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Ранно лимфоцитно възстановяване като независим предиктор за изход от алогенна стволово-клетъчна трансплантация при пациенти със злокачествени хематологични заболявания

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Early lymphocyte recovery as an independent predictor of allogeneic stem cell transplantation outcome in patients with hematological malignancies

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РЕЗЮМЕ:

Алогенната стволово-клетъчна трансплантация (АСКТ) е терапевтична процедура, която има потенциала да подобри резултатите при лечението на редица злокачествени и доброкачествени хематологични заболявания. Въпреки значимият напредък в цялостното реализиране на АСКТ, значим проблем остават развитието на остра или хронична реакция на присадката към рецепиента, инфекциозните усложнения и риска от рецидив на заболяването. Медицината продължава да бъде в търсене и моделиране на рисковите фактори пряко свързани с подобряване на изхода от АСКТ. Решаващо значение за подобряване на общата преживяемост и намаляване на смъртността без рецидив след АСКТ има навременната и функционално адекватна имунната реконституция.

ABSTRACT:

Allogeneic stem cell transplantation (ASCT) is a therapeutic procedure that has the potential to improve outcomes in the treatment of a variety of malignant and benign hematological diseases. Despite the significant progress in the overall implementation of ASCT, a significant problem remains the development of an acute or chronic graft versus host disease, infections, and the risk of disease recurrence. Medicine continues searching and modeling of risk factors directly related to improving the outcome of ASCT. Timely and functionally adequate immune reconstitution is crucial to improve overall survival and reduce non-relapse mortality after ASCT. A surrogate marker for this is the restoration of the donor lymphoid system, represented by the lymphocytes circulating in the peripheral blood. Early lymphocyte recovery (ELR) is a proven

Сурогатен маркер за това е възстановяване на донорната лимфоидна система, представена от циркулиращите в периферната кръв лимфоцити. Ранното лимфоцитно възстановяване (РЛВ) е доказан, биологично значим предиктор за изхода от трансплантацията. Настоящият обзор представя преглед на известните в литературата данни, проблеми и клинични проучвания, изучаващи мястото и значимостта на РЛВ като прогностичен фактор за изхода от АСКТ.

Ключови думи: алогенна стволовоклетъчна трансплантация, хематологични заболявания, имунна реконституция, ранно лимфоцитно възстановяване.

biologically significant predictor of transplant outcome. This review provides an overview of the data, problems and clinical studies known in the literature examining the place and importance of ELR as a prognostic factor for ASCT outcome.

Key words: allogeneic stem cell transplantation, hematological diseases, immune reconstitution, early lymphocyte recovery.

Introduction

Allogeneic stem cell transplantation is a potentially curative procedure which can improve outcomes in a wide variety of diseases, including leukemia, lymphoma, myeloproliferative disorders, myelodysplasia, bone marrow failure syndromes, congenital immunodeficiencies, enzyme deficiencies, and hemoglobinopathies. Unfortunately, it's still associated with significant morbidity and mortality. Relapse and nonrelapse mortality (NRM) remain to be the major reasons of treatment failure. The goal of ASCT is a lifelong engraftment of the administered cells, resulting in some or all the recipient's lymphohematopoietic system being derived from the hematopoietic stem cell graft [1]. The antileukemic effect of ASCT is dependent on two components: (1) the conditioning chemotherapy contributing to tumor reduction by killing off chemosensitive cells and (2) the strong adoptive graft versus leukemia (GVL) response mediated by the immunocompetent cells in the stem cell graft, which eliminates minimal residual disease resulting in decreased rate of leukemia relapse. The importance of the GVL effect has been known since its first description by the Seattle group in the 1970s and has been highlighted by the success of nonmyeloablative allogeneic transplants [2,3]. It's evident that GVL is associated with acute and chronic graft versus host disease (GVHD). However, GVL effect is not entirely dependent on GVHD. The effector mechanism of GVL and GVHD are complex and incompletely understood. It's known that GVL effect happens very early post-ASCT [4]. This period is the most critical as the disease burden is lowest at this time and chances of eliminating it completely through immune mechanism are highest. During the early post-transplantation period most of the peripheral blood mononuclear cells are NK cells that are capable of mediating cytotoxicity without prior sensitization and may be responsible for most of early antileukemic activity of allograft but also to reduce GVHD [5,6]. Unlike recovery of other hematopoietic lineages, which typically occurs over the course of weeks after ASCT, and except for NK cells, lymphocyte recovery is a prolonged process. Reestablishment of immunocompetence requires at least several months, and some patients continue to show immune deficits for several years after ASCT. In general, NK cells are the first lymphocyte subset to recover, followed by CD8 T cells, which often reach normal levels within 2-8 months. Subsequently, B cells and ultimately CD4 T cells recover [8-11]. It's still unknown why donor lymphocytes vary in their recovery in the leukemic host post-infusion. It is very likely to be multifactorial process. Possibly there are factors like patient age, in vivo or ex vivo T cell depletion and donor type that may affect immune reconstitution early after ASCT [7,8], however graft source is considered the most important one [9].

There is accumulating data indicating that lymphocyte recovery is a universal factor

associated with outcomes of hematologic malignancies after chemotherapy, autologous BM transplantation, and ASCT. Diverse studies have been designed to investigate the influence of immune reconstitution and lymphocyte recovery on ASCT outcomes. They have suggested that an earlier recovery of lymphocytes after ASCT is strongly associated with a lower relapse rate (RR) and NRM in patients with hematologic malignancies [10-13]. It's well-known that immune reconstitution plays a pivotal role in the protection against fatal opportunistic infections, which are directly related directly to treatment related mortality (TRM). Lymphocytopenia has already been accepted as the main risk factor for the development of cytomegalovirus disease [14-16]. The early ALC may be regarded as an indicator that defines groups at high risk for NRM or relapse after ASCT [17]. However, most of the studies included cohorts with few patients, proposed a wide range of arbitrary time points and thresholds with conflicting findings on relapse and survival, and incorporated stem cells from different graft sources.

Review of published clinical trials concerning the theme.

Powels et al performed the first study on lymphocyte recovery, including 201 AML patients who received allogeneic bone marrow transplantation after myeloablative (MA) conditioning from matched related donor (MRD). The probability of relapse was calculated as a function of the absolute lymphocyte count (10^9/L) on days 27 to 30 posttransplant (<0.1 v >/=0.1, <0.2 v >/=0.2, and <0.3 v >/=0.3). In each of these 12 comparisons, the probability of relapse was higher for the group with the lower lymphocyte count. Because the difference was most significant (P = .004) for an absolute lymphocyte count of <0.2 on day 29 (3-year relapse probability, 42%) versus >/= 0.2 (16%), this variable was included in a Cox model to determine factors independently affecting relapse. Multivariate analysis showed that conditioning regimens other than melphalan-TBI, a low lymphocyte count on day 29, French American-British (FAB) subtypes M4-7, and a nucleated cell dose of > 2.42 x 10(8)/kg was associated with a higher risk of relapse. They concluded that slow lymphocyte recovery after allogeneic BMT, to < 0.2 x 10^9/L on day 29, appears to be associated with a higher risk of relapse in patients with AML. This group of patients may benefit from posttransplant immune manipulations such as abbreviated GVHD prophylaxis, donor cell infusion (DLI) or cytokine administration to enhance GVL to reduce relapse [18].

Rigoni at al have a retrospective study on early lymphocyte recovery after ASCT in 100 patient with acute leukemia and myeolodysplastic syndrome after myeloablative and nonablative conditioning with different source of stem cells . Twelve patients received peripheral blood stem cells, 3 units of umbilical cord blood, 85 patients received bone marrow as stem cell source. Excluding criteria were refractory disease at transplantation, thymoglobulin or alemtuzumab administration as part of the conditioning regimen or steroid prophylaxis for acute GVHD.They analyzed the role of absolute lymphocyte count (ALC) at days 21 and 30 after ASCT in predicting the transplant outcome regarding to risk of opportunistic infections, death, and recurrence of the original disease; the number of lymphocytes below or above 300 103/mL was correlated with OS, DFS, RR, and TRM at 5 years.The main result of the study was to demonstrate an increased mortality (TRM and NRM) of 2.2-fold among patients with lymphocytes <300 10^3/mL at D+30 compared with patients with values of >300 10^3/mL. With regard to TRM, to have ALC of <300 10^3/mL at D+30 was associated with a risk 3.76 times greater compared with those with values of >300 10^3/mL. Interestingly, the group of patients with lymphocytes >300 10^3/mL exhibited a lesser incidence of acute GHVD compared with the group below this threshold. However, no difference was noted in the incidence of chronic GVHD. Over a medium follow-up of 20 months OS, DFS, and NRM were similar between the groups.They concluded that patients delayed lymphocyte recovery after ASCT was a predictor of early death post-ASCT[19].

Kim et al. conducted the largest cohort study to date assessing the impact of ALC early after ASCT including 1109 adult patients who underwent a first allogeneic transplantation between 2003 and 2009. The median age

was 51 years (range, 18 to 74) with 52% undergoing reduced-intensity conditioning and 48% undergoing myeloablative conditioning with T celle replete peripheral blood stem cells (93.7%) or marrow (6.4%) grafts, haplo and UCB were excluded. The median follow-up time was 6 years. To determine the threshold value of ALC for survival, the entire cohort was randomly split into a training set and a validation set in a 1:1 ratio, and then a restricted cubic spline smoothing method was applied to obtain relative hazard estimates of the relationship between ALC at 1 month and log hazard of progression-free survival (PFS).Based on this large cohort, they have identified an ALC threshold value of .2 109 cells/L as the most predictive of outcomes across different diseases. For patients with low ALC at 1, 2, or 3 months after HSCT, the overall survival (OS) (P .0001) and PFS (P .0002) were significantly lower and nonrelapse mortality (NRM) (P .002) was significantly higher compared with patients with ALC > .2 10^9 cells/L at each time point. The 5-year OS for patients with low ALC was 28% versus 46% for patients with ALC > .2 10^9 cells/L, P < .0001; the 5-year PFS was 21% versus 39%, P < .0001, respectively and 5-year NRM was 40% versus 18%, P < .0001. This result remained consistent when other prognostic factors, including occurrence of grade II to IV acute graft-versus host disease (GVHD), were adjusted for in multivariable Cox models stratified by conditioning intensity: hazard ratio (HR) for OS: 1.52; P .0001; for PFS: 1.42; P ¼ .0008; and for NRM: 2.4 P < .0001 for patients with low ALC. Low ALC was not significantly associated with relapse (HR, 1.01; P ¼ .92) in the multivariable model. The effect of low ALC is stronger in MAC HSCT than in RIC. The reasons are unclear, but it is possible that the ALC early after MAC HSCT is more useful because it reflects mainly donor lymphocyte reconstitution, whereas in RIC HSCT, the ALC in the first 3 months very likely reflect a mixed chimera of both donor and host lymphocyte populations. ALC at 1, 2, and 3 months after HSCT may have significant prognostic implications. Low ALC early after HSCT is an independent risk factor for increased NRM and poor survival independent of grade II to IV acute GVHD. Univariable and multivariable analyses were performed to assess baseline factors that are associated with low ALC at1, 2, or 3 months after HSCT. In univariable analysis, significant risk factors for developing low ALC were mismatched HLA type (P ¼ .001), bone marrow graft source (P ¼ .01), nonsirolimus-based prophylaxis (P ¼ .009), low CD34 cells infused (P ¼ .005 for 5-unit decrease), and ATG use as part of conditioning (P ¼ .01) (Table 1). However, only mismatched HLA type (odds ratio [OR], 3.09; 95% confidence interval [CI],1.78 to 5.35; P <.0001), low CD34 cells infused (OR, 1.34 for a 5-unit decrease; 95% CI, 1.11 to 1.63; P ¼ .003), and ATG use (OR, 3.22; 95% CI, 1.48 to 7.01; P ¼ .003) were significant in multivariable analysis. These findings suggest that ALC could potentially be used as a readily available metric for identifying patients within 100 days of HSCT who are at increased risk for NRM, who could thus be observed more closely for infections, GVHD, and other transplantation complications [20].

Damlaj et al performed a retrospective analyses 72 patients ≥ 14 years of age with AML or ALL who underwent ASCT included patients receiving myeloablative (MAC) or reduced intensity conditioning (RIC) from related or unrelated donors where exclusion criteria were for patients who received a bone marrow graft or cord blood stem cell source, second transplant and those who underwent in vivo or in vitro T-cell depletion.The optimal ALC threshold and timeline was analyzed using receiver operator characteristics (ROC) and area under the curve (AUC). They report that ALC > 0.3 × 10^8/kg on day +14 post ASCT for acute leukemia is an independent factor predicting decreased CIR at multivariable analysis. They also observed a trend towards improved PFS and OS; however this did not meet statistical significance. NRM was not significant between both cohorts, however both the incidence of aGVHD and cGVHD related deaths were more frequent in the ELR (early lymphocyte recovery) group. Incidence of cGVHD related deaths was 37.5% (3/8) in the ELR group compared to 12.5% (3/24) in the DLR (delayed lymphocyte recovery) group. This perhaps explains the lack of statistical significance seen for PFS and OS. They observed that infused allo-graft cellular con-

tent predicts ASCT reconstitution and the higher T-cell and absolute lymphocyte content was significantly associated with ELR [21].

