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T Cell Activation: Surface Markers in Clinical Transplantation

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INTRODUCTION

The success story of organ transplantation started back in the 1950s when Joseph Murray for the first time transplanted a kidney between identical twins (1). This unique immunological situation with genetically identical subjects made it possible to get along without immunosuppressants. However, today organ transplantation is possible between subjects who are genetically not identical. It has become a routine procedure for end stage organ failure particularly for heart, liver, and kidney malfunction. In contrast to the homogeneic condition with monozygous twins we therefore usually encounter an allogeneic situation in which the transplanted organ is rejected by the recipient's immune system.

The players of the immune system involved in organ rejection comprise antigen presenting cells (APC), B cells, antibodies, T cells, natural killer cells, monocytes/macrophages, and the complement as well as coagulation system (Table 1). The following report will focus on T cells. If a donor organ (allograft) is transplanted donor alloantigens are presented to the recipients T cells in secondary lymphatic organs such as lymph nodes and the spleen. Upon recognition of the alloantigens displayed on major histocompatibility complex (MHC) molecules of APC such as dendritic cells or macrophages T cell get activated and home to the graft as effector T cells where they start to destroy it (2).

Table 1.
Players involved in graft rejection

1.	**Antigen presenting cells** • Dendritic cells • Macrophages • Activated B cells
2.	**B cells and antibodies** • Preformed antibodies • Natural antibodies • Preformed antibodies from prior sensitization • Induced antibodies
3.	***T cells*** • Effector CD4+ cells (T helper cells) • Memory CD4+ cells • Effector CD8+ cells (cytotoxic T lymphocytes) • Memory CD8+ cells
4.	**Other cells** • Natural killer cells • Monocytes/macrophages
5.	**Complement system**
6.	**Coagulation system**

In this event two types of T cells are involved namely CD8+ cells which are activated by antigens presented on MHC I molecules and CD4+ T cell which are mainly activated by antigens presented on MHC II molecules. CD8+ T cells become cytotoxic effector T cells whereas CD4+ T cells turn into T helper cells which support humoral immunity. From both T cell populations memory T cells are formed (3).

Allorecognition and T cell activation can be triggered by two pathways. Donor APC contained in the graft either directly present the alloantigens to the recipient T cells (direct allorecognition) or the recipients APC process

proteins from the transplanted graft before they are presented to the recipients T cells (indirect allorecognition) (4) (Figure 1).

T CELL ACTIVATION AND IMMUNOSUPPRESSION

For T cells to become activated a close contact to APC is needed. First the T cell must recognize the antigen presented on MHC molecules of the antigen presenting cell by its T cell receptor and second a co-stimulatory signal is needed which is triggered by the interaction of peptides presented by MHC molecules on APC and a complementary binding partner on the T cell surface (5). The most well known pairs are CD80/86 (antigen presenting cell) and its ligand CD28 (T cells) or CD40 (antigen presenting cell) and CD40 ligand (T cells) also called CD154 (Figure 1). To achieve full activation of the T cell a third signal is required which is provoked by cytokines released by the antigen presenting cell or in an autocrine fashion by the T cell itself such as IL-2 and type I interferon (6).

Because T cell activation is a crucial step for the rejection reaction immunsosupprressant drugs (ISD) are mainly aimed at inhibiting this reaction. All currently used ISD prevent T cell activation by either interfering with the signals needed for full activation or by blocking T cell proliferation. The calcineurin inhibitors Cyclosporine and Tacrolimus block T cell receptor mediated IL-2 production, the recombinant protein Belatacept binds to CD 80/86 on APC cells thereby interrupting co-stimulation, humanized antibodies (basiliximab) against the IL-2 receptor prevent IL-2 binding, mTOR inhibitors (Sirolimus and Everolimus) and Mycophenolic Acid (MPA) prevent T cell proliferation by arresting the cell cycle (7). The crucial breakthrough to make transplantation a routine therapy for many end stage organ failures was the introduction of these immunosuppressants besides a refinement of the surgical techniques and the aftercare in high tech intensive care units. However, most pharmacological ISD are so called narrow therapeutic index drugs which need dose individualization based on therapeu-

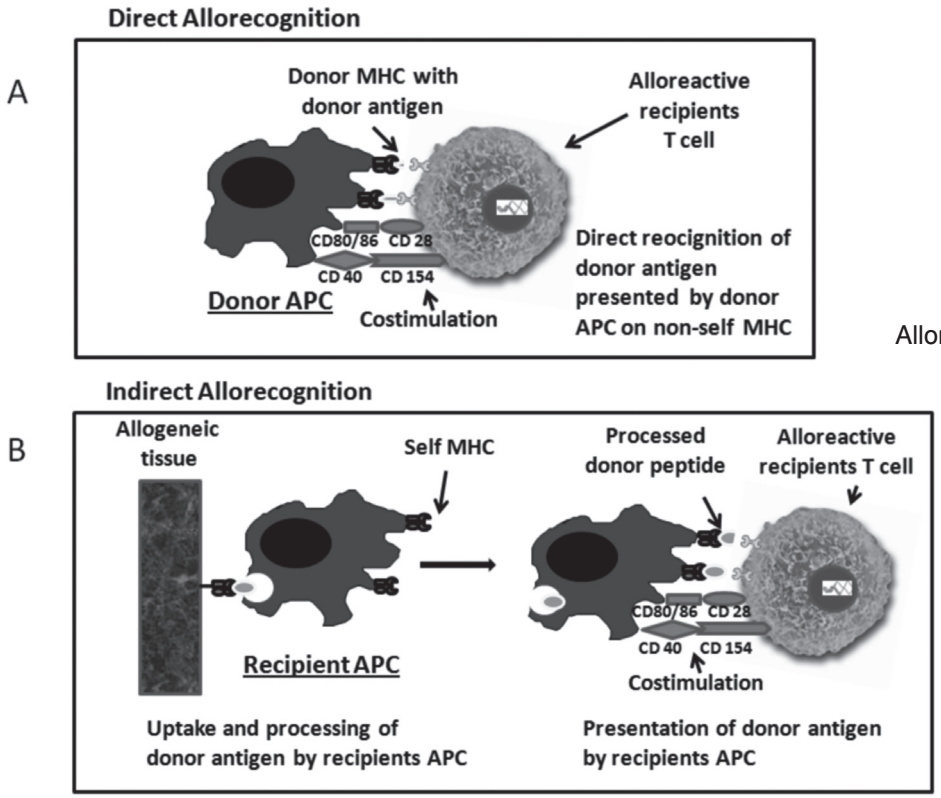

Figure 1
Allorecognition and T cell activation. Panel A shows the direct activation of T cells by donor antigens presented on donor antigen presenting cells (APC), panel B indirect activation by donor antigens processed and presented to T cells by the recipients APC. CD40-CD134 and CD80/86-CD28 are common co-stimulatory ligands on APC and T cells which are crucial for full T cell activation

tic drug monitoring (TDM) to avoid over- and under-immunosuppression (8).

BIOMARKERS TO COMPLEMENT THERAPEUTIC DRUG MONITORING

Although TDM has certainly significantly contributed to increase both patient and graft survival particularly in the early phase after solid organ transplantation it does not allow to adjust the therapy to the particular immunological situation of the individual patient. Target therapeutic ranges are derived from cross-sectional studies not considering patients who respond weaker or stronger to the standard therapy. It is well known that rejection episodes occur as an indication of under-immunosuppression albeit patients are compliant and their blood concentrations of ISD are very well within the therapeutic range. On the other hand, signs of over-immunosuppression such as infections, leucopenia, anemia, and malignancies occur although the therapy is guided by TDM. Besides chronic rejection, the latter clinical complications are particularly limiting for the long term success of organ transplantation (9).

To better personalize the immunosuppressive therapy the medical community is looking for diagnostic tools complementary to TDM which allow a better fine tuning. Pharmacodynamic biomarkers either specific for the action of the drug or general non-specific biomarkers reflecting the immune status are emerging (10). Because T cell activation is critical for organ rejection the assessment of surface markers reflecting the activated state of T cells may be a suitable non-specific approach reflecting the net state of immunuosuppression exerted by drug combinations.

T cells up-regulate a variety of surface proteins upon stimulation triggered though either antigens presented on APC in vivo or mitogens such as phorbol esters or concanvalin A in vitro (Figure 2). These surface markers on activated T cells can be clustered into receptors for a variety of proteins or peptides, chemokine receptors, co-stimulatory proteins, or adhesion molecules (11). The following paragraphs we will focus on CD25 (alpha-chain of the IL-2 receptor), CD26 (dipeptidyl peptidase IV), CD30 (tumor necrosis factor receptor SF8), CD71 (transferrin receptor 1), CD154 (CD40 ligand), IL-2, and interferon ɣ to discuss whether they are suitable biomarkers to reflect the net state of immunosuppression.

