emotional drives (that is, their temperament) and their capacity for effective mental self-government (that is, their character) [Cloninger et al., 1993]. Much prior work has shown that disorders like burn-out that are characterized by anxious and depressive symptoms are likely to be associated with hypersensitivity to aversive stimuli as measured by the TCI dimension of Harm Avoidance (i.e., being pessimistic, fearful, shy, and fatigable) [Cloninger et al., 2010]. However, our tendency to become exhausted and cynical in response to punishment and frustrative non-reward can be modulated by healthy character traits and persistence [Cloninger et al., 2012]. In addition, the psychological climate to which the person must adapt must be taken into consideration because people are inseparable from their environment [Cloninger, 2004].

These questions require us to ask what are the characteristics of a healthy and resilient person? We know that healthy character traits include mature development of Self-directedness (i.e., purposeful and resourceful), Cooperativeness (i.e., helpful and forgiving), and Self-transcendence (i.e., unselfish and virtuous), but how many of us know how to develop and maintain these characteristics under the stress of modern life? [Cloninger, 2004]. We need to know more about what are the characteristics of a salutogenic and supportive institutional environment, as is carefully considered in this monograph. Surely these are among the most important questions that all of us need to ask in facing the challenges of modern life.

Fortunately the authors have begun to paint a clear picture of healthy people, salutog enic institutional climates, and what a person can do to develop greater resilience and well-being. What we see emerging is a set of observations that indicate that personal well-being is an inseparable component of the collective well-being of institutions. The take-home message is that each of us needs to be both generous and self-reliant, thereby working with generosity and kindness in a way that is respectful of others and their intrinsic value as human beings, thereby creating a mutually supportive and secure psychological climate for one another. If we view ourselves as separate and live defensively or apprehensively, we are vulnerable to disengagement from work and other people in a way that deprives us of the experiences that give our life its meaning and satisfaction.

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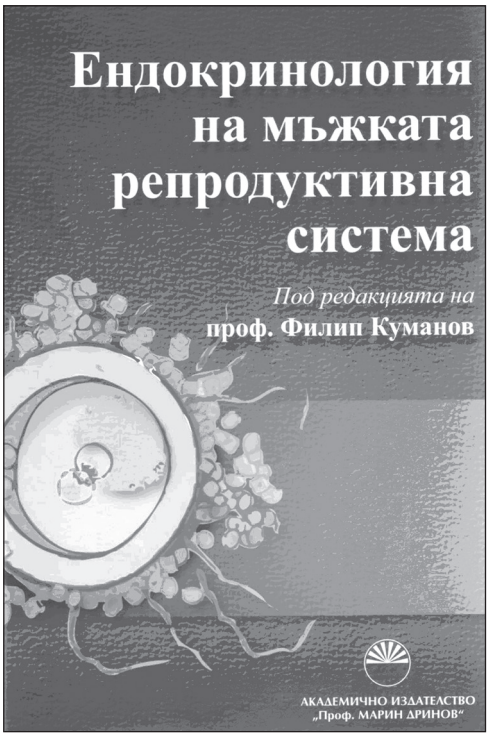

„ЕНДОКРИНОЛОГИЯ НА МЪЖКАТА РЕПРОДУКТИВНА СИСТЕМА“

От авторски колектив под редакцията на проф. д-р Филип Куманов, дмн

Настоящата монография е посветена на мъжката репродуктивна система и отговаря на належаща нужда от ново съвременно българско четиво в тази област на ендокринологичното познание. Последните по-подробни ръководства по тази тематика са издавани преди повече от десетилетие. Монографията на проф. д-р Филип Куманов и сътр. представлява монументален труд, който съчетава последните достижения на съвременната андрологична наука и десетилетния клиничен опит на повечето от авторите. Така е постигнат рядко добър баланс между научно-изследователските интереси на авторите и възможността за непосредствена приложимост в клиничната практика. Авторският колектив ни превежда последователно през данните за физиологията на мъжката репродуктивна система и пубертетното развитие, диагностиката, клиничната картина и лечението на хипогонадизма в неговите разновидности, както и през по-редките хромозомни болести и синдроми. Изключително актуални са разделите, посветени на сперматогенезата, на съвременната концепция за лечение с производни на тестостерона, на влиянието на факторите на околната среда и повишеното телесно тегло върху мъжката репродуктивна система. За първи път у нас се коментират проблемите при приложението на анаболни стероиди, растежен хормон,

както и свързания с това допингов контрол. По този начин монографията последователно и в подробности обхваща пълния спектър на мъжките ендокринни проблеми.

