BULGARIAN MEDICINE ISSN 1314-3387

Българска медицина

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Microsatellite Instability and CpG Island Methylator Phenotype as Prognostic Factors in Patients with Colorectal Cancer

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Роля на микросателитната нестабилност и фенотипът на метилираните CpG-острови като прогностични фактори при пациенти с колоректален карцином

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РЕЗЮМЕ

В патогенезата на колоректалния карцином (КРК) са описани поне 3 механизма: на хромозомна нестабилност, микросателитна нестабилност (МСН) и фенотип на метилираните CpG острови (CIMP). ЦЕЛ: Да се оцени влиянието на МСН и CIMP върху прогнозата на болните с КРК. МЕТОДИ: Проследени са постоперативно в продължение на 5 г. 82 болни. Екстрахирана е ДНК, анализът на МСН е извършен чрез стандартен панел от 2 мононуклеотидни (BAT 25, BAT 26) и 3 динуклеотидни (D2S123, D5S346, D17S250) маркера. Метилирането на гените hMLH1, CDKN2A, TIMP3 и TPEF/HPP1 е оценено количествено чрез пиросеквениране. РЕЗУЛТАТИ: Общата преживяемост на КРК с МСН и липса на такава е съответно 41.0±6.6 и 49.6±3.3 месеца (p=0.69, тест на Kaplan-Meier). Преживяемостта на болните с МСН в резултат на метилиране на hMLH1 е 22.6±23.6 месеца спрямо 49±15.1 месеца за тези с МСН без метилиране (p=0.028). CIMP(+) се асоциира с по-лоша преживяемост: 24.8±23.3 месеца спрямо 40.3±19.7 месеца за CIMP(–)(p=0.035). Пациентите без МСН и проведена адювантна 5-FU-базирана химиотерапия имат по-дълга преживяемост спрямо тези, лекувани само хирургически– 44.2±16.3 спрямо 33.2±22.4 месеца (p=0.046), докато за МСН такава разлика не бе наблюдавана (съответно 46.8±8.6 и 30.5±10.2 месеца, p=0.78). ЗАКЛЮЧЕНИЕ: Възможно е прогнозата и избора на лечение при болните с КРК да се повлияят от наличието на МСН и CIMP, но са необходими повече проучвания сред българската популация.

Ключови думи: колоректален карцином – микросателитна нестабилност – CIMP – прогноза

ABSTRACT

Colorectal cancer (CRC) has become a highly relevant condition nowadays. In Bulgaria it ranks second among all human neoplastic disorders with incidence of 56.6 per 100 000 inhabitants for 2010 (1). Surgical treatment alone is curative in early stages I and II, but in high-risk patients and in locally and systemically advanced disease 5-Fluoruracil-based adjuvant chemotherapy (ChT) should be considered (14). Despite the improved 5-year survival chemotherapy-related systemic toxicity represents a serious problem and may necessitate treatment discontinuation (9). Therefore, careful selection of patient who might benefit from this treatment is of great importance.

The TNM classification remains the gold standard of prognostic factors in CRC patients whose 5-year survival is highly dependent on TNM stage. The latter was initially developed to predict prognosis but eventually has evolved to aid in the choice of treatment (21). However, CRC should be considered a heterogenous, multi-pathway disease, and recent data suggest that even histologically identical tumors from the same stage may have different prognosis and response to therapy (12). Different molecular and protein markers such as venous and lymphatic invasion, tumor grading, tumor buds and borders, loss of 18q, components of the cell cycle, apoptosis, proliferation, EGFR, VEGF, etc. have been studied to reveal high-risk patients but their use has not been validated outside scientific research (27).

The advances in understanding the molecular characteristics of CRC could become the key for adequate treatment in the near future. Three major pathways have been identified so far: the suppressor or chromosome instability pathway (CIN), the mutator or microsatellite instability pathway (MSI), and the methylator or CpG Island Methylator Phenotype (CIMP) (17,19). Patients with Lynch syndrome, the hallmark of which is MSI, tend to form metastases less frequently and show better prognosis than sporadic CRCs but higher recurrence rate (6). Patients with sporadic MSI tumors also have a better survival compared to their MSS counterparts (23). At the same time data assessing the role of CIMP show either presence or absence of survival benefit of adjuvant chemotherapy for tumors with heavily methylated genes (18,26). So far in Bulgaria no study assessing the potential role of MSI and CIMP as prognostic and predictive factors has been carried out.