Other studies involved only patients with bone marrow graft source.

Kumar et al performed a retrospective review of 43 patients with ALL who underwent matched related allogeneic BMT in order to examine whether the rate of lymphocyte recovery after transplantation had any prognostic value in ALL. They found that patients with an ALC of 175x 10^6 /l or less on day 21 were more likely to relapse than those with ALC greater than 175x 10^6 /l (relative risk, 4; 95% confidence interval, 1.5–11.2), showing a significantly lower relapse-free survival than those with faster recovery (P ¼ 0.0028). Validation of this phenomenon for ALL is important especially because previous studies have indicated that GVHD has a less protective effect on relapse in patients with ALL than in those with acute myelogenous leukemia or chronic myelogenous leukemia. Another study on 87 AML patients who received allogeneic BMT, excluding haplos and syngeneics donors, finds that patients with absolute lymphocyte count (ALC) <150 × 106/l by day +30 had a 3.5-fold higher risk of relapse (P = 0.0088) and a lower overall survival (P = 0.0079) than patients with a higher ALC. Patients receiving prednisone had a significantly lower ALC at day +30 than those who did not receive prednisone (289 vs549 × 106/l, P = 0.002). They conclude that a slow lymphocyte recovery after allogeneic BMT for AML is strongly predictive of subsequent relapse and that the type of GVHD prophylaxis should be considered when analyzing [22,23].

Bayrakyar et al performed another study searching for the optimal threshold and time of absolute lymphocyte assessment for outcome prediction after BMT. The study involved 518 patients who underwent BMT for acute leukemia or myelodysplastic syndrome between 1999 and 2010 were divided into training and test sets to assess the prognostic values of ALC on days 30, 60, 90, 120, 180, as well as, the first post-transplant day on which a patient achieved ALC of 100, 200, 300, 400, 500, and 1000/μL.In the whole patient cohort, multivariable analyses demonstrated significantly better OS, RFS, NRM, and lower incidence of graft-versus-host disease among patients with ALC >300/μL on day 60, both including and excluding patients who had developed graft-versus-host disease prior to day 60. Among the patient-, disease-, and transplant-related factors assessed, only busulfan-based conditioning was significantly associated with higher ALC counts on day 60 in both cohorts [24].

Confirmations are also found in the literature for consistent association between lymphocyte recovery and transplant outcome after cord blood transplantation (CBT).

Amandine Le Bourgeois and her team managed a single-center retrospective study aimed to report the impact of early hematopoietic and immune recoveries after a standard total body irradiation, cyclophosphamide, and fludarabine (TCF) reduced-intensity conditioning (RIC) regimen for double umbilical cord blood (dUCB) ASCT in adults. They analyzed 47 consecutive patients older than 17 years who engrafted after a dUCB TCF allo-SCT performed between January 2006 and April 2013 in our department. Median times for neutrophil and platelet recoveries were 17 (range, 6 to 59) and 37 days (range, 0 to 164), respectively. The 3-year overall (OS) and disease-free survivals, relapse incidence, and nonrelapse mortality were 65.7%, 57.2%, 27.1%, and 19%, respectively. In multivariate analysis, higher day +30 monocyte (≥615/mm3; hazard ratio [HR], .04; 95% confidence interval [CI], .004 to .36; P < .01) and day +42 lymphocyte (≥395/mm3; HR, .16; 95% CI, .03 to .78; P = .02) counts were independently associated with better OS. These results suggest that early higher hematopoietic and immune recovery is predictive of survival after dUCB TCF RIC ASCT in adults. Factors other than granulocyte colony–stimulating factor, which was used in all cases, favoring expansion of monocytes or lymphocytes, should be tested in the future as part of the UCB transplantation procedure [25].

Sara K Tedeschi and collegeus reviewed the records of 40 consecutive CBT patients to determine the impact of lymphocyte recovery on transplant outcome. The majority of pati-

ents (83%) received CBT for hematologic malignancies. Patients with ALC ≥150/μL at 30 days post-CBT had decreased non-relapse mortality (NRM) (P = 0.011) and improved survival (P = 0.013) compared with ALC <150/μL. Patients with ALC <100/μL at 30 days post-CBT had a significantly higher rate of graft failure than those with ALC ≥100/μL (four of 10 versus one of 29; P = 0.011). ALC was positively correlated with the nucleated cell dose and inversely correlated with the patient's age. There was no relationship between disease risk, type of conditioning regimen, anti-thymocyte globulin and number of cord units on ALC recovery. The results indicate that ALC 30 days post-CBT is a surrogate for engraftment, and that low ALC (<150/μL) identifies an 'at-risk' population of patients after CBT. Studies are needed to determine ways to increase ALC cell numbers post-CBT, including ex vivo-expanded natural killer cells using adoptive immunotherapy, which might improve outcome after CBT [27].

There is also data on the importance of lymphocyte recovery for transplant outcomes restricted to AML patients.

Le Blank and colleagues studied the relationship between LC30 and outcome in 102 ASCT patients with MUD after MAC for myelogenous leukemia between 1996-2009 year. LC30 was low (\0.2 109 /L) in 18 patients, intermediate (0.2-1.0 109 L) in 67, and high (.1.0 109 /L) in 17 patients. In multivariate analysis, independent factors associated with high relapse-free survival (RFS) were high LC30, high CD34 cell dose, and absence of acute graft-versus-host disease (aGVHD) grades II-IV. When analyzed as a continuous variable in multivariate analysis, a higher LC30 was associated with a lower transplant-related mortality (TRM; relative hazard [RH] 5 0.87, P\.05), higher relapse-free survival (RH 5 3.42, P 5.036), and improved survival (RH 5 4.53, P 5.016, excluding GVHD). In patients with high, intermediate, and low LC30, overall survival (OS) was 91% versus 60%, versus 36% (P 5.02 and .001, respectively). This significant relationship was maintained in patients who did not develop GVHD by day 30. Significant risk factors to develop low LC30 was chronic myelogenous leukemia (CML; hazard ratio [HR] 0.73, P 5.001), prophylaxis with granulocyte colony-stimulating factor (G-CSF; HR 0.81, P 5.02) and aGVHD (HR 0.84, P 5.05). These results indicate that LC30 is an independent prognostic factor for transplant outcome in matched unrelated ASCT for myelogenous malignancies [28].

Michelis et al also evaluated the impact of lymphocyte recovery at 28 d post-ASCT only in AML patients, but using only peripheral blood stem cells as graft. 191 patients were divided into those with absolute lymphocyte count (ALC) ≥0.5 9 109 /L (n = 111, 58%; high ALC group) and those with ALC <0.5 9 109 /L (n = 80, 42%; low ALC group), at day 28 post-transplant. The cut off value was chosen arbitrarly, the time point was based on the mediana number of days to achieve ALC500 at day 28 (48%).With a median follow-up of 49 months, overall survival (OS) was signifificantly improved in the high ALC group (59% at 3 yr) vs. patients with low ALC (40% at 3 yr, P = 0.03). Cumulative incidence of relapse (CIR) was signifificantly lower in the high ALC group (16% at 3 yr) vs. low ALC group (36% at 3 yr, P = 0.001). Multivariable analysis for CIR demonstrated high ALC group as an independent factor decreasing relapse risk (P = 0.03, HR = 0.49, 95% CI = 0.26–0.92). Multivariable analysis for OS and non-relapse mortality did not demonstrate ALC ≥0.5 9 109 /L at 28 d post-transplant to be predictive. They conclude that lymphocyte recovery with ALC ≥0.5 9 109 /L at day 28 post-transplant is associated with less relapse in AML patients undergoing allogeneic peripheral blood ASCT, but without survival benefifit [29].

It is important to be evaluated the role of graft manipulation on lymphocyte recovery and transplant outcomes. To further explore the relationship between lymphocyte recovery and outcome in patients receiving T cell-depletion, Savini et al analyzed lymphocyte counts and other engraftment parameters in 157 patients with leukemia (48 acute myelogenous leukemia, 80 chronic myelogenous leukemia, and 29 acute lymphoblastic leukemia [ALL]) receiving T cell-depleted myeloablative ASCT from an HLA-identical sibling. In multivariate analysis the day 30 absolute lymphocyte count (LC30) above the median of 450/L was associated with improved survival

(71% 5% versus 38% 6%, P < .0001), less relapse (21% 5% versus 44% 7%, P .009), less nonrelapse mortality (NRM; 9 3 versus 36% 6%, P < .0001) and less acute graft-versus-host disease (aGVHD) (34% 5% versus 51% 6%, P .025). The beneficial effect of a higher LC30 influenced outcome in patients with both standard and high-risk disease but did not affect survival and relapse in ALL. We found that a higher LC30 correlated with higher lymphocyte counts at all time points between 30 and 90 days post-SCT and also with more rapid neutrophil and platelet engraftment. These results indicate that LC30 is a surrogate for robust engraftment and identifies an „at-risk" population of patients after T cell-depleted ASCT [30].

There are 2 studies which evaluate the relationship between lymphocyte recovery and long-term outcome by using the ALC on day 100, because it is not influenced by early events after transplant. This could be a novel time point that would provide information to follow patients without early events after transplant.

Yamato et al have explored the significance of lymphocyte recovery on day 100 after ASCT in patients with AML/ALL/MDS who underwent MA or RIC with all sources of stem cells from MRD or MUD. An absolute lymphocyte count 500/L was defined as lymphocytopenia. They found a signifcant relationship between lymphocytopenia and advanced disease at ASCT or corticosteroid administration within 100 days. Lymphocytopenia on day 100 (hazard ratio [HR]: 2.4; 95% confidence interval [CI]: 1.3 – 4.5; p 0.006) and advanced disease (HR: 2.2; 95% CI: 1.3 – 3.9; p 0.005) were prognostic factors for overall survival by multivariate analysis. Advanced disease was signifi cantly associated with relapse (HR: 2.8; 95% CI: 1.5 – 5.4; p 0.002), while lymphocytopenia was an independent predictor of non-relapse mortality (HR: 2.8; 95% CI: 1.1 – 6.8; p 0.027). These results suggest that lymphocyte recovery on day 100 may be an important predictor of late complications in patients receiving ASCT for hematologic malignancies [31].

On the other hand, DeCook and colleagues looked for the impact of day 100 lymphocyte and monocyte recovery on the outcomes of ASCT in patients with hematologic malignancies only after RIC conditioning. They hypothesized that lymphocyte and monocyte recovery would have a similar impact on survival in the reduced intensity setting. To test this hypothesis, they analyzed clinical data from 118 consecutive fludarabine/melphalan-conditioned patients by correlating peripheral blood absolute lymphocyte counts and monocyte counts (ALC and AMC, respectively) at days +15, +30, +60 and +100 with the outcomes. Multivariate analysis revealed that day +100 AMC (risk ratio (RR) 0.22, 95% confifidence interval (CI) 0.07–0.73, P ¼ 0.01) and mild chronic GVHD (RR 0.09, 95% CI 0.005–0.43, P ¼ 0.008) were independently associated with survival. To explore whether the patterns of lymphocyte and monocyte recovery had a prognostic value, was performed unsupervised hierarchical clustering on the studied hematopoietic parameters and identifified three patient clusters, A–C. Patient clusters A and B both had improved OS compared with cluster C (77.8 months vs not reached vs 22.3 months, respectively, P<0.001). No patient in cluster C had a day +100 AMC >300. Both severe acute GVHD and relapse occurred more frequently in cluster C. These data suggest that patients with low AMC by day +100 post fludarabine/melphalan conditioned ASCT may be at risk for poor outcomes [32].

There are several studies exploring the role of lymphocyte recovery on ASCT outcomes in pediatric patients and conforming that ELR is a statistically significant predictor for better survival after transplantation.

Ishaqi et al have a large single center study of 136 pediatric patients with ALL receiving allogeneic ASCT between 1994 and 2005 at the Hospital for Sick Children, Toronto, Canada, found that delayed lymphocyte recovery as reflected by an ALC of 0.3 x 10^9 per liter at days 21 and 30 post-ASCT is associated with a significant increase in relapse. Patients with an absolute lymphocyte count (ALC) <0.3 x 10^9 per liter at day 21 (n ¼ 104) had more than five times risk of relapse compared to those with ALC >0.3x 10^9 per

liter (n ¼ 32) (hazard ratio (HR) 5.3; P ¼ 0.002) and had inferior 3-year event-free survival, (EFS), 0.42 (95% confidence interval (CI) 0.32, 0.51) compared to 0.66 (95% CI 0.48, 0.82; P ¼ 0.02). Similarly, patients with an ALC <0.3x 10^9 per liter (n ¼ 48) at day 30 were more than twice as likely to relapse compared to those with an ALC >0.3 10^9 per liter (n ¼ 88) (HR 2.2; P ¼ 0.01) and had an inferior 3-year EFS, 0.30 (95% CI 0.18, 0.45) compared to 0.57 (95% CI 0.46, 0.68; P ¼ 0.0001). Interestingly, increasing ALC at days 21 and 30 was not associated with increased incidence of acute or chronic GVHD or transplant-related mortality (TRM) [33].

