ISSN 2409-9988

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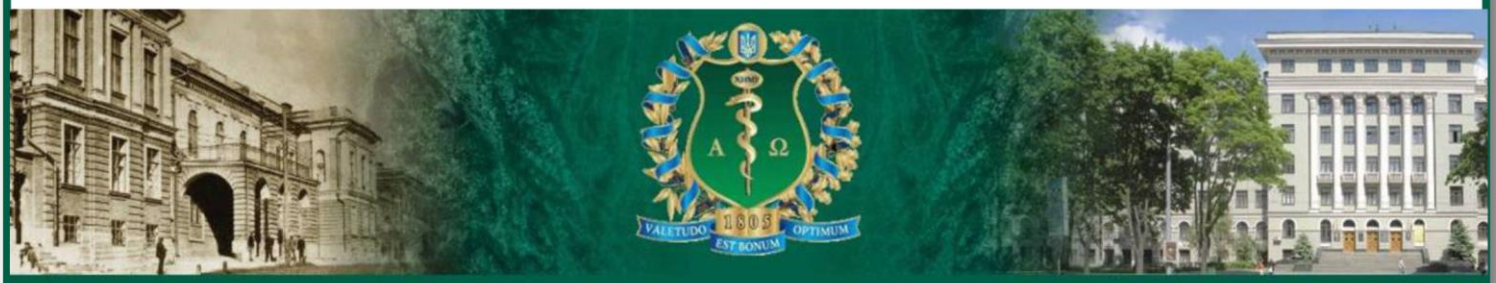

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2017

№3(4)

INTER COLLEGAS

2017

Vol. 4 No.3

OFFICIAL JOURNAL OF
KHARKIV NATIONAL MEDICAL UNIVERSITY
ISSN 2409-9988

Recommended for publishing
by Scientific Council of Kharkiv National Medical University

19 - Oct - 2017

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URL:
http://inter.knmu.edu.ua/pub

Periodicity:
4 times a year

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SURGERY

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THE BI-DIRECTIONAL MIGRATION OF A DYE TRACER INJECTED AT THE EDGE OF PRIMARY OR SECONDARY LUNG TUMORS DURING SURGERY. INITIAL STUDY ON 33 PATIENTS AND CLINICAL IMPLICATIONS

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4 - Biotech
5 - Interventional Drug Delivery Systems and Strategies (ID2S2)

Abstract: Purpose. To assess the loco-regional distribution pattern of a blue dye tracer, as a surrogate for a chemotherapeutic agent, injected in the invasion edge of resectable lung tumor; to evaluate the technique efficacy at staining the lung-tumor interface and the metastatic pathways. Methods. Between November 2014 and September 2015, we enrolled 33 patients (17 women, 16 men; 52-87 years old) presenting with 31 primary lung carcinomas and 2 metastases. We injected in vivo (n=17) or ex vivo (n=16) the innermost side of the tumor invasion edge with 1.3ml methylene blue dye. We performed the injection alone (n=12) or combined with a focal freezing (n=21). We assessed the stain distribution into the invasion-edge, the tumor, the lung or the node(s) at gross and microscopic examination. Results. At gross examination, we observed a quick, intense staining of the invasion edge, and a concomitant staining of the tumor and the lung. The staining pattern was heterogeneous in the tumor, homogeneous in the invasion edge and the lung irrespective of the focal freezing, tumor type, size, or blood perfusion status. The microscopic examination evidenced the staining of the matrix, vessel lumens, and tumor cells, except for lymph nodes. Conclusions. The inner side of the invasion edge looks a suitable location for directly injecting and distributing the methylene blue tracer within the interstitium and related draining pathways during the resection of primary or secondary lung tumor. Fresh resection specimens are convenient to evaluate new edge-targeting injections techniques for the diagnostic or therapeutic management of cell dissemination during surgery.

KeyWords: freezing-assisted injection, lung tumor, methylene blue, surgery, tumor edge injection.

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INTRODUCTION

The resection of the primary tumor and loco-regional lymph nodes is the best curative option for stage I to IIIA NSCLC, but the rate of loco-regional and local plus distant recurrences after curative surgery, respectively 17% to 27% and 39% is high [1]. Adjuvant systemic chemotherapy (ACT) has demonstrated modest survival benefit largely confined to patients with stage II disease [2].

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Many studies suggest that surgery has a pro-metastatic effect potential, likely affecting the disease free survival (DFS) and the overall survival (OS) rates [3, 4, 5, 6]. The search for new multimodal anti-metastatic therapeutic strategies has lead oncologists to consider the initiation of adjuvant chemotherapy during the perioperative period, regarded as a "window of opportunity [3], and/or the loco-regional administration of active agent (s) [7]. Many advocate a more systematic use of the combination of adjuvant chemotherapy and resection for early lung cancer [8].

The metastatic dissemination, arising from a growing tumor, a surgical resection [5, 6] or a biopsy [9] involves cells shedding within the tumor interstitium and the aerial, hematogenous and/or lymphatic drainage pathways, [10,

11]. Thus, the tumor interstitium has increasingly become a target for various diagnosis and therapeutic agents [12]. The peritumoral (PT) and/or intratumoral (IT) injection of chemotherapeutic (CT) agents has emerged as a useful and efficacious method in controlling lung tumors [13, 14,]. The advantages of local over systemic chemotherapy [CT] are an elevated local drug concentration, little or no side effects, and the modulation of local plus distant antitumor immunity [15].

Whether the tumor approach is surgical, endoscopic or per-cutaneous, the gross tumor edge is the usual landmark for assessing the location of the injection needle (s), since it is a marker of the procedure realization and efficacy evaluation [16]. However, the spatial positioning of the needle is based on a rough estimate of the tumor edge, as exemplified with the high variability of results currently observed for lung cancer lymphatic mapping [17, 18]. Chemoablation, a therapeutic method that injects cytotoxics directly in multiple IT and PT sites shows undeniable local cell kill efficacy [14, 19]. Still the procedure lacks a precise spatial reference for the peritumoral needle insertion and therefore remains very operator-dependent. In this translational study, we propose to use a readily locatable region of the tumor edge as a spatial reference for the injection (s); a tumor region that interfaces with the adjacent lung parenchyma and possesses similar interstitial fluid transport characteristics [20].

We describe here the direct injection of a fixed dose of methylene blue dye (MB) in the innermost side of the tumor invasion edge (IE). MB is a small, weakly basic drug, a known localization-tracer for a lung tumor [21], a photosensitizer [22], and a lymphatic tracer [23]. This mono-institutional study includes 33 human patients presenting with resectable stage I-IIIA primary (n=31) or metastatic tumors (n=2). The primary objective was to investigate the MB migration rate, direction and pattern within the tumor and the lung draining pathways. A secondary goal was to assess the seamless integration of the procedure within the workflow of conventional surgery. We evaluated various injection strategies, whether injection was the sole modality or a combination with a nearby focal tumor freezing, and whether the procedure took place during or after the surgical resection. Therefore, we could compare the tracer migration in perfused, in vivo, and non-perfused, ex vivo, lung-tumor samples. The simultaneous focal freezing-and-injection aimed at evaluating whether the combined procedure would affect the dye migration pattern compared to the injection alone, as previously demonstrated in pre-clinical studies [24, 25].

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purposes. Our primary goal was to develop a reliable injection technique of the inner side of the invasion edge of resectable lung tumors. We investigated at gross and microscopic examination the migration rate, direction and pattern of methylene blue (MB) within the tumor and the lung; we compared the staining results whether the injection was the sole modality or was associated with a nearby focal tumor freezing, and whether the procedure took place during or after the surgical resection. . Another goal was to assess the seamless integration of the procedure within the workflow of conventional surgery. The ultimate objective of our research is to use the knowledge gained from this study for the development of intraoperative, antimetastatic local drug delivery techniques during the surgery of lung tumors.

2.2 Subjects & Methods

This study was approved by the Ethics Committee of the Department of Thoracic Surgery, Wroclaw Medical University, Poland. Between November 2014 and September 2015, 33 operable patients had their tumor resected at thoracotomy (Table 1). The patients were chemotherapy naive. They provided their informed consent before the procedure. The clinical suspicion of malignancy was confirmed with preoperative biopsy (n=6), intraoperative incisional (n=20) or excisional biopsy (n=3)-, or core needle biopsy (n=4). The pathology was adenocarcinoma (ADC, n=16), squamous cell carcinoma (SCC, n=7), Large cell carcinoma (n=5), carcinoid (n=1), carcinosarcoma (n=1), small cell carcinoma (n=1), non-pulmonary metastasis

(n=2). Twenty-two of 33 patients presented with IA to IIB stage disease: IA (n=5), IB (n=7), IIA (n=5), IIB (n=5), or with IIIA stage disease (n=6).

Table 1.

Patients, tumors and disease stage

Patients, (33)	
mean age (range), years	*64 (52-87)*
Sex, Male, Female, (n)	*M (16), F (17)*
Histology	
ADC	*16*
SCC	*7*
Large Cell Ca	*5*
Carcinoid	*1*
carcinosarcoma	*1*
Small cell Ca	*1*
Meta (not lung)	*2*
Tumor Stage	
IA	*5*
IB	*7*
IIA	*5*
IIB	*5*
IIIA	*6*
IIIB	*2*
IV	*3*
Surgery	
Lobectomy	*25*
Segmentectomy	*2*
Wedge Resection	*4*
Pneumonectomy	*2*

UICC-Union for International Cancer Control;
ADC-Adenocarcinoma; SCC-Squamous Cell Carcinoma.

Surgery: Table 1 shows the surgical procedures. Except for the two metastasectomy, we performed a mediastinal lymph node dissection (MLD) in 29 patients and a mediastinal lymph node sampling at the hilar and mediastinal level in two. Following the biopsy, and ten minutes after the completion of the injection, lymphovascular dissection and resection procedure were conducted regardless of the staining results. Care of not disrupting the tumor lymphovascular draining pathways during the allotted migration time of the tracer off the injection side was taken. In most but not all patients, the pulmonary artery was ligated before the pulmonary vein. On average, it took 90 minutes from the end of the injection to the resection of the lung-tumor specimen. The total duration of the surgery was 141 minutes (ranging from 90 to 198 min). After the specimen resection and before the closure of the wound, the thoracic cavity was flushed with one liter of saline solution at room temperature.

Injection needle and cryoprobe: The prerequisites for the study were the selection of readily available user-friendly, low-cost instrumentation and drug tracer. For the injection, we used a commercial a 23 G, 50mm needle (BD, http://www.bd.com/pl/) and a self-made depth stop that makes the needle easier to manipulate and keep steady at a known depth, 15mm to 20mm, within the tumor edge, as seen in Figure 1. The needle was connected to a small bore extension line and a 3ml plastic syringe; the fluid line and needle were debubbled and primed before needle insertion; for the tumor edge freezing, a separate cryoprobe (Cp) with a cooling tip-3mm wide, 25mm long, was connected to a nitrous oxide powered console (CRYO-S-II electric, Metrum-CryoFlex, Warsaw, Poland). The cryosystem full functionality was checked prior to any clinical use. We had previously conducted in vitro simulations of the simultaneous freeze-and- injection, i.e. a freezing-assisted injection procedure to determine the temporospatial parameters of the fluid delivery illustrated at Figure 3. We determined that 3 minutes of continuous cooling make an average 3ml ice zone (IZ) in a hydrogel medium; the IZ is impervious to a solution of MB 1%; a 1.5ml volume of MB spreads over about 40% of the ice margin (Le Pivert, data not shown). We assessed in ex vivo freshly resected and deflated lung tumor samples the formation of a similar IZ shape and volume with the same cryoprobe and freeze duration (data not shown).

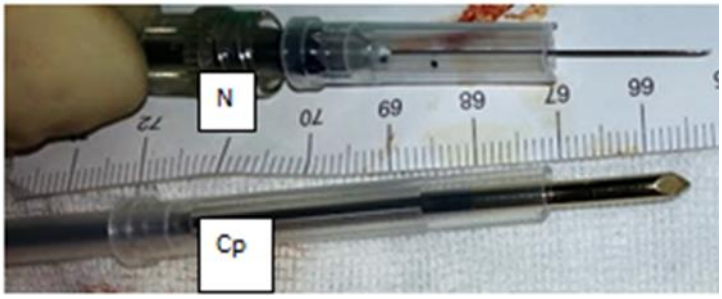

Fig. 1. (Left) Self-made needle (N) depth-stop for adjusting the insertion depth, ≤20mm. The cryoprobe (Cp) is inserted about 10mm apart from the needle. (Right) During surgery, the 23 G needle is seen located in the palpable edge of a peripheral lung tumor.

Methylene blue dye: Methylene blue (MB, American Regent, NY, USA) is a small (MW 319), nanosized molecule (5nm) that has a known safety, and tracing ability in lung tumor [26] and lymphatics [17, 26]. Our method delivers manually and continuously a fixed dose, 1.3 ml of undiluted 1% MB into the tumor invasion edge (IE) over a two minutes period. The dye dosing was calculated as the lowest amount susceptible to migrate within the IE interstitial fluids, the tumor and/or the lung parenchyma as demonstrated or inferred from previous studies [18, 27]. The MB is a weakly basic molecule that resembles some cytotoxics and tends to aggregate in acidic environment, a characteristic of the invasion edge fluids.

Injection procedure: We modelled the fluid space of the tumor invasion edge (Figure 2) as a torus having a mean thickness of 10mm (range: 7mm to 13mm). The torus center line is the tumor gross edge that comprises two fluid compartments: one stretches in the tumor inner side of the gross edge, 1mm [27] to 5mm thick; the other pervades the peritumoral and lung side of the gross edge, 6mm to 8mm thick [28]. It is the region of NSCL cancer microscopic extension. Based on literature [29, 30, 31], a common fluid space for both compartments, each having similar fluid pressure, hydraulic conductivity, and flow velocity was assumed. On a deflated lung, one inserts the needle, equipped with the depth stop, in the innermost side of the visible and/or palpable tumor edge, i.e. 1mm to 5mm inside the margin and 15mm to 20mm deep. We inject the tumor side that faces the interlobar fissure or hilum, a location estimated best for a rapid transport of the tracer in this direction, as shown in Figure 2.

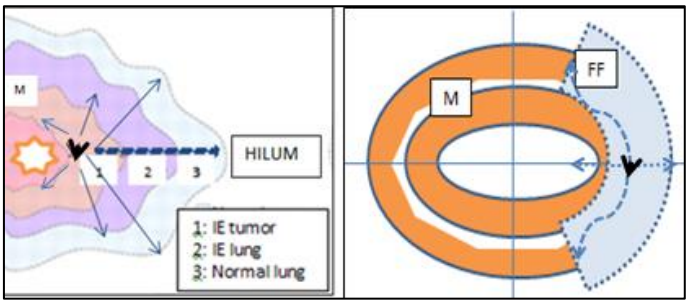

Fig. 2. (Left) Schematic representation of the invasion edge (IE) fluid compartments and injection strategy. (Left) Regions 1 and 2 are the inner and outer interstitial compartments of the gross tumor edge (M) that artificially distinguishes them. The needle (arrowhead) injects the tracer in the innermost side of region 1, and in the tumor quadrant facing the hilum. For the freezing -assisted injection procedure, we insert the cryoprobe (star) between the tumor center and the needle. The frozen tumor tissue surrounding the probe tip acts as an impervious mass to the penetration of the co-injected tracer [24, 25]. (Right) Our model assumes a similar fluid flow (FF) in the interstitial fluid compartments of the edge (M, white thick line), along with a similar tracer distribution rate, and pattern. The tracer migrates through the interstitial fluid pathways and the vascular drainage (thin dotted arrows and drawing area) towards the normal lung -3- and the hilum. The injection pressure drives a convergent fluid flow towards the tumor and a divergent flow towards the lung.