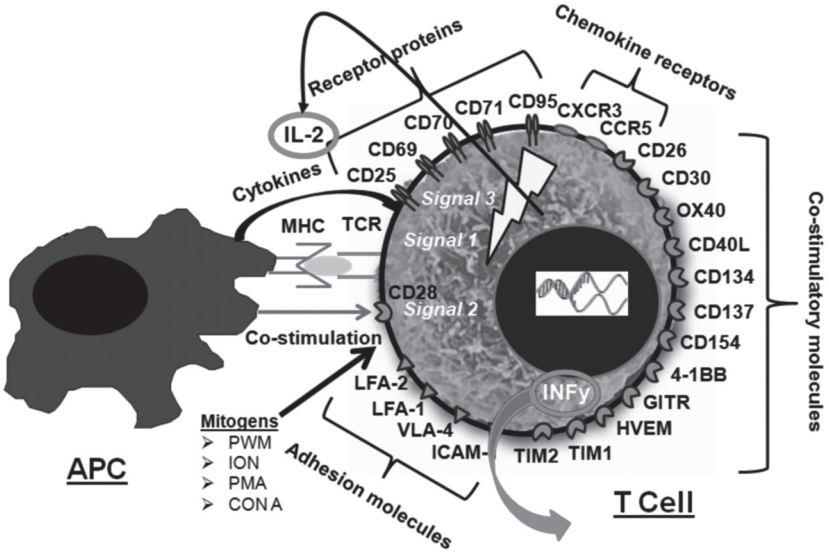

Figure 2.
A selection of surface markers, which are up-regulated on T cells after activation through either contact to APC or mitogens. PWM = pokeweed mitogen; ION= ionomycin; PMA= phorbol-12-myristate-13-acetate; Con A= concanvalin A

CD26/DIPEPTIDYL PEPTIDASE IV

Our group has focused recently on the T cell surface marker CD26 or dipeptidyl peptidase IV (DPPIV) wherefore we take the liberty to make a short excursion. CD26 is a transmembrane glycoprotein and a member of the S9B serine peptidase protein family (12). It is expressed on activated T cells and a variety of non-immune cells e.g. renal, prostate, liver, and small intestinal epithelium (13). Its extracellular domain possesses

DPPIV activity. DPPIV has an important modulatory activity on a number of chemokines, neuropeptides and peptide hormones including the glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) (14). Therefore, DPPIV inhibitors are used to treat diabetes mellitus by increasing the half-life of these incretin hormones (15). About 90% of the DPPIV activity found in serum is considered to originate from the membrane of CD26 expressing cells (16).

A particularly important aspect for clinical transplantation is the role of CD26/DPPIV in immune regulation. Multiple studies in recent years have demonstrated a link between this molecule and signaling pathways and structures involved in T cell activation. CD26 is preferentially expressed on memory T cells and is up-regulated after T cell activation. Besides being a marker of T cell activation, CD26 is a costimulatory molecule for T cell activation (17).

EFFECTS OF IMMUNOSUPPRESSANT DRUGS ON T CELL ACTIVATION MARKERS *IN VITRO*

The first step to examine whether T cell activation markers can reflect the effect of ISD is to perform in vitro experiments with stimulated cells in the presence and absence of these drugs. For this purpose leukocytes are isolated and incubated in the presence of mitogens or antigens. T cell activation can then easily be followed by flow cytometry with labeled antibodies against the respective surface markers (18). Alternatively stimulation can be performed in whole blood which facilitates the procedure because the time consuming and laborious cell isolation step using Ficoll-Hypaque density gradient centrifugation can be ommitted (19). It has been shown that the calcineurin inhibitors Cyclosporine and Tacrolimus, the mTOR inhibitors Sirolimus and Everolimus, and Mycophenolic Acid were all able to inhibit expression of CD25, CD26, CD71, CD154, IL-2, and interferon ɣ in a time and dose dependent manner in different models either alone or in combinations (20–24). It can be therefore concluded that the inhibitory effect of all currently used pharmacological ISD on T cell activation can be followed by surface marker expression and cytokine release. Before this knowledge derived from *in vitro* experiments can be translated into a clinically useful tool for guiding immuosuppression the important question to answer is whether these T cell activation markers are associated with clinical events *in vivo*?

T CELL ACTIVATION MARKERS IN TRANSPLANT PATIENTS *IN VIVO*

In order to assess the effect of the immunosuppressant therapy on T cell activation markers *in vivo* an approach complementary to that applied for the in vitro experiments which served as a proof of principle is usually performed. Several authors have isolated lymphocytes from the blood of transplant patients treated with ISD and performed incubations steps in the presence of mitogens or antigens (25–27). However, as mentioned above it is advantageous if this step can be waived to save time and to make the diagnostic assay more convenient. Therefore, whole blood approaches have also been pursued (28,29). The clinical events recorded in studies with the assessment of T cell activation markers were of course rejection as an indicator of under-immunosuppression but also infections and leucopenia as signs of over-immunosuppression.

Lun et al. have shown that CD25 expression was higher both on CD4+ and CD8+ T cells in liver transplant patients who experienced an acute rejection (30). Our group recently reported data on an association between low CD26 expression on T cells and freedom of rejection during the first 3 month after kidney transplantation (31). In the meantime we have observed that CD26 is up-regulated on T cells of kidney transplant patients without previous *ex vivo* stimulation and can therefore be directly assessed in whole blood by flow cytometry. Kidney transplant patients who suffered from acute rejection episodes demonstrated not only a significantly higher percent of CD26 positive CD8+ T cells early after transplantation but also

a different time course of these cells over the first 2 weeks compared to patients without rejection (32). A low CD26 expression on CD4+ T cells was in contrast associated with a risk to develop leucopenia (33). This risk was increased if the concentration of the immunosuppressants Tacrolimus and MPA were high (Figure 3). This is an example of how a biomarker can complement TDM in estimating the risk for the occurrence of an undesired adverse event after kidney transplantation.

CD26 assessed as DPPIV activity in serum was lower in patients after transplantation compared to their pre-transplantation status as well as to healthy controls. No association between DPPIV activity and clinical events was noted. This points to the fact that DPPIV activity in serum is not a mirror of CD26 expression on T cells and cannot be used as a marker of T cell activation to complement TDM.

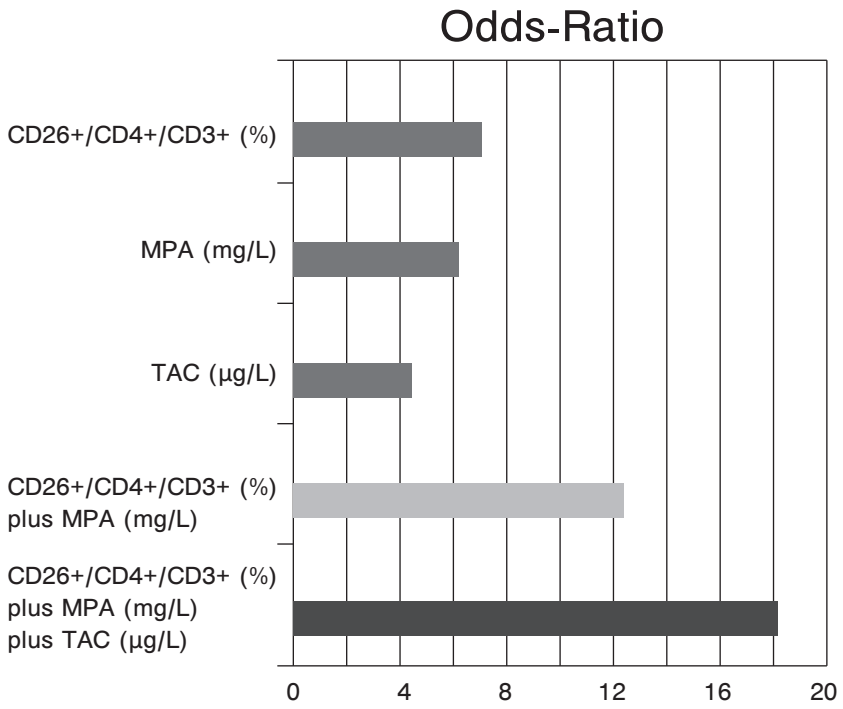

Figure 3
Risk to develop leucopenia (<4000/mL) within the first 6 months after kidney transplantation in 70 patients. Odds ratios are given for CD26 expression on CD+ cells alone and in combination with drug concentrations of MPA and Tacrolimus. Surface markers were monitored by flow cytometry in whole blood, drug concentrations by HPLC and LC-MS/MS respectively.

However, with CD71 expression on CD4+ T cells we have observed in the same kidney transplant population that CD71 was lower in patients with infections (10). Ashokkumar et al. and Boleslawski et al. have shown that CD154 expression on CD4+ T cells and IL-2 production by CD8+ T cells respectively were both related to acute rejection in liver graft recipients (34,35).

CD30 is commonly not assessed as a surface marker but in its circulating form called soluble CD30 or sCD30 in serum. A convincing amount of data mainly generated by Süsal and colleagues suggests that sCD30 is a suitable biomarker to guide the immunosuppressive therapy because it has been shown to be associated with both under- and over-imunosuppression (36). It also nicely reflects the strength of the immunosuppressive regimen (37).

The last biomarker we want to address is interferon ɣ. Interferon ɣ production and release is a hallmark of T cell activation. However, it cannot be directly assessed on or within circulating T cells. Although it needs cell isolation and *in vitro* incubation it has the advantage that assay platforms are commercially available, the so called IGRA (Interferon-Gamma-Release Assays). The most commonly used form is the ELISPOT (Enzyme Linked Immuno Spot Assay). A capture antibody against interferon ɣ is coated onto a membrane in a microplate and lymphocytes are plated out at varying densities, along with antigen or mitogen, and then placed in an incubator for about 24 hours. The interferon ɣ released by the activated T cells is then directly captured by the immobilized antibody. A second bi-

otinylated antibody forms a sandwich and after addition of a streptavidin conjugate visible spots develop. The number of spots is then counted and an indicator of T cell activation. The assay is known to be very reproducible in different locations and thus allows comparisons between laboratories and multi center trials (38). Using either peripheral blood mononuclear cells from living or splenocytes from respective deceased kidney donors as the source of donor specific antigens Bestard et al. have shown that the T cell activation state assessed by the ELISPOT was correlated with kidney graft function (39). In addition, in a recent paper the same authors used the ELISPOT results before transplantation and 6 month after transplantation to guide the immunosuppressive therapy. Patients with a lower T cell activation were given a milder calcineurin inhibitor or steroid free therapy as compared to those with strong T cell activation. Patients with a lower ELISPOT result and milder calcineurin inhibitor or steroid free therapy had similar rejection rates but a better kidney function (40).