Afzal et al published data on 136 children who received ASCT for ALL and showed that early lymphocyte recovery is a powerful indicator for survival by GVL effect without increase in GVHD. Lately they extended the cohort to 207 consecutive children with acute leukemia by adding 71 children with AML who received 75 HSCT's between 1994 and 2005. All patients received myeloablative regimens. Stem cell sources were: matched sibling donor in 40 patients, mismatched related donor in eight patients, matched unrelated donor in 25 children and two children received cord progenitor stem cells. In AML, absolute lymphocyte count <0.3 × 109/l or >0.3 × 10 ^9/l on days 21 and 30 were not predictive of relapse with a hazard ratio at day 21=0.88; P=0.8, and hazard ratio at day 30=0.5; P=0.2 [34].

Han et al have evaluated 69 children transplanted for acute lymphoblastic leukemia (ALL) (n=34), acute myeloid leukemia (AML) (n=26), chronic leukemia (n=7) and juvenile myelomonocytic leukemia (n=2) between 1996 and 2008 at the Chonnam National University Hospital, Korea. The patients were grouped based on absolute lymphocyte counts (ALC) <500/μL or ≥500/μL at D+21 and D+30 after transplant. The cut off value was based on preliminary analyses of ALC 200, 300, 400, 500. Patients with a High ALC at D+21 and D+30 had a faster neutrophil and platelet engraftment. The High at D+30 group had a better 5 year overall survival (71% vs. 53%, p=0.043) and event-free survival (72% vs. 53%, p=0.065) than the Low at D+30 group. The incidence of grade II-IV acute and chronic graft-versus-host disease (GVHD), and relapse rate did not differ by the ALC counts. However, the Low at D+30 group had a significantly increased risk for transplant-related mortality (p=0.019). The univariate analysis showed that the factors associated with decreased survival were a Low ALC at D+30, patients with high risk ALL, and grade II-IV aGVHD in patients with ALL and AML [35].

Conclusion

Diverse studies have been attempted to investigate the influence of immune reconstitution and lymphocyte recovery on ASCT outcome, however, reports in the literature are conflicting. Several found an association between low ALC and relapse and NRM, whereas other studies found an association between low ALC and NRM, but not with relapse. Furthermore, these studies are mostly small, limited to certain disease type, donor type, conditioning regimen and graft source. They cover a wide range of post-transplantation assessment time points (days 21 to 100 after ASCT) and proposed varying threshold values for defining low ALC (.175 x 10^9cells/L to .5 x 10^9 cells/L). Timely identifification of patients at high risk of relapse or death early in the posttransplant period is important because it could potentially allow targeted intervention such as a rapid taper of immunosuppressive therapy with the goal of triggering a GVL reaction, use of DLI, or initiation of immunomodulatory biological agents, such as interferon or interleukins (eg, IL-2 or IL-12). Early lymphocyte count measurement is reliably and widely measured in most transplant centers, and can be retrieved from retrospective transplant data. Analyses of much larger population of patients with wide spectrum of hematologic malignancies, transplanted with different regimens, donor types and graft sources, should be done to determine the general predictive value of ALC. Such studies might define the types of diseases and transplant approaches that have the most impact from the pattern of early lymphocyte recovery and lead to development of patient specifific strategies to improve outcome in those who fail to achieve satisfactory lymphocyte counts in the first month posttransplant.

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Нарушена свързаност на предната инсула при психотични и афективни разстройства

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Impaired anterior insula connectivity in psychotic and mood disorders

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РЕЗЮМЕ:

Известно е, че инсуларният кортекс участва в поддържане на съзнанието и различни функции, свързани със състрадание, емпатия, самосъзнание, когнитивно функциониране, междуличностно преживяване и осъзнаване. Предната и задната част на инсулата поддържат различни функции. Съвременната постановка е, че основна функция на предната част на инсулата (ПИ) е посредничеството на динамичните взаимодействия между широкообхватните мозъчни мрежи, ангажирани с външно ориентирано внимание и самопознание. ПИ е основен компонент на мрежата за значимост (салиентната мрежа - СМ), където поддържа идентифицирането на важни за индивида събития. Освен това е известно, че ПИ играе ключова роля в превключването между други широкомащабни мрежи за насърчаване на достъпа до вниманието и работната памет. Тя е отговорна и за регулирането на вегетативния отговор към салиентни стимули. Тези функции, свързани с инсулата, често са нарушени при психиатрични разстройства и не е изненадващо, че са докладвани открития за нарушения в структурата, функцията и свързаността ѝ при редица психични заболявания. Настоящият обзор се фокусира върху най-новите изследва-

ABSTRACT:

Insular cortex is known to be involved in consciousness and a variety of functions linked to compassion, empathy, self-awareness, cognitive functioning, interpersonal experience, and awareness. Anterior and posterior parts of the insula have been suggested to support different functions. A major function of the anterior part of the insula (AI) has been proposed to be the mediation of the dynamic interactions between large-scale brain networks engaged in externally oriented attention and self-cognition. It is a core component of the salience network (SN) where it is supporting the bottom-up identification of salient events. Moreover, AI is known to play a key role in the shifting between other large-scale networks to promote access to attention and working memory. It is responsible as well for the adjustment of the autonomic response to salient stimuli. These insula-related functions are often impaired in psychiatric disorders, and not surprisingly findings of structural, functional and connectivity abnormalities have been reported in a range of mental illnesses. The current review focuses on the most recent findings of both common and distinct AI connectivity disturbances in major psychotic and mood disorders, namely schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD). At the end,

ния както на общите (конвергентни), така и на различните (дивергентни) нарушения на свързаността на ПИ при основните психотични разстройства и разстройства на настроението, а именно шизофрения (Ш), биполярно разстройство (БР) и голямо депресивно разстройство (ГДР). В заключение е описан обяснителен модел, в който нарушената свързаност на ПИ (заедно с нейните структурни и функционални увреждания) като част от СМ води или до преобладаване на екстернализиращи ментални репрезентации, водещи до психотични симптоми, или до свръхпредставено интернализиране, водещо до саморазрушителните депресивни симптоми при разстройствата на настроението. Освен това, неспособността на СМ да изпълнява адекватно основната си функция на динамично превключване между мрежата на режима по подразбиране и централната изпълнителна мрежа може да е в основата на добре известните когнитивни симптоми и при двете групи пациенти.

Ключови думи: предна инсула, свързаност, шизофрения, биполярно разстройство, голямо депресивно разстройство.

an explanatory model is described in which the disturbed connectivity of the AI (along with its structural and functional impairments) as part of the SN results in either predominance of externalizing mental representations leading to psychotic symptoms or an overrepresented internalizing leading to self-defeating depressive symptoms in mood disorders. Moreover, the inability of the SN to adequately perform its main function of a dynamic switch between the default mode network and the central executive network might underly the well-known cognitive symptoms in both patient groups.

Key words: Anterior insula, connectivity, schizophrenia, bipolar disorder, major depressive disorder.

Introduction

Insula or insular lobe is a part of the cerebral cortex located deep within the lateral sulcus in each hemisphere. It is commonly divided into anterior insula (AI), and posterior insula baring distinct functions and connections. There are direct projections from the ventral medial thalamic nucleus and the central nucleus of the amygdala to the anterior insula which in turn projects to the amygdala. The posterior insula projects predominantly to the lateral and central nuclei of the amygdala. In contrast, the anterior insula projects to the anterior amygdaloid region as well as medial, cortical, accessory basal magnocellular, medial basal, and lateral amygdaloid nuclei (Uddin, Nomi et al. 2017).

Insular cortex is involved in consciousness and plays a role in a variety of functions linked to emotion or the regulation of the body's homeostasis. It has been suggested to play a role in compassion, empathy, taste, perception, motor control, self-awareness, cognitive functioning, interpersonal experience, and awareness of homeostatic emotions such as hunger, pain, and fatigue (Shura, Hurley et al. 2014).

Recent functional studies suggest that the AI is mediating the dynamic interactions between large-scale brain networks engaged in externally oriented attention and self-cognition. As mentioned earlier insular cortex is involved in a variety of cognitive, affective, and regulatory processes, including interoception, emotional reactions, and empathy. These functions are supported by the bottom-up identification of salient events, the shifting between other large-scale networks to promote access to attention and working memory when a salient event is detected, and the involvement of the anterior and posterior parts to adjust autonomic response to salient stimuli (Uddin 2015).

Thus, the salience network (SN) with its main hubs including AI and anterior cingulate cortex (ACC) enables different brain regions to generate appropriate behavioural reactions to salient stimuli (Menon and Uddin 2010). The perception of both visual, and auditory emotional information, pain, and subjective projections of the self are all insula-related functions that are disrupted in major psychiatric disorders such as schizophrenia (SCZ), bipolar (BD), and major depressive disorder (MDD).

Whereas structural connectivity studies provide evidence of the anatomical connections between brain regions, functional connectivity (FC) reflects the coactivation of brain areas not necessarily anatomically connected (based on functional MRI time series data) with the area of interest (seed or voxel). FC can be measured during resting state (known as well as intrinsic functional connectivity) or during specific task-related conditions. Effective connectivity (EC), on the other hand, provides an estimate of the influence that one neural system exerts over another thereby reflecting the directionality and the type (inhibitory or excitatory) of the causal connections (Friston 2011). In the following lines we will discuss the most recent findings regarding the connectivity of the anterior insula in patients with psychotic and mood disorders.

Anterior insula connectivity in schizophrenia

SCZ is amongst the most devastating and socially significant diseases affecting people mainly in late adolescence or early adulthood, therefore leading to a considerable functional impairment in personal, social, and professional life of those affected and their families (Montgomery, Liu et al. 2013). Despite decades of dedicated research, the exact pathophysiological mechanisms underlying the development of SCZ remain elusive. One of the most prominent recent hypotheses is the so called dysconnectivity hypothesis of SCZ reflecting the supposed abnormal functional integration of brain processes (Stephan, Friston et al. 2009).

As already noted, AI is considered to be a key node in the Salience Network which regulates the dynamic switch between the Default Mode Network (DMN) and the Central Executive Network (CEN) thus providing the rapid change of focus between internal and external stimuli. By integrating sensory, emotional, and cognitively charged information, the SN engages in complex processes such as communication, social behaviour, and self-awareness (Menon and Uddin 2010). Impaired functional connectivity (FC) in the nodes of the SN as well as aberrant interactions of the SN with other large brain networks has been reported in both schizophrenia patients and individuals with high-risk for psychosis (Manoliu, Riedl et al. 2014, Wotruba, Michels et al. 2014).

In line with the dysconnectivity hypothesis, reduced functional connectivity of the SN has been reported during information processing and reward prediction in SCZ (White, Joseph et al. 2010). It is suggested that inaccurate evaluation of stimuli which would usually be assessed as irrelevant might be the source of abnormal salience processing in individuals with psychosis. In this way, subthreshold stimuli become excessively attention-getting, which is referred to as "aberrant salience" by Kapur (Kapur 2003). As the author states, this process could explain the onset and relapses of psychotic symptoms, whereby hallucinations are a direct consequence of the aberrant salience of internal representations, and delusions are a cognitive attempt to make sense of these aberrantly salient perceptions. On the neurotransmitter level, the aberrant salience is a product of the well-known hyperdopaminergic state in subcortical brain areas (Howes and Kapur 2009).

In a recent study of our group, we observed an excitatory connection from the ACC to the AI in the SCZ group during rest suggesting that patients stay in a resting-state of „aberrant salience" which may interfere with the function of the Default Mode Network (DMN) (Aryutova, Paunova et al. 2021). These assumptions find support in our previous study, where the results showed a strong involvement of the DMN during task performance (Stoyanov, Aryutova et al. 2021). Since the SN provides the dynamic switching between the states of rest and cognitive load, this over-engagement with internal stimuli at

rest (hyperactivity of the SN) disturbs the appropriate activation within the DMN. As a result, the DMN stays active during tasks, which might provide an explanation of the cognitive deficits observed in SCZ individuals. Interestingly, the dysconnectivity between AI and ACC was found to be significantly correlated with the severity of emotion withdrawal, cognitive impairment, negative symptoms, poor psychosocial functioning, and longer duration of illness (Tian, Bousman et al. 2018, Tian, Zalesky et al. 2019).

In our most recent transdiagnostic study on effective connectivity in schizophrenia and mood disorders, we have been able to demonstrate the differential diagnostic potential of the brain connectome features involving major nodes of the SN, CEN, and the Limbic system (Kandilarova, Stoyanov et al. 2021). Interestingly, the self-inhibitory connection of the AI emerged as a feature of both mood disorders and SCZ and it was capable of distinguishing them both from healthy controls. This led us to the assumption that the disrupted self-regulation of this key hub of the SN might represent a shared mechanism of both affective and psychotic disorders.