Freezing-assisted injection procedure: Our focal freezing-assisted injection procedure (FAI) derives from prior pre-clinical [24, 25] studies that demonstrated the transient imperviousness of the tissue undergoing freezing, i.e. the ice zone (IZ), to a locally co-injected tracer solution; we hypothesized that the IZ "barrier" would facilitate the channeling of the tracer in the low fluid-pressure region.

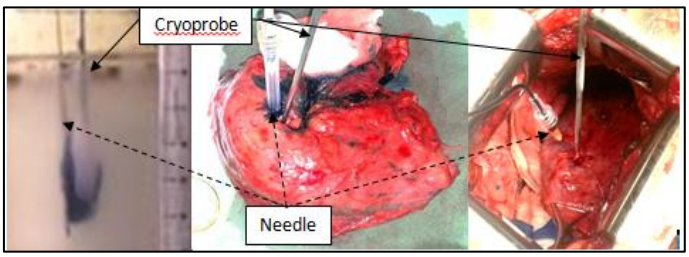

Fig. 3. Examples of freezing-assisted injection procedures. (Left) In vitro simulation in 0.6% agar hydrogel: the 3ml ice zone has an ovoid shape about the cryoprobe and excludes the 1.3ml MB solution that

distributes at the ice-hydrogel interface [37]. There is a 10mm gap between the injection needle and the cryoprobe; (Middle) ex vivo procedure: the needle depth stop sets a 15mm insertion depth and the cryoprobe-needle gap in a freshly resected specimen. (Right) Intraoperative digital photograph of the freezing-and-injection procedure of a peripheral lung tumor conducted on a collapsed lung, before the vascular ligature.

Study groups: In the in vivo group (n=17) - intraoperative freezing and MB injection (n=11) or the MB injection alone (n=6) preceded the vascular dissection and tumor resection. In the ex vivo group (n=16), ten freshly resected tumors were frozen-and-injected to evaluate the MB dye transport and distribution in the non-perfused lung-tumor interface and peritumoral tissue; six tumors were injected ex vivo without simultaneous freezing, as seen in table 2.

Table 2.

Patients Study Groups

SERIES	PROCEDURE		Tumor Volume Vt (cm3)	MB Dose % (Vt)	Ice Zone % (Vt)	Migration Time (min.)
	IN-JECT	FREEZE-INJECT				
In vivo (n=17)	6	11	15.8 (4.1-317)	9 (0.1-46)	19 (1-107)	15 (90)
Ex vivo (n=16)	6	10	17.8 (5.3-84.8)	7 (2-24)	15 (4-57)	15

The median tumor volume Vt, (range) is calculated with the formula: 4/3 pi(r1*r2*r3); the methylene blue (MB) dose and ice zone (IZ) are estimated as a volume percentage of Vt (range). The migration time is the time during which the MB can distribute into the tumor and the lung. In vivo, the grander migration time is due to the tracer transport in the perfused tissue followed by a migration in the non-perfused tissue following the intraoperative vascular ligature-section.*

The intraoperative procedure was as follows: the tumor biopsy was performed far from the injection site, before the injection procedure. On the deflated lung, the needle equipped with its depth stop was inserted in the inner side of the visible and/or palpable edge. The continuous injection of the 1.3ml MB dose took about 2 minutes, an injection rate of about 0.70ml/minute. For the freezing-and-injection procedure, we inserted the cryoprobe tip (Cp) inside the palpable tumor edge; The Cp was always located closer to the tumor center than the needle, as shown in Figure 2. Upon its activation the Cp froze, stuck and helped with keeping the tumor steady during the needle insertion in the tumor inner edge, about 10 to 15 mm apart. We initiated the tracer injection after 30 sec of freeze, and we pursued the freezing during the MB injection for 2 minutes. Next, the active thaw detached t the cryoprobe from the tumor within 2 to 3 seconds. The freeze-injection procedure took about 15 minutes from start to completion. The time available for the evaluation of the tracer distribution into the vascularized tumor and/or the lung parenchyma (Table 2) was about 15 minutes before any lymphovascular dissection, and about 90 minutes before the resection. We recorded the staining dynamics with time-stamped digital photos.

For the ex vivo procedure, at the completion of surgery, we injected sixteen freshly resected samples in the operative room with the prescribed techniques and allowed a 15 minutes migration time for the tracer as seen in table 2. The injection site was not massaged.

Staining evaluation: Following the procedure, the lung-tumor specimen was cross-sectioned in a vertical plane defined by the needle and the probe tracks, and a horizontal plane passing in the middle of the tumor. We measured and took digital photographs of vertical and horizontal cross-sections of the lung-tumor specimen. A macroscopic visual assessment of the staining pattern, localization, and spread, including the previously frozen region was made. The MB dose and the ice zone volume were similar in order to evaluate whether the tumor characteristics and/or their perfusion status would affect the MB distribution pattern. Frozen sections of the blue stained tumor and edge were measured to determine the microscopic distribution of the tracer. The microscopic examination was completed with a conventional formalin fixation and HE staining on all specimen.

Post-operative therapy and follow up: All the patients presenting with stage II to IV disease (n=21) were treated with cisplatin-based doublet adjuvant chemotherapy (ACT), 3 to 4 weeks after the surgery. External beam radiotherapy was associated for one patient. Eleven patients had no adjuvant therapy.

Statistics

Given the limited number of cases and the qualitative aspect of the study, we did not conduct any statistical evaluation.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

The staining rate, localization and pattern of methylene blue (MB) within the edge interface, the tumor and the lung exhibited large variations.

Staining rate and spread: The MB constantly stained the lung-tumor interface and migrated within tumor and the surrounding lung. At gross examination of the tumor cross sections the dye was spreading over 30% to 50% of the tumor perimeter for 27/33 (81%) cases, and over 50% of the perimeter for the rest. The stained area was grander, >50%, in the tumor core or in the contiguous lung, respectively for 7/33 (21%) and 6/33 (18%) procedures. This intra- and extra-tumoral localization of the MB tracer was similar for the in vivo and ex vivo cases, regardless of the MB migration time; a time that was inevitably longer in vivo compared to ex vivo as shown in Table 2. In all cases, the MB stained the cryoprobe site either during the thaw of after the full melting of the frozen tissue, but never during the freezing.

Staining pattern: the gross staining pattern was heterogeneous, patchy and mosaic-like, or confluent in the tumor; strikingly, it was homogeneous in the tumor edge and the contiguous lung, as exemplified in table 4 and figure 4. We observed an equivalent pattern in all specimens, regardless of the injection technique -freeze assisted or not- , the tumor pathology, dimension, or perfusion status.

Table **3.**

Lung-tumor interface MB staining.

Tumor + Edge + Lung	ADC	SCC	Large Cell C	Met	Ca.S	Small Cell C	C.oid	**Total**
L + M + S	3	1	2	---	1	---	---	7
M + M + M	10	4	2	2	---	1	1	20
S + L + L	4	2	---	---	---	---	---	6
Total	17	7	4	2	1	1	1	33

On fresh tumor gross sections at visual examination, the MB distributes more largely within edge and tumor in 7 cases (upper row) and within edge and contiguous lung in 6 cases (lower row). In all cases, the tumor edge staining is constant and bidirectional: towards the tumor core and towards the lung, regardless of the tumor characteristics, the blood perfusion status, or the simultaneous freeze. We grade the stain spread on the tumor cross sections (left column) as large (L: >50%), medium (M: 30% to 50%), or small (S: <30%). In 20 cases, the M+M+M category, the stain distributed equally in the tumor, the edge and the lung. ADC: adenocarcinoma; SCC: squamous cell carcinoma; Ca.S: carcinosarcoma; C.oid: carcinoid.

The tracer distributed within the tumor active and necrotic zone (s), within the thawed zone and into the lung parenchyma.

The ice zone (IZ) surrounding the cryoprobe, was purposely of small size, about 15% to 19% of the tumor volume as seen in table 2; we calculated it to be 40% to 50% of the torus equivalent invasion edge model, for the ex

vivo or in vivo procedures (data not shown). Although the IZ was impervious to the simultaneously injected tracer, it did not prevent the dye from migrating towards the tumor core and away from it towards the lung in an injection only-like pattern.

Table 4.

Lung-tumor interface MB staining.

Pat-tern	ADC	SCC	Large Cell C	Met	Ca. S	Small Cell C	C.oid	Total
Con-fluent	11	4	2	1	---	1	1	20
Patchy	6	3	2	1	1	---	---	13
Total	17	7	4	2	1	1	1	33

The tumor-staining pattern is independent of the injection procedure (freezing-assisted or not), tumor characteristics and/or blood perfusion status. ADC: adenocarcinoma; SCC: squamous cell carcinoma; Ca.S: carcinosarcoma; C.oid: carcinoid.

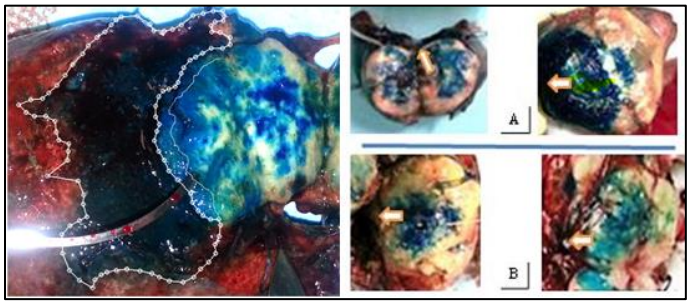

Fig. 4. Staining localization and pattern observed in lobectomy specimens post injection or post freeze-injection. Left: freehand ROI delineation of the homogeneous inner and outer edge staining compared to the patchy staining, >50%, of an ADC tumor core. Right: the homogeneous and constant staining of the invasion edge (arrows) and of the contiguous lung departs from the tumor core patterns: mosaic-like in A, confluent in B. The Mb distributes on both sides of the invasion edge. ADC: adenocarcinoma.

Microscopy: The microscopic examination showed similar in vivo and ex vivo aspects: the dye distributed in the tumor edge matrix, interstitial fluid spaces and randomly within the cells and nuclei. The tumor structures, including the freezing zone, remained recognizable. The necrotic zones and post-freeze alterations were unremarkable as illustrated in Figure 5.

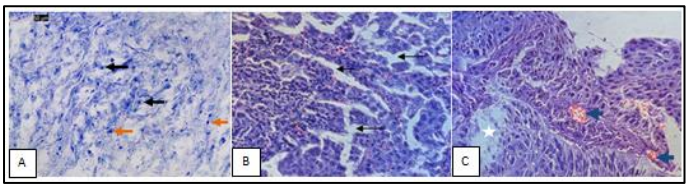

Fig. 5. A: the frozen section (Scale Bar-100µm) of an ADC injected ex vivo evidences a uniform tracer distribution in the stroma, and the random staining of the tumor cells (black arrows) and nuclei (orange arrows). B: an H&E stained ADC section (200X) previously frozen and injected, evidences a predominant papillary structure and an identifiable grading (G3); large intercellular spaces (black arrows) due to post-freeze interstitial edema are also visible. C: an H&E stained SCC section (200X) shows necrotic zones (white star), and early thrombosis of vessel lumens (blue arrows).

Staining dynamics: The tumor and the lung staining was fast and visible within 10 minutes of the injection; however the tracer was not detected in the interlobar, hilar or mediastinal region and lymph nodes at the time of resection, 90 minutes after the injection.

Injection associated devices: The needle depth stop facilitated the injection procedure. In the beginning of our study, we found out that the tumor contours and the edge were not always easy to delineate or palpate; an additional difficulty was to insert a bare needle in the tumor edge while insuring that it did not transfixed the tumor. The self-made depth stop of figure 1 helped with setting an insertion depth and maintaining the needle still during the injection. We also used the sticking effect of the activated cryoprobe to manipulate the tumor and ease the needle insertion during the freezing injection procedure. There was no significant bleeding during or after the removal of the Cp from its tract.

The injection procedure(s) blended well with the normal surgical workflow: The inclusion of the freeze-injection procedure added an average 17 minutes (range, 15-20) to the operative time; it went uneventfully on the 17 in vivo patients. There was no significant loss of MB dose from reflux or leakage. In 6/33 cases a reflux estimated at <100ul for, i.e. 6% of the MB dose, occurred

during the needle removal, and the lost dose was not compensated for. In one case, a minor leakage of the dye occurred in the bronchial tree during a wedge resection. The procedure was not associated with any side effects or intraoperative or postoperative adverse event.

DISCUSSION

Our study primary objective was to investigate the intraoperative distribution pattern of a blue dye tracer injected in the inner side of resectable primary or secondary lung tumors stage I to IV. We selected MB dye as a surrogate for a cytotoxic agent. The ability of a concomitant focal freezing to drive the directional flow of the tracer was explored, and the influence of the blood perfusion status on the dye migration was compared. A secondary objective was to evaluate how well the procedure integrated with the conduct of a conventional surgery. The ultimate objective of our research is to use the knowledge gained from this study for the development of intraoperative, antimetastatic edge-targeting injection techniques during the surgery of lung tumors.

Our results, illustrated in table 3-4 and figure 4, show that the dye distributed constantly and homogeneously within the edge and the contiguous lung; this migration reached also the tumor core where the staining pattern was heterogenous. The tracer localization rate, spread and distribution pattern was unrelated to the injection technique, the volume, pathological characteristics, or the vascular perfusion status of the tumor. The ice zone, conversely to the post-thaw zone, excluded the tracer. In all cases, the dye stained the interstitium of the lung-tumor interface.

The homogeneous staining pattern of the IE, contrasting with the heterogenous tumor staining was striking but predictable. Indeed, when selecting the inner side of the IE for the injection we assumed equivalent fluid transport properties in the edge interstitial fluid space, a space estimated to stretch over the innermost and outermost side of the tumor gross edge [27, 28]. We also hypothesized higher odds of reaching the fluid dissemination pathways with injecting the inner side rather than the outer side of the edge, where watershed regions [32] might have pooled the injected fluid. Given the known properties of the edge interstitium, including similar low interstitial fluid pressure (IFP), interstitial fluid flow (IFF), pore structure and hydraulic conductivity [27], we inferred that the small hydrophilic MB tracer would disperse homogeneously and convectively from the inner edge injection site outwards [33, 34]. Remarkably, a study by Vignaud et al. [26] demonstrated similar homogenous dye distribution pattern at the edge-lung interface, along with a heterogeneous tumor staining. The authors injected trans-bronchially a single low dose of MB, 0.75ml, into lung tumors a few minutes before surgical resection. Although they were targeting the tumor core, their injection-and-pull technique likely reached the tumor inner and outer margin instead. The tumor staining, 29%, was quite large for the injected dose; a fact probably due to the slow injection rate, 0.37ml/min, known for improving the distribution volume [33]. The two-dimensional dye spread observed in our study, although not quantifiable, looks similar; we infer that the needling technique and the site of injection contributed the tracer distribution more than the dose or the injection rate, that was twofold higher compared to Vignaud [26].