CONCLUSIONS AND OUTLOOK

T cell activation markers hold promise to become complementary biomarkers to TDM for guiding immunosuppression. Major drawbacks are so far the time consuming *ex vivo* stimulation steps required for many analytical approaches as well as the lack of standardization between laboratories. In addition, most assays require freshly isolated cells. Exceptions to these rules are the assessment of CD26 expression on T cells directly in whole blood by flow cytometry, the measurement of sCD30 in serum and the highly standardized ELISPOT approach (41) which can be performed with cryopreserved and thawed PBMC without loss of functional activity (42). In addition to T cell surface markers there a variety of other biomarkers under investigation such as the assessment of cell free donor DNA in the recipients plasma (43) or pharmacodynamic assays which directly examine the effect of ISD on their target molecules such as inosine monophosphate dehydrogenase (IMPDH) activity for MPA (44) or the inhibited phosphorylation of the ribosomal S6 protein as a marker of the mTOR effect (45). Gene signatures and expression patterns which can be assessed by array technologies are also under investigation (46). It can be expected that the field will rapidly develop and that more biomarkers will be evaluated in multi center trials. Biomarker development and validation is part of clinical trials organized by consortiums in the USA and Europe such as Clinical Trials in Organ Transplantation (CTOT; https://www.ctotstudies.org/) or BIOmarker-Driven personalized IMmunosuppression (BIO-DrIM; http://www.biodrim.eu/index.html).

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The influence of the extent of tumor resection on executive functioning and quality of life of brain tumor patients

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Влияние на обема на туморната резекция върху екзекутивното функциониране и качеството на живот при пациенти с мозъчни тумори

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РЕЗЮМЕ

ЦЕЛ

Да се проследи влиянието на обема на туморната резекция върху екзекутивните функции и качеството на живот при пациенти със супратенториални мозъчни тумори.

МАТЕРИАЛ И МЕТОДИ

Извършено е трикратно невропсихологично изследване чрез тестове с доказанана чувствителност към екзекутивни дисфункции при 38 пациенти, оперирани по повод на супратенториални

ABSTRACT

AIM

The object of the current study is to investigate the impact of the extent of tumor resection on executive functioning and quality of life in patients with supratentorial brain tumors.

MATERIALS AND METHODS

Three point neuropsychological assessment was carried out by means of widely used cognitive tests sensitive to executive dysfunction in 38 patients operated on for supratentorial brain tumors. Two

мозъчни тумори. Приложени са трикратно и две скали за оценка на функционалния статус и качеството на живот. Пациентите са разпределени в две подгрупи за сравнение: 1. Пациенти с тотално отстранени мозъчни тумори (N=24) и 2. Пациенти с не-тотално отстранени мозъчни тумори (N=14).

РЕЗУЛТАТИ

Пациентите с тотално отстранени мозъчни тумори са показали значимо по-добро и трайно възстановяване на екзекутивните си функции за целия период на проследяване, измерени чрез тестовете за свързване на линии ($p<0.05$), фонемна флуентност ($p<0.001$) и теста за рисуване на часовник ($p<0.05$), в сравнение с пациентите с не-тотално отстранени мозъчни тумори. Пациентите с тотално отстранени мозъчни неоплазами са показали и значимо по-добро цялостно качество на живот ($p<0.01$) и функционален статус ($p<0.05$) за целия период на проследяване, измерено чрез съответните оценъчни скали.

ЗАКЛЮЧЕНИЕ

Тоталното отсраняване на супратенториалните мозъчни тумори е предпоставка за по-добро и трайно възстановяване на екзекутивните функции и подобрено качество на живот в следоперативния период при тези пациенти.

Ключови думи: обем на отстраняване, мозъчен тумор, екзекутивни функции, качество на живот

scales for assessment of functional status and quality of life were also applied. Patients were divided into two groups for comparison: 1. Patients with totally resected tumors (N=24) and 2. Patients with non-totally resected tumors (N=14).

RESULTS

Patients with totally resected brain tumors experienced significantly better and permanent recovery of executive functioning for the entire follow-up period measured by the Trail-Making Test Part B ($p<0.05$), Phonemic Fluency Test ($p<0.001$) and the Clock Drawing Test ($p<0.05$) compared to the patients with non-totally resected brain tumors. They have also achieved higher scores on the scales assessing functional status ($p<0.01$) and overall quality of life ($p<0.05$).

CONCLUSION

The total resection of supratentorial brain tumors is precondition for better and permanent recovery of executive functions and improved quality of life of the patients in the postoperative period.

Key words: extent of resection, brain tumor, executive functions, quality of life

INTRODUCTION

Executive function deficit is observed early in the course of well-known neurological disorders such as Parkinson's and Alzheimer's diseases [1,9]. On the other hand, more than 90% of brain tumor patients demonstrate impairment in at least one cognitive domain and executive dysfunction is observed in approximately 78% of cases [11]. Executive functions are of great importance for patient's safety and ability to perform planned actions in his/her daily living [13]. Cognitive impairments may negatively influence quality of life (QOL), family and interpersonal relationships [3,8].

The aim of this study is to investigate the impact of the extent of tumor resection on executive functioning and quality of life in patients with supratentorial brain tumors.

MATERIAL AND METHODS

Materials: The study included 38 adult patients who were operated on for supratento-

rial brain tumors at the Clinic of Neurosurgery, St George University Hospital – Plovdiv between 2010 and 2012. Patients were selected by inclusion and exclusion criteria and after signing an informed consent. Mean age was 55.08±1.67 (SD 10.27); mean years of education were 10.82±0.41 (SD 2.51). Patients were divided into two subgroups for comparison: 1. Subgroup of totally resected tumors (N=24) and 2. Subgroup of non-totally resected tumors (N=14) which included the cases with subtotal, partial resection and biopsy. The reasons for non-total tumor removal were the lack of clear tumor borders to the adjacent normal brain tissue as well as the tumor extension in two or more brain lobes in the cases of intraaxial infiltrative primary neoplasms; infiltration of eloquent brain areas and/or entrapment of important arterial and venous vessels which once injured can result in development of neurological disability. According to their histology based on the Classification of Central Nervous System Tumors of the WHO from 2007, the study included 12 cases of Meningioma Gr.I and 3 cases of Meningioma Gr. II&III; 1 case of epidermoid tumor (cholesteatoma); 4 cases of low-grade glioma (Gr. II); 13 cases of high-grade glioma (Gr. III&IV); and 5 cases of metastatic brain tumors.

Methods: Preoperative and postoperative computed tomography (CT) and/or magnetic-resonance imaging (MRI) with contrast enhancement was performed in all cases in order to register the extent of tumor resection (EOR). The lack of contrast enhancement on the postoperative imaging studies was accepted as a proof for total tumor removal. Patients were followed up for a period of 7 months post surgery. Neuropsychological and QOL assessments were applied threefold: before operative treatment, at 1st and 7th postoperative month. We used three neuropsychological tests reported to be sensitive to impairment of executive functions: Trail-Making Test Part B (TMT-B), Phonemic Fluency Test (PFT) and Clock Drawing Test (CDT). Functional status was evaluated by the Karnofsky Performance Status Scale (KPS) (varying 0–100) and QOL was assessed by the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire version 3.0 (QLQ-C30). The EORTC QLQ-C30 (version 3.0) is a 30-item questionnaire composed of multi-item scales and single items that reflect the multidimensionality of the QOL construct. It combines five functional scales {physical (PF), role (RF), emotional (EF), cognitive (CF) and social functioning (SF)}, three symptom scales {fatigue (FA), pain (PA), and nausea/vomiting (NV)}, a global health and QOL scale, six single items assessing additional symptoms commonly reported by cancer patients {dyspnea (DY), appetite loss (AP), sleep disturbance (SL), constipation (CO) and diarrhea (DI)}, as well as the perceived financial impact (FI) of the disease and treatment.

Statistical analyses: Descriptive, parametric, nonparametric, correlation and ANOVA statistical analyses were made by SPSS software (version 17.0). Graphic analyses of data were performed using MS Office Excel 2003. Scores were expressed as mean (±SE). Kolmogorov-Smirnov Test was used to test for normality of distribution. Most of the scores were nonnormally distributed and were, therefore, compared by nonparametric methods. The numerical comparisons between consecutive measurements (dependent groups) were assessed by Friedman within the whole group comparisons and by Wilcoxon test in pairwise comparisons. The pairwise comparisons between two independent groups were made by Mann–Whitney U test. A $p<0.05$ was considered to be statistically significant.

RESULTS

The subgroup of totally resected tumors (STRT) demonstrated significantly better and permanent improvement in executive functions at the

7th postoperative month (p<0.05) measured by the TMT-B than the subgroup of non-totally resected tumors (SNTRT) (Fig.1). ANOVA showed that the EOR is a factor which influences the results from the TMT-B at the end of the follow-up period (F=4.39; p=0.05).

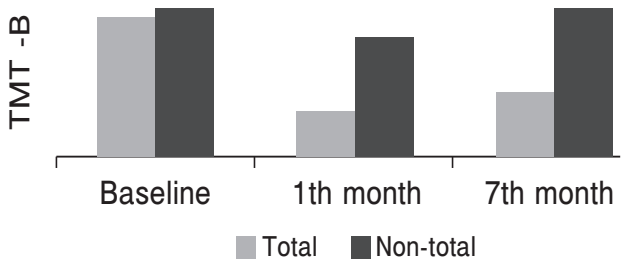

Fig. 1.
Dynamics of the executive functions assessed by the TMT-B.