Converging evidence supporting the crucial role of the AI in psychosis comes from a recent study using combined voxel-based morphometry and resting-state FC where early-stage SCZ patients have been found to have significantly reduced gray matter volume in both bilateral AI and ACC when compared to healthy subjects (Pu, Li et al. 2012). Moreover, significantly reduced FC within the SN was found to be a characteristic feature of the patient group. In addition, these convergent morphological and functional deficits in the SN were significantly associated with hallucinations (Pu, Li et al. 2012). In line with these findings, the positive symptom scores of the Positive and Negative Syndrome Scale were correlated with the FC within the right AI during the state of psychosis (Manoliu, Riedl et al. 2014).

In summary, the results of ours and other similar connectivity studies contribute to the understanding of schizophrenia as a behavioural disorder caused by disintegration across the key brain networks, namely, abnormal activation of the Salience network during rest which explains the hyperactivity of the Default mode network during cognitive load. In support of this understanding are the recent findings of reduced FC between the left ventral AI and other SN regions in subjects with At-Risk-Mental-State (ARMS) along with reduced structural connectivity in terms of fractional anisotropy (FA) and axial diffusivity of white-matter tracts, including frontal-striatal-thalamic circuits and the cingulum. Additionally, symptom severity correlated with the FA measures extracted from these disrupted white-matter regions. Moreover, FC between the bilateral insulae and FA at the forceps minor were further reduced in subjects who transitioned to psychosis after 2 years which adds a prognostic value of the combined structural and functional SN studies (Wang, Ji et al. 2016).

Anterior insula connectivity in major depressive disorder

Depression is recognized as one of the most common and disabling psychiatric disorders with increasing prevalence, social, and economic burden (Sartorius 2001). The signs and symptoms of depressive disorders span across several psychopathological domains including mainly affective (increased negative and reduced positive affect), and cognitive components (reduced concentration, memory, executive function etc) (Joormann and Quinn 2014). Accordingly, functional neuroimaging, and particularly connectivity studies have been concentrated mainly on these domains with a variety of task-related, and resting state research revealing disruptions in specific brain areas (Wang, Hermens et al. 2012).

Decreased FC within the SN has been demonstrated in depression, with the additional finding of strong correlation between the severity of symptoms and the decreased intrinsic FC of the right AI (Manoliu, Meng et al. 2013). Moreover, decreased FC between dorsolateral prefrontal cortex (DLPFC) and insula was found in subjects with subthreshold depression compared to healthy controls (Hwang, Egorova et al. 2015). In a previous study of our research group, we have found decreased effective connectivity between the

AI and the DLPFC as well as an aberrant connection (non-existent in healthy individuals) from the amygdala to the AI in a sample of patients with unipolar or bipolar depression (Kandilarova, Stoyanov et al. 2018). Our findings were convergent with the reports of increased activity of the SN in depression (Uddin 2015).

Moreover, a meta-analysis of resting state studies by Mulders er al. confirmed an increased connectivity between the SN and the anterior DMN (Mulders, van Eijndhoven et al. 2015). Kaiser et al. reported mixed meta-analytical results, concerning the connectivity between the SN and nodes of both the CEN and DMN. The pattern of altered SN connectivity in their study included both hypo- and hyperconnectivity, suggesting that the nature of the disturbance in MDD may depend on additional factors. As the authors comment, the nature of communication between networks involved in salience and attention may be affected by the presence of environmental cues that correspond to the content of internal thoughts (Kaiser, Andrews-Hanna et al. 2015).

In addition, symptom severity of depression have been found to be positively associated with decreased intrinsic FC within the right AI (Manoliu, Meng et al. 2013), while the amplitude of low-frequency fluctuations (ALFF) of the left insula demonstrated a negative correlation (Zhu, Lu et al. 2012). In our study, we have demonstrated negative associations between AI self-regulation and the Montgomery Aasberg Depression Rating Scale score (Kandilarova, Stoyanov et al. 2018) which is in accordance with the report of Manoliu et al. We suggest that this association might be interpreted as additional evidence for the importance of the self-regulating capacity of the AI in the development and worsening of the depressive symptoms. This finding implies that the more depressed the patient is, the less effective is the self-inhibition of the AI. As already mentioned, the insula acts as the monitor of emotional stimuli of the SN, and the disturbed regulation would lead to inadequate attribution of attention to indifferent stimuli which can explain the prominent negative bias in depression (Gotlib, Krasnoperova et al. 2004).

Anterior insula connectivity in bipolar disorder

The differential diagnosis between unipolar and bipolar depression is a major unresolved clinical challenge in psychiatry with great consequences for the patients affected. Thus, it is not surprising that there is an abundance of studies comparing these disorders in search for potential structural, functional or connectivity markers for differential diagnosis. As reported in a recent review by Han et al., the most convergent findings involve regions such as the amygdala, the anterior cingulate cortex, and the prefrontal cortex, mainly DLPFC (Han, De Berardis et al. 2019).

Earlier studies on resting state connectivity demonstrated that BD was associated with decreased amplitude of low-frequency fluctuations in the left posterior insula and superior parietal lobule and increased ALFF in the right dorsal AI compared to patients with MDD (Liu, Ma et al. 2012). In a more recent report, patients with bipolar depression demonstrated significantly altered right anterior insula FC with the nodes of the CEN (inferior parietal lobule) when compared to MDD patients and healthy control. Notably, the connectivity values significantly discriminated patients with bipolar depression from both other groups (Ellard, Zimmerman et al. 2018).

Recent dynamic FC study by Pang et al. reported decreased dynamic functional connectivity (dFC) between the right ventral AI (rvAI) and right ventrolateral prefrontal cortex that was common for BD and MDD. However, some distinct features were detected such as the MDD-related increases in dFC between the rvAI and right precuneus, temporal pole, and left dorsolateral prefrontal cortex, and the BD-related increases in the dFC between the right dorsal AI (rdAI) and left inferior parietal lobule and right middle occipital gyrus (Pang, Chen et al. 2018). On the other hand, Han et al. reported that BD and MDD patients shared decreased network switching rate of key hubs in DMN while only in MDD decreased switching rate in salience network and striatum was detected (Han, Cui et al. 2020).

Most recent study comparing MDD to BD found that unipolar depression was associated with increased FC between rdAI and right

superior frontal gyrus, along with increased FC between left posterior insula and right precentral gyrus and right thalamus. Notably, machine learning based on the combined FC of ACC, bilateral insula and bilateral amygdala seeds with the whole brain discriminated BD from MDD with an accuracy of 91.30% (Yu, Li et al. 2020). Similarly, in our study, we have identified that abnormalities in resting-state neural connectivity of the anterior insula, amygdala and prefrontal cortex may be a useful marker for differentiating the depressive states of MDD and BD with an overall accuracy of 80.4% (Kandilarova, Stoyanov et al. 2021).

Moreover, the study of Yuan et al. reported that resting state FC between the right AI and the left dorsolateral PFC played a crucial role in the early antidepressant effect, and was linked to the treatment response (Yuan, Zhu et al. 2020). Thus, the AI region might be considered as a potential target for drug, stimulation or other types of treatment. Interestingly, in patients with refractory focal epilepsy, only the stimulation of dorsal AI was able to reproduce an ecstatic aura (Bartolomei, Lagarde et al. 2019), and again the dAI was the most commonly implicated region demonstrating significant increase of FC values in the period immediately following the stimulation.

Conclusion

The impaired structure (Goodkind, Eickhoff et al. 2015), function (Uddin 2015) and connectivity of the SN and its AI node appears to be a key feature of both SCZ and depression and provides a plausible mechanism explaining the symptom formation and the clinical presentation in these major psychiatric disorders. It is suggested that in SCZ the abnormality of the SN results in predominance of externalizing mental representations leading to psychotic symptoms (delusions and hallucinations), while in depression it causes an overrepresented internalizing leading to self-defeating depressive symptoms (the negative bias in depression). Moreover, the inability of the SN to adequately perform its main function of a dynamic switch between the DMN and the CEN produces the well-known cognitive symptoms in both psychotic and mood disorder (Bora, Yücel et al. 2010).

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Влиянието на образованието и пола върху резистентността към лечението при болни с шизофрения

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The effect of education level and sex differences on resistance to treatment in patients with schizophrenia

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РЕЗЮМЕ:

Въведение: Шизофренията е хронично психично разстройство, засягащо в почти еднаква степен както мъже така и жени без да се влияе от нивото на образование. Симптомите на шизофренията са групирани като положителни, отрицателни и когнитивни. Значителен процент от болните /между 30 до 50 %/ са резистентни към прилаганите медикаментозни режими. Влиянието на пола и нивото на образование върху предразположеността към резистентност е важно за прогнозата, както и за терапевтичните подходи, избрани в тези случаи.

Методи: Анализирана е група от 105 пациенти с шизофрения. Разпределението по пол показа, че 39 са мъже и 66 жени. Направена е оценка на нивото на образование. Резистентността е изследвана с помощта на установения консенсусен модел за резистентност при пациенти с

ABSTRACT:

Background: Schizophrenia is a chronic psychiatric disorder affecting almost equally men and women, with different level of education and characterized with positive, negative and cognitive symptoms. A significant percentage, 30 to 50 % of all patients, are resistant to the applied treatment regimes. How sex and education level affect resistance predisposition is important for the prognosis as well for the treatment measures chosen in these particular cases.

Methods: A group of 105 patients with schizophrenia were analyzed. Distribution by sex was 39 men and 66 women. Level of education was assessed. The resistance was examined using consensus guidelines for resistance in patients with schizophrenia. Clinical evaluation was done with PANSS and BPRS scales.

Results: Of the total number of patients, 45 have resistant schizophrenia and 60 are in

шизофрения. Клиничната оценка беше направена със скали PANSS и BPRS.

Резултати: От общия брой пациенти 45 са с резистентна шизофрения и 60 са в клинична ремисия. В групата с резистентност към лечението има 20 са мъже като останалите 25 са жени. В групата пациенти в клинична ремисия 19 са мъже и 41 жени. Разпределението на степента на образование в двете групи пациенти показва, че в групата с резистентност 33 /73.3%/ лица са със средно образование, а 12 /26.7%/ са със завършено висше образование. В групата в клинична ремисия - 4 /6.7%/ пациенти са с основно образование, 36 /58.3%/ пациенти със средно, 20 /33.3%/ пациенти с висше и един пациент /1.7%/ е с докторска степен.

Заключение: Открихме по-висок процент пациенти от мъжки пол в групата с резистентност към лечението с сравнение с групата в клинична ремисия. Не открихме разлики в нивото на образование при двете наблюдавани групи пациенти.

Ключови думи: шизофрения, резистентност, резистентна шизофрения, образование, образователно ниво, пол

clinical remission. There are 20 men in the resistance group and the other 25 are female. In the group of patients in remission, 19 are men and 41 are women. The distribution of the level of education in the two groups of patients showed that in the group with resistance, 33 /73.3%/ persons have secondary education and 12 /26.7%/ have completed higher education. In the group in clinical remission - 4 /6.7%/ patients are with primary education, 36 /58.3%/ patients with secondary, 20 /33.3%/ patients with higher and one patient /1.7%/ has a PhD degree.

Conclusion: We found a higher percentage of male patients in the treatment resistance group than in the clinical remission group. We did not find differences in the level of education in the two observed groups of patients.

Key words: schizophrenia, resistance, resistant schizophrenia, education, education level, gender, sex prevalence

Background:

Schizophrenia is a chronic mental disorder associated with impaired integration and a state of disconnection between brain regions leading to the formation of specific clinical symptoms. Disturbed associative relationships between brain areas have been established in numerous studies (Stoyanov D, Kandilarova S, et al., 2018; Stoyanov D, Aryutova K, et al., 2021; Nyatega, Charles O., et al., 2021). The described disorders are also established by analysis of the morphology of the corpus callosum and the underlying/associated atrophic changes in it (Innocenti, G., et al. 2003; Katherine L. et al., 2000).

The established changes in the connecting systems between the different brain regions give grounds for some authors to consider schizophrenia as a disconnection syndrome (Friston, K., et al., 2016). On the other hand, it should be noted that gender differences in brain size have been found, as well as not very convincing differences in the associative connections between individual neuronal centers and lateralization in men and women (Lise Eliot, et al., 2021).

These data give us the right to ask whether these uncertain gender differences in the organization of brain structures and functions, which in the analysis of different researchers show different data, are relevant to the schizophrenic process in men and women. There is evidence that the disease begins earlier in men than in women, and there are some differences in the course of the clinical setting (Han M, Huang XF, et al., 2012; Fine C. 2014; Ingalhalikar M et al., 2014). These studies indicate that the course of the schizophrenia process is more severe in males than in females without a specific analysis of resistance to therapy using the accepted criteria for its evaluation.