The heterogeneous staining pattern of the tumor core, illustrated in figure 4, is not new [24], confirming the heterogeneous structure of most solid tumors. Such heterogeneity complicates the proper delivery of intralesional chemo-gene- or immuno- therapies, which require that these agents reach all tumor cells within the target [14, 19]. Only multiple local injection sites and/or repeated treatment sessions fulfill in part this objective [13, 35], increasing health care costs and constraints for the patients. The bidirectional tracer migration from a single site of injection was unexpected in light of the published techniques of lung tumor chemoablation [13, 14, and 35] that require both intra- and extra-tumoral injections. To the best of our knowledge, it is the first time that the direct injection of MB in the innermost edge of a lung tumor spreads the tracer in this edge and from there in the tumor and in the lung, as illustrated in figure 2. We think that the

injection pressure and resulting pressure gradient created in the edge is the main driver of the drug flow. For Zhang [36] such flow commences at a 24mmHg infusion pressure threshold; over this threshold, the tumor interstitial fluid channels, usually poorly connected, would open and interconnect. We infer that the convergent flow of the tracer towards the tumor core is due to an injection pressure grander than the interstitial fluid pressure. In vivo the IFP is about 25mmHg in the tumor core, and is slightly positive or close to zero mmHg in the edge [12]; ex vivo, in an integral tumor specimen [33] the IFP is also low, ~3mmHg. The higher migration rate of the dye outwards in the lung, although not quantified, would have a similar ground. The low IFP in the edge-lung region would promote a higher migration spread of the dye, a trend seen in Table 3, due to a larger fluid pressure gradient in this region.

The similar staining pattern and migration, observed in vivo and ex vivo, points to the well-known rapid transport of the small tracer into the interstitium [18]; its clearance through the aerogenous and lymphovascular drainage pathways, probably combines equally with the blood capillary clearance, and may explain the absence of specific accumulation in the nodes. The small dose of tracer or the single site of injection [17] may have been additional accumulation-limiting factors. Nevertheless, the presence of the dye within the interstitial fluids warrants its uptake and migration within the lymphovascular network [29].

The successful but unmodified interstitial transport of the dye during the simultaneous focal freezing and injection of the tumor edge was predictable. No injection failure due to needle freezing and fluid crystallization was observed, a confirmation that we had met with the spatial and temporal parameters for a proper freezing-assisted fluid delivery, as previously demonstrated [24, 25] and illustrated in figure 3. The ice zone, although impervious to the co-injected fluid, as expected [24, 37], could not prevent the dye from migrating around the ice margin. The IZ size was likely too small, about 17% of the tumor volume (Table2), to affect the interstitial fluid pressure gradients and the resulting general direction of the flow.

The tumor edge delineation and the needle insertion were two crucial steps of the procedure. The gross margin was the beacon for the needle insertion, but sometimes it was not directly visible or palpable. The use of atraumatic Duval clamps helped with presenting the tumor edge to the needle; as did the cryoprobe, which could stuck to, lift and orientate the tumor, as described by others [38, 39].

Overall, we estimated the spatial positioning of the needle to be within ± 3mm. In seven in vivo cases, the lung was injected due to an unwanted needle motion off target, and we had to reposition the needle; a fact that lead us to make a depth stop for that small needle diameter. Intraoperative ultrasound for the determination of the tumor edge and more precise needle guidance was not used, due to the likely prolongation of anesthesia and known limitations of ultrasound imaging in the lung [16]. Despite our rough estimate of the exact needle tip location, the consistent patterns of edge staining observed in our study may indicate that the whole edge fluid space is a proper target for an interstitial injection. However, the width of this interstitial fluid space is an estimate [28, 40], and we could not assess a posteriori the exact location of the needle tip due to the rapid spread of the dye.

MB was selected as a surrogate for a chemotherapeutic agent that we could inject in similar conditions. MB is a weak basic drug that gets protonated in the acidic environment of the tumor edge [41] and therefore may disperse mostly in the interstitial fluid space of the edge, as it seems from our study. We anticipate that the chemotherapeutics doxorubicin, mitoxantrone, vincristine, and vinblastine, which are also protonated in acidic environment, and display a decreased cellular uptake [42], would behave like the MB [43]. Additionally the MB tracer could serve as a co-marker of the distribution pattern for the above drugs, except mitoxantrone, a known chromophore. We successfully demonstrated in an animal tumor model the freezing-assisted injection and distribution of MB combined with epirubicin, another weak basic cytotoxic, at the tumor edge; the cell kill was predominant at this stained area [24].

Both injection procedures integrated well within the conduct of conventional surgery at open thoracotomy

approach. Even though the freezing-assisted injection procedure took longer than the single injection, its duration was in the range of published results for intraoperative lymphatic mapping [18]. Overall, the absence of procedural complications, even in the rare occurrence of dye leakage in the bronchial tree, one in our study confirms the safety of the technique [14, 19, 35].

We are aware of some limitations of the study, such as the small number of patients, and the qualitative evaluation due to the heterogeneity of the sampled tumors; both prohibited any statistical analysis. We evaluated the MB distribution pattern by direct visualization at the macroscopic level on a limited number of tumor sections, thus making impossible a precise distribution volume estimate. A specific preparation of the fixated, paraffin-embedded sample [26] might have brought additional microscopic details, compared to those reported only on frozen sections.

Overall, we think this simple study has important clinical implications. The first of which relates to the relative imprecision of the peritumoral techniques of injection, such as used for lymphatic mapping or chemoablation. In light of these preliminary results, any objective analysis of an intraoperative injection made at the tumor edge, either for diagnostic or therapeutic purpose, should use a readily locatable site marker evidencing the needle location; the mere description of this location looks insufficient to analyze a possible injection site and distribution related effect. The second implication relates to the likely but unknown rate and spread of edge staining during conventional peritumoral, multi-quadrant injection for intraoperative lymphatic mapping. A prospective clinical study using blue dye tracer(s) should be conducted; which might bring valuable information on the drug transport in the edge fluid space, and the tumor; further contributing to the development of novel intraoperative antimetastatic edge-targeting therapeutic injection techniques. Such targeting with cytotoxic drug(s) could be the initial rather than the final step of the chemoablative methods currently in use. The outer edge is already the target of no-touch thermal or non-thermal tumor ablation techniques that aim at decreasing the intraoperative cell dissemination [44]. The third implication is a procedural confirmation that the ice margin must cover the whole tumor edge to prevent the co-injected dye from permeating the frozen tumor. However, the post thaw region behaves as a trap for the dye, and therefore a possible modulator of the drug pharmacokinetics during resection [24].

CONCLUSIONS

The inner side of the invasion edge of resectable primary or secondary lung tumors looks a suitable location for directly injecting and distributing the methylene blue tracer within the interstitium and fluid-draining pathways of the lung tumor interface. The edge interstitial fluid space pools and disperses the MB dye bi-directionally within the tumor and the lung, regardless of injection technique, tumor characteristics or blood perfusion status. Fresh resection specimens are convenient tools to investigate further the edge injection parameters, and optimize the drug transport effectiveness to the interstitial fluid pathways of cell dissemination during surgery.

LIST OF ABBREVIATIONS

IT: Intra tumor; PT: peritumoral; IZ: Ice zone; MB: Methylene blue; Cp: cryoprobe; FAI: Freeze-assisted injection

DECLARATIONS

The Study received clearance from the Ethics Committee of the Department of Thoracic Surgery, Wroclaw Medical University, Wybrzeże L. Pasteura 1, 50-367 Wrocław, Poland, NIP 896-000-57-79.

All the patients provided their informed consent before the procedure.

All data generated or analyzed during this study are included in this published article

FUNDING

The Study was conducted under a grant # ST 790 from: Wroclaw Medical University, ul. Grabiszyńska, 105 53-439 Wroclaw, Poland. Tel. 71 33 49 400 or 71 334 94 75; Fax. 71 334 96 03; E-mail: barbara.mroz@umed.wroc.pl or adam.rzechonek@umed.wroc.pl

AUTHORS' CONTRIBUTIONS

AR contributed to the study design, the surgical data

collection, data analysis, and manuscript revision; conducted the surgical procedures. PB and MM contributed equally to the study data collection and analysis. BMB, JA and LF contributed equally to the pathological data collection and analysis. WB contributed to the study coordination, data analysis, and manuscript revision. PLP conceived the study and the delivery technique, contributed to the study design and coordination, data analysis, and writing the manuscript. All authors read and approved the final manuscript.

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Received: 13-Jun. – 2017
Accepted: 21-Sep. - 2017

INTER COLLEGAS, VOL. 4, No.3 (2017)
ISSN 2409-9988

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A CLINICAL CASE OF REMOVING A RESIDUAL FOREIGN BODY FROM THE LEFT SUPRACLAVICULAR REGION

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Abstract: Residual foreign bodies in soft tissues are one of the main causes of chronical infection lesions and decrease in life quality. Surgical treatment is the most common way to relieve the patient from a foreign body. Often there is a question whether to remove a foreign body? On the one hand, all foreign bodies that are in the human body must be removed. On the other hand, in the absence of symptoms, the risk of surgery performed for the purpose of removal exceeds the risk associated with finding the foreign body. We would like to describe a practical case of removing a foreign body (Kirschner`s wires) from the left supraclavicular region. The young patient lived with a fragment of Kirschner's wire left after the osteosynthesis of the fractured clavicle for 5 years. Surgery to remove the residual foreign body was successful. On the 7-th postoperative day the patient was discharged from the hospital under the supervision of surgeons at the place of residence.

KeyWords: foreign body in soft tissue, Kirschner`s wire, surgical treatment.

INTRODUCTION

Foreign bodies (corpus alienum) in soft tissues are common in the surgical practice. The main mechanism of entering soft tissues is domestic, mine explosion, and occupational injuries. In many cases, foreign bodies remain in the patient's body after the surgical treatment. As a rule, these are metal objects (frame plates, wires, etc.) after traumatological surgical interventions [1, 2, 3]. According to the International Red Cross Committee, foreign bodies lying deep in soft tissues should not be removed. Exceptions are as follows:

- foreign bodies causing dysfunction of vital parts (larynx stenosis, hollow organ perforation, bleeding, intestinal obstruction, etc.);
- all foreign bodies accessible during initial wound handling (around 10 % of all foreign bodies);
- foreign bodies causing significant functional disorders or exerting pressure on vessels and nerves;
- indications for late removal of foreign bodies (in case of partial or complete healing of the wound channel) may include sustained wound infection, fistula formation, repeated bleeding, pronounced painfulness.

We have faced a clinical case of a residual foreign body (fragment of Kirschner`s wire) in the soft tissues after osteosynthesis of the left clavicle and would like to share our observations.

A 25-year-old patient presented to the hospital of State Enterprise "V.T. Zaitsev Institute of General and Emergency Surgery of the National Academy of Medical Sciences of Ukraine" with pain in the left supraclavicular region when lifting her 10-kg-baby, which is probably due to the irritation of nerve plexuses. At the age of 20, the patient underwent surgery for clavicle fracture and osteosynthesis with Kirschner`s wires was performed. It was also found out that the frame wire was fractured during removal, and its medial part migrated to soft tissues. The patient lived with a foreign body in the left supraclavicular region for 5 years without any complaints. The patient was examined at the Institute hospital. Laboratory tests were unremarkable. Computer tomography of the thorac-

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ic organs showed that a 70 mm long and 3 mm wide fragment of wire with metal density was visualized in the soft tissues of the left supraclavicular region between the 1st rib and the scalene. The medial end of the wire was attached to C7 left half. Consolidated fracture of the outer third of the left clavicle was also visualized. Figures 1 and 2 show CT scans visualizing a foreign body (Kirschner's wire) in the left supraclavicular region.

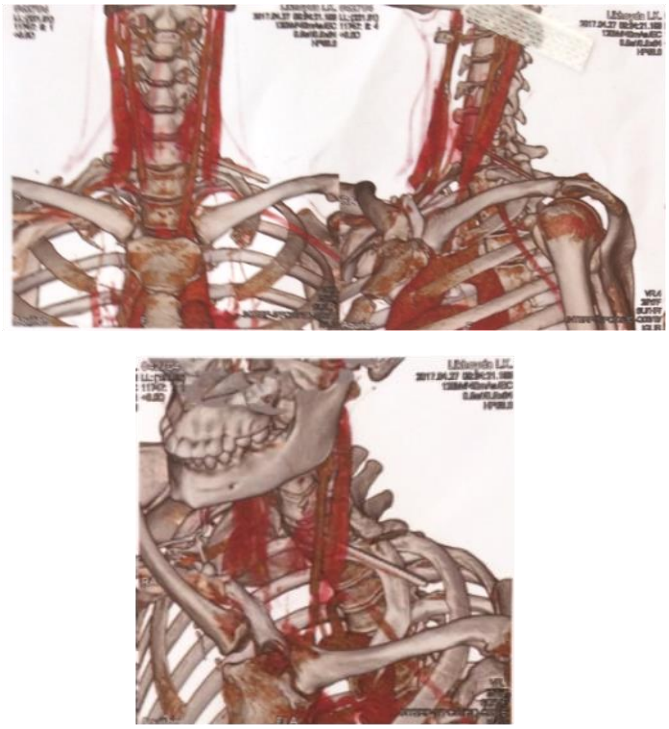

Fig. 1. CT scans visualizing a foreign body (Kirschner`s wire) in the left supraclavicular region.

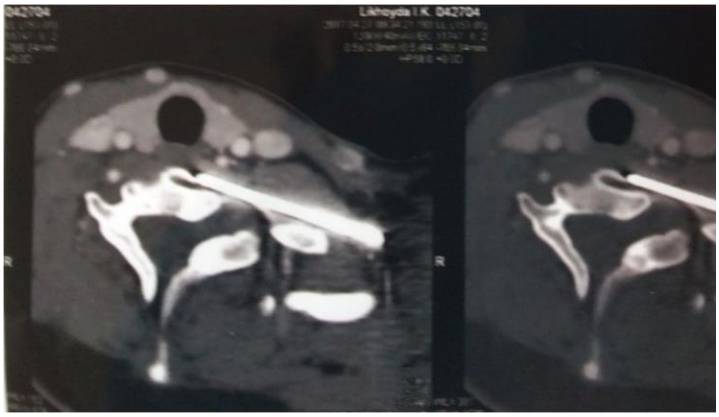

Fig. 2. CT scans visualizing a foreign body (Kirschner`s wire) in the left supraclavicular region.

The foreign body was marked and its depth in the soft tissues of the left supraclavicular region was measured under ultrasound control. Many authors recommend marking the foreign body to avoid technical difficulties during its removal [3, 4].

On 17 May 2017, the foreign body in the left supraclavicular region was removed under general anesthesia. The skin and subcutaneous tissue over the foreign body were lanced under ultrasound control by the projection route based on the prior marking. During the instrumental inspection of the foreign body location from its lateral edge, the foreign body end was identified 2-2.5 cm deep under the skin, seized with the Kocher's forceps and removed (Fig. 3.). Hemostasis was dry. The post-operative wound was sutured layer-wise. The wound was drained with rubber tube drainage. Iodine. Aseptic bandages.