Significantly better results were scored on the PFT by the STRT at the 1st (p<0.001) and 7th postoperative month (p<0.001) again confirming the substantial improvement in executive functioning in this subgroup. (Fig.2.).

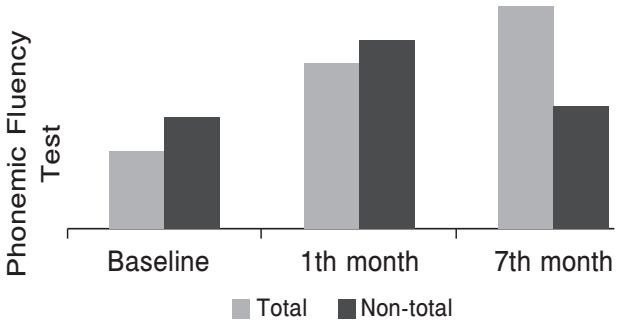

Fig. 2.
Dynamics of the executive functions assessed by the PFT.

The ability for planning within executive functions assessed by the CDT in the STRT also showed considerably better improvement at the 1st (p<0.05) and 7th postoperative month (p<0.05) compared to the SNTRT (Fig.3). ANOVA showed that the EOR is a factor which influences the results from the CDT at the end of the follow-up period (F=5.36; p=0.03).

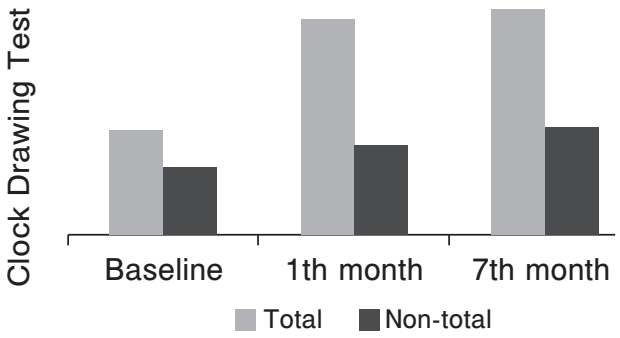

Fig. 3.
Dynamics of the planning ability assessed by the CDT.

The patients from STRT reported significantly better improvement in their functional status (p<0.01) and global QOL (p<0.01) measured by KPS and QLQ-C30 for the entire follow-up period than the patients from the SNTRT. (Fig 4 and 5).

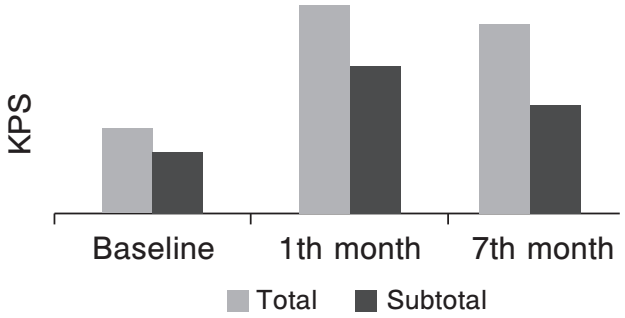

Fig.4.
Dynamics of the functional status evaluated by the KPS.

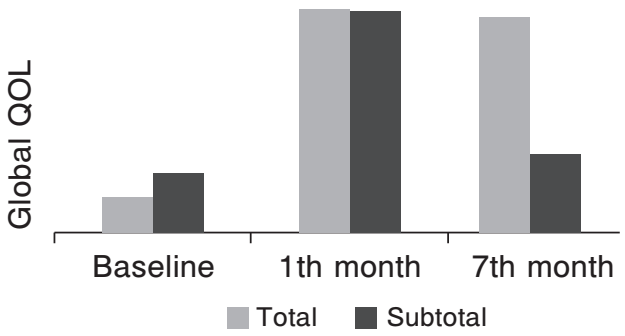

Fig.5.
Dynamics of the global QOL evaluated by the QLQ-C30.

DISCUSSION

The comparison of the results between the patients from STRT and SNTRT provides evidence that patients with totally resected brain tumors experience greater improvement in terms of divided attention and executive functions including the planning ability. The overall improvement in executive functioning within the STRT reaches 63% and 48% assessed by the PFT and the CDT, respectively. Considerable improvement is also observed in terms of the TMT-B for the entire follow-up period. Improvement of these cognitive domains is also registered in the SNTRT but to a much lesser extent and this dynamics is not statistically significant. There are many publications discussing the impact of the extent on tumor resection on the overall survival of patients with brain tumors but those studying the effect of the EOR on cognitive deficits are rare [10, 12].

Yoshii et al. (2008) emphasize that the radical removal of hemispheric gliomas results in alleviation of cognitive deficit. Meanwhile, they also point out that in elderly patients (above 75 years) operated on for meningiomas in the dominant hemisphere there was no improvement in cognitive functions and in cases where the tumor was near to the left cingulate gyrus and the left part of corpus callosum there had been substantial risk for cognitive deterioration [14].

The patients from the STRT reported considerably better and permanent improvement in their functional status (17%) and global QOL (70%) for the entire follow-up period compared to the patients from the SNTRT who improved with only 4% and 6%, respectively. ANOVA demonstrated that the EOR is a factor influencing the functional status and global QOL. The overall dynamics of the functional status measured by the KPS is strongly correlated to the overall dynamics of the executive functions assessed by the TMT-B (r_s=-0.55; p=0.007). Similar influence of the extent of brain tumor resection on patient's quality of life is also reported by others [2,4,5,6,7].

CONCLUSION

Radical but safe resections of supratentorial brain tumors can result in improved executive functioning and QOL in the patients harboring such neoplasms. The series we followed up consists mainly of cases with brain tumors located outside the eloquent brain areas of greatest importance. Further studies are needed in order to define the effect of the EOR on cognitive functions in cases where the lesions are located near or within the eloquent areas such as the speech area.

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Comparative study of burnout and psychological climate among toxicology wards employees

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РЕЗЮМЕ

Професиите в здравеопазването са безспорно високорискови по отношение на стреса. Проучвания в областта, както в България, така и в Европа отбелязва голям брой служители в здравната система със синдрома на професионално изпепеляване. Тази безспорна информация е базисна за промяна управлението на човешкия ресурс в тази сфера.

Цел на изследването е да определи нивото на Бърн аут синдромът сред работещите в токсикологични звена съпоставими с други интензивни сектори, предпоставящи увеличаване на стреса. Това проучване има за задача да сравни и открои съществуващите разлики сред определените групи медицински работници, както и съществуващата корелационна зависимост между нивата на Бърн аут, определени личностови характеристики и психологическия климат на работното място.

Ключови думи: стрес, Бърн аут.

ABSTRACT

Health professions certainly have high levels of stress. Studies both in Bulgaria and in Europe noted a large number of employees in the health system with burnout syndrome . This indisputable information is basis for the change of the management of human resources in this field.

Aim of the study is to determine the level of burnout syndrome among workers in toxicology units comparable to other intensive sectors with increased stress . This study aims to compare and highlight the existing differences among certain groups of medical professionals and the existing correlation between the levels of burnout, certain personality characteristics and the occupational psychological climate.

Keywords: Stress , Burnout

Healthcare professions are certainly high-risk in terms of stress. Studies both in Bulgaria and in Europe indicated a large number of healthcare system employees suffering from the burnout syndrome. This information serves as the basis for change of human resources management in this field [1].

Studies in the field of occupational and organizational psychology raise the problem of the relationship between psychosocial factors of the environment, quality of work and individual health. [1]

Empirical studies have shown that the negative organizational environment is a prerequi-

site for emotional dissonance. Healthcare employees are at risk of developing high levels of stress, less job satisfaction, implicating mental health [2, 3, 4]. Inability to quickly change the work environment in degraded psychological climate is a risk factor for professional burnout [5, 6].

Work-related stress itself does not lead to burnout. Generally, professionals can operate at high levels of exhaustion if their work provides positive feedback. However, those who operate under highly stressful environment may develop higher levels of anxiety, anger, behavioral disorders and depression symptoms. [7]

Social climate in the workplace is associated with burnout in a downgrade manner, but the support of the team leader and the team itself may prevent the occurrence of the syndrome. Garrett and McDaniel, claim that the perception of uncertainty in the environment predicts burnout [8]. In their study, Bellani et al. found that interpersonal relationship ability and teamwork are the important factors which determine the profile of severally "burnout" and "reduced personal accomplishments" of healthcare professionals [9]. Another study in the field found that improvements in the psychological climate also affect the reduction of "burnout" levels with healthcare professionals [10].

Working hypothesis: We assume that the negative psychological climate affects the levels of professional burnout. Based on this study on the levels of toxicology wards healthcare employees professional burnout and psychological climate, we consider that there is an organizational predictor implicating the development of burnout with these particular employees.

Environment selection. Of particular interest is the group of employees working in the toxicology field as environment with recurring stress situations. A large group of healthcare staff employed in these wards are tutors of students and interns. Despite their small number, this group is very important for the individual patient and the quality of medical training.

Subject of the study is the dynamic relationship between professional burnout and organizational characteristics in toxicology medical practice.

The observation units are healthcare professionals working in the toxicology wards of Medical University Plovdiv and Medical University Pleven.

Observation parameters are the demographics, gender and age, and psycho-emotional determinants – emotional burnout, depersonalization and the pursuit of career and personal achievements, as well as individual and group work environment factors.

The objective of the study is to determine the level of burnout syndrome among toxicology wards employees in comparison to healthcare employees in psychiatric wards. The study aims to compare and highlight the differences that exist among healthcare professionals and the existing correlation dependency between the burnout levels and certain organizational environment characteristics.