A study of patients with psychotic disorders showed that there were no differences in the level of education between patients and their parents, however, the authors indicated a higher level of education in patients with psychosis than their parents. In those living in urban areas, there were no large differences in the level of education (Frissen, A., Lieverse, R., et al., 2015).

However, other studies on the level of education have found a link with the development of psychotic disorder. A study in Sweden showed that low levels of education are associated with the likelihood of developing schizophrenia (MacCabe JH, Lambe MP, et al 2008). Other analyses showed that if the presumed level of education was not reached at the age of 14, the probability of future hospitalizations increased. The authors did not establish a link with a specific psychotic disorder (Isohanni I, Jarvelin MR, et al., 1998).

Their research showed that poor performance in art and craft schools, but not academic performance, is a risk factor for schizophrenia [Cannon M, Jones P, et al., 1999]. The analysis of another team of authors found another association. The analysis of school performance up to the age of 16 established a link between poor performance at that age and the likelihood of developing schizophrenia between the ages of 17 and 31(MacCabe JH, et al., 2008). An analysis conducted in China showed that with the increase in educational qualifications, the probability for onset of schizophrenia decreased. The authors pointed out that this relationship was more pronounced in women than in men (Luo Y, Pang L, et al., 2020).

Working hypothesis: We believe that gender as well as the level of education will be factors related to the likelihood of resistance to treatment in patients with schizophrenia.

Methods:

A total of 105 patients with schizophrenia have been observed. Of these, 45 have resistant schizophrenia and the remaining 60 are in clinical remission.

The diagnosis has been made according to the criteria of ICD, 10 and DSM, 5 (DSM 5, 2013).

Including criteria for patients with resistant schizophrenia are those who have met the resistance criteria of the published consensus on resistant schizophrenia (Howes OD, McCutcheon R, et al., 2017). They are:

1. Assessment of symptoms with the PANSS and BPRS scale (Overall JE, Gorham DR. 1962; Kay SR, Fiszbein A, Opler LA, 1987).
2. Prospective monitoring for a period of at least 12 weeks.
3. Administration of at least two antipsychotic medication trials at a dose corresponding to or greater than 600 mg chlorpromazine equivalents.
4. Reduction of symptoms when assessed with the PANSS and BPRS scale by less than 20% for the observed period of time.
5. The assessment of social dysfunction using the SOFAS scale is below 60 (Mirosini PL et al 2000).

The exclusion criteria are:

1. Mental retardation
2. Presence of organic brain damage
3. Concomitant progressive neurological or severe somatic diseases.
4. Expressed personality change
5. Score of MMSI below 25 points

The statistical software package SPSS was used for statistical data processing. Because we use nominal variables, and limit group numbers, chi-square test in non-parametric tests was chosen for comparing the groups. The data were analyzed by Chi-square test.

Results:

Distribution by gender

Of all patients observed, 66 /62,9%/ are female and 39 /37.14%/ are male. We observed a predominance of female patients. This fact can be viewed from the standpoint of the inclusion and exclusion criteria in relation to the requirements related to education, level of intelligence, lack of progressive CNS diseases and the need for a lack of pronounced personality change that has begun to dominate in the patients' clinical setting. All these features were observed predominantly in males, which would not allow their inclusion and conducting

a comparative study on the established criteria.

In patients with resistant schizophrenia, it was found that the distribution by sex is as follows: 20 /44.4%/ of the patients were male and the remaining 25 /55.6%/ were female.

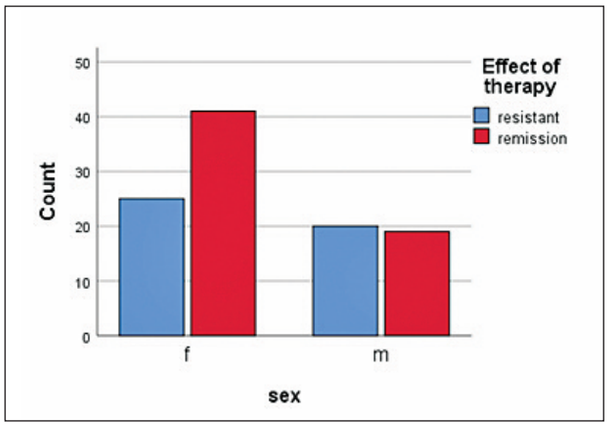
In the patients in remission, the distribution by sex was: 41 /68.3%/ were female and 19 /31.7/ were male.

In patients with resistant psychotic symptoms there was a small (to insignificant) difference between the sexes in the sample, while in those in remission we registered more than 2 times difference in favour of females (Table 1, Figure 1).

Table 1. Distribution of patients by sex in the resistance group and in the clinical remission group

		Effect of therapy		
		Resistant	Remission	Total
gender	f	25	41	66
	m	20	19	39
Total		45	60	105

Figure 1. Distribution of patients by sex in the resistance group and in the clinical remission group



These results from the distribution by gender in both groups of patients show tendencies males to be more likely to be resistant to treatment than females.

Distribution by education

The assessment of the distribution by educational level shows that out of all 105 patients, 4 have primary education, 68 have secondary education, 32 have higher education /in this group we have included persons with completed bachelor's and master's degrees/ and one patient with a PhD degree.

Of the patients with RS, it was found that 33 /73.3%/ persons have secondary education and 12 /26.7%/ have higher education.

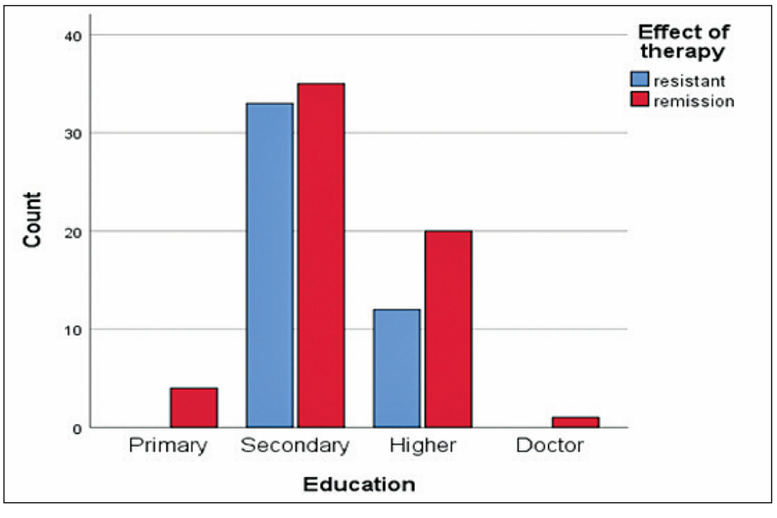
Of the patients in clinical remission - 4 /6.7%/ patients have primary, 36 /58.3%/ patients are with secondary, 20 /33.3%/ patients are with higher education and one patient /1.7%/ is with PhD level of education.

It is noteworthy that patients with primary education and patients with a PhD level are from the group of patients in clinical remission /Figure 2/

Table 2. Table of statistical significance of the result of the distribution by education

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1,798[a]	1	,180		
Continuity Correction[b]	1,293	1	,256		
Likelihood Ratio	1,793	1	,181		
Fisher's Exact Test				,222	,128
N of Valid Cases	105				

Figure 2. Result of the distribution by education



The results show that the education factor cannot be deduced as influencing the likelihood of resistance to treatment.

Relationship between education and gender distribution

The analysis of this relationship showed that in the persons with primary education we found more women (3) and only one man.

In the group of patients with secondary education, 68 in total, we found 40 women and 28 men.

In the group of patients with higher education (32), 22 were female and 10 were male. With a PhD educational and scientific level there is one patient and she is female.

From this distribution we can say that there is no significant difference between the patients in terms of educational qualifications between males and females. The statistical analysis did not reveal a significant difference in the use of non-parametric methods for estimating the data.

Table 3. Relationship between gender and educational attainment in patients with schizophrenia

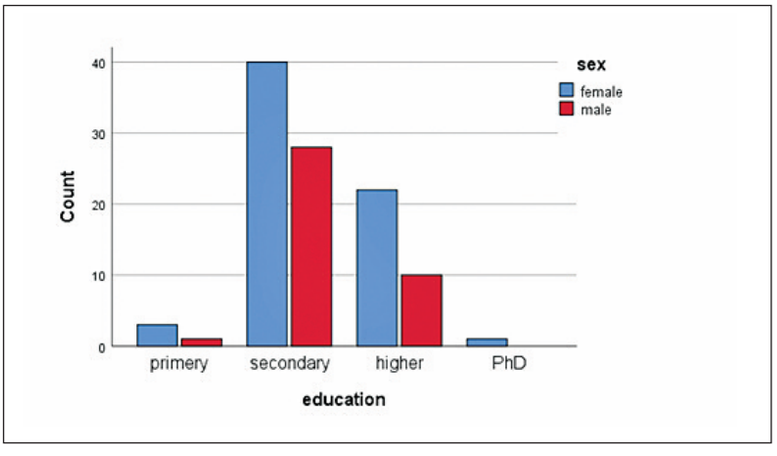
		sex		
		f	m	Total
Education level	Primary	3	1	4
	Secondary	40	28	68
	Higher	22	10	32
	PhD	1	0	1
Total		66	39	105

Statistical analysis

Table 4. Statistical analysis of relationship between gender and educational attainment in patients with schizophrenia

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1,793[a]	3	,616
Likelihood Ratio	2,152	3	,541
N of Valid Cases	105		

Figure 3. Relationship between gender and educational attainment in patients with schizophrenia



We did not find gender differences in educational attainment in our patients with schizophrenia. We also did not find differences in educational qualifications between patients with resistance to treatment and those in clinical remission. In our study, females predominate. The distribution in the groups in terms of the effect of treatment shows that there is a statistical difference with a predominance of males in the group with resistance to treatment.

Discussion:

Males patients with schizophrenia are more likely to be resistant to treatment. These data were confirmed by many other authors (Lieberman J., Jody D., Geisler S., et al. 1993; Robinson DG., et al. 1999 Szymanski S., et al. 1995) who concluded that males had shorter life expectancy and more acute course of various diseases, including mental ones. In this sense, the increased incidence of resistant cases in males could be considered as a special case of the general trend in the course of diseases in both sexes (Vlassoff C, 2007) or to be appraised as an effect of the earlier onset of psychosis in men, found in various studies (Stilo, S. A., & Murray, R. M. 2010). We can accept the results as a consequence of the influence of both processes.

The results show that the "education" factor cannot be deduced as influencing the likelihood of resistance. This result emphasizes that resistance is not significantly affected by social status and lifestyle, reflected in the educational qualifications of patients. i.e. it (resistance) cannot be simply deduced and explained by "psychologizing" the clinical symptoms and the psychopathological phenomena observed in it.

On the other hand, the analysis of the education factor on the development of the schizophrenic process needs to be conducted in a larger group of patients in connection with the established different levels of education and the need to group patients into smaller subgroups would be sufficient to derive clinically relevant results.

Conclusion:

We found that males were more likely to be resistant to treatment than females. The level of education achieved did not affect the development of resistance to treatment. The gender differences we identified were not related to the acquired level of education. These results indicated that the analysis of the underlying mechanisms associated with resistance was most likely associated with underlying biological mechanisms.

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Сравнителни антропометрични критерии при пациенти с резистентна шизофрения

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Comparative anthropometric criteria in patients with resistant schizophrenia

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РЕЗЮМЕ:

Въведение: Шизофренията е хронично психично заболяване с разнообразна клинична картина, свързано с изкривено възприятия за реалността. Значителен процент от пациентите, въпреки използването на различни терапевтични подходи, остават резистентни към използваното лечение. Идентифицирани са различни фактори, свързани с резистентността. Особеностите на различните антропометрични показатели при пациенти с шизофрения и възможната резистентност към лечението ни дадоха основание да търсим връзка между тях.

Методи: Проведен е корелационен анализ. Наблюдавани са 105 пациенти с шизофрения с пореден психотичен епизод. От тях 45 са с резистентност към лечение, а останалите 60 са в клинична ремисия. Направена е оценка на ръста, теглото, ИТМ /индекс на телесна маса/ и хабитуса на пациентите.

Резултати: При оценката на ръста на болните установихме, че средната височина при пациенти с резистентност е 170 cm, а при тези в ремисия е 167 cm. Теглото на пациентите и в двете групи е съответно при резистентните болни -76,09, а при тези в ремисия 76,12 кг. Анализа на ИТМ

ABSTRACT:

Background: Schizophrenia is a chronic mental illness with a diverse clinical presentation associated with distorted perceptions of reality. A significant percentage of patients, despite the use of different therapeutic approaches, remain refractory to the treatment used. Various factors related to resistance have been identified. The peculiarities of the different anthropometric indicators in patients with schizophrenia and the possible resistance to treatment gave us reason to look for a connection between them.

Methods: Correlation analysis was conducted. We observed 105 patients with schizophrenia and another psychotic episode. Of these, 45 showed resistance to treatment and the remaining 60 achieved clinical remission. The height, weight, BMI and habitus of the patients were assessed.