Fig. 3. A fragment of Kirschner's wire

Figure 4 shows the fragment of Kirschner`s wire as compared to the size of surgical forceps. During the post-operative period, the patient received antibacterial, anti-inflammatory, and infusion therapy leading to progressive improvement. She was discharged from the in-patient department 7 days later.

As a rule, Kirschner`s wires are used to fix thin bones, including clavicles. After such interventions, wires should be removed 8-12 months after the surgery because clavicles usually need longer and more stable fixation [1, 5, 6].

Fig. 4. A fragment of Kirschner`s wire as compared to the size of surgical forceps.

There are cases of unsuccessful removal when the wire is fractured and its medial part migrates into soft tissues. A foreign body unnoticed or left in soft tissues becomes an infection lesion around which infiltrate or abscess is likely to form. It is also likely that a fistula may form around the foreign body. Originally, sterile foreign bodies, such as Kirschner`s wires, get encapsulated after osteosynthesis without abscess, however, there is a risk of infection [7, 8, 9, 10].

CONCLUSIONS

Based on the data obtained, it can be concluded that the risk of large vessel damage and constant irritation of the nerve plexus causing clinical symptoms in patients justifies surgical interventions for the removal of residual foreign bodies in soft tissues.

CONFLICT OF INTERESTS

There is no conflict of interests.

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Received: 08-May. – 2017
Accepted: 21-Sep. - 2017

INTER COLLEGAS, VOL. 4, No.3 (2017)
ISSN 2409-9988

THERAPY

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STATE OF HUMORAL IMMUNITY IN PATIENTS WITH ASTHMA COMBINED WITH OBESITY

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Abstract: It was found out in patients having asthma combined with obesity that in cases of a higher body mass index versus patients with asthma and healthy persons the "waist/hip volume" ratio was reliably increased. An examination of the state of humoral immunity indices in patients with asthma found out an increase of non-specific (with rising concentrations of immunoglobulins Ig A, M, G) and specific (with a rising level of Ig E) immunity. Patients with comorbidity of asthma and obesity revealed differently directed changes in the concentration of the main immunoglobulins: with a decrease in the levels of IgA and IgM there was a significant increase in the concentration of IgG. Those changes were accompanied by a significant reduction in the number of circulating immune complexes and an increasing concentration of lymphocyte antibodies in the blood of patients with comorbidity of asthma and obesity. This fact may indicate an aggravating effect of obesity on the course of asthma and a change in the direction of the pathological process to the autoimmune one that should be taken into consideration when treating such patients.

KeyWords: asthma, obesity, humoral immunity.

INTRODUCTION

In recent years the attention of researchers and doctors of different specialities is more and more attracted by the problem of comorbidity, which means a combination of several chronic diseases in one patient [9, 15]. Modern studies of the incidence of asthma in patients with different levels of an increased body mass index (BMI) have revealed a direct dependence of the increased rate of asthma development upon an increase of the BMI [12, 21]. Asthma and obesity are prevalent disorders, each with a significant public health impact, and a large and growing body of literature suggests an association between the two. Meanwhile it has been found out that overweight and obesity occur in asthma cases twice more frequently than in the population on an average [13].

GINA (2014) recommendations point out the necessity of the personalized approach with regard for individual peculiarities of the asthma course in each particular patient and draw a parallel between the success in achieving control over asthma and comorbid states, which can influence difficulties in diagnosis and efficacy of the given therapy [11, 14].

An imbalance of the subpopulation structure of T lymphocytes that underlies pathogenesis in asthma facilitates development of a chronic local inflammation with participation of cellular and humoral reactions [2, 18]. The current focus on the fatty tissue as the source of both energy and proinflammatory mediators, which are also mediated by T helpers (Th) type 2 [7, 17, 20], causes a more thorough study of the immune system in patients having asthma combined with obesity. Cellular immunity changes are accompanied with disorders in the humoral component of the immune system.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose of this work is to study to study the state of humoral immunity indices in patients having asthma combined with obesity.

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The study was conducted in compliance with the asthmasic plan of research and development (R&D) of the State Institution "Kharkiv National Medical University" and is a fragment of the R&D subject "Factors of the development and progression of different phenotypes of bronchial asthma, chronic obstructive pulmonary disease and community-acquired pneumonia: peculiarities in the course, comorbid states, their prognosis and prevention" (State registration No. 0113U002280).

2.2 Subjects & Methods

The research was conducted on 121 patients with a moderately severe course at the age of (51.6 ± 4.7) years, including 51 (42,2 %) men and 70 (57,8 %) women. Of the examined patients, there were 46 cases with ASTHMA and normal body weight (group I) and 75 cases having asthma combined with obesity (group II). The control group consisted of 21 healthy donors of the same age and gender. Asthma was diagnosed according to Order of the Ministry of Health of Ukraine No. 127 dated March 19, 2003; the presence of obesity was determined by calculation of the BMI. All the examinees had their waist circumference (WC) and hip circumference (HC) measured and WC/HC ratio calculated.

The performed studies involved the state of the cellular and humoral components of immunity and phagocytosis with help of revealing: subpopulations of T and B lymphocytes (CD3, CD4, CD8, CD16, CD22) in absolute and relative values using "NVL Granum" diagnosticum (Ukraine); levels of IgA, IgM and IgG of blood serum by the Mancini technique [16] with help of reagents of the Federal State Unitary Enterprise "Microgen Scientific Production Association" (Ministry of Health of the Russian Federation, Russia); circulating immune complexes (CIC) using the technique developed by V. Haskova et al. and modified by Yu.A. Grinevich and A.I. Alfiorov [1]. Phagocytosis indices (phagocyting neutrophils, phagocyte number and neutrophil activation index) were studied by the principle of the ability of polymorphonuclear leukocytes and monocytes of peripheral blood to bind on their surface, absorb and digest microbe test cultures, NBT test modified by B.S. Nagoev [5]. A computer data asthma of the obtained indices was created in Microsoft Excel. The study materials were statistically processed with use of SPSS 19 program for Windows. Infinite variables are shown in the form of the median (Me) and values 25-75 (Q25-Q75). The critical level of significance in checks of statistical hypotheses was accepted equal to 0.05. Dependencies between the variables were studied with use of the Spearman's rank correlation coefficient. The results are presented as (M±m), where M– is the mean value of the index and m– is the standard error. The reliability of the difference of mean values between the groups by quantitative indices during a distribution close to the normal one (the Kolmogorov-Smirnov test) for independent samples was calculated using the Student's t-test.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

The BMI of the patients from group I averaged with Me = 23.4 (respectively, Q25-Q75 = 22.5-24.3; $p<0.001$) that was higher than the control values (Me = 21.7, Q25-Q75 = 21.3-22.8). No reliable difference in WC of the patients from group I versus the healthy persons was detected, though their HC (Me = 101 cm, Q25-Q75 = 98-103 cm) was reliably ($p<0.001$) less than the same index in the healthy people (Me = 111.6 cm, Q25-Q75 = 109.9-114.4 cm) by 9.0 % with the resultant increase of the WC/HC ratio in the patients from group I versus the practically healthy persons by 7 % ($p<0.001$). Despite the fact that BMI in the cases from group I did not exceed the limits of the generally accepted norm, those persons revealed a tendency to increase their body weight versus the practically healthy people. These data coincide with results of studies on an increased rate of excessive body mass in patients with asthma [10, 11, 19]. The cases from group II were diagnosed an excessive body mass with Me of the BMI value equal to 28.9 (respectively, Q25-Q75 = 27.9-30.1) that was reliably higher ($p<0.001$) than the value in group I. In the patients from group I, Me of the WC value was 78 cm (Q25-

Q75 = 75-84 cm, respectively), in group II it being 99.5 cm (respectively, Q25-Q75 = 89-102 cm), which was by 21.5 cm or 27.6 % higher than in group I. In the latter group, Me of the measurement of HC in the patients was 101 cm (Q25-Q75 = 98-103 cm, respectively), while in group II it was 115 cm (respectively, Q25-Q75 = 100-118 cm), which was on an average by 14 cm or 13.9 % higher than in group I. Increases of WC and HC in the patients from group II versus those from group I was also reflected on an increase of their WC/HC index 1.2 times ($p<0.001$); respectively, Me = 0.89 and Me = 0.77.

All the examinees did not reveal any significant differences in analyses of values of their clinical blood test and glucose content.

It should be noted that Me of the IgE level in the patients from group I was 140 IU/l (Q25-Q75 = 120-170 IU/l), it being 2.3 times reliably higher versus the control group (Me = 60 IU/l, Q25-Q75 = 50-65 IU/l). In cases from group II their concentration of IgE (Me = 250 IU/l, Q25-Q75 = 170-290 IU/l) exceeded the control one 4.2 times ($p<0.001$) and the same value in group I 1.8 times ($p<0.001$); this fact could reflect an increasing influence of the accompanying obesity on the state of the systemic allergic inflammation in ASTHMA [22].

Me of the content of IgA in blood of the patients from group I was 4.1 g/l (Q25-Q75 = 3.1-4.9 g/l) and was 1.4 times higher than the control values (Me = 2.9 g/l, Q25-Q75 = 2.8-3.0 g/l) ($p<0.001$). The concentration of IgM in blood of the patients from group I (Me = 1.9 g/l, Q25-Q75 = 1.7-1.9 g/l) exceeded the control one (Me = 1.5 g/l, Q25-Q75 = 1.45-1.6 g/l) too, but less significantly, 1.3 times ($p<0.001$).

The levels of IgA (Me = 3.12 g/l, Q25-Q75 = 2.23-3.56 g/l) and IgM (Me = 1.56 g/l, Q25-Q75 = 1.45-1.76 g/l) in the patients from group II were reliably lower than those from group I (IgA with Me = 4.10 g/l and IgM with Me = 1.90 g/l), respectively, by a factor of 1.3 and 1.2 ($p<0.001$). The value of IgG in cases with combined ASTHMA and obesity (group II: Me = 20 g/l, Q25-Q75 = 18-22 g/l) was 1.5 times higher than that of the control group (Me = 13 g/l, Q25-Q75 = 12-14 g/l), ($p<0.001$), though did not differ significantly from the similar value in the patients from group I (Me = 19 g/l, Q25-Q75 = 18-20 g/l).

The above fact demonstrated that asthma was characterized by an increase of nonspecific immune defence [3]. When asthma was combined with obesity, changes of the blood immunoglobulin levels had different directions: lowering levels of IgA and IgM versus a significant elevation of the concentration of IgG.

The number of lymphocyte autoantibodies in the patients from group I (Me = 11.0 %, Q25-Q75 = 10.0-13.0 %) exceeded the norm 3.7 times ($p<0.001$), and in group II (Me = 15.5 %, Q25-Q75 = 14.0-17.0 %) it was significantly (5.2 times, $p<0.001$) higher than the control value (Me = 3.0 %, Q25-Q75 = 2.0-4.0 %) and 1.4 times higher than the same index in group I ($p<0.001$). The increase in the number of autoantibodies versus lymphocytes, on the one hand, demonstrates the development of the autoimmune component of inflammation [4] in patients with asthma and its further stimulation by the presence of the accompanying obesity and, on the other hand, facilitates explanation of the nature of formation of the secondary immune deficiency at the expense of the cellular component of immunity in asthma [3], this deficiency being also detected in another pathology of internal organs in conditions of its combination with obesity [15].

The blood concentration of the total number of CIC in the patients with asthma (Me = 91 %, Q25-Q75 = 89-93 %) was reliably higher versus the practically healthy people (Me = 93 %, Q25-Q75 = 92-94 %). The above data confirm previously conducted studies of the content of CIC in asthma with different degrees of severity [3, 5] taking into consideration the biological role of these complexes [2]. Herewith the content of CIC in the patients from group I was higher than the similar one in asthma combined with obesity (Me = 89 %, Q25-Q75 = 87-91 %) by 2 % ($p<0.001$). Side by side with an increased number of lymphocyte autoantibodies, the tendency to a reduced content of CIC in patients having asthma combined with obesity can highlight pathogenetic changes in components of a chronic inflammation from immune complex to autoimmune as more aggressive. Such changes in mediators of the chronic

inflammatory process in asthma combined with obesity versus the same ones revealed in patients with asthma, can demonstrate, on the one hand, the aggravating effect of the accompanying obesity on the course of asthma [4, 6, 8] and a potential risk of the development of complications of the disease and, on the other hand, direct the rational and pathogenetically grounded medical influence.

CONCLUSIONS

1. BMI and WC/HC ratio in patients having asthma without obesity are found higher than in practically healthy people. BMI in cases with asthma and obesity reliably exceeded the same index both in the control group and in the patients with asthma.

2. In asthma, increases of the nonspecific and specific components of the humoral immune defence are observed. In combinations of asthma and obesity changes of blood immunoglobulin levels had different directions: with lowering levels of IgA and IgM the concentrations of IgG and IgE significantly rose.

3. Side by side with a reduction in the total number of CIC, a more significant elevation of the level of lymphocyte antibodies in the blood of patients having asthma combined with obesity versus asthma cases without obesity reveals formation of the autoimmune component of inflammation in the comorbidity of asthma and obesity and can affect changes in the cellular component of immunity.

Thus, asthma and obesity have a number of common potential formation mechanisms, among them immunological factors, systemic inflammation, mechanical factors and concomitant diseases.

Further researches will deal with a comparative in-depth study of peculiarities in the immune system mechanisms in patients having asthma and asthma combined with obesity.

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Received: 07-Jul. – 2017
Accepted: 28-Sep. - 2017

THERAPY

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CLINICAL FEATURES OF PSORIASIS WITH COMORBID ARTERIAL HYPERTENSION

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Abstract: The study involved an assessment of medical history data and clinical features of psoriasis in 230 patients, of whom 182 suffered from isolated dermatosis and 48 from psoriasis with comorbid hypertension. The psoriasis group with concomitant arterial hypertension was found to have a significantly higher frequency of stressful situations (81% of cases as compared to 62%) and infectious diseases were registered less frequently (6% vs. 28%). Relapses of psoriasis in this group occurred more often, out-of-season type was observed more than 1.5 times more frequently and seasonal type of dermatosis was registered 2 times less often. Moreover, rapid dissemination of rash during exacerbations in patients with psoriasis with concomitant hypertension was observed two times as frequently (28% of cases vs. 16%), and cases of slow and gradual spread were more rare.

KeyWords: psoriasis, arterial hypertension, history taking, clinical characteristics

INTRODUCTION

The study of the association of psoriasis and cardiovascular diseases is now at the center of scientific interest of professionals around the world. Importance of clinical, social and economic aspects of this issue results in worldwide trials and objective multicenter researches of comorbidity of psoriasis and cardiovascular pathology. Their results allow to consider psoriasis as a risk factor for a wide range of cardiovascular diseases (hypertension, coronary heart disease, myocarditis, damage of the heart valves, atherosclerosis), which often develop at young age and, with prolonged course, lead to congestive heart failure and even death [1-5]. Some recent studies have shown clinical and metabolic disorders with violation of laboratory indications, specifical for comorbid psoriasis, which may have a pathogenic significance [6-13]. Our prior studies revealed a high degree of comorbidity of psoriasis and arterial hypertension (more than 50%), among psoriatic inpatients. Although we identified a definite comorbidity between psoriasis and different metabolic syndrome components, the degree of association of psoriasis and hypertension was the highest [14-15].