MATERIAL AND METHODS

The Maslach Burnout Inventory (MBI) and psychological questionnaire concerning the psychological climate were applied in this study. The studied subjects were divided into three levels of professional burnout – mild, moderate and severe. Correlation analysis was applied for data analysis. The analysis examines the psycho-social environment and its effect on toxicology wards employees. The study covers 16 employees from Medical University Plovdiv and Medical University Pleven. The group of toxicologists was compared to 18 healthcare employees in psychiatric wards.

RESULTS AND DISCUSSION

After the analysis of the results and the comparison of the two groups of employees in toxicology and psychiatric wards, we established a statistically significant difference in terms of emotional burnout (F=4.47; p<0.5) (Table 1). Healthcare employees in toxicology wards have notably lower levels of emotional burnout ($\overline{X}$ = 14.62 ± 2.04) in comparison with those in the psychiatric wards where moderate levels were established ($\overline{X}$= 21.72 ± 2.97). Another difference we found concerns depersonalization, where toxicology wards employees again exhibited lower levels ($\overline{X}$= 4.69 ± 1.09) as opposed to psychiatric ward, where the levels were moderate. For the personal achievements scale we did not establish a statistically significant difference (F=0.51; p>0.5). The variances analysis confirmed the presence of statistically significant differences between psychiatric and toxicology wards regarding the organizational factors: trust (F=5.41; p<0.5) and support (F=9.59; p<0.01).

In the results analysis of professional burnout levels between the two studied groups, we established that 56.3% of respondents within toxicology wards healthcare employees fall into the category of low levels of emotional burnout, while for the psychiatric wards employees this ratio is 36.8%. The distribution in the moderate emotional burnout category is similar, toxicologists – 33.1% and psychiatrists – 21.1%. Regarding high levels of emotional burnout, we established lower levels, hence less professional burnout, in the toxicology specialists group with 12.5% in comparison with 36.8% for psychiatry employees.

The depersonalization levels analysis showed that 75% of the toxicology ward employees have low levels in comparison with 42.1% for psychiatric wards. An interesting fact is that there are no persons with moderate levels of depersonalization working in toxicology wards. Regarding the high levels of this scale, we established that 12.5% of toxicologists have higher levels in comparison to psychiatrists 10.5%.

Regarding performance and personal achievements, we established that the group of toxicology wards employees had 43.8% for the high levels, while for those working in psychiatric wards, this percentage was 47.4%. The moderate levels percentage is 37.5% for the first group and 31.6% for the second. Striving for personal achievements in the lower levels is again higher for toxicologists – 18.8% in comparison with psychiatrists – 15.8%.

The last part of this study concerns our task to investigate whether there is an organizational environment predictor, which implies an increase of the burnout levels in toxicological wards employees. As result of the correlation analysis, we established a moderate reverse correlation dependency of depersonalization with the organizational factor "trust at work" (R= -0.49; p<0.5). The more the levels of support and trust in the working environment are increased, the more the negative attitude of the toxicology employees towards themselves and others are reduced, as the degree of social withdrawal and hostility is also reduced. We established a moderate correlation dependency of emotional burnout with the organizational factor "pressure at the workplace" (R= 0.55; p<0.5). This factor implies that the pressure from supervisor, colleagues, time and specific tasks increases the premise of toxico-

Table 1.
MBI subscales comparison
between the Toxicology and Psychiatry groups

Scale	N	Mean ± SE Toxicology	N	Mean ± SE Psychiatry	F	P
Emotional burnout	16	14.62 ± 2.04	18	21.72 ± 2.97	4.47	<0.05
Depersonalization	16	4.69 ± 1.09	18	7.67 ± 1.17	0.50	>0.05
Personal achievements	16	31.62 ± 1.36	18	31.22 ± 1.38	0.51	>0.05

logical wards healthcare employees to exhaust their energy resources more quickly.

DISCUSSION

In conclusion, we can summarize that the pressure of the environment and the lack of trust and support towards toxicology wads employees is a premise for emotional exhaustion, negative self-image, non-humane attitude towards patients and clearly pronounced burnout.

The comparison between the toxicologists and psychiatrists groups indicated that the toxicology wards employees are less emotionally exhausted and have higher performance levels and personal career achievements, but also have higher levels of depersonalization.

In the analysis we established statistically significant differences between the groups compared in regard to issues of emotional burnout, trust and support.

The obtained results give us basis information regarding management approaches which are needed to overcome burnout in those employed in toxicology wards, namely distinct environment of trust and support, tailored to each employee's personal and temperamental characteristics.

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Mediation in healthcare-unknown method for alternative dispute resolution

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Медиацията в здравеопазването – един непознат начин за извънсъдебно решаване на спорове

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РЕЗЮМЕ

Анализът разглежда един сравнително нов метод за извънсъдебно решаване на спорове, който се използва в САЩ и Европа, но все още не е толкова популярен в България. Статията преглежда уредбата на медиацията в страни от ЕС, както и в САЩ, посочва нейните ползи и резултати.

Дискутират се няколко различни случая на правни спорове, възникнали в здравеопазването – между лекар и пациент, между лекар и лечебно заведение, между лечебно заведение и служители, като посочва резултатите от съдебните спорове и предлага решения през погледа на медиацията.

Изложението предлага начини за въвеждане на медиацията като метод за решаване на спорове и проблеми от изпълнители на болнична помощ, посочва затрудненията, които срещат държави от ЕС при прилагане на медиацията. Предлагат се идеи за развитие и популяризиране на медиацията в един чувствителен сектор, като здравеопазването.

ABSTRACT

Mediation as a comparatively new method for alternative dispute resolution, used in EU and USA and not very popular in Bulgaria is analyzed. The article follows the legislation regarding the mediation in the EU countries and USA, proving its efficiency and results.

Several different case studies of legal disputes in the healthcare, between a doctor and patient, a patient and a provider of hospital care and a provider of hospital care and an employee, are presented and the results of the court disputes are discussed. Possible results of those cases are presented from the mediation point of view.

The study suggests ideas to implement the mediation as a method for dispute resolving, points the difficulties of the EU countries and offers suggestions for development and popularization of mediation in a very sensible branch as **healthcare.**

As the toxicology is among the medical specialties, where the doctors meet one of the most difficult and conflict patients/relatives more often, as well as the staff is overloaded, the information

Тъй като токсикологията е специалност, при упражняването на която лекарят с голяма честота среща конфликтни пациенти/близки, свързана е с голямо натоварване на служителите, работещи в такива отделения/клиники. Информацията за идеите и целите на медиацията, като способ за решаване на конфликти и извънсъдебни спорове, може да бъде изключително полезна.

Ключови думи: конфликти; медиация; извънсъдебно решаване на спорове; правна уредба в страни от ЕС/САЩ;

about mediation as a successful method for alternative dispute resolution and the ideas, supported by the mediators, could be really useful. The information about the ideas and aims of the mediation, as a method for alternative dispute resolution, could be very useful.

Key words: conflicts; mediation; dispute resolution; legislation in EU/USA;

INTRODUCTION

Mediation is one of the methods for alternative dispute resolution with the help of a mediator, who helps the conflicting parts to resolve the argument, reaching satisfying agreements between them.

This method is unknown in the hospitals in Bulgaria and thus, it is not commonly used. However, mediation provides effectively resolution of social and economical problems in different field of medicine, especially those with problematic characteristic as Toxicology.

CASE STUDIES:

The analysis represents two cases, helping to study the mediation thoroughly:

V.D, 69 years old starts a legal process against a big University hospital. The claim for non monetary and monetary remedy reached the amount of 6000 BGL. Mrs. D. stated that she was accepted in the Clinic with a specific diagnosis. On the third day of her stay she felt acute pain in her back due to a fall on the floor. She claimed that nobody had paid attention to her complaints. Ten days after she was discharged, she went in another hospital, where she was diagnosed with a broken vertebra. During the court case it was discovered that an X-ray had been made in the hospital and it didn't show a broken vertebra. The claim was dismissed. Mr. D had to pay for the expenses, made by the hospital during the court case (1000 BGL) as well as she had to burden her own expenses (940 BGL).

Dr. A is a doctor without medical specialty in a Clinic in a big hospital. Short after being appointed on this position conflicts between her and staff started. She had several postgraduate qualification courses in foreign countries, and she had domineering attitude to her colleagues, argues with them very often. The escalating problems ruin the working environment in the Clinic and she was fired. She started a legal dispute and the court judged in favor of her claim. Three days after that she was fired again. The expenses of the hospital made during the legal process reached the amount of 580 and 1500 BGL should have been paid as compensation.

Both cases show that the Court decides on the case and judges in favor of one of the arguing parties, and therefore one of them remains unsatisfied.

DISCUSSION:

What would happen of the parties would have tried to resolve the dispute with the help of mediator?

V.D agreed to mediation. An expert was allowed to evaluate the medical help, delivered to the patient. He explained to Mrs. D that the X-ray do not show any evidences of broken vertebra during her stay at the hospital. It was

also explained that the lady suffers of osteoporosis, which increases the pain. The mediator helps the parties to realize that the problem was caused by a lack of attention and special care, although all the medical protocols were completed. The hospital offers to provide extra tests and examination by endocrinologists. The parties settled.

During the second meeting with the mediator, Dr. A was sure that she had been fired due to her unfriendly colleagues, she claimed she was a good professional, who was not evaluated and the staff deliberately caused problems. The Head of the Word described Dr. A as a very conflict person, who doesn't communicate easily with the rest of the staff. She would also argue with superiors and do not follow their decisions. The mediator analyzed the problem and finally both parties decided that they should resolve the problem according to the patients' interest. Dr. A understood that her behavior is the reason to change the working environment, which influenced the quality of the services. Prof. P insisted Dr. A to change her model of communication and finally the parties settled. Dr. A decided to change her job and accept compensation from the hospital. The case was closed.