Results: In assessing the height we found that in the observed patients of both groups the average height in patients with resistance was 170 cm, and in those in remission it was 167 cm. The weight of patients in both groups was 76.09 and 76.12 kg, and in relation to BMI the values were 26.60 in the group with resistant schizophrenia and 27.22 in those in remission, respectively. The results regarding the assessment of the habitus showed that in

показа че стойностите са съответно 26,60 в групата с резистентна шизофрения и 27,22 при тези в ремисия. Резултатите от оценката на хабитуса установи, че при пациенти с резистентност към лечението 25 /55,6%/ имат астеничен хабитус, 14 /31,1%/ са с нормостеничен и 6 /13,3%/ с пикничен. При пациентите в ремисия -17 пациенти /28,3%/ са с астеничен хабитус, 26 /43,3%/ са с нормостеничен и 17 /28,3%/ са с хабитус за пикничен.

Заключение: Регистрирахме приблизително два пъти по-голям процент пациенти с астеничен навик в групата пациенти с резистентност към лечението. Не открихме значителни отклонения в телесното тегло, височината на пациентите и ИТМ. Установихме някои тенденции за по-слаба вътрешногрупова динамика на телесното тегло при пациенти с резистентност без достигане на статистическа значимост.

Ключови думи: шизофрения, резистентна шизофрения, ИТМ, тегло, височина, хабитус, астеничен хабитус, терапевтична резистентност

the patients with resistance to treatment 25 /55.6%/ have asthenic habitus, 14 /31.1%/ have normosthenic and 6 /13.3%/ have picnic one. Among the patients in remission -17 patients /28.3%/ have asthenic habitus, 26 /43.3%/ have normosthenic and 17 /28.3%/ have picnic habitus.

Conclusion: We registered approximately twice the percentage of patients with asthenic habit in the group of patients with resistance to treatment. We did not find significant deviations in body weight, height of patients and BMI. We found some tendencies for weaker intra-group dynamics of body weight in patients with resistance without reaching statistical significance.

Key words: schizophrenia, resistant schizophrenia, BMI, weight, height, habitus, asthenic habitus, treatment resistance

Introduction

Schizophrenia is a chronic mental illness in which the clinical symptoms are divided into three main groups /positive, negative and cognitive/. The disease is associated with high disability and increased mortality (Hoang U, et al. 2011; Bitter I et al. 2017). In addition to the characteristic mental symptoms in patients with schizophrenia, changes in metabolism, immune and opioid systems have been found (Tanaka, M. Tóth, F. et al., 2021; Correia, Banny SB, João V. Nani, et al., 2021 ; Moustafa SR, Al-Rawi KF, Stoyanov D, 2020). On the one hand, impaired connectivity between different brain regions has been established (Stoyanov D, Kandilarova S, et al., 2018; Stoyanov D, Aryutova K, et al., 2021), and on the other hand, metabolic disorders have been registered, most likely as a result of impaired psychosomatic signalling. Of interest is the fact that low levels of lipids are found not only in patients with schizophrenia, but also after the use of psycho-stimulants (Correia, Banny S.B., João V. Nani, et al., 2021). These studies suggest that schizophrenia is considered a more extensive pathology associated with metabolic and immunological changes throughout the body. Moreover life expectancy in these patients is approximately 15-20 years shorter than in the general population (WHO, 2016; Saha S, Chant D, McGrath J., 2007). These features in patients with schizophrenia have led some researchers to assess the body weight and BMI index in these patients as well as its dynamics during treatment. Several large studies and meta-analyses have found strong links between BMI and mortality due to a variety of causes; most have described a U-shaped relationship with minimal mortality in the healthy weight range (20–25 kg/m2) (Aune D Sen A et al 2016; Berrington de Gonzalez A Hartge P et al 2010). It has been found in various studies that in patients with schizophrenia there is an increase in body weight as well as BMI. BMI in patients was 32.11 wereaf in the control group it was 27.62. (Annamalai, A., Kosir, U.,

& Tek, C., 2017). On the other hand, there are studies showing that increased BMI is associated with lower expression of negative symptoms (Wang, J., Zhang, Y., Liu, Z. et al. 2020). Clinical and epidemiological studies dating back to the early 20th century suggest a link between height (H) and SCZ (Burchard, 1916; Gunnell et al., 2005; Kemali et al., 1976; Nopoulos et al., 1998; Perrin et al., 2007; Zammit et al., 2007). The largest study, a study of 720,000 Swedish men and women, found an inverse relationship between height and the risk of schizophrenia (Gunnell et al., 2005). These findings are confirmed by the largest study to date on the relationship between the risk of developing schizophrenia and height from a large epidemiological study in Sweden in 1.35 million men (Zammit et al., 2007). Combined with the high heredity of schizophrenia (Sullivan et al., 2003) and height (Yang et al., 2010), these epidemiological findings suggest that both height and schizophrenia share common genetic variants that increase height and are likely to be related to reduce the risk of schizophrenia, i.e. the effect of the variants on the two phenotypes is in opposite direction (i.e. inconsistent).

There have been many attempts since the advent of medicine as a science to connect certain nosological units with a certain shape and characteristic of the body. In 1966, Pinillos et al. (Pailhez G, Bulbena A. 2010; Pinillos JL et al. 1966) summarized the results of five studies on physique in mental disorders published between 1920 and 1940. In support of Kretschmer's theory, the authors found a link between schizophrenia and leptosomal physique, and between manio-depressive psychosis and picnic physique. In support of the classical hypothesis, Pivnicki & Christie found the opposite physique in schizophrenia and affective disorders, with differences in the prevalence of individual somatotype components (Pivnicki D, Christie RG. 1968). In two studies from southern China in the 1970s, Singer et al. (Singer K, Chang PT 1972; Singer K, et al. 1976) compared the anthropometric performance of patients with schizophrenia, neurosis, and affective disorder with healthy individuals of similar age and socioeconomic status. In both sexes, they found greater body linearity in schizophrenia compared with both healthy controls and patients with affective disorders. Additionally, the authors found a correlation between linearity in bodybuilding in schizophrenia and early onset of psychosis. In 2009, in a Spanish study with a similar design, Pailhez et al. (Pailhez G, 2009) found significantly more ectomorphic categories among patients with schizophrenia than controls. In the spirit of Kretschmer's early observations, the Soviet constitutional school of the last century studied the role of somatotype in the clinical manifestation and course of schizophrenia. According to Kornetov, chronic-progressive forms of the disease with pronounced negative symptoms are characteristic of asthenic physique, recurrent forms - for picnic, and forms with frequent relapses and remissions - for normosthenic (Kornetov NA. 1987; Kornetov NA. 1991). According to the authors, somatotype has nothing to do with the risk of developing schizophrenia, but only modifies the course of the disease (Ritsner MS, et al 1990).

Working hypothesis: We have not found studies that attempt to distinguish the differences in anthropometric data between resistant schizophrenia and those in clinical remission. We expect differences in anthropometric indicators between the two groups of patients.

Methods:

A total of 105 patients with schizophrenia have been observed. Of these, 45 have resistant schizophrenia and the remaining 60 are in clinical remission.

Including criteria for patients with resistant schizophrenia are those who have met the resistance criteria of the published consensus on resistant schizophrenia (Howes OD, McCutcheon R, et al., 2017). These are:

1. Assessment of symptoms with the PANSS and BPRS scale (Overall JE, Gorham DR. 1962; Kay SR, Fiszbein A, Opler LA, 1987).

2. Prospective monitoring for a period of at least 12 weeks.

3. Administration of at least two antipsychotic medication trials at a dose corresponding to or greater than 600 mg chlorpromazine equivalents.

4. Reduction of symptoms when assessed with the PANSS and BPRS scale by less than 20% for the observed period of time.

5. The assessment of social dysfunction using the SOFAS scale is below 60.

The exclusion criteria are:

1. Mental retardation
2. Presence of organic brain damage
3. Concomitant progressive neurological or severe somatic diseases.
4. Expressed personality change
5. Score of MMSI below 25 points

The statistical software package SPSS was used for statistical data processing.

Descriptive analyses, correlation analysis, dispersion analysis /Anova/

and a non-parametric statistical method were used /Mann Whithney U test/, (Mann, Henry B.; Whitney, Donald R. 1947).

Results:

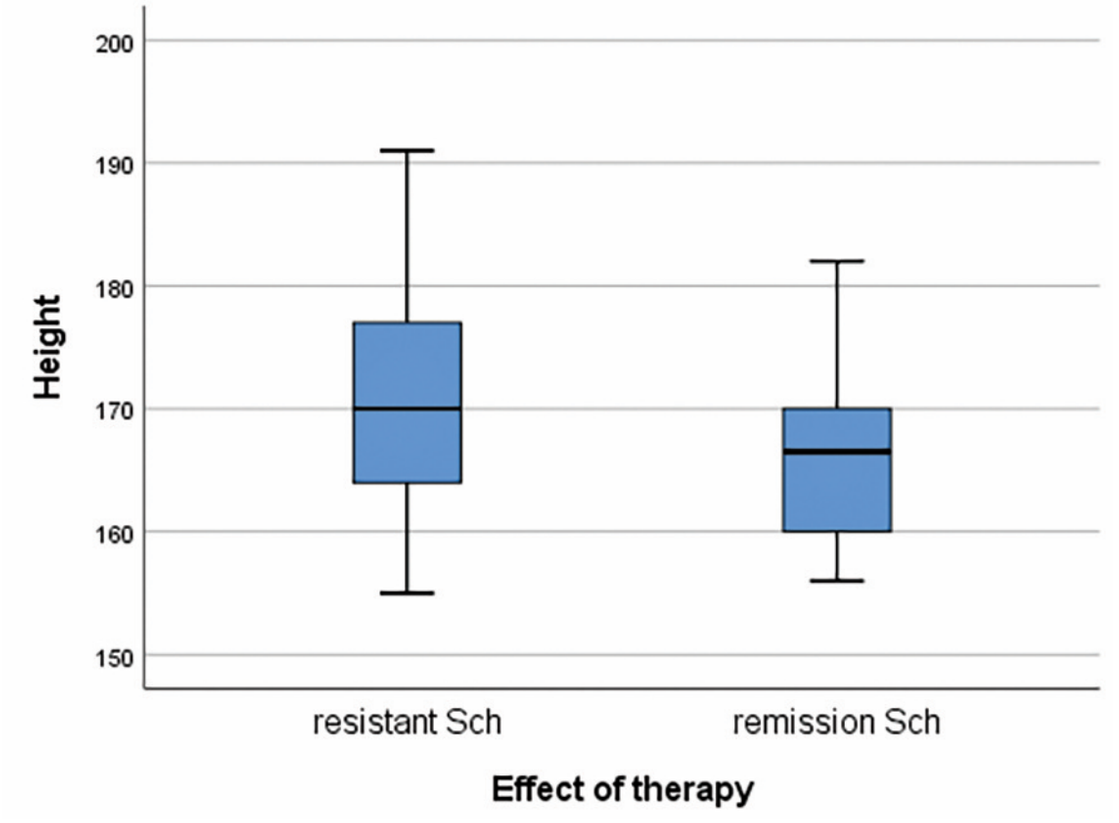
Height

The average height of the patients in the study was 168.55 cm with a minimum height of 155 cm and a maximum of 191 cm.

The average height of females is 164.62, while the average height of males is 175.21 cm. These results are comparable to the results obtained from a survey in 2014, analyzing the height of individuals in Bulgaria. This analysis shows that the average height of females is 164.8 and that of males is 178.2. The result shows that in the patients we studied no differences have been observed compared to the data characteristic of the main population (NCD Risk Factor Collaboration (NCD-RisC, 2016).

In patients with resistant schizophrenia it was found that the average height was 170.11 cm with a standard deviation of 8,896, while in patients in remission the average height was 167.38 cm with less standard deviation - 7,190 cm (Figure 1).

Figure 1. Relationship between the height of patients and the effect of therapy



There was no statistically significant difference in the height of patients from the two groups (p> 0.05).

Weight

The mean weight measured in all patients with schizophrenia was 76.10 kg. Their weight varied from the lowest 48 kg to the highest 124 kg. In the group of patients with resistance to treatment the average weight was 76.09, and in the group of patients in remission it was 76.12.

While in the group with resistance the standard deviation was 14,998, in those with remission it was 17,289. On the other hand, the minimum and maximum weight in patients with RH varied in a narrower range - in the range between 50 and 105 kg, while in those in remission it was in a wider range - 48 and 124 kg, respectively.

There was no difference in the average weight of patients from the two groups (p>0,05).

BMI /Body Mass Index/
in both groups of patients

The analysis of BMI in both groups of patients showed that in the group of those with resistant symptoms the average BMI was 26.60, and in the group with remission it was 27.22. On the other hand, most probably by analogy with the data related to the body weight of patients with BMI, greater variability was observed in the group of patients with remission.

The lowest BMI in the group with resistant schizophrenia was 18.37 and the highest was 38.06.