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A particular problem is the treatment of psoriasis associated with hypertension, since some antihypertensive drugs reportedly exacerbate the course of dermatosis and may even trigger psoriasis [16-18].

However, the data published on that subject are not sufficient to get a full understanding of the clinical and prognostic significance of this nosology syntropy. The pathogenic and clinical relationship of this impairment is indisputable, which proves the need for better understanding of clinical implications of this comorbidity.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose of the research was to study the clinical features of psoriasis with comorbid arterial hypertension.

2.2 Subjects & Methods

The study involved two groups of patients with confirmed psoriasis, who were under examination and treatment in the inpatient department of Kharkiv Hospital of Skin and Venereal Diseases No. 5. Etiology and disease duration were established on the basis of patient presentation, history taking and clinical examination. Particular attention was drawn to medical history data on comorbid diseases. The main ones included arterial hypertension (AH), atherosclerosis and coronary heart disease. The

severity of dermatosis was calculated using the PASI [19-20] and the study of dynamic clinical status of patients implied evaluation of vital functions, severity of focal neurological and somatic symptoms of cardiovascular, peripheral and central nervous systems, vasculature, muscle system and the musculoskeletal system. AH was iagnosed in cases of diagnosis "Hypertension" established by a physician, or intended antihypertensive therapy or diagnosed high blood pressure (BP) when measuring blood pressure during the examination. High blood pressure was considered SBP> 130 mmHg or DBP> 85 mmHg (the criteria for metabolic syndrome, National Cholesterol Education Program USA (NCEP ATP III, 2001; metabolic syndrome criteria International Diabetes Federation (IDF, 2005)). For at least one week before study, the patients stopped using inhibitors of angiotensin-converting enzyme and / or angiotensin receptor blockers AT 2 and other antihypertensive drugs. Registration ECGs were performed in 12 standard leads with additional leads on the electrocardiograph 6 NEK-4 (Germany). Contractile properties of the myocardium were investigated using ultrasound cardiograph in M and B modes on TI-628 device (Ukraine). All the patients were consulted by clinicians of different specialties. Clinical blood tests and urinalysis were performed by standardized methods.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

The total number of the patients with psoriasis included 230 patients, of them mild severity was diagnosed in 115 (50 %), moderately severe condition in 88 (38 %) and severe in 27 patients (12%). The age of the patients ranged from 40 to 65 years, an average of 52.7 ± 1.3. The study included 122 male (53 %) and 108 female (47 %) patients. The largest group consisted of patients aged 40-50 years (54 %), that was the most efficient period. The duration of the disease before this study in Kharkiv Hospital of Skin and Venereal Diseases No. 5 ranged from 5 to 30 years. The patients with disease duration of 5 years were distributed as follows: 2 to 6 months - 4 patients, 7 to 11 months - 17, from one year to five - 20. The vast majority of patients suffered from dermatosis from 6 to 20 years. 129 (56 %) patients indicated that they had developed psoriasis before 25 years, 101 patients (44 %) after 25 years.

Assessment of history data determined that 152 patients (66 %) had exacerbation of the pathological process in winter, 41 patients (18 %) in summer; 37 patients (16 %) did not notice any seasonal exacerbation. Most patients (202 (88 %) reported annual exacerbations. Frequent exacerbations of dermatosis, requiring hospitalization, were typical for 87 patients (38 %). The study of family history showed that 127 patients had relatives of the 1st and 2nd degree of relationship with psoriasis, family history was revealed in 21 patients (9 %).

The study of clinical features of dermatosis revealed psoriatic erythroderma in 34 patients, pustular psoriasis in 46, palmoplantar in 39 and exudative form in 55. The majority of patients received different treatments according to their presentation. Thus, 191 patients (83 %) were repeatedly treated in an outpatient department, 175 (76 %) in an inpatient department, 46 (20 %) received spa treatment. Short time effectiveness of previous treatment was marked in 179 patients (78 %), no positive effect of treatment in 21 (9 %). Exacerbations occurred once in several years in 12 patients (5%); 1 per year in 39 (17 %); 2-3 times a year in 69 (30 %). Continuously relapsing course with refractoriness to therapy was observed in 110 patients (48 %).

According to survey data of 182 patients with isolated psoriasis 113 (62 %) patients associated the onset of dermatosis with psychoemotional stress, 51 (28 %) with previous infectious viral disease, 18 (10 %) with injuries and surgical manipulations. According to survey data, 48 patients with psoriasis associated the onset of dermatosis with AH, in 39 (81 %) patients the condition was caused by emotional stress in 3 (6 %) by infectious and viral diseases, trigger factor in other patients remained unknown.

A close study of disease history as well as additional tests (biochemical and instrumental) showed that patients with isolated psoriasis suffered from pancreatitis, calcu-

lous cholecystitis, biliary dyskinesia 1.3 times more frequently than patients with psoriasis, associated with AH (29 % and 22 % respectively). Endocrine diseases were not significantly predominant in patients suffering from psoriasis, associated with AH (12 % and 17 %, respectively). Gastrointestinal diseases (gastritis, colitis, malabsorption syndrome) were often recorded in patients with psoriasis without AH. According to abdominal cavity ultrasound examination report hepatobiliary pathology was diagnosed in 45 (20 %) patients. In particular, 25 (11 %) patients had chronic cholecystopancreatitis, 14 (6 %) patients had fatty hepatosis and 5 (4 %) patients had cholelithiasis.

Average PASI in group of psoriasis without concomitant hypertension was 33.8 ± 3.9 and 37.5 ± 4.0 in group with hypertension. In most patients the disseminated psoriatic process was diagnosed (224 – 97,5 %), and 6 (2.5 %) patients had localized condition. Clinical examination of patients at the time of clinical trial showed that 6 patients had limited cutaneous process as single plaques with different localization on the skin of the trunk and extremities with PASI not more than 10. Disseminated skin process with PASI 10 to 50, with a tendency to erythroderma was observed almost equally in all groups of the patients under investigation. Impairment of nail plates was found in 25 (14%) of psoriatic patients without AH and 8 (17%) of patients suffering from psoriasis, associated with AH had “oil spot” symptom, “thimble” symptom, onychogryphosis and onycholysis.

AH was observed in 48 (20.8 %) patients with psoriasis out of 230. Depending of the level of blood pressure the patients were distributed as follows: mild hypertension (I degree) was diagnosed in 18 patients (37.5 %), with average systolic blood pressure accounting for 158.4 mmHg, diastolic blood pressure 97.3 mmHg. Moderate AH (Ⅱ degree) was observed in 30 patients (62.5 %) of the following indices: systolic blood pressure of 178.5 mmHg, diastolic 108.2 mmHg. Electrocardiographic studies also showed signs of early ventricle repolarization syndrome in 32 patients (67 %), including 14 (29 %) men and 18 (37.5 %) women.

Depending on the degree of the target organ damage, the patients were divided according to stages of hypertension. However, only 9 patients (19 %) had the first stage of the disease. Other patients were found to have signs of the target organs damage of varying degrees of severity and second stage of the disease was established in 39 (81 %) patients. Family history from both parents was detected in 7 patients (14.5 %), from one parent in 12 (25 %), from the second-degree relative in 4 (8 %). Thus, 19 patients (40 %) were found to have family history from the first-degree relatives.

Obesity of varying degrees of severity was noted in 67% of men and 60 % women. Type 2 diabetes was observed in 4 patients. Regular stress was noted in 23 (48 %) patients. However, stress in the family, which worsened the progress of hypertension, was noted in 17 (35 %) of women and only 5 (10 %) men, but stress at work in 15 (31 %) men and 11 (30 %) women. Low physical activity was observed in 7 (15 %) patients according to their own estimation and in 26 (54 %) patients according to the doctor’s estimation. Overuse of salt was reported by 7 (15 %) patients.

4 CONCLUSIONS

Assessment of the features of clinical manifestations and course of psoriasis in patients with AH as compared to patients without AH showed significantly higher incidence of stress (81 % of cases versus 62 %) and lesser incidence of infections (6 % vs. 28 %), medication intake, allergies and alcohol abuse as trigger factors of psoriasis. Moreover, patients with AH comorbid psoriasis were found to have relapses more frequently. These patients more than 1.5 times more frequently had off-seasonal type and 2 times less seasonal type of dermatosis. Attention is drawn to the fact that rapid dissemination of skin lesions during exacerbation in patients with psoriasis, associated with AH, was observed 2 times more often (28 % of cases versus 16 %) and cases of slow and gradual dissemination of rash were rarer.

Thus, medical history data and clinical presentations of 230 psoriasis patients, including cases of comorbid arterial hypertension, are heterogeneous, aggravating by each other in various combinations that requires further study and systematization of key parameters.

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Received: 07-Jun. – 2017
Accepted: 03-Sep. - 2017

INTER COLLEGAS, VOL. 4, No. 3 (2017)
ISSN 2409-9988

PEDIATRICS

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IRON DEFICIENCY ANEMIA IN CHILD WITH LEFT-SIDED DIAPHRAGMATIC HERNIA (case report)

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Abstract: Diaphragmatic hernia is a common pathology of the digestive system in children. The most dangerous complications in surgical practice include inflammation of hernia, strangulation of hernia, bleeding and intestinal obstruction. In pediatric practice complications of diaphragmatic hernia are as follows: gastroesophageal reflux disease, peptic ulcer, pyothorax, pneumonia, cardiac arrhythmias, dysuric disorders, and deficiency anemia. Since diaphragmatic hernias in children are characterized by poor clinical symptoms, they cause difficulties in diagnosis. In examination of patients with refractory forms of anemia, it is necessary to consult a gastroenterologist and a hematologist to exclude digestive tract abnormalities, perform therapeutic correction and provide adequate therapy for this pathology. Clinical observation of a 7-year-old child who underwent inpatient treatment in the Regional Children's Clinical Hospital and was diagnosed with iron deficiency anemia of moderate severity and left-sided diaphragmatic hernia.

KeyWords: diaphragmatic hernia, anemia, clinical case, children.

This problem is relevant not only in connection with the increased uncidence, but also the high probability of complications. According to the statistics, more than 700 000 children have been born with diaphragmatic hernia since 1 January 2000. Diaphragmatic hernia occurs with a frequency of 1 per 1700. Mortality in this disease is 1-3% of the total infant mortality rate, and during the first year of life in 10% of deaths due to malformations.

Illustrative is the data that 147 children are born with this disease every day, that is, a child with diaphragmatic hernia is born every 10 minutes [1].

Hiatal hernia is more common at older age. Hiatal hernia affects about 0.5% of the total adult population [2].

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A 7-year-old boy was admitted to hospital presenting with pallor, weakness, decrease in appetite, dysgeusia. He developed the abovementioned symptoms a year ago. According to his medical history he was registered for pediatric consultation this year, and was administered bivalent iron preparations, but without effect. He did not seek hematology consultation.

On examination: state of moderate severity, pale skin, epithelial changes (trophic disorders of the skin, nails, hair, mucous membranes).

On auscultation: vesicular breathing, murmur in the left side of the chest. Loud and rhythmic heart sounds. Soft and painless abdomen, parenchymal organs are not enlarged.

Due to atypical auscultation findings above the left lung the patient was referred to chest X-ray. Chest X-ray findings: lung fields without focal changes. Heart, mediastinum shifted to the right. Left diaphragmatic cupula and gas-filled gastric fundus are at the level of the 4-th rib. Right, left sinuses are clear. Relaxation of the left diaphragmatic cupula. Conclusion: left-sided diaphragmatic hernia.

Laboratory findings. Complete blood count: RBC-3.4 * 1012/L; HGB - 85g/L; MCH - 0,7; PLT - 180 * 109/L; Retic - 0,2%; WBC - 4.0 * 109/L; BSR-15.

Biochemical blood assay: serum iron - 8mcm /l; total iron binding capacity - 50mcm/L; latent iron binding capacity - 45mcm/L; serum ferrites - 10 mcm/L.

Diagnosis: Iron deficiency anemia of moderate severity. Left-sided diaphragmatic hernia.

Therapy. Operative correction: laparotomy, surgical repair of the diaphragmatic cupula, with local tissues.

After surgery he was prescribed bivalent iron supplements at a dose of 5 mg per kg per day for 6 months. The child's condition improved significantly, no complaints, laboratory indices (RBC-4.0 1012/L; HGB – 110 g/L; MCH – 0.98). He received hematological consultations for a year, after which he was deregistered.

There are various complications of diaphragmatic hernias which include inflammation of hernia, strangulation of hernia, bleeding and intestinal obstruction. The most common complications in pediatrics are gastroesophageal reflux disease, peptic ulcer, pyothorax, pneumonia, cardiac arrhythmias, dysuric disorders, and deficiency anemia.

Major pathogenic mechanisms of anemia development in diaphragmatic hernias include gastrointestinal bleeding in strangulation, disruption of iron absorption [3].

In physiological conditions absorption occurs mainly in the duodenum and first part of the jejunum. In iron deficiency the absorption zone extends distally. Iron is absorbed both as heme (10% of the absorbed iron) and non-heme (9%). The degree of its assimilation is determined by a number of factors, which may both interfere and promote iron absorption. Most of ferric iron (III) forms insoluble salts, for example, with phytin, tannin and phosphate present in food, and is excreted in the feces. Bioavailability of ferric iron in food and synthetic hydroxide iron complexes (III) is determined by iron release rate and the concentration of iron-binding proteins such as transferrin, ferritin, mucins, integrins and mobilferrin.

The amount of iron absorbed by the body is strictly controlled by the mechanism, the details of which have not yet been fully studied. Absorption of iron from ion compounds depends on iron ions valence. Iron is absorbed by mature enterocytes mainly in the form of ferro-ions (Fe2 +). Ferric iron (ferric ions) is partially imported into enterocytes, but the majority is reduced to ferro-ions. Ferric ions (Fe3+) interact with mucin and ß3-integrin and are imported into intracellular space of enterocyte villi of duodenal mucosa membrane by extracellular chaperone, namely calreticulin-like mobilferrin. A certain part of Fe3 + ions on apical surface of the villous epithelium under the impact of membrane-bound ferrireductase enterocyte brush border (duodenal cytochrome b - Dcytb) is reduced to the ferrous state (ferro-ions Fe2+). Full iron absorption in the duodenum occurs only if mucosa of the intestine functions normally. If a person has gastrointestinal diseases, it will provoke a damage of the intestinal mucosa, thus reducing the inflow rate of iron in the body.

Malabsorption of iron can be triggered by inflammation, cicatrical or atrophic processes in the small intestine, resection of the small intestine and the presence of gastrointestinal hernias. Clinical manifestations include pallor, lethargy, loss of appetite and taste perversion [4].

The development of iron deficiency has a clear staging. Sequentially developing stages of iron deficiency are as follows:

- Latent iron deficiency is characterized by a decrease in iron accumulation and the beginning of iron deficiency erythropoiesis;
- Iron deficiency anemia is characterized by a combination of sideropenic and anemic syndromes (Table 1) [5].