Table. 1.
Comparison between the methods:

	Legal disputes	Mediation
Procedure	Formal	Non formal; The parties participate personally;
Principles	Competition; public hearings;	Equality; voluntarily; neutrality of the mediator; impartial mediator; confidentiality;
Expenses	Taxes are 4% of the claimed damages; The party who loses the case pays the expenses of the other one;	Low taxes; free mediation is some cases;
Dispute resolution	The court decides instead of the parties in favor of one of the party; The other one is unsatisfied	The mediator helps the parties to settle. The parties settle according to the interest of both of them and they are all satisfied;
Final document	Court decision	Settlement

The cases describe different approach to the dispute, according to the method, chosen by the parties to be resolved. In the first two cases, the dispute was resolved by the court and the second two cases were settled with the help of mediation. The differences between those to methods could be specified as follows:

The healthcare system is defined as a one of the most problematic spheres, causing "blame-oriented culture" as it is mention by the European Hospital and Healthcare Federation. Usually argues are caused by differences between the expectations of both parties. The same problems could be found in the relations between staff, due to the stressful routine and the lack of financial resources. The mediation provides the opportunity to discuss more emotional aspects of the disputes, offering "therapeutic sense of closure".

The survey conducted by HOPE investigated in which healthcare mediation is used in each country. In the majority of the countries such as Belgium, Denmark, Estonia, France, Hungary, Latvia, Malta, Slovenia, Spain and the UK mediation is used to resolve disputes between patient and patients' relatives and healthcare provider. In some of those countries the use of mediation is also diffused in case of collective labor disputes, while in countries such as Estonia, Malta, Slovenia mediation is used to solve individual labor disputes as well. Finally, mediation may also be used to solve conflicts between healthcare provider and other legal entities as suppliers, public sector etc.

Methods for alternative dispute resolution are very common in USA and only 10%-15% of all the legal disputes reach a trial. The rest of them are settled before that. For example, a survey conducted by **New York City health and Hospital Corporation** studied the satisfaction of the mediation in cases of medical malpractice. The results are as follows (see Attachment № 1).

The average time spent on mediation ranged from 1 to 4.5 hours in comparison with 36 hours preparation of the attorneys before

trial. The conclusion is that the attorneys spent 1/10 times less, when the case is resolved with the help of mediator. It is interesting to mention that 10 out of 26 cases had been resolved after an apology was made. During that survey it was found out that the amount of money that will settle the case were reduced after the apology and the parties agree on different alternative ways for compensation such as free medical services.

The results of HOPE survey show that the importance of mediation in the healthcare sector is raising and it is progressively acknowledged as a method to solve conflicts and to reach solutions which are more satisfying to all parties. In Denmark, for instance, a new law on patients complains has been implemented and now the healthcare providers have to offer a local dialogue with the complainer. In Luxemburg, a project for e new law on patients' rights is pending. One of its chapters concerns mediation as a specific field of healthcare.

In Slovenia, mediation in healthcare matters was codified by the Patient Rights Act in 2008 and the Rules on mediation on area of healthcare regulate it in more detail. The patient who considers that any of the rights from this act has been infringed is entitled to a hearing of the alleged violation, at first at the healthcare provider. If at this stage an agreement on the method of dispute resolution is not reached, the patient may file a request for treating the infringement of his right before the Commission of the Republic of Slovenia for protection of patients' rights. Irrespective of the options offered by the legislation, the mediation began to develop under the auspices of the Association of Health Institutions of Slovenia. The Association is aware that disputes are an integral part of working environments and greatly affect quality and wellbeing of both providers and users of healthcare services. Therefore, the Association acts towards introducing mediation as a verified good method for healthcare institutions environment. In the field of mediation the Association has undertaken a vision of establishing the Centre for communication and mediation in healthcare (hereinafter referred to as the Centre), that started operating in 2010. Within the frames of mediation, the Centre offers its members counseling, assistance and guidance in relation to the use of mediation for resolving disputes in healthcare sector.

In the UK, the House of Commons' Health Select Committee recently reported on the working of the NHS complaints system in England. The use of mediation was not specifically addressed; rather the emphasis was on securing speedy local resolution of the complaint. Mediation certainly forms part of a local NHS organization's portfolio of tools to achieve prompt and amicable local resolution, and as the focus is concentrated on the rising number of complaints about NHS services, the length of time taken to resolve these complaints and the costs involved, it is sensible to conclude that the benefits of mediation will be discussed more widely at national and a local level.

If we go back to the research, conducted in New York, we would discover that all the participants view mediation as fair and satisfying and responsive to their interests. The costs are decreased.

Bulgaria is not very active in mediation in healthcare. At the same time it could be very efficient way to resolve disputes, especially between patients and doctors/provider of healthcare and we can even discuss the mediation as a part of the patient care. The role of health mediator is considered as an intervention between patients from specific social groups and healthcare providers and public bodies. This model of health mediator was accepted in Bulgaria in 2001. The pilot project involved NGOs working with Roma society. The work of those mediators is connected more with health promotion and resolving specific problems of the vulnerable part of the society, and was not considered as a alternative dispute resolution method.

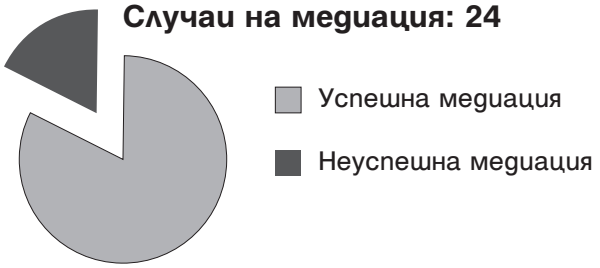
The Act of Mediation was issued in 2004, regulating the principles, procedures, requirements and settlement. In countries such as Mal-

ta, Finland, Sweden and Estonia This legislation generally aims to provide a ground for solution of both individual and collective labor disputes, whatever the sector or industry in which they occur be. In some cases, general legislation also addresses the use of mediation in civil matters. Special act, relating the mediation in healthcare is issued in countries like France, Belgium and Slovenia. In Estonia, disputes between trade unions and employers are resolved according to the Collective Labour Dispute Resolution Act ; disputes between employer and member of healthcare staff are resolved accordingt o the Individual Labour Dispute Resolution Act, whereas the Reconciliation Act regulates reconciliation in civil matters and by voluntary basis.The mediation process in Belgium, Denmark, France, Luxemburg, UK, Spain and Sweden is free of charge. In Bulgaria the mediation is free in some of the cases.

CONCLUSIONS:

1. The mediation is very useful method for alternative dispute resolution between patient and doctors/healthcare providers. During those procedures conflicts not only to be solved without going into an expensive and long trial, but to develop new relations between patients and doctors, based on trust.
2. Mediation helps to analyze the conflicts deeply and thoroughly, to "see" from different point of view, without exacerbation of the dispute.
3. We could recommend the hospitals to initiate more procedures based on mediation in cases of medical malpractice complaints.

Фиг. 1.
Дял на медиацията при спорове тип "лекарска грешка: 29 спора, 24 от тях преминали през медиация; Share of mediation in disputes in cases of medical errors: 29 disputes, 24 of them mediated



Фиг. 2.
Резултат от медиация: 24 общо преминали случая, 17 от тях приключили със споразумение; Results from mediation: 24 cases, 17 of them finalized with agreement

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Medication associated Gianotti – Crosti syndrome. Clinical case

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Асоцииран с медикаменти синдром на Gianotti – Crosti. Клиничен случай

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РЕЗЮМЕ

Синдромът на Gianotti-Crosti е рядко срещано характерно за детската възраст заболяване, чиято етиология се свързва преди всичко с инфекциозни агенти и клинично се манифестира с типичен по своята морфологична характеристика и локализация екзантем .

ABSTRACT

The Gianotti – Crosti syndrome is a rare disease mainly occuring in children. It's etiology is related to infectious agents and it is clinically manifested with a typical in it's localisation and characteristics exanthema.

В медицинската литература съобщения за различна от инфекциозната етиология на синдрома, особено при лица от други възрастови групи почти липсват.

Ето защо представеният от нас клиничен случай би предизвикал интереса на работещи в различни области клиницисти – алерголози, дерматолози, токсиколози, инфекционисти и други.

Ключови думи : синдром на Gianotti-Crosti, симетричен акрален екзантем, токсо-алергични реакции, медикаментозна алергия.

Data of etiology of the syndrome different than the infectious one, especially in people of other age groups is almost completely absent in medical literature. That is why the presented clinical case would attract the attention of clinical workers in different areas like allergologists, dermatologists, toxicologists, infectious diseases specialists etc.

Key words: Gianotti – Crosti syndrome, symmetric acral exanthema, toxoallergic reactions, medication allergy.

INTRODUCTION:

The disease was first described by Gianotti in 1955 and is named after its discoverers Ferdinando Gianotti and Agostino Crosti (1,2). The papuloerythematous dermatitis localised on the face and limbs, paracortical hyperplasia of lymph nodes and the common association of the disease with non – icterous form of acute viral hepatitis are reckoned to be the most typical. The morphology of the exanthema, described by the discoverers of the syndrome is characterised by papular or papulovesicular rash with or without itching (4). This syndrome is reckoned to affect children from 3 months to 15 years of age, it is most common to be manifested before the 4th year of the child (3,4,5). Later on this concept was changed. The first publicated cases of adults diagnosed with the syndrome date from 1975 – 1977 (6,7,8). However the etiology of the disease is still related mainly to viral or bacterial iinfection. The most common cause of the syndrome in the USA is reckoned to be the Ebstein – Barr virus. In specialised medical literature there occur reports of another etiology of the disease like vaccinations (10). But the onset of the disease is rarely connected to use of medications.