Авторският колектив включва най-изтъкнатите у нас изследователи, които се занимават и практически насочено с „мъжките проблеми“. Приносът на чуждите автори също е значителен – не само с качеството на изложението, но и с подкрепата, която те като водещи международни авторитети в областта на андрологията оказват за появата на настоящето издание. С участието си те потвърждават стойността на българския изследователски и клиничен опит в областта на мъжката репродуктивна ендокринология.

Монографията излага балансирано най-съвременните становища по разглежданите проблеми, но съдържа и голям обем собствени проучвания и резултати. Представени са данните от най-голямото в последните десетилетия проучване при 6200 момчета на възраст до 19 години. Коментирани са отделни клинични случаи. Така монографията съдържа силен елемент на оригиналност. Като оригинален, артистичен елемент присъстват исторически и литературни препратки. По този начин авторският колектив е оставил своя неповторим отпечатък върху настоящия труд.

Изложението е написано на прекрасен и разбираем български език; то е интересно, увлекателно и съдържателно.

Обобщавайки чудесните си впечатления от представената монография на проф. Ф. Куманов и сътр., бих искал горещо да я препоръчам на потенциалните читатели. Това е балансиран труд на най-високо съвременно ниво, който дава ясни указания за поведение в клиничната практика на ендокринолога. Монографията може да бъде от голяма полза и за педиатри, уролози, гинеколози, както и за общо практикуващи лекари.

Проф. д-р Михаил Боянов, дмн

The Bulgarian Medicine Journal, official edition of the Bulgarian Academy of Science and Arts, Science Division, Research Center for Medicine and Health Care is published in 4 issues per year. It accepts for publication reviews, original research articles, case reports, short communications, opinions on new medical books, letters to the editor and announcements for scientific events (congresses, symposia, etc) in all fields of fundamental and clinical medicine. The journal is published in English with exceptional reviews on significant topics in Bulgarian. The detailed abstracts and the titles of the articles, the names of the authors and institutions as well as the legends of the illustrations (figures and tables) are printed in Bulgarian and English. Bulgarian medicine is available online at the website of the Academy, publications section.

The manuscripts should be submitted in two printed copies, on standard A4 sheets (21/30 cm), double spaced, 60 characters per line, and 30 lines per standard page.

The size of each paper should not exceed 10 pages (up to 5 000 words) for original research articles, 12 pages for reviews (7 500 words), 3 pages for case reports, 2 pages for short communications, 4 pages for discussions or correspondence on scientific events on medical books or chronicles. The references or illustrations are included in this size (two 9x13 cm figures, photographs, tables or diagrams are considered as one standard page).

The abstracts are not included in the size of the paper and should be submitted on a separate page with 3 to 5 key words at the end of the abstract. They should reflect the most essential topics of the article, including the objectives and hypothesis of the research work, the procedures, the main findings and the principal conclusions. The abstracts should not exceed one standard typewritten page of 200 words.

Списание „Българска медицина", издание на Българската Академия на Науките и Изкуствата, Отделение за наука, Научен център по медицина и здравеопазване, излиза в четири книжки годишно. „Българска медицина" е достъпна онлайн на сайта на БАНИ, раздел издания.

В него се отпечатват оригинални научни статии, казуистични съобщения, обзори, рецензии и съобщения за проведени или предстоящи научни конгреси, симпозиуми и други материали в областа на клиничната и фундаменталната медицина. Списанието излиза на английски език с подробни резюмета на български и английски. Изключения се правят за обзорни статии по особено значими теми. Заглавията, авторските колективи, а също надписите и означенията на илюстрациите и в таблиците се отпечатват и на двата езика.

Материалите трябва да се предоставят в два еднакви екземпляра, напечатани на пишеща машина или на компютър, на хартия формат А4 (21 х 30 см), 60 знака на 30 реда при двоен интервал между редовете (стандартна машинописна страница). Освен това могат да бъдат изпратени като прикачени файлове по електронната поща на адресите, посочени по-долу.

Обемът на представените работи не трябва да превишава 10 стандартни страници за оригиналните статии (или 5000 думи според стандарта на англосаксонските издания) 12 страници (7 500 думи) за обзорните статии, 3–4 страници за казуистичните съобщения, 4 страници за информации относно научни прояви в България и в чужбина, както и за научни дискусии, 2 страници за рецензии на книги (монографии и учебници). В посочения обем се включват книгописът и всич-ки илюстрации и таблици. В същия не се включват резюметата на български и английски, чий-то обем трябва да бъде около 200 думи за всяко

The basic structure of the manuscripts should meet the following requirements:

TITLE PAGE

The title of the article, forename, middle initials (if any) and family name of each author; institutional affiliation; name of department(s) and institutions to which the work should be attributed, address and fax number of the corresponding author.