The lowest BMI in the remission group was 18.34 and the highest one was 44.14.

No difference was found between the two groups in terms of BMI.

Habitus

From the observation it is clear that 42 patients /40%/ have an asthenic habitus, 40 /38.1%/ have a normosthenic habitus and 23 /21.9%/ have a picnic habitus. There is an prevalence of on patients with asthenic habitus.

The analysis of the habitus in patients with refractoriness and in those without refractoriness shows that there are differences in the distribution of patients by the criterion of habitus in the two groups:

In patients with resistance 25 /55.6%/ have an asthenic habitus, 14 /31.1%/ - normosthenic and 6 /13.3%/ - picnic habitus.

In patients with remission -17 patients /28.3%/ have asthenic habitus, 26 /43.3%/ have normosthenic and 17 /28.3%/ have picnic habitus.

Approximately 2 times higher rates of patients with asthenic habitus are observed in patients with resistance to treatment than those in clinical remission (p <0.05) (Table 1, Table 2, Figure 2).

Table 1. A link between habitus and the effect of therapy

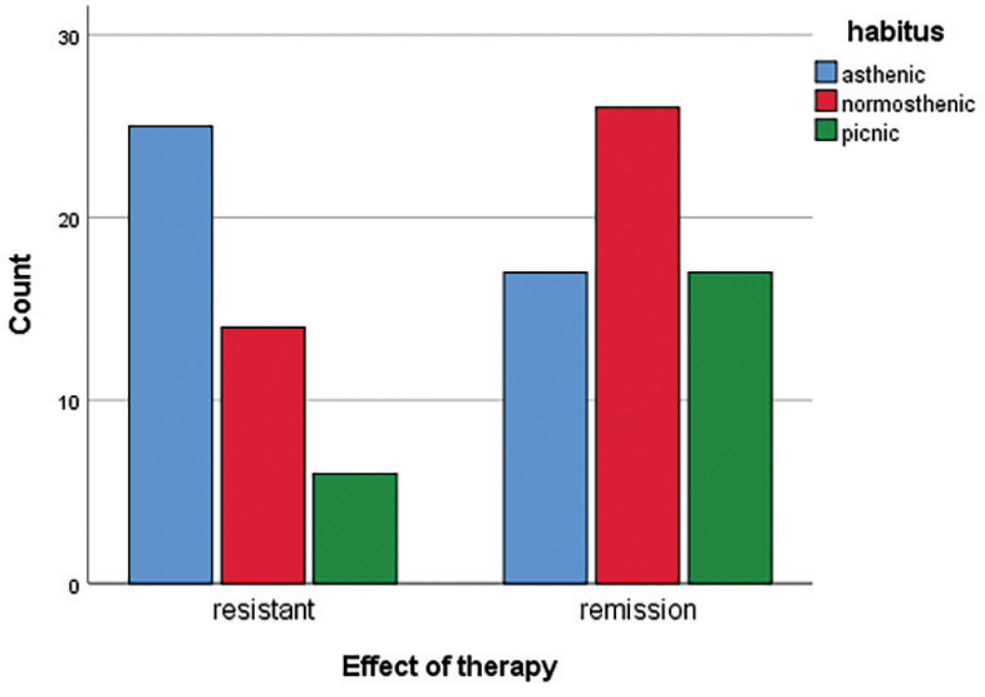
Count

		Effect of therapy		
		resistant	remission	Total
Habitus	asthenic	25	17	42
	normosthenic	14	26	40
	picnic	6	17	23
Total		45	60	105

Table 2. Statistical relationship between the effect of therapy and the habitus of patients

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	8,414[a]	2	,015
Likelihood Ratio	8,521	2	,014
Linear-by-Linear Association	7,744	1	,005
N of Valid Cases	105		

Figure 2. A link between habitus and the effect of therapy



The analysis of anthropometric indicators in the patients we observed shows that patients with resistant schizophrenia have a predominantly asthenic habitus and it is associated with slightly taller height and lower body weight variation compared to patients in clinical remission.

Discussion:

Our results in terms of patient height are comparable to the data obtained from a study in 2014, analyzing the height of individuals in Bulgaria. The analysis shows that the average height of females is 164.8, and for men it is 178.2. Our data show that the patients we studied did not show statistically significant differences compared to the data typical of the main population in our country (NCD Risk Factor Collaboration (NCD-RisC, 2016)). We observed shorter height in patients with schizophrenia.

With this observation, we also confirm the

data found by other authors concerning shorter height in patients with schizophrenic disorders compared to the general population (Burchard, 1916; Gunnell et al., 2005; Kemali et al., 1976; Nopoulos et al., 1998; Perrin et al., 2007; Zammit et al., 2007; Gunnell et al., 2005; Zammit et al., 2007). Our observations are on a relatively small number of patients, but we did not find significant differences in the height of patients from both groups. We found a slightly shorter height in the group in clinical remission, which shows that we cannot derive the height of patients as an indicator associated with the development of resistance to treatment.

The analysis of body weight demonstrates that there is a weaker trend for dynamics in body weight in resistant patients /there is a smaller range between the minimum and maximum registered weight/. An explanation about that phenomenon can be found in the accumulated data that weight gain is usually associated with the start of treatment and is particularly pronounced in the first psychotic episode (Kinon BJ, et al., 2005; Kahn RS, et al., 2008; Citrome L, et al., 2011). On the other hand, in resistant patients there is less adherence to treatment and the associated lower weight gain.

The results of the physical habitus analysis showed that asthenic habitus is predominant in patients with resistant schizophrenia. It is associated with slightly taller height and lower variation in body weight compared with patients in remission (Kornetov NA, Gubernik V., 1980). However, the analysis of this factor is also difficult to make in some cases, especially those with a long duration of the disease. The reason for this is that the analysis of body weight revealed that most patients were overweight and generally occupied an "intermediate" position between "obese" and overweght according to the WHO classification of BMI. In this case, a patient who has an asthenic habitus during treatment and especially when it comes to a long period of time /measured in years/ with weight gain, there is a change in the assessment of the habitus, especially in cases where height is not tall. In these cases, the lack of change in the habitus (respectively BMI, as an influencing factor for the assessment of the habitus) can be considered a guiding sign. In addition to this, and in support of this analysis, we found that within the group the body weight of resistant patients varied to a lesser extent.

Our study was conducted with 105 patients with schizophrenia. To assess height and weight, a larger number of patients is usually required to derive clinically relevant results. We found certain trends both in terms of patient height and in terms of body weight variability. Given that these are quantitative indicators, a detailed assessment requires analysis of a large number of patients. With regard to habitus, we confirm the results from studies showing that linearity in body composition is more common in patients with schizophrenia.

We found that this linearity is more characteristic of drug resistance. This fact gives grounds in clinical practice to make an early assessment of the habitus and to approach with caution asthenic patients in the preparation of the therapeutic plan.

Conclusion:

We found that in the group with resistance to therapy asthenic habitus and lower dynamics of body weight during treatment are more characteristic. Our results showed that the analysis of anthropometric data in the therapeutic process outlined certain trends that are guiding in terms of the results of treatment. On the other hand, the general change in anthropometric parameters should be taken into account and is a factor related to adherence to therapy and thus could indirectly affect the outcome of treatment in patients without therapeutic resistance. These changes in anthropometric parameters are important to take into account when designing a treatment plan for patients with schizophrenia.

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Измерители и подходи за измерване на болничния продукт

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Measurements and approaches to measuring of the hospital product

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РЕЗЮМЕ:

Най-точният подход за определяне на разходите в една болница е „Методът АВС". При него всяко болнично звено се дефинира като разходен център „произвеждащо"някакъв междинен или краен продукт. Към настоящия момент все още няма методика, по която да се отчита и остойностява труда и на лекарите, и на медицинските специалисти на равнище вложен труд за конкретен пациент, както в България, така и в международен аспект. Индивидуално определими разходи на равнище конкретен пациент са за храна, медикаменти, консумативи, лабораторни изследвания и някои други. Разходите от типа „Среден разход за пациент с диагноза „Х" или „Среден разход за пациент от Диагностично-свързана група „Z", могат да се определят с достатъчна точност за практическите цели. Чрез подхода „Среден разход за пациент с диагноза „Х" и „Среден разход за пациент от Диагностично-свързана група „Z", могат да се определят както локалните разходи за всяка болница, така и Националните средни разходи.

Ключови думи: болничен продукт, краен продукт, междинен продукт, Метод „АБС", локални и национални разходи.

ABSTRACT:

The most precise method and approach to determine the expenses in a hospital is the „ABC method", known for the fact that any hospital ward or a devision is defined as an expense-center, „cultivating" some kind of intermediate or a final product. Up to the moment there is not existing a method, according which the work of the medical specialists could be calculated - both in Bulgaria, and abroad. If we speak about an individual patient, the expenses are for food,medical consumatives and supply, lab tests and checking, etc. The expenses of the kind „Mean expenses for a patient X", or „Mean expenses for a patient of diagnostic-connected group Z", could be checked most precisely practically. Using the approach „Mean expenses for a patient X", and „Mean expenses for a patient of diagnostic-connected group Z", could be possible to count the local expenses for any hospital, as well as the National mean expenses.

Key words: Hospital product, final product,intermediate product, „ABC – method" local and National expenses.

Introduction:

There are 2 reasons, which make the measurements of the hospital product important. The first one is that the hospitals themselves are commercial cooperations and economic subjects, making and suggesting own, product(s) to another (other) economical subjects. The second reason is that there are already formed economical subjects, ready to buy these specific hospital products. Those are the National Healthcare Insurance System, Cooperations and Companies for healthcare insurance on a volunteers" principle, Private Healthcare Companies, as well as people, paying directly for a certain health and hospital product.

The final product of a hospital is the treatment of a patient. The treatment itself is a mixture of many and different deeds, done for the patients „sake and security in the hospital. All these deeds come to be intermediate products of the hospital, so, they determine its" structure into several parts – in order to make the management easier and more effective, and all.

Finally-the thorough definition of the final and intermediate products, proposed by the hospital are of great importance, so is the accounting of any subdivision of the structure of the hospital. The book-keeping of the expenses is usually done on the shelf of several levels, like:

1st level – expenses for a certain patient;

2nd level – expenses for a certain ward or department;

3rd level – expenses for a hospital.

On the other side, the expenses are devided into constant and variable, like:

- Constant – do not change in accordance to the volume of activities;

- Variable - in direct proportion, according to the volume of activities.

The expenses must be disposed thoroughly among the intermediate products of the hospital in order to check the calculation of the final product. The process of accumulating of all expenses of the intermediate products, used by the patient leads us to the point, concerning the expenses of any patient. The general expenses, done for a patient in a hospital is a sum, equal to the certain and specific so-called patients" expenses, i.e.- medicaments, food, manipulations, check-ups, lab tests, procedures,consultations, rehabilitations, etc. Thus, the hospital management gets known about all the expenses, made for everybody.

Material and methods:

The whole hospital work – diagnostic, theurapetic, paraclinical examinations, etc., are classified into several subdivisions, groups and subgroups, so the result is a list of items, nomenclatures of the hospital works. These nomenclatures are based for a certain hospital, National and International level. There are different types, such as for 10, 15, 100 and over 1000 nomenclature items, while the division of the expenses of the administrative layers in accordance to those, supplying the real medical procedures is done by 4 methods:

- method 1 – division in groups.

We may use the following formula for making known about the expenses of each branch, i.e.:

- Ka = Xa I (X+X+....Xn) I, so Ka = coefficient for division towards branch „a",

- Xa = quantity of the intermediate products, used by the branch.

- method 2 – a direct method for division;

- method 3 – comes to be a method for stepping division;

- method 4 – simulative method for division.

Results and discussion:

1. Approaches for measuring the expenses of a certain unit hospital product. We suggest 5 levels, i.e., one by one:

- level 1 – a method for separative calculating of the expenses.

According to the quantity of the product and the expenses come in view the „expenses for a unit product", „mean expenses for a patient", „expenses for a bed-day", „expenses for an examination", „general expenses for the examination rooms", clinics, wards and for the whole hospital. The specific point of the trend here is all the expenses for the laboratory deeds, administration work, additional nonhealthy staff are devided into the whole expenses of the clinics and wards. This approach is a simple one.

- level 2 – calculating the expenses objective plan.

The approach increases the preciseness, the exactness, in calculating the expenses.Along with the expenses of the clinics and wards, there are expenses of the other parts for reaching the so-called intermediate product. There is a possiibility to check the expenses for a certain examination, for a manipulation, for an X-ray examination, etc. All these expenses could be added into those for a concrete clinic, or an ward - in accordance to the specific product, thus to increase the preciseness of the analysis.

- level 3 – ABC method.

The specific here is that any hospital particulate is devided as a final expenses centre, „producing" some kind of intermediate or a final product. The whole expenses are re- calculated and thus the final expenses of final hospital product are checked. This comes to be the most exact approach for calculating the expenses in a structural and unit-source point of view.