The main criteria for diagnosis in children: peristaltic noises in the lungs on auscultation, increasing fatigue, lethargy, lack of presentation typical for diaphragmatic hernia.

According to statistics deficiency anemia is observed in 15% of children, they vary widely - some are related to the lack of B vitamins, while others - with folic acid deficiency, but the overwhelming majority of anemia cases develop because of iron deficiency, these types are called iron-deficiency anemia (IDA), and they are the most common (about 80% of anemia cases) [6].

Table 1

Stages of iron deficiency states and their main characteristics

The stage of iron deficiency	Main characteristics
The first stage **Latent iron deficiency** **Decreased accumulation of iron.**	• Decrease in tissue stores of iron. • Parameters of the iron transport fund (serum iron, total iron binding capacity, latent iron binding capacity, ferric iron saturation ratio) within the limits of age norms. • Hb concentration is normal. • In adults, there is a compensatory increase in iron absorption in the intestine. • In children, the absorption of iron from food decreases due to reduced activity of enzymes involved in the absorption of iron in the intestine. • There are no clinical manifestations. • Laboratory criteria: a decrease in serum ferritin concentration, an increase in the concentration of soluble transferrin receptors.
The second stage **Latent iron deficiency** **Iron deficiency erythropoiesis.**	• Decrease in tissue stores of iron. • Reduced content of deposited iron and iron transport fund. • Gradual decrease in the activity of enzymes containing iron. • Hb synthesis rate, its concentration, total number and saturation of Hb red blood cells are not changed, so there is no anemia. • There are clinical manifestations, caused by a decrease in the activity of enzymes containing iron (sideropenic syndrome). • Laboratory criteria: decreased serum ferritin concentration, increased concentration of soluble transferrin receptor, increased total iron binding capacity; serum iron concentration may be normal.
The final iron deficiency stage. **Iron-deficiency anemia** **Clinically manifested state.**	• Iron stores are depleted. • Hb synthesis and its concentration decrease. • Zinc protoporphyrin increases. • There are morphological changes in erythrocytes: microcytosis, anisocytosis, and poikilocytosis. • Reduced saturation of Hb erythrocytes and as a result, increased hypochromia. • Development of anemic hypoxia. • Dystrophic changes in tissues and organs.

According to the World Health Organization (WHO), more than 500 thousand people in the world suffer from IDA.

The prevalence of IDA in children in Ukraine and developed European countries is approximately 50% in preschool children and 20% in teenagers [7].

Iron deficiency leads to various pathological states, infectious diseases of the gastrointestinal tract and respiratory system; brain structures cannot function normally without iron and psychological development is disturbed. Children diagnosed with iron-deficiency anemia in infancy, at the age of 3-4 years are found to have disruption of the transmission of nerve impulses from the brain centers to the organs of hearing and visual impairment due to violations of myelination and, as a consequence, violation of nerve conduction [8].

Establishment and elimination of its causes are crucial in the treatment of iron deficiency anemia. Therapy only with iron preparations in the presence of underlying disease that led to the IDA does not bring good results. Complete absence of any complaints typical for gastrointestinal disorders was a clinical feature of the abovementioned clinical case where the only symptom of diaphragmatic hernia was anemia with leading sideropenic syndrome [9, 10].

4. CONCLUSIONS

Gastrointestinal abnormalities may be one of the factors triggering iron deficiency anemia and thus, patients with prolonged iron deficiency require comprehensive examination of the gastrointestinal tract.

CONFLICT OF INTERESTS

There is no conflict of interests.

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Received: 08-Jun. – 2017
Accepted: 12-Sep. - 2017

INTER COLLEGAS, VOL. 4, No. 3 (2017)
ISSN 2409-9988

PEDIATRICS

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CONDITION AFTER HEMOLYTIC-UREMIC SYNDROME IN A CHILD WITH 3RD STAGE CHRONIC KIDNEY DISEASE (case report)

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Abstract: Currently, hemolytic-uremic syndrome is one of the frequent causes of acute kidney failure in children, so the timeliness of diagnosis and treatment determines the outcome of the disease. In the given clinical case, a set of certain factors that lead to an unfavorable outcome of the disease and the progression of chronic renal failure are presented. Clinical case of a 14-year-old child K., who was admitted to the nephrology department of the Regional Children's Clinical Hospital with the diagnosis: 3rd stage CKD, subcompensated stage of chronic renal failure and condition after hemolytic-uremic syndrome.

KeyWords: hemolytic-uremic syndrome in children, chronic kidney disease.

Hemolytic-uremic syndrome is a polyetiological disease secondary to other diseases and usually leading to severe damage to the endothelium of the vessels of the target organs. For reasons of origin, it can be divided into infectious and non-infectious forms. Early identification and the initiation of the best maintenance care with a microbiological contribution to pathogen detection lead to a favorable outcome in most patients [1]. Hemolytic-uremic syndrome occurs throughout the world. The annual incidence in children under five years is 2-3 cases per 100,000 children. According to both foreign and Ukrainian clinicians, this syndrome is most typical for infancy and early age (from 6 months to 4 years). In addition, hemolytic-uremic syndrome is one of the frequent causes of disability of patients with the deveelopment of chronic renal failure [2]. The incidence of hemolytic-uremic syndrome and its complications according to the Regional Children's Clinical Hospital from 2011 to 2016 recorded 5 cases of hemolytic-uremic syndrome.

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A 14-year-old girl K. diagnosed with 3rd stage chronic kidney disease, subcompensated stage of chronic renal failure, congenital anomaly of the urinary system (horseshoe kidney), condition after hemolytic-uremic syndrome (2003), secondary chronic pyelonephritis, remission period and polycystic disease.

Past history: 3rd pregnancy child, 2nd childbirth, term birth, birth weight 2800 g, height 50 cm, Apgar score: 8-9 points. She grew up and developed according to her age. She often has acute respiratory-viral diseases. She was administered Proteflazidum for Epstein-Barr virus infection (Epstein-Barr virus DNA in saliva +++) from 12.04.09 to 12.07.09. In October 2009 she was treated for anemia. Bilateral sinusitis in September 2012. She did not have children's infections. Heredity in nephropathy is not compromised.

At the age of 7 months, she developed hemolytic-uremic syndrome, secondary to acute intestinal infection and congenital anomaly of the kidneys (horseshoe kidney). These changes were confirmed by radioisotope renography and renoscintigraphy. The course of hemolytic-uremic syndrome was complicated by secondary chronic pyelonephritis, secondary glomerulonephritis with 1st stage chronic renal insufficiency, long anuric stage during the onset of

the disease (anuria for more than 10 days), which was managed by 6 sessions of peritoneal dialysis. She was discharged with improvement for a follow-up observation of the nephrologist. Thus far (within the last 5 years), relapses of pyelonephritis were observed every year, for which the child received appropriate therapy. Since September 2012, recurrence of urinary tract infection has not been reported and the child continues to be observed for 2nd stage chronic kidney disease. She receives antihypertensive, renoprotective, and anti-relapse therapy with uroseptics. In 2016 the child was diagnosed with polycystic kidney disease, which is one of the factors contributing to the progression of chronic kidney failure.

Criteria for the diagnosis of hemolytic-uremic syndrome [3]:

- microangiopathic hemolytic anemia
- kidney failure
- thrombocytopenia

Pathophysiological aspects of hemolytic-uremic syndrome development:

Glomerular thrombotic microangiopathy, a thickening of the wall of the renal vessels with edema of the endothelium and accumulation of proteins in their subendothelial layer is one of the main factors triggering kidney damage in hemolytic-uremic syndrome.

Moreover, pathophysiological mechanisms include the development of glomerular ischemia, which, in combination with thrombosis, leads to multifocal or diffuse necrosis of the cortex, followed by their occlusion with fibrin clots [4].

Classification [5]**:**

Infectious:

- verotoxin-producing E. coli
- Shigella dysenteriae
- microorganisms secreting neuraminidase (Str. Pneumoniae, etc.)
- HIV infection, etc.

Non-infectious:

- Idiopathic hemolytic-uremic syndrome
- Hereditary hemolytic-uremic syndrome (autosomal recessive, autosomal dominant)
- Drug hemolytic uremic syndrome (cyclosporin A, mitomycin C, bleomycin, duanorubicin, cytosine-arabinoside, cyclophosphamide, carboplatinum, doxorubicin, chlorozotocin, oral contraceptives, etc.);
- Hemolytic-uremic syndrome associated with pregnancy;
- Hemolytic-uremic syndrome associated with organ transplantation;
- Hemolytic-uremic syndrome associated with systemic lupus erythematosus;
- Hemolytic-uremic syndrome associated with tumors;
- Hemolytic-uremic syndrome, associated with scleroderma;
- Hemolytic-uremic syndrome, associated with malignant hypertension;
- Hemolytic-uremic syndrome, layered on glomerulonephritis.

Clinical and laboratory criteria of diagnosis [6]**:**

- Intoxication syndrome
- Anemic syndrome
- Hemorrhagic syndrome
- Kidney syndrome

Prognosis [7, 8]**:**

- Polyuric stage of acute renal failure (1-1.5 months) is a favorable outcome of the acute stage of hemolytic-uremic syndrome.
- Causes of deaths: central nervous system involvement, cardiopulmonary and multi-organ failure.
- The level of mortality ranges from 5 to 15%, in underdeveloped countries to 70% depending on the adequacy and timeliness of medical care,.
- The analysis of follow-up data shows that up to 85% of patients restore renal function.
- In 5-7 years after hemolytic-uremic syndrome 5% patients develop chronic renal failure, in 15 years more than 25% of patients suffer from chronic renal failure development. Unfavorable prognostic signs are: early anuria and its duration more than

2 weeks, progressive involvement of the central nervous system, urinary tract infections, microthrombi in more than 60% glomeruli, leukocytosis more than 20x109/l, atypical form of hemolytic uremic syndrome, age from 6 months and up to 4 years, as well as urinary system abnormalities/

Follow-up [9]:

- control of blood pressure;
- control of kidney function (serum creatinine, urine analysis (proteinuria level).

In a number of cases, chronic renal failure after hemolytic-uremic syndrome develops after a certain period of well-being. Progressive kidney damage can be suggested by persistence or development of proteinuria after a certain period after recovery, accompanied with or without arterial hypertension.

The closest or long-term prognosis of the disease is directly related to the severity of the acute period. The most reliable criterion is undoubtedly the duration of the oligoanuric period, which determines the formation of pathomorphological changes in the kidneys and the incidence of chronic renal failure [10].

4. CONCLUSIONS

Thus, according to the analyzed data, unfavorable outcome of hemolytic-uremic syndrome with the development and progression of chronic renal failure in our patient were determined by the following reasons: prolonged oligoanuric stage during the onset of the HUS, the early age of the child, urinary system abnormalities, and the urinary tract infection.

CONFLICT OF INTERESTS

There is no conflict of interests.

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Received: 08-Aug. – 2017
Accepted: 21-Sep. - 2017

INTER COLLEGAS, VOL. 4, No. 3 (2017)
ISSN 2409-9988

PSYCHIATRICS & MEDICAL PSYCHOLOGY

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MODERN SYSTEM OF MEDICAL AND PSYCHOLOGICAL SUPPORT OF INTERNS AT THE STAGE OF POSTGRADUATE EDUCATION

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Abstract: The study deals with the assessment of individual-personal and socio-psychological factors, mechanisms and conditions for psychological adaptation of interns for professional activity. The authors distinguished objective and subjective criteria of the interns' adaptation efficiency to professional activity. A high level of maladaptation was detected in 9.2% of male and 12.5% of female interns; severe level of maladaptation in 10.3% of male and 14.0% of female interns; a moderate level of maladaptation in 36.2% and 42.1%, respectively. According to the findings medical interns were found to have such clinical and psychological manifestations of adaptation disorders as asthenic (25.5%), hyperesthetic (21.6%), depressive (16.2%), psychosomatic (14.2%), astheno-apathic (11.4%), addictive (11.1%) types of maladaptive reactions. The findings were used to elaborate a system of medical and psychological support for physicians at the stage of postgraduate education with a differentiated use of a set of psychotherapeutic methods and psychoeducation, reflecting formation mechanisms of the disorders of adaptation to the professional activity of doctors.

KeyWords: psychological adaptation, professional activity, maladjustment, psychotherapy, psychoeducation.

INTRODUCTION

Postgraduate education is a specialized improvement in education and professional training aimed at extension, development and update of professional knowledge, skills and abilities, or obtaining another specialty on the basis of previous qualification and practical experience [1, 2].

Changes in higher medical education and its integration into the European educational sphere require a new approach to postgraduate training for physicians. Under current conditions the main objectives of postgraduate education for physicians are both to improve professional training of interns and to provide medical and psychological support to physician during adaptation to professional activities [3, 4].

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The problem of professional development is one of the most challenging problems of psychological science. And not only because it is a complex and very broad topic, but also because different views on this process are complementary and greatly deepen scientific ideas on psychological nature of not only professional formation, but also on personal development [5, 6].

One of the most important educational tasks of postgraduate education institutes is work with interns for quicker and more successful adaptation of their professional activities to a new system of social relations [7, 8].

The study of adaptation is the subject of research both of natural and social sciences and is an important area of research on the verge of various branches of knowledge, such as physiology, psychology, pedagogy, ecology, medicine, social psychology, etc. Each of these sciences are peculiar to our own understanding regarding the allocation of substantial emphasis, specific study of the processes of adaptation and maladaptation in all spheres of life making high demands on resources and psycho-physiological adaptation reserves. Professional activities of a doctor are characterized by increased stress related to work in terms of increased intellectual and psycho-emotional stress, lack

of time and information, high level of responsibility [9, 10, 11].

The abovementioned points out the necessity of the development and evaluation of an up-to-date system of medical and psychological support for interns in conditions of adaptation to professional activity in order to prevent maladaptive states.

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose was to study specific signs of psychological maladaptation of interns during professional training and medical and psychological support during professional specialization training.

2.2 Subjects & Methods

In order to achieve this goal, we carried out a comprehensive medical psychological and psychodiagnostic examination of 256 doctors-interns of Kharkiv National Medical University, both sexes, aged 23-30 years, in compliance with the principles of bioethics and deontology.

Psychodiagnostic method included the use of "Evaluation of Occupational Maladjustment" questionnaire (A. N. Rodina, 1995, adapted by M. A. Dmitrieva, 1997), Hamilton Depression Rating Scale (M. Hamilton, 1967), adapted to ICD-10 (G. P. Panteleyev, 1988) (HDRS) and quality of life assessment using the questionnaire developed by H. Mezzich, Cohen, Ruiperez, Liu & Yoon, 1999 in the modification of N. A. Maruta, 2004; scales determining the level of anhedonia SHAPS (Snaith-Hamilton Pleasure Scale, 1995).

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

Yhe findings showed a high level of maladaptation requiring the use of urgent measures (psychological and medical) in 2.3% of the interns under investigation; severe level of maladaptation, requiring mandatory psychological intervention and rehabilitation in 10.1%; a moderate level of maladaptation, with advisory medical support in 26.2%.

At the same time, women were found to have a higher level of adaptation disorders during their professional activity, as compared to men.