TEXT OF THE ARTICLE

Titles and subtitles should be standardized. The original research reports should have the following structure: introduction (states the aim, summarizer the rationale for the study), subjects and materials, methods (procedure and apparatus in sufficient detail, statistical methods), results, discussion, conclusions (should be linked with the aims of the study, but unqualified statements not completely supported by research data should be avoided). These requirements are not valid for the other types of manuscripts. Only officially recognized abbreviations should be used, all others should be explained in the text. Units should be used according to the International System of Units (S. I. units). Numbers to bibliographical references should be used according to their enumeration in the reference list.

Illustrations

Photographs should be presented both in the text body to indicate their location and in separate files as saved in jpeg, tif or bitmap formats.

The figures, diagrams, schemes, photos should be submitted in a separate file with: consecutive number (in Arabic figures); titles of the article and name of the first author. The explanatory text accompanying the figures should be presented along with the respective number of the figure in the main text body with space left for insertion of the figure.

(25–30 машинописни реда). Резюметата се представят на отделни страници.Те трябва да отразяват конкретно работнатахипотеза и целта на разработката, използваните методи, най-важните резултати и заключения. Ключовите думи (до 5), съобразени с „Medline“, трябва да се посочат в края на всяко резюме.

Структурата на статиите трябва да отговаря на следните изисквания:

ТИТУЛНА СТРАНИЦА

а) заглавие, имена на авторите (собствено име и фамилия), название на научната организация или лечебното заведение, в което те работят. При повече от едно за ведение имената на същите и на съответните автори се маркират с цифри или звездички;

б) същите данни на английски език се изписват под българския текст.

Забележка: при статии от чужди автори българският текст следва английския. Точният превод от английски на български се осигурява от редакцията. Това се отнася и за останалите текстове, включително резюметата на български.

Основен текст на статията. Заглавията и подзаглавията следва да бъдат уеднаквени и различими.

Оригиналните статии задължително трябва да имат следната структура: увод, материал и методи, собствени резултати, обсъждане, заключение или извод.

Методиките следва да бъдат подробно описани (включително видът и фирмата производител на използваните реактиви иапаратура). Същото се отнася и за статистическите методи.

Тези изисквания не важат за обзорите и другите видове публикации. В текста се допускат само официално приетите международни съкращения; при използване на други съкращения те трябва да бъдат изрично посочени в текста. За мерните единици е задължителна международната система SI. Цитатите вът-ре в текста е препоръчително да бъдат отбелязвани само с номерата им в книгописа.

References

The references should be presented on a separate page at the end of the manuscript. It is recommended that the number of references should not

Exceed 20 titles for the original articles and 40 titles for the reviews; 70 % of them should be published in the last 5 years. References should be listed in alphabetical order, English first, followed by the Bulgarian ones in the respective alphabetic order. The number of the reference should be followed by the family name of the first author and then his/her initials, names of the second and other authors should start with the initials followed by the family names. The full title of the cited article should be written, followed by the name of the journal where it has been published (or its generally accepted abbreviation), volume, year, issue, first and last page. Chapters of books should be cited in the same way, the full name off the chapter first, followed by"In:" full title of the book, editors, publisher, town, year, first and final page number of the cited chapter.

Examples:

Reference to a journal article:

1. McLachan, S. , M. F. Prumel, B. Rapoport. Cell Mediated or Humoral Immunity in Graves' Ophthalmopathy? J. Clin. Endocrinol. Metab., 78, 1994, 5, 1070–1074.

Reference to a book chapter:

2. Delange, F. Endemic Cretenism. In: The Thyroid (Eds. L. Braveman and R. Utiger). Lippincott Co, Philadelphia, 1991, 942–955.

Submission of manuscripts

The original and one copy of the complete manuscript are submitted together with a covering letter granting the consent of all authors for the publication of the article as well as a statement that it has not been published previously elsewhere and signed by the first author. The procedure should be complemented via electronic submission. Manuscripts of articles accepted

Илюстрации и таблици

Снимките – освен в Word, за да се знае местоположението им, следва да бъдат предоставени и като отделни файлове във формат jpg, tif или bitmap.