The diagnosis is based on a constellation of exclusion or inclusion criteria. Clinical criteria, morphology of the rash and its localization are key. The clinical manifestation and the characteristics of the exanthema in adults don't always correspond to the ones in children. Etiologic treatment is absent at the moment. The itchiness could be relieved by the use of antihistamines but most commonly the rash disappears by itself in 2 to 8 weeks.

MATERIALS AND METHODS:

Source of information is the official medical documentation of the patient – medical history of the disease, the results of the conducted medical tests and epicrisis.

A 56 year old male was hospitalised in the Occupational diseases and allergology department of the St. George University hospital in Plovdiv.

Medical history data: First the patient was referred to the Infectious diseases clinic by a general practicioner after which people close to him noticed he turned yellow. After seeing the infectionist he was admitted in a surgical unit with the diagnosis of mechanical jauntice. The patient didn't have any subjective complaints but a small spotted rash localised mainly on the abdomen was present. Treatment with H1 and H2 antagonists was conducted in the outpatient unit to treat the exanthema but the rash was not influenced by the medications. After exclusion of acute surgical abdomen and counselling with an allergologist the patient was hospitalised in the unit to be treated and diagnosed.

After taking a full medical history it turned out that the patient had been taking Aspirine C effervescent tablets and Fervex sachets sevral times a day over a long period of time (over 6 months) due to frequent colds. It is known that one effervescent tablet of Aspirine C contains 400 mg acetylsalycilic acid and one Fervex sachet for adults contains 500 mg Paracetamol (Acetaminophen).

Family history: no immuno-allergic diseases in the family. The patient didn't report alcohol abuse.

Physical exaination: good general appearance. Normal state of consciousness. Adequate. Afebrile. Subicterous sclera. Strongly itchy maculopapular urticarial rash on the face and the hairy part of the head, abdomen, back, upper and lower limbs, the rash was confluent on some parts (pictures 1 – 3).

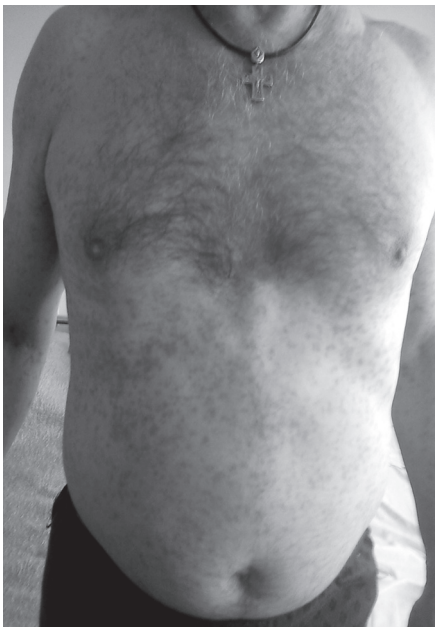
Peripheral lymph nodes could not be palpated. Pathologic changes of the respiratory and cardiovascular systems could not be objectified by the physical examination. The abdomen was over the level of the thorax, not tender on palpation. Palpable liver that was enlarged with 3 to 4 centimeters at the medioclavicular line, sharp edged and slightly tender on palpation. The spleen was not palpable. The muscolosceletal system was without pathologic changes.

The based on medical history, clinical manifestation, physical examination and test results working diagnosis was urticaria with acute onset, tight development and unknown etiology.

Systemic treatment with corticosteroids, antihistamines, H2 antagonist in proper doses was conducted. The result was reduction of the rash and tendency to fading of the vast erythematous areas, the itchiness was relieved.

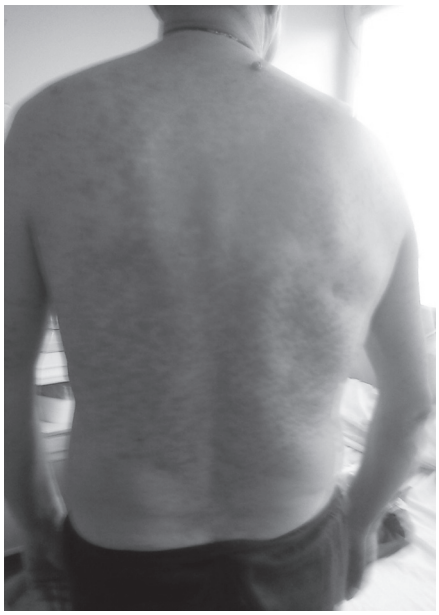
After counseling a gastroenterologist the patient was referred to and hospitalized in a gastroenterologic clinic so as to discover the etiology of the disease and for further treatment.

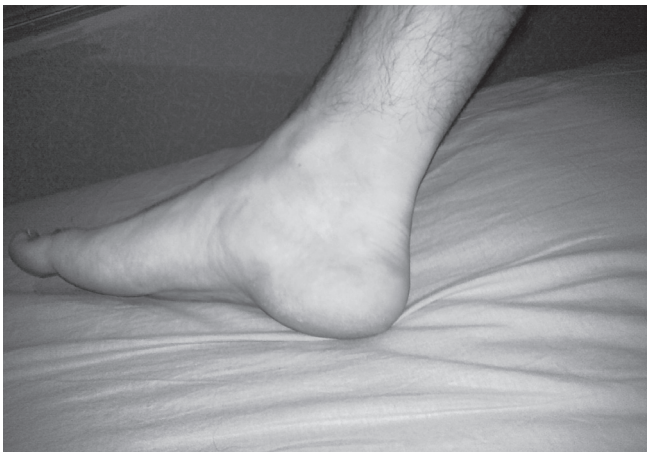
Photographic material objectifying the characteristics and localization of the rash in the patient:



Hematologic, biochemical and immunological tests

Hematology	Differential blood count	Biochemistry	Immunology
HGB – 149 g/L	Neut. – 49.6%	gluc – 6.5 mmol/l	HAV IgM /–/ omp.
RBC – 4.74 T/L	Lymph. – 22.4%	t.prot – 69 g/l	HBsAg /–/ omp.
HCT – 0.466	Eos. – 17.6 %	alb – 39 g/l	HBc IgM /–/ omp.
MCH – 31.5	Mono – 7.9%	t.bill – 80.1 mkmol/l	Anti – HCV /–/ omp.
		d.bill–38.20 mkmol/l	
MCV – 83.5	Baso – 0.4%	AST – 137 U/l	
WBC – 9.47 G/L		ALT – 521 U/l	
		GGT – 509 U/l	
MCHC – 320		urea – 5.0 mmol/l	
PLT – 260 G/L		crea – 96 mkmol/l	
ESR – 6 mm		UR AC – 242 mkmol/l	
RDW – 12.4%		K – 4.5 mmol/l	
MPV – 10.7 fL		Na – 137 mmol/l	
		Cl – 101 mmol/ l	





DISCUSSION:

The Gianotti – Crosti syndrome is a disease with mainly infectious etiology and typical acral localization of the papular exanthema. The rash usually occurs in childhood but however there are few published cases of adult patients. Although the etiology is unknown it is rarely discussed to be different than infection.

The main factor that triggered the onset of the syndrome in the presented here clinical case was the usage of the previously mentioned medications. The absolute exclusion of concomitant or previous infectious genesis is impossible because of the broad spectrum of infectious agents that are thought to cause the disease – Ebstein –Barr virus, viral hepatitis (especially HBV), cytomegalovirus, coxsackie virus, ECHO viruses, bacterial infections. Another reason is the big number of serologic and immunologic test that must be conducted to exclude infection. Viral hepatitis that is thought to be the most often cause of the syndrome is excluded in the presented case (9, 10).

Regardless of the age of the patient and the numerous reports of infectious etiology in literature the clinical manifestation with the usual localisation and morphology of the exanthema as well as the lack of apparent influence by the antiallergic medications give us a reason to consider the presented case to be the Gianotti – Crosti syndrome.

In that matter the taken by the patient medications (Aspirine and Pracetamol) over a long period of time are a basis and a factor contributing to the development of the syndrome. It is known that the acetylsalicylic acid causes type I allergic reactions as well as pseudoallergy. More interesting and poorly studied are the mechanisms of paracetamol causing allergic reactions. Presumably glutathione reductase deficiency has a leading role. Such a deficiency is observed when the medication is used in toxic doses or due to terapeuthic overdose which is present in the presented case. Enzyme deficiency or hypermedication could release a toxoallergic reaction similar to the cytotoxic and immunocomplex immune reactions that include activation of the complement by non- immune mechanisms (11).

The concomitant hepatitis in this case is most probably caused by the long-term use of paracetamol even though it was in terapeuthic doses. This is related to the hepatotoxicity of the medication that is known to develop with the use of doses of 10 to 15 g. for adults. In such cases a glutathione deficiency develops, glutathione deactivates the highly reactive and toxic metabolite N-acetyl-p-benzoquinineimine. A result of all this is the increased production and accumulation of free radicals – a process that is one of the reasons for the development of toxic medicamentous hepatitis.

Apart from the mentioned above facts, we reckon that the information given by the patient after dehospitalization from the gastroenterologic clinic is a reason for our terapeuthic approach. The patient reported that after the conduction of different terapeuthic procedures he was discharged with the diagnosis of toxic hepatitis and favourable outcome. The exanthema reached a point of almost complete involution.