Clinical manifestations of anxiety were detected in 15.8% of the examined women, as compared to 7.2% of men. Subclinical manifestations of anxiety were observed in 16.3% and 15.5%, respectively. Clinical manifestations of depression were typical for 2.4% of women and 1.4% of men, and subclinical manifestations of depression for 20.1% and 16.0%, respectively.

According to our findings, medical interns were found to have such maladaptive reactions as asthenic (25.5%), hyperesthetic (21.6%), anxiety-depressive (16.2%), psychosomatic (14.2%), astheno-apathic (11.4%) and addictive (11.1%). Asthenic type, characterized by asthenic component, both physical and mental, reduces the capacity and interest in the external environment, persistent fatigue and weakness. Hypersthenic type is a tendency to transient or prolonged affective reactions, increased sensitivity to previously neutral stimuli. Anxiety-depressive type is characterized by effeminate background affecting mood and involving sadness, groundless anxiety with inability to relax, frustration. Psychosomatic type is manifested by the development of psychosomatic diseases. Astheno-apathetic type is manifested by fatigue, weakness, exhaustion, inactivity, indifference, lack of interest in communication secondary to depressed state, irritability, apathy. Addictive type is characterized by excessive consumption of alcohol, narcotic and toxic substances, gradual loss of situational control when taking psychoactive substances, as well as formation of different non-chemical types of addiction.

In accordance with the established features of adaptation disorders development in interns, we have developed and tested a system of medical and psychological support of interns at the postgraduate education stage, which includes personality-oriented psychotherapy (B. D. Karvasarsky, G. L. Insurina, V.A. Tashlykiv, 1994), individual and group cognitive-behavioral therapy (A.T. Beck, 2006), rational psychotherapy (classic version by P. Dubois 1912).

Psycho-educational work occupies an important place in

the system of medical and psychological support (N.O. Maruta, G.M. Kozhina, V.I. Korosty, 2010, 2011), which includes the use of informational modules, trainings for positive self-perception, increase of involvement, formation of communicative skills, solving problems of interpersonal interaction and problem-oriented discussions.

Evaluation of the system for medical and psychological support showed improvement in the emotional state in 83.8% of the surveyed with adaptive disorders, an increase in social and professional functioning (66.2%), and an increase in the quality of life index on all scales, which indicated a high efficiency of the proposed system for medical and psychological support of interns at the stage of postgraduate education.

The obtained data concerning adaptation disorders in doctors related to their professional activity correlate with data provided by Ukrainian scientists, but their attention is more closely focused on adaptation disorders in physicians who work in the specialty for more than 5 years. The results of the study allowed us to expand and supplement existing scientific ideas on adaptation of doctors to professional activity on the model of doctors-interns.

4 CONCLUSIONS

Thus, according to the results of the study the period of adaptation to professional activity in interns was characterized by asthenic (25.5%), hyperesthetic (21.6%), anxiety-depressive (16.2%), psychosomatic (14.2%), asthenoapathic (11.4%), addictive (11.1%) types of maladaptive reactions, with clinical manifestations determining the specifics of psychotherapeutic intervention and medical and psychological support.

The system of medical and psychological support of interns at the postgraduate education stage should include the use of personality-oriented psychotherapy, individual and group cognitive-behavioral therapy, rational psychotherapy and psycho-education.

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Received: 01-Aug. – 2017
Accepted: 27-Sep. - 2017

INTER COLLEGAS, VOL. 4, No. 3 (2017)
ISSN 2409-9988

PSYCHIATRICS & MEDICAL PSYCHOLOGY

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MODERN APPROACHES TO MEDICAL AND PSYCHOLOGICAL SUPPORT OF FAMILIES WITH INFANTS WITH SEVERE CRANIOCEREBRAL TRAUMA

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Abstract: The study involved a comprehensive survey of 137 families (mother and father) of children with severe somatic disease aimed at the development and evaluation of the system of medical and psychological support of families with a somatically challenged child. The main group comprised 97 families participating in the program of medical and psychological support, and the control group included 40 families who did not receive psychological support. According to our findings, a serious disease of the child became a psychotraumatic situation for all the parents, resulting in the development of anxiety-depressive reactions and conditions. Psychodiagnostic examination showed that the parents had mild, moderate depressive and anxious episodes on the Hamilton Rating Scale; high levels of situational and personal anxiety according to the C.D. Spielberger Inventory, a high level of neuropsychic stress on T.A. Nemchin Scale. The couples under investigation noted tensions in family relationships, family conflicts, related to the treatment of the child and escalation of pre-existing interpersonal and marital problems that led to distancing and a decrease in internal family resource. Based on these data, we have developed a system of medical and psychological support of the families with somatically challenged child, which consisted of four consecutive phases and included the use of individual cognitive-behavioral therapy (Beck AT, 2006), family therapy (Eidemiller E. G., 2003), rational therapy (classic Dubois P., 1912) and psychological educational programs. Case monitoring in the main group following the employment of the proposed system of medical and psychological support showed a stable positive pattern of psychological state with a statistically significant total reduction of anxiety-depressive states and the harmonization of the marital relationship.

KeyWords: Medical and psychological support, anxiety, depression, family interactions, infants with severe craniocerebral trauma.

INTRODUCTION

Protection of mental and physical health of the mother and child is one of the priorities of the state social policy in our country. Epidemiological studies of craniocerebral trauma incidence in children are conducted in many countries and indicate general trends with slight fluctuations in rates. In the CIS countries this figure is about 2%. Traumatic brain damage in newborns is 2%, 25 - 25.9% in infants, 7.1 - 8% in toddlers, 20% in preschool age children and 45% in school age children. Of all the children affected by craniocerebral trauma infants comprise 27.9% [1, 2, 3]. Serious diseases in children have a psycho-traumatic effect on parents, manifested by disorders of adaptation and anxiety-depressive states.

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Craniocerebral trauma is one of the most important and actual problems of pediatric traumatology, which has great social and medical significance due to its prevalence and severity of consequences [4, 5]. Parents of an infant with severe craniocerebral trauma are under high psychological pressure, resulting in psycho-emotional impairments and other manifestations of psychosocial maladaptation. During this period, it is particularly relevant to search for sources of medical and psychological support, to increase the psychological adaptation resource of parents [6, 7].

Psycho-emotional state of the parents is closely associated with changes in physical and mental condition of a sick child. At the same time, psychological well-being of the child depends on the mental state of his parents, in particular, those who are emotionally closer. Thus, a serious illness of a child is a powerful stressful situation for the whole family, which dramatically changes family functioning [8, 9, 10].

Destabilization occurs even in resourceful and well-adapted family-based systems; however, family has a pow-

erful potential support and gradually tries to adapt and develop new strategies of internal family interactions in case of long-existing crisis. We should also emphasize that the harmonious development of the child is inextricably linked to the welfare of the family, sense of security, support and protection [11, 12, 13].

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose of the research was to develop and evaluate a system of medical and psychological support of families with infants with severe brain injury.

2.2 Subjects & Methods

To achieve the goal, we carried out a comprehensive survey of 137 families (mother and father) of infants with severe craniocerebral trauma treated at the Children's Neurosurgical Department of A.I. Meshchaninov Kharkiv City Clinical Emergency Care Hospital.

The main group consisted of 97 families who took part in medical and psychological support program. The control group consisted of 40 families who did not receive psychological support.

The study involved the employment of the following research methods: history taking; psychodiagnosis using the questionnaire of mental stress (T. A. Nemchin, 1984), Hamilton Depression Rating Scale (M. Hamilton, 1967), adapted to ICD-10 (G. P. Panteleyev, 1988), C. D. Spielberger State-Trait Anxiety Inventory (adapted by Yu. L. Khanin, 1981), methods of lifestyle index diagnosis (adapted by L. S. Wasserman, O. F. Yerishev, Y. B. Klubova (1998)), methods of stress-overcoming behavior assessment “Ways of coping” (adapted by T. A. Krukova, 2002), Thomas-Kilmann Model of Conflict Management Styles, adapted by N. V. Grishina (D. J. Raigorodsky, 2002).

Methods of mathematical statistics, with results presented in the form of an average value ± the representativeness error at the probability level of $p < 0.05$.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

The findings showed that craniocerebral trauma in infant was a traumatic situation for all the parents, which provoked a whole range of difficult issues, namely the need for decisions related to the treatment of the child; concern about the impact of injury and surgical treatment on physical and mental development of the child; experiences associated with planned operational intervention; disruption of family functioning; aggravation of family, marital, interpersonal and intrapersonal conflicts; the need for adaptation to stay in a medical institution (medical procedures, everyday aspect); exclusion from the professional activities of the caring family member.

The most significant issues for parents at the stage of admission to neurosurgical hospital and examination of the child were the questions of actual surgical intervention, effectiveness of treatment and its impact on physical and mental development of the child; concern over the result of the operation, its consequences; fear of anesthesia, its side effects.

In the postoperative period, the most severe concern is the care, rehabilitation and exclusion from social functioning in need of the child’s care, redistribution of responsibilities at the time of treatment. Parents had to adapt to conditions of functioning in the hospital and adapt the child to them.

The range of stress experiences varied in women and men. While staying at a hospital, the mother was near the sick child and her duties included care for the child, while men were forced to engage in financial and social aspects.

According to the findings obtained in the study, parents (mother and father) had low mood (97.6% of patients), depression (66.2%), a sense of sadness and sorrow (73.5% of respondents), anxiety, constant internal stress with inability to relax (67.4%), state of confusion (36.3%), fears and concerns associated with weather conditions (87.3%), a sense of danger and failure (69.8%).

According to the Hamilton Depression Rating Scale, 53.6% of the surveyed had mild (16.4 ± 1.3 points) and 32.3% had moderate (24.6 ± 1.7 points) depressive episodes. According to the Hamilton Anxiety Rating Scale, 55.4% of the parents

had mild (16.6 ± 1.3 points) and 40.2% had moderate (24.9 ± 1.8 points) anxiety episodes.

Psychodiagnostic assessment showed high levels of situational and personal anxiety in the surveyed parents by C. D. Spielberger method (58.89 and 59.19 points, respectively) with higher rates among mothers, high level of severity of mental stress on the scale of T.A. Nemchin (69.41 points).

Analysis of applied coping strategies concerning behavioral method helping to cope with the situation, showed that most families used strategies aimed at emotion (57.1 ± 5.6 points), avoidance (51.7 ± 5.7 points), social distraction and adjustment (50.9 ± 7.2 points, respectively), $p<0.05$.

The families under investigation noted tension in family relationships, family conflicts, both related to the treatment of the child, and escalation of previously existing interpersonal and marital problems, which led to distancing and reducing the intra-family resource.

Thus, consequences of an infant's severe craniocerebral trauma for parents included development of intense psychological reactions to the stressful situation (82.3%); transformation of psychological reactions into expressed anxiety-depressive disorder (79.4%); maladaptive behavior during the stages of treatment (61.1%); psychosocial maladjustment (40.1%); disturbance of interpersonal relationships (87.2%); deformation of family interaction (72.3%).

According to our findings, we have elaborated a system of medical and psychological support for families of infants with severe craniocerebral trauma, which was regulated by the targets of medical psychological effects and consisted of four consecutive phases: 1st phase – compliance development, aimed at the establishment of a productive contact between the physician and the parents of the infant with severe craniocerebral trauma; 2nd phase – correction of intense mental reactions to stressful situations and change in anxious and depressive attitudes, formation of adequate ideas on postoperative period prognosis, effectiveness of treatment and impact on physical and mental development of the child; 3rd phase – the stage of correction of emotional responses to the child's condition, surgery, the need to stay in hospital, aimed at reduction of anxiety and depressive symptoms, correction of family relations; the 4th phase – establishment and maintenance of the results by potentiation of positive emotions, fixation on the improved health of the child, specifics of rehabilitation.

The psychotherapeutic complex of the proposed system of medical and psychological support included the use of individual cognitive-behavioral therapy (A. T. Beck, 2006), family therapy (E. G.Eidmiller, 2003), rational psychotherapy (classic version by P. Dubois, 1912).

Psychological education was chosen to be the sense-making element of the developed model. Psycho-educational classes were held in closed groups of 8 to 10 parents, lasting for 45 minutes (twice a week during the entire stay of the parents with the child in the neurosurgical department). The main issues proposed during psychological education included the concept of craniocerebral trauma, the necessity and methods of neurosurgical treatment, the needs of the child during treatment, possible consequences (physical and mental) of craniocerebral trauma, psychological state of the family members of the child; self-regulation of mental state.

Case monitoring in the main group following the employment of the proposed system of medical and psychological support showed a stable positive pattern of psychological state with a statistically significant total reduction of emotional disorders in parents, $p<0.05$: reduction in anxiety level in 73.5% of the mothers and in 83.6% of the fathers; leveling of depressive symptoms in 71.1% of the mothers and 88.6% of the fathers; a decrease in family conflicts in 72.5% of families; harmonization of marital relationship in 65.28% of the couples.

In the control group aggravation of psychopathological symptoms was diagnosed in 35.4% of the mothers and 11.2% of the fathers, 64.6% of the mothers and 88.82% of the fathers had stable presentation of anxiety-depressive disorders, and deterioration of family interactions was observed in 42.3% of the families.

4 CONCLUSIONS

The obtained results allowed us to substantiate the expedience of medical and psychological support of the families of infants with severe craniocerebral trauma.

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Received: 08 - Jun. – 2017
Accepted: 23 - Sep. - 2017

PSYCHIATRICS & MEDICAL PSYCHOLOGY

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INDIVIDUAL-PSYCHOLOGICAL AND PHYSIOLOGICAL MANIFESTATIONS OF MALADJUSTMENT TO EDUCATIONAL ACTIVITIES

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Abstract: In the course of work with the purpose of studying the psychophysiological features of adaptation disorders in students of medical University had conducted comprehensive psychodiagnostic and psychophysiological examination of 603 students of Kharkiv national medical University, of both sexes, aged between 17 and 24 years. As shown by the results of the evaluation of students ' adaptation to educational activity and 4.5% of the surveyed students revealed a high level of maladjustment, 13.3% higher, at 36,2% - moderate in 20.2% - low level of maladjustment; 25.8% in the absence of signs of maladjustment. In the course of work systematizes the main manifestation of the states of maladjustment in medical students. Mental , manifested by deterioration of psychological well-being, growth, asthenia, anxiety and depressive disorders, decrease of activity, violation of interpersonal relations, increased intrapersonal conflicts. Psychophysiological, decreased mental performance, impaired memory, decrease in productivity of attention, fatigue, decreased speed of information processing, a greater period of sensorimotor reactions and a low level of coordination and significant deterioration of the described indicators is influenced by physical activity.

KeyWords: students, maladjustment, psychological state, physiological state.

INTRODUCTION

The problem of the search of regularities and mechanisms of the students' adaptation to training in high school inevitably leads to the need for analysis of the whole complex of factors determining peculiarities of educational activity [1, 2, 3].

The relevance of the study of the disruption of adaptation process to educational activity is determined by the fact that the course of study is considered to be particularly strenuous and the learning process takes place in conditions of information and emotional stress, significant physical and mental stress. Deterioration of physical and mental health of students stated recently, reduction of stress and cognitive functions have become a subject that receives growing attention from researchers [4, 5, 6].

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Student age is a special period in an individual' development in point of the "saturation crisis" (exam stress, age-related problems, awareness of the content of professional activities as self-realization and self-actualization, etc.), which is also rich in opportunities for the maximum development of one's abilities and potential [7, 8, 9].