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Книгописът се представя на отделен лист. Броят на цитираните източници е препоръчително да не надхвърля 20 (за обзорите до 40), като 70 % от тях да бъдат от последните 5 години. Подреждането става по азбучен ред (първо на латиница, после на кирилица), като след поредния номер се отбелязва фамилното име на първия автор, след това инициалите му; всички останали автори се посочват с инициалите, последвани от фамилното име (в обратен ред) до третия автор, последвани от съкращшениетоet Al. Следва цялото заглавие на цитираната статия, след него названието на списанието (или общоприетото му съкращение), том, година, брой на книжката, началната и крайната страница. Глави (раздели) от книги се изписват по аналогичен начин, като след автора и заглавието на главата (раздела) се отбелязват пълното заглавие на книгата, имената на редакторите (в скоби), издателството, градът и годината на издаване, началната и крайната страница.

for publication will not be returned to the authors.

Peer-review process: following the international standards in the field, the Editorial board has adopted double-blind peer-review policy assigned to independent referees. The authors are encouraged to submit the names of three potential referees for editorial consideration

PUBLICATION ETHICS

Editors' obligations

The editor is responsible for deciding which of the articles submitted to the journal should be published.

The editor may be guided by the policies of the journal's editorial board and constrained by such legal requirements as shall then be in force regarding libel, copyright infringement and plagiarism. The editor may confer with other editors or reviewers in making this decision.

An editor at any time evaluate manuscripts for their intellectual content without regard to race, gender, sexual orientation, religious belief, ethnic origin, citizenship, or political philosophy of the authors.

The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

Authors' obligations

The authors should ensure that they have written entirely original works, and if the authors have used the work and/or words of others that this has been appropriately cited or quoted.

An author should not in general publish manuscripts describing essentially the same research in more than one journal or primary publication. Submitting the same manuscript to more than one journal concurrently constitutes unethical publishing behaviour and is unacceptable.

ПРИМЕРИ:

Статия от списание:

1. McLachlan, S., M. F.Prumel, B. Rapoport. Cell Mediated or Humoral Immunity in Graves' Ophthalmopathy? J. Clin. Endocrinol. Metab., 78, 1994, 5, 1070–1074.

Глава (раздел) от книга:

2. Delange, F. Endemic Cretenism. In: The Thyroid (Eds. L. Braveman and R. Utiger). Lippincott Co, Philadelphia, 1991, 942–955.

Адрес за кореспонденция с авторите

Той се дава в края на всяка статия и съдържа всички необходими данни (вкл. електронна поща) на български език за един от авторите, който отговаря за кореспонденцията.

Всички ръкописи трябва да се изпращат с придружително писмо, подписани от авторите, с което потвърждават съгласието си за отпечатване в сп. „Българска медицина". В писмото трябва да бъде отбелязано, че материалът не е бил отпечатван в други научни списания у нас и в чужбина. Ръкописи не се връщат.

ПРОЦЕДУРА ПО РЕЦЕНЗИРАНЕ:

С оглед спазване на международните стандарти, редакционната колегия е приела процедура по 'двойно сляпа' рецензия от независимио референти. На авторите се предоставя възможноста да предложат на вниманието на редакционния екип три имена на специалисти в тяхната област като потенциални рецензенти.

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Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. Where there are others who have participated in certain substantive aspects of the research project, they should be acknowledged or listed as contributors.

The corresponding author should ensure that all appropriate co-authors and no inappropriate co-authors are included on the paper, and that all co-authors have seen and approved the final version of the paper and have agreed to its submission for publication.

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Peer review assists the editor in making editorial decisions and through the editorial communications with the author may also assist the author in improving the paper.

Any manuscripts received for review must be treated as confidential documents. They must not be shown to or discussed with others except as authorized by the editor.

Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

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Ethical regulations: reports with experiments on human subjects should specify whether the procedures were conducted in accordance with the ethical norms if the responsible committee on Human experimentation (local or regional) and/or with the Helsinki Declaration, as revised in 2000. Respective guidelines for animal experimentation should be considered.

PROCESSING CHARGES

Following acceptance for publication the authors are charged 5 euros per page for language editing and corrections.

ADDRESS FOR SENDING OF MANUSCRIPTS AND OTHER EDITORIAL CORRESPONDENCE

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1431 Sofia, Zdrave str. 2, University Hospital for Endicrinology

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WITH COPY FOR THE SCIENTIFIC SECRETARY –

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Рецензиите следва да се придържат към обективни стандарти на оценка. Лични нападки срещу авторите са неприемливи. Критичните забележки следва да бъдат подкрепени с аргументи.

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