CONCLUSIONS:

1. The presented case shows that the Gianotti – Crosti syndrome could be released by the use of certain medications.
2. The pathophysiologic factors and pathogenetic mechanisms through which the used by a patient medications could cause the disease are well described in specialized medical literature.
3. The period over which the medications were used is a predispositon to terapeuthic overdosage and disturbance of the liver and kidney functions is of importance in the presented case. Those organs are responsible for the biotransformation, detoxication and ellimination of the taken medications.
4. The thorough knowledge of pharmacokinetics and toxokinetics of the medications as well as the pathogenetic mechanisms of the toxoallergic reactions are necessary for the diagnosis and adequate treatment of such cases.

*The photographic material is published with the written consent of the patient. His personal data is protected by bulgarian law and normative legislation of the University hospital.

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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;

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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.

Илюстрациите към текста (фигури, графики, диаграми, схеми и др. черно-бели копия с необходимия добър контраст и качество) се представят на отделни листове (без обяснителен текст), в оригинал и две копия за всяка от тях. Текстът към фигурите със съответната им номерация (на български и на английски език) се отбелязва вътре в основното текстуално тяло на статията под съответния номер на мястото, където трябва да се разположи при предпечатната подготовка.Таблиците се представят с готово написани обяснителни текстове на български и на английски, които саразположени над тях; номерацията им е отделна (също с арабски цифри).

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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 съкращшениетоет 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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При това редакторът се съобразява със законови ограничения, свързани с въздържане от дискредитиране, нарушаване на авторски права или плагиатство.

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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.

Obligations of the reviewers

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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Unpublished materials disclosed in a submitted manuscript must not be used in an editor‘s own research without the express written consent of the author.

All authors should disclose in their manuscript any financial or other substantive conflict of interest that might be construed to influence the results or interpretation of their manuscript. All sources of financial support for the project should be disclosed.

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Всички ръкописи, получени за рецензиране следва да се считат за поверителни материали и тяхното съдържание на следва да се разкрива пред никого, освен с разрешението на редактора.

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

Prof. Dr Philip Kumanov
1431 Sofia, Zdrave str. 2, University Hospital for Endicrinology

And the next electronic addresses:

Prof. Dr Philip Kumanov, Editor-in-chief:
phkumanov@lycos.com

With copy for the scientific secretary –

Prof. Drozdstoj Stoyanov:
stojanovpisevski@gmail.com

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

КОНФЛИКТ НА ИНТЕРЕСИ

Непубликувани материали не могат да бъдат използвани в собствени изследвания на редактора без изричното писмено съгласие на авторите.

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След положителна рецензия и одобрение на редколегията, авторите на статията дължат заплащане в размер на 10 лв. за всяка стандартна машинописна страница, с оглед на покриване разноските по ангийска езикова редкация на текста и коректури

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1431 София, ул. Здраве 2, УСБАЛЕ

Или на следния електронен адрес:

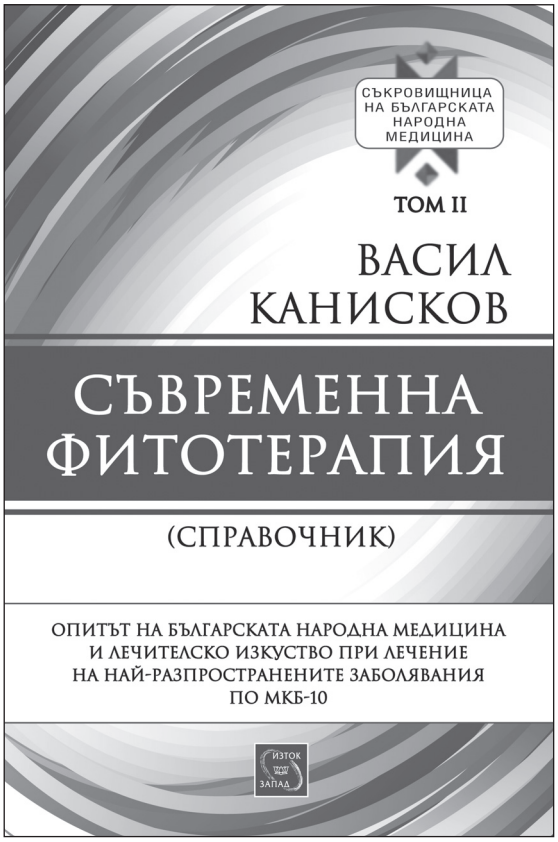
Проф. Д-р Филип Куманов, главен редактор:
phkumanov@lycos.com

С копие до научния секретар –

Проф. д-р Дроздстой Стоянов:
stojanovpisevski@gmail.com

Търсете

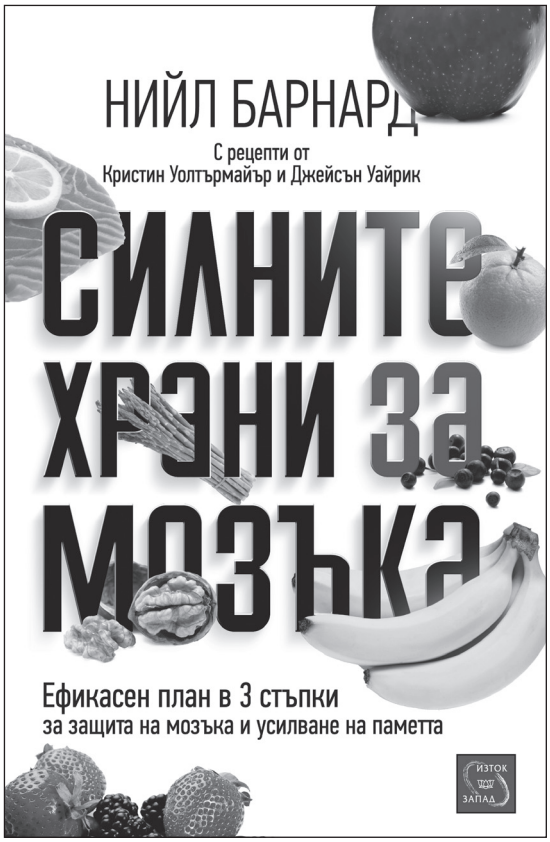

д-р ПЕТЯ АРНАУДОВА
МАЛКА
МЕДИЦИНСКА
ЕНЦИКЛОПЕДИЯ
ЗА ВСЕКИ
ИЗТОК ЗАПАД


СЪКРОВИЩНИЦА НА БЪЛГАРСКАТА НАРОДНА МЕДИЦИНА
ТОМ II
ВАСИЛ КАНИСКОВ
СЪВРЕМЕННА ФИТОТЕРАПИЯ
(СПРАВОЧНИК)
ОПИТЪТ НА БЪЛГАРСКАТА НАРОДНА МЕДИЦИНА
И ЛЕЧИТЕЛСКО ИЗКУСТВО ПРИ ЛЕЧЕНИЕ
НА НАЙ-РАЗПРОСТРАНЕНИТЕ ЗАБОЛЯВАНИЯ
ПО МКБ-10
ИЗТОК ЗАПАД


КРИС УИЛЯМС
БАРИ РАЙТ
КАК ДА ЖИВЕЕМ С АУТИЗЪМ И СИНДРОМ НА АСПЕРГЕР
ПРАКТИЧЕСКИ СТРАТЕГИИ ЗА РОДИТЕЛИ И СПЕЦИАЛИСТИ
ДЕТЕТО ЗДРАВЕТО СВЕТА
ИЗТОК ЗАПАД

Търсете


СИДХАРТ МУКХЪРДЖИ
ИМПЕРАТОРЪТ НА ВСИЧКИ БОЛЕСТИ
НОСИТЕЛ на наградата ПУЛИЦЪР
БИОГРАФИЯ НА РАКА
ИЗТОК ЗАПАД


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


БИБЛИОТЕКА
Красив ум
АНТОНИО ДАМАЗИО
ИЗГРАЖДАНЕ НА СЪЗНАТЕЛНИЯ МОЗЪК
ИЗТОК ЗАПАД

Търсете


МЕЛАНИ
ТЪРНСТРОМ
ХРОНИКИ
НА
БОЛКАТА
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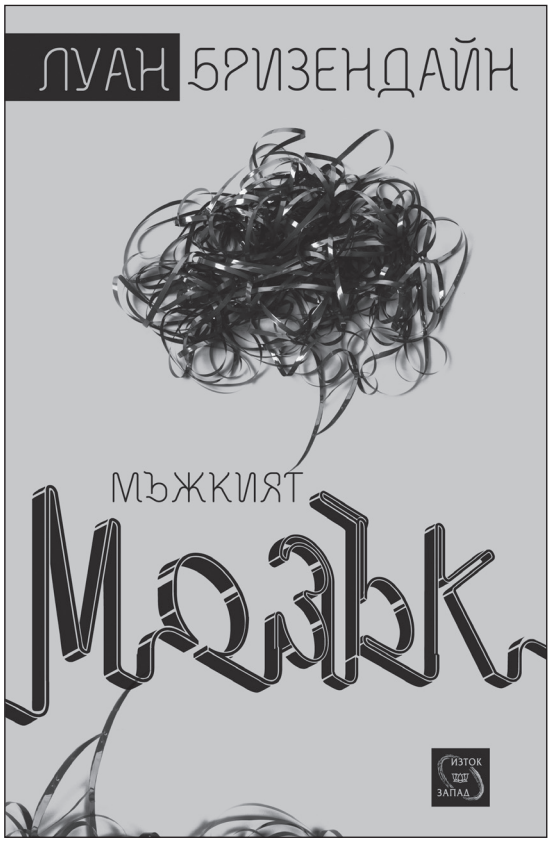
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БИБЛИОТЕКА здраве
КАК АЛТЕРНАТИВНАТА МЕДИЦИНА НИ БАЛАМОСВА
РОУЗ ШАПИРО
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