An interest in activities was shown to be the basic psychological condition for implementation of personal development. Depending on how implemented potential psychological possibilities of man, his inclinations, interests determined by the professional level of specialists [10, 11, 12].

The students ' adaptation to learning in higher education must be viewed as dynamic, multidimensional and integrated process skills meet those requirements that apply to the student during the period of training and education in high school [13, 14].

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose

To study psychophysiological characteristics of adaptation disorders in students of Medical University.

2.2 Subjects & Methods

Study population

To address this goal in compliance with the principles of bioethics and deontology, we conducted a comprehensive survey of 603 students of Kharkiv National Medical University, of both genders, aged between 17 and 24 years.

During the study we used the following research methods: clinical history taking; psychodiagnosis using the questionnaire "Evaluation of occupational maladjustment" (Rodina, A. N., 1995, adaptation Dmitrieva M. A., 1997), Hamilton Depression Rating Scale (M. Hamilton, 1967), adapted to ICD-10 (G. P. Panteleyev, 1988) (HDRS); neuro-mental stress questionnaire (T. A. Nemchin, 1984), asthenic condition scale (L. M. Fucking and T. G. Malkova 1981), Zung Depression Self-rating Scale (adapted by T. N. Balashova, 1984); psychophysiological "Questionnaire to identify signs of vegetative changes" and "Study design for detecting signs of autonomic disorders" (A. M. Weiner, 1981). The study involved an assessment of the complex psycho-physiological parameters at rest and their changes occurring under the impact of pre-dosed physical loads. It included a quantitative assessment of visual memory, evaluation of attention span, the balance of processes of excitation and inhibition in the cerebral cortex (Korobchansky V. A., 2005), determination of time of simple sensorimotor (Schmidt, Thews.G., 1983); methods of mathematical statistics.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

The students' adaptation to learning in higher education must be viewed as dynamic, multidimensional and integrated process, with performance indices including the following: functional stability of the student's body (absence of severe disruptions of most physiological functions); absence of apparent signs of fatigue when carrying out training activities; absence of emotional problems; educational success.

As shown by the results of the evaluation of the students' adaptation to educational activity with the questionnaire "Assessment of occupational maladjustment" (Rodina, A. N., 1995, adapted by Dmitrieva M. A., 1997) and 4.5% of the surveyed students demonstrated a high level of maladjustment requiring urgent measures (psychological and medical); 13.3% showed severe level of maladjustment, requiring mandatory rehabilitation program from psychologists; 36.2% revealed moderate level of distress, requiring consultations from specialists; 20.2% had low level of maladjustment; 25.8% had no signs of maladjustment.

Students with high, evident and moderate level of maladjustment were included into the first study group, students with low levels or absence of maladjustment signs were assigned to the second group.

Diagnostic examination of the first group students showed that 15.8% had clinical symptoms of anxiety (according to clinical scales of anxiety and depression), 16.3% had subclinical manifestations, as compared to 3.5% and 8.2% of the second group students, respectively. Clinical manifestations of depression were typical for 5.4% of the first group students and 2.1% of the second group students; subclinical symptoms of depression were detected in 20.1% and 9.5%, respectively.

The first group students had higher average levels of asthenic state according to L. M. Malkova and T. G. Chertova scale (54.12±1.98, $p<0.05$), neuro-mental stress according to T. A. Nemca scale (48.38±1.79, $p<0.05$) and gotm according to Zung scale (50.30±1.66, $p<0.05$) as compared to the second group students who had the lowest results of 41.97±1.73, 38.24±1.22 and 44.51±1.96 ($p<0.05$), respectively.

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The results of objective study of the vegetative status of the students according to the method of A. M. Vein showed that the first group students mainly had autonomic disorders, cardiovascular and respiratory diseases as a single syndrome with psychovegetative disorders and high meteosensitivity as a consequence and manifestation.

Physiological studies revealed that the first group students had the worst performance concerning the majority of psychophysiological methods as compared to the students who adapted well.

This was manifested, in particular, in a smaller total volume of performing three-minute corectura samples made up 615,93±10,37 ($p<0.05$) character of the students of the first group and 638,46±of 2.51 ($p<0.05$) – in group II. Also, significant differences existed in the dynamics and quality of performance of the sample - patients in the first group showed less pronounced decrease in the volume of the sample in the third minute of the sample, higher precision and performance of its implementation. Under the influence of physical activity was significant deterioration in all indicators of attention to students of the first group (attention span decreased by 27.24%, accuracy - by 10.95%, productivity - by 37.22%, resistance - by 36.82%) compared to the significant improvement in the rate of the sample - the students of II group.

The time of simple sensorimotor reaction of the students of the second group was 0.20±0.02 ($p<0.05$), patients in the first group it was slower by 95% (to 0.39±0.02, $p<0.05$). Under the influence of physical activity was slight increase in the time of sensorimotor reactions from the students of the first group (0,31±0,03 $p<0,05$) and decrease in the second group (0,18±0,04, $p<0,05$).

Conducting a sample coordination revealed significant differences between the different groups surveyed, the time during which surveyed the first group were able to maintain coordination in the course of the trial, amounted to 18,33±2,61, examined the second cluster is within 50,87±1,43 ($p<0.05$). Under the influence of physical activity there was a reduction in the execution time of the samples, more pronounced in the examined first and second groups.

As shown by the results of the study the severity of the manifestations of maladjustment in the process of learning has certain gender differences: it is the students it connected with the manifestation of fatigue, increase of signs of insufficiency of cerebral circulation, increasing complaints about the state of the cardiovascular and nervous systems. From male students, this factor is less pronounced and is primarily a manifestation of general fatigue and increased signs of cerebrovascular insufficiency.

Thus the overall deterioration of self-rated health of female students is affected by insufficiency of cerebral circulation and the cardiovascular system, fatigue. In male students the process of adaptation is associated with increasing fatigue and deteriorating physical condition.

The emergence of non-adaptive state is accompanied by an increase and strengthening of the relationships between indicators of mental state, and their transformation is presented as a factor that weakens the maladjustment of students. In male students - changes in the indices of maladjustment is accompanied by complication of relations between them, the female students – a qualitative reorganization of the structure of relationships.

Revealed that men and women have the qualitative and quantitative differences in the relationship between emotional state and performance accuracy, and productivity of mental work.

For male students tend lack of relationship between accuracy of work performed and measures of emotional status, while among women this pattern is not observed. The accuracy of the performed mental work depends on self-esteem health and well-being. Performance, on the contrary essentially depends on increased activity and well-being of female students, in male students from the health, activity, anxiety, mood.

4 CONCLUSIONS

Thus, the results of our study allowed us to characterize main manifestations of maladjustment states in medical students.

Mental problems are manifested by deterioration of psychological well-being, growth, asthenia, anxiety and

depressive disorders, decrease of activity, violation of interpersonal relations, increased intrapersonal conflicts.

Psychophysiological, decreased mental performance, impaired memory, decrease in productivity of attention, fatigue, decreased speed of information processing, greater period of sensorimotor reactions and a low level of coordination and significant deterioration of the described indices is influenced by physical activity.

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Received: 11-Jun. – 2017
Accepted: 23-Aug. - 2017

PSYCHIATRICS & MEDICAL PSYCHOLOGY

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EVALUATION OF THE IMPACT OF ART THERAPY ON THE PROGRESS OF SOCIAL FUNCTIONING IN SCHIZOPHRENIC PATIENTS

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Abstract: Based on the results of a comprehensive survey of 86 patients with schizophrenia, the effectiveness of art therapy in complex rehabilitation of patients was assessed. The high effectiveness of art therapy is established in comparison with the traditional therapy of schizophrenia. There is a positive dynamics in quality of social functioning of patients by the general behavioral dysfunction scale, dysfunction in the performance of social roles in society scale, functioning of patients in the hospital scale and the dysfunction of modifying factors. Art-therapeutic program in the structure of complex therapy of schizophrenia promotes rapid social reintegration of patients. It mobilizes internal reserves, restoring self-esteem, changing the attitude of patients to their disease.

KeyWords: schizophrenia, social functioning, art therapy

INTRODUCTION

Schizophrenia is one of the most important mental diseases and its average incidence is 1% of the population. The disease is characterized by a long-term duration, quite often resulting in the reduction or loss of physical capability, with essential social consequences. Disability of patients suffering from schizophrenia constitutes 40% to 80% in different regions, which testifies to the high level of the patients' maladaptation [1, 2, 3].

The modern stage of the development in psychiatry is characterized by an extensive use of atypical neuroleptics which in a rather fast way stop productive and negative psychopathological symptoms, improve cognitive deficits and have minimal side effects. The possibility of rapid restoration of life quality and social functioning in patients with schizophrenia is an extremely important factor [4, 5].

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Schizophrenia is the most expensive of all mental disorders with regard to the cost of treatment, loss of working capacity and public spending on the mentally ill people, support for their disability-specific costs. There is evidence of a significant cost of schizophrenia treatment for society: up to 90% of medical costs are spent on inpatient care, about 30% of all costs are spent on pharmacotherapy [6, 7, 8].

Schizophrenia is considered to be one of the most serious and quickly disabling diseases but it does not always triggers severe outcomes. It is possible to stop acute symptoms in a short period of time, to achieve full recovery of social adaptation in the case of timely diagnosis, using modern pharmacotherapy, combined with methods of social rehabilitation and psychotherapy [9, 10].

The rehabilitation of mentally disabled people is not limited to elimination of psychopathologic symptoms and is aimed at the creation of the optimum social functioning conditions, improvement of life quality, ability to have independent active life and in modern conditions this problem becomes even more topical [11, 12].

Research carried out in our country and abroad has showed the prospects and therapeutic effectiveness of art therapy dealing with inpatients and outpatients of Psychiatric Departments over the last few years [1, 4].

The majority of authors consider that art-therapeutic methods in psychiatric practice are relevant because they can influence patients' problems which can not be solved by other methods of psychotherapy. The following factors of therapeutic and corrective impact in art therapy are considered to be the most important: creative activity, psychotherapeutic relations and the patient's and the specialist's feedback [13, 14].

2 PURPOSES, SUBJECTS and METHODS:

2.1 Purpose of the research was to study the progress of the level of social functioning in schizophrenic patients under the influence of art therapy.

2.2 Subjects & Methods

To reach this goal, we carried out a comprehensive survey of 86 male and female inpatients aged 18 - 65 years with diagnosed schizophrenia according to F 20 rubric (ICD 10) in the period of stabilization. Art-therapeutic correction was used along with psycho-pharmacotherapy complex therapy.

The study involved the employment of clinico-psychopathological, clinico-anamnestic and psychodiagnostic research methods using socially-oriented and social functioning scales "Personal and social functioning - PSP (Mezzich, Cohen, 2001)", hospital psychologist's conclusion and mathematical statistics methods.

Conflict of interests

There is no conflict of interests.

3 RESULTS AND DISCUSSION

The main goals of art therapy were: patients' preoccupancy through their involvement in purposeful activities; development and maintenance of their creative skills; sensory stimulation; abreaction of feelings and experience of positive emotions associated with creative activity and its results; Support and development of communication skills, independency and self-organization; psychological integration of patients.

The main tasks of art therapy include: reduction of intellectual and esthetic anhedonia through the relation of cognitive logico-analytical, expressive, emotional and behavioral game components into art-therapeutic activities oriented toward success, mastering the skills of emotional self-regulation, behavior through the development of the ability to self-observation, self-instruction, coping with inner dialogue and self-expression of the proposed visual means; strengthening of communicative orientation in collective group creativity; studying effective strategies for solving interpersonal problems through graphic and art-plastic role modeling of standard social situations.

Art-therapy sessions were conducted twice a week lasting 1.5 hour for 1.5 months and consisted of 2 consecutive stages: the main (intensive) at the inpatient stage of treatment and supportive at the outpatient stage.

The course of the main stage lasted 1 month, the supporting stage lasted 3 weeks.

The inpatient stage of 8 sessions of individual art therapy was provided for 1.5 hour twice a week.

The outpatient stage of 3-4 group sessions lasted 1.5-2.0 hours once or twice a week.

Sessions with patients were conducted at a certain time in a specially equipped art-therapy center with a full set of necessary materials and tools.

The main factors and psycho-therapeutic effects in art therapy included the following: the factor of artistic expression, the factor of intra-group communication processes and relationships and the factor of interpretation and verbal feedback.

The study showed the following progress of artistic expression in the process of art therapy: image data created at the initial stages were characterized by amorphous, vague boundaries, changes of normal and initial forms, mixing of different styles and image data created at the last stages of art therapy acquired symbolic, archetypal character, greater structure and completeness.

Moreover, there was an apparent positive progress of intra-group processes and relationships. Thus, at the beginning of the therapy schizophrenic patients depended on the spearheading activity of the art therapist; assuming

the role of a "wingman". The patients had a desire to establish personal relationships with the leader while relations with the rest members of the group were less important. The process of art-therapeutical work was characterized by the following changes: gradual development of interpersonal relationships, strengthening of orientation toward general group phenomena and activation of communicative processes, a tendency towards an increase in the level of verbal communication of the group participants with each other and with the leader up to active participation in debates.

At the first research level the results of social functioning study of the patients under investigation showed disturbance of general behavioral dysfunction in the society: obvious in 24.2%, serious in 26.5% and very serious in 28.1%. Dysfunction in social functioning (social roles) in society: obvious in 24.8%, serious in 27.4%, very serious in 28.6%. Dysfunction of patients in the hospital: 2.4% without dysfunction, 10.9% with minimal dysfunction, 27.1% with obvious, 33.5% with serious and 25.9% with very serious dysfunction. Dysfunction of modifying factors in patients (positive qualities of the patient): 3.4% without dysfunction, 13.1% with minimal, 25.6% with obvious, 24.1% with serious and 34.2% with very serious dysfunction.

The study showed that the level of total social behavioral dysfunction in the main group was improved up to 87.4%, to 66.2 % in the control group; dysfunction while performing social roles in the society to 75.1 % and in the control group to 39.3%, malfunction in the patients' performance in hospitals to 73.7 % and in the control group to 72.5%; dysfunction of modifying factors to 82.5%, and in the control group to 65,4 % ($p < 0.05$) at the second stage of art therapy completion, according to the results of social functioning examination of the patients with schizophrenia.

The obtained data testify that the complex approach in the therapy of schizophrenia which included psychopharmacotherapy in combination with art therapy leads to restoration of social activity and successful resocialization of patients.

The obtained data on the effectiveness of art therapy in therapy and psychosocial rehabilitation of mentally ill correlated with the data of Ukrainian scientists and confirmed data on the positive effects of art therapy of psychosocial reintegration of patients with schizophrenia and indicated the need for further development and implementation of art therapeutic measures in the system of psychosocial rehabilitation of mentally ill.

4 CONCLUSIONS

The study showed evident positive progress of social functioning level in patients with schizophrenia, which included art therapy in traditional complex of treatment and rehabilitation measures according to the scales of general behavioral dysfunction, dysfunction in social functioning in society; the functioning of patients in the hospital and the dysfunction of modifying factors.

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Received: 14-Jul. – 2017
Accepted: 27-Sep. - 2017