- level 4 – checking the mean expenses according to the different illnessess groups.

The results are: indexes of the kind: „mean expenses for a treatment of a patient from disease X", (or a group of diseases), or "mean expenses for a treatment of a patient from a „diagnostic -connected group Z". The approach gives the opportunity to check precisely the mean expenses for a treatment of a patient – on the basis of the stylistic economical accounting – concerning any hospital clinic, ward and the hospital as a whole. The expenses for patients with similar diagnoses, or equal such, are getting to the mean prefixes, then – mean expenses are getting on.

- level 5 – approach „Individual expenses".

Here the individual expenses for every patient are calculated. That is why there are 2 types of calculation, i.e.:

- approach 1 – using a „pricelist" and nomenclature of the hospital medical deeds. Any procedure for a certain patient A,B,C,etc. is registered and checked thoroughly. The mean expenses are forwarding calculated in a „pricelist", a part from the nomenclature. Then the individual expenses for a patient A,B,C, etc. are summed up, for every performed procedure.

- approach 2 – a „subject" method for calculating the individual expenses for a hospital treatment.

The achievement is as it follows:

A – calculating the expenses for medical and all staff labour – for a certain patient.

B - calculating the expenses for a general hospital treatment, administrative -community expenses, etc.

C - expenses, precisely well being checked, as: food, medicaments, consumatives, lab - checkings, procedures, interventions. The final result is the sum of expenses for a patient A,B,C,etc.

2. Distribution of the expenses for a unit intermediate product:

- 1 st stage: checking the intermediate products – for later expenses;

- 2 nd stage: forming groups of these intermediate products into several basic groups;

- 3 rd stage: declaring different types of expenses, according to the groups;

- 4 th stage: an estimation of the mean consumption of expenses for each group, thus – checking the mean coefficients;

- 5 th stage: distribution of the done already expenses, according to an unit product, by the help of mean coefficients, registered in part 4.

3. Measuring the final product of the hospital.

When the expenses of the intermediate medical products are ready, and the volume of an unit intermedia of the product is on, then the next step is they both to be checked and used for calculating the final medical product for a patient in a hospital. So, then summing up of all the expenses for the used intermediate products is going on. The all general expenses for a patient comes to be a sum of used by him (her): medicaments,food, manipulations, lab – tests, procedures, rehabilitations, etc. Finally, every period of time should be registered by different sums of money, for the performed in the hospital procedures. In this way the administration of the hospital takes great care of all the expenses for every patient. That is why there is a great need of an automatic informative system - for checking the expenses of the final product. It is necessary all the intermediate product to be presented, thus the calculation of the registered expenses should be done early and precisely.

The total sum of the expenses of the final product depend not only on the already done intermediate products, but on also some other

particularities,like – total number of recovered patients, types of treated illnessess, financial management of the hospital, inflation index, etc.

The calculation of the final product of the hospital is done for a certain period of time – a month,3 months, 6 months,an year.

4. Any kinds of problems in checking the National and local expenses:

Finally, there is one more problem, to be dissolved here – that for the local and National expenses. Every hospital has the opportunity to check its „own expenses for the done already hospital deeds by its" own nomenclatures and methods, and approaches.Thus, the results are registered as „local expenses" for these deeds. So, they should be used to some extent by the government of the hospital. Let's imagine that all the hospitals should use one and the same, equal nomenclatures and methodological approaches for estimating and calculating the expenses, so the final local expenses for a unit performance should be Nationally comparing. This will increase partly the abilities of the hospital management.

If, on a basis of local expenses, using different methods and experts opinions are calculated units for expenses for the whole country – for a unit hospital performance, then we gain the so-called National expenses.

So, the National expenses could be able to be used for different management aims:

- comparing the local with National expenses in order to extend to the optimum management decissions;

- distribution of the resources in a regional and National aspect;

- payment to the hospitals by: National Health Care System, „Municipalities, Cooperations for Volunteers" Health Supply, the Ministry of Health, etc. - directly to the hospital.

5. Discussing about possible precise agree of the expenses checking for a treated patient in a hospital:

- the discussion itself must diverse between the 2 edges – expenses and effectiveness.

- the preciseness of the process of accouning the expenses of a certain hospital product, do increases the abilities for effective management of the hospital – in general, and of any its particular district. Effective management of a hospital means less expenses for a unit product – during appropriate sircumstances. The most precise effectiveness in measuring the expenses needs more informative resources – from medical side. Finally, we came to the point – and the point is that the health manager must look for a rational balance between the 2 edges – the expenses and the effectiveness. That's why we suggest several basic background dots in the process for looking for such a balance:

- A. Due to the essense of the hospital expenses, the maximal preciseness in calculating the expenses for a unity product, comes to be absolutely limited. For example, let"s regard he hypothetic patient X.Y.Z. and discuss the individual expenses for his treatment,so they are: - expenses for medical labour – comes to be practically uncounted and unappropriate marked. There is not still such a method, according which, one can do that.

- expenses for energy,heat water, fuels, economic, etc. The same situation.

- expenses like: food,medicaments, consumatives, lab tests, etc. - they are individually encounted.

B. The expenses of the type „mean expenses for a patient X", or „mean expenses for a patient", belonging to a diagnostic- connected group Z', could be checked preciselly, practically. In this way could be encountered both – the local, and the National mean expenses. One should analyse the preciseness of the approach „mean expenses for a patient X', in comparision to the approach „mean expenses for a patient in group Z". For the first one there is not need of great economic money funds as far methods and information facilities are concerned. Up to the moment there are no data for evaluating the necessary investments for the approach „mean expenses for a patient in group Z".

C. If we intend to include nomenclatures for the medical deeds, like these nomenclatures for lab tests, manipulations, surgical interventions,etc.,on the basis of a certain hospital, this should be done very carefully, because:

- doing all that comes to be very expensive;

- soon or late there will be such nomenclatures on a National level, so there will be a need for synchronisation between the local and National nomenclatures.

D. Using National nomenclatures should be

done very seriously, with abilities to join them to the European and Internaional such, and to similar standards. As a matter of fact, such practise already exists in the European Union.

E. Initiating in Bulgaria the principles and rules for approaches in checking the expenses of the medical deeds, must become compulsory one. Only then the local expenses of the different hospitals for one and the same medical product could be compareable in a National site. For example, here we may show the experience of Great Britain.

Conclusions:

1. The most precise method for checking the expenses in a hospital is „ABC method", according which, a hospital department is defined like an expense – centre, „producing" somekind of intermediate or a final product.

2. Expenses for labour. Still there is not exist such a precise method for encounting the medical staff labour.

3. The expenses for food, medicaments, consumatives, lab tests, etc., are individually one.

4. The expenses of the type „mean expenses for a patient X", or „mean expenses for a patient in a group Z", could be precisely checked, practically.

5. Using the approach „mean expenses for a patient X", or „mean expenses for a patient in a group Z", could be checked both the local expenses of any hospital, as well as the National expenses.

6. Using the National nomenclatures should be done very carefully, with intention to attach them to such European and International nomenclatures and standards.

7. Initiating in Bulgaria the principles and rules for approaches in checking the expenses of the medical deeds must become compulsary one. Only then the local expenses of the different hospitals for one and the same medical product could be compareable in a National site. For example, here we may show the experience of Great Britain.

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Изисквания към авторите

Списание Българска медицина е издание на Българската академия на науките и изкуствата (БАНИ), Отделение наука, Научен център по медицина и здравеопазване. Излиза 4 книжки годишно. Списанието е достъпно електронно на сайта на БАНИ, раздел издания.

В списание „Българска медицина" се отпечатват оригинални статии, казуистични съобщения, обзори рецензии и съобщения за проведени или предстоящи научни форуми – симпозиуми, конгреси, или други в областта на клиничната и фундаментална медицина. Списанието излиза на английски език с подробни резюмета на английски и български език. Изключения се правят за обзорни статии по особено значими теми. Заглавието, авторските колективи и надписите и означенията на илюстрациите се отпечатват и на двата езика.

Материалите трябва да се представят в два еднакви екземпляра, на шрифт Times New Roman, размер 12, разстояние между редовете 1.5 линии. Обемът на всяка статия е до 10 страници, 12 страници за обзорните статии и 3-4 страници за казуистичните съобщения. Библиографията и илюстрациите са включени в този обем. За информация за научни прояви обемът е до 4 страници, за рецензии на книги – до 2 страници. В този обем не се включват резюметата на английски и български език, чийто обем трябва да бъде до 200 думи с 3-5 ключови думи. Резюметата трябва да отразяват конкретната работна хипотеза, използваните методи, получените резултати и заключение.

Структурата на статиите трябва да отговаря на следните изисквания: заглавие, имената на авторите (собствено име и фамилия), название на научната организация или лечебното заведение, в което работят Оригиналните статии трябва да имат следната структура: въведение, методи, резултати, обсъждане и заключение или изводи. Методиките трябва да бъдат подробно описани, както и статистически методи, използвани в изследването. В теста се приемат само официално приетите съкращения, останалите трябва да бъдат обяснени.За мерните единици се използва системата SI. Илюстрациите се представят като отделни файлове и се посочва мястото им текста за улеснение при предпечатната подготовка.

Тези изисквания не важат за другите научни публикации (обзори, казуистика или съобщения и рецензии).

Книгописът се представя на отделна страница подреден по азбучен ред първо на английски език, после източниците на български език. Броят на цитираните източници не трябва да надвишава 20 за оригиналните статии, до 40 за обзорните статии и до 10 ца казуистичните случаи. Подреждането на библиографията става по следния начин:

За списание: автори, заглавие на статията, списание, година, том, страници от..до.

За книга: автори, заглавие на главата, В: заглавие на книгата, в скоби редактори, издателство, година, страници от…до.

Адрес за кореспонденция се дава в края на всяка статия и съдържа данните на кореспондиращия автор, включително адреса на електронната му поща. Всички ръкописи се изпращат с придружително писмо подписано от авторите, в което се отбелязва, че тя не е била предлагана на друго списание и не е отпечатвана у нас или в чужбина. Ръкописите не се връщат.

Процедура по рецензиране: С оглед спазване на международните стандарти, редакционната колегия е приела процедура по „двойно сляпо" рецензиране от независими референти. На авторите се предоставя възможността да предложат на вниманието на редакционния екип три имена на специалисти в тяхната област като потенциални рецензенти.

ПУБЛИКАЦИОННА ЕТИКА:

Задължения на редактора: редакторът носи отговорност за вземане на решението коя от изпратените статии да бъде

публикувана. Редакторът се съобразява със законовите ограничения, свързани с въздържане от дискредитиране, нарушаване на авторски права или плагиатство. Редакторът оценява интелектуалната стойност на един труд без оглед на възраст, пол, расова принадлежност, сексуална ориентация, религиозни убеждения и др. форми на дискриминация. Редакторът не разкрива информация то отношение на ръкописа на други лица освен рецензентите, авторите за кореспонденция, издателя и другите членове на редакционната колегия.

Задължения на авторите: Авторите следва да предложат оригинални произведения, в които не са използвани трудове и изрази на други автори, без да бъдат цитирани. По принцип авторите не следва да публикуват многократно материал, който повтаря по същество дадено изследване в други списания или първични публикации. Не се приема представянето на един и същ ръкопис в повече от едно списание едновременно. Трудовете и приносът на други автори, относими към предмета на ръкописа, трябва да бъдат отразени под формата на цитирания. Всички лица, които са дали своя принос за концепцията, литературния анализ, дизайна, изпълнението или интерпретацията на данните, следва да бъдат посочени като съавтори. Авторът за кореспонденция носи отговорност за това всички съавтори да бъдат запознати и да са изразили своето одобрение за съдържанието на предлагания за публикуване материал.

Задължения на рецензентите: Рецензентите подпомагат редактора при вземане на решение, като те могат да подпомогнат автора за повишаване качеството на статията. Всички ръкописи, получени за рецензиране следва да се считат за поверителен материал и тяхното съдържание не следва да се разкрива пред никого, освен с разрешението на редактора. Рецензентите следва да се придържат към обективните стандарти за 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. Авторите следва да обяват всички финансови или други съществени конфликти на интереси, които могат да окажат влияние върху интерпретацията на техните резултати. Всички източници на финансиране на проведените проучвания следва да бъдат обявени.

Етически съображения по отношение на самите изследвания: всички трудове, които отразяват клинични проучвания следва да имат подписано информирано съгласие от пациентите и получено разрешение за изследването от съответната Етична комисия в съответствие с Декларацията от Хелзинския комитет. Експерименталните проучвания следва да имат също разрешение от съответната Етична комисия и от Българската Агенция по безопасност на храните и лекарствата.

След положителна рецензия и одобрение на редколегията, авторите на статията дължат заплащане в размер 10 лв на страница на статията си, с оглед покриване на разноските по английската езикова редакция на текста и коректури.

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Delange F, Endematic Cretenism. In: The thyroid (Eds. L. Braveman and R. Utiger). Lippincot Co, Philadelhia, 2001, 942-955.

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