The aim of this study is to examine whether MSI and CIMP could affect the survival and the risk of metachronous cancer among Bulgarian patients with CRC.

Key words: colorectal cancer – microsatellite instability – CIMP – prognosis

Introduction

At least 3 different pathways have been discovered in colorectal cancer (CRC) carcinogenesis: chromosomal instability, microsatellite instability (MSI) and CpG Island Methylator Phenotype (CIMP). AIM: To evaluate MSI and CIMP as prognostic factors in patients with CRC. METHODS: For an average of 5 years postoperatively 82 Bulgarian patients were followed up. DNA was extracted, and MSI was performed by the standard panel containing 2 mononucleotide (BAT 25, BAT 26) and 3 dinucleotide (D2S123, D5S346, D17S250) markers. Methylation of hMLH1, CDKN2A, TIMP3 and TPEF/HPP1 was analyzed quantitatively by pyrosequencing. RESULTS: The overall survival of MSI and MSS CRCs was 41.0±6.6 and 49.6±3.3 months, respectively (p=0.69, Ka-

plan-Meier test). The survival of patients with MSI due to methylation of hMLH1 was 22.6±23.6 months vs 49±15.1 months for patients with MSI and unmethylated gene (p=0.028). CIMP(+) phenotype was associated with worse survival: 24.8±23.3 months compared to 40.3±19.7 months for CIMP(–)(p=0.035). Patients with MSS tumors on adjuvant 5-FU based chemotherapy showed better survival than those treated surgically only – 44.2±16.3 vs 33.2±22.4 months respectively (p=0.046), while for MSI tumors no difference was observed (46.8±8.6 months vs 30.5±10.2 months, p=0.78). CONCLUSION: MSI and CIMP could modify their treatment plan and prognosis in patients with CRC but more studies are needed to confirm these results in the Bulgarian population.

Materials and methods:

Materials: The present study included 82 patients undergone elective surgical resection for CRC between May 2005 and May 2006. All participants signed an informed consent prior entering the study. Information regarding age, sex, tumor location along the colorectum, histology and TNM classification was gathered postoperatively. Subjects were scheduled for adjuvant 5-FU based chemotherapy for cancer of the colon with or without radiotherapy for rectal cancer according to their TNM status. All patients were followed-up until August 2010. The primary endpoint was the overall survival.

Methods: *DNA extraction:* DNA was obtained from formalin-fixed paraffin-embedded blocks which were deparaffinized and rehydrated in xylol and ethanol. Normal and tumor tissues were separated and DNA was extracted using a Qiagen kit according to protocol.

Microsatellite instability analysis: Paired normal and tumor tissues were tested for microsatellite instability according to the National Cancer Institute Workshop (4). Two mononucleotide (BAT 25 and BAT 26) and three dinucleotide (D2S123, D5S346, D17S250) markers were used, and PCR products were run on automated ABI Prism 3100 sequencer. Samples with 2 unstable markers were classified as MSI-high, those with instability in 1 marker – as MSI-low, while tumors lacking instability were classified as microsatellite stable (MSS).

Bisulfite treatment, PCR and quantitative analysis of promoter methylation: Bisulfite conversion of 1 μg DNA was performed using a Qiagen kit according to protocol. For methylation analysis promoters of 4 genes: hMLH1, CDKN2A ($p16^{INK}$), TIMP3 and TPEF/HPP1 containing 4 CpG islands were amplified using biotinilated forward or reverse primers (Biotage, Uppsala, Sweden). Presence of an amplified product and absence of contamination were determined by 2% agarose gel electrophoresis, after which the remaining product was analyzed quantitatively for presence of methylation by pyrosequencing. The latter represents a real-time sequencing in which the incorporation of a nucleotide by the DNA polymerase activates an enzymatic cascade and results in light emission. The quantity of the emitted light corresponds to the level of methylation of each CpG island.

Statistical analysis: Pyrosequencing measures the level of methylation of several CpG islands in the promoter of each gene which usually show concordance. A mean methylation level in percentage for each gene in every sample as an average of methylated cytosines in every CpG island is calculated.

The overall survival is calculated in months from the day of entering the study until reaching the end date (August 2010) or death of the patient. Survival curves were generated using the Kaplan-Meier method, and survival was compared using the Log-rank test. Proportion analysis was performed using odds ratio and $\chi 2$-test. Qualitative data (mean age) were compared using non-parametric Mann-Whitney test. A $p<0.05$ was considered as statistically significant.

Results

Microsatellite instability was found in 18.3% (15/82) of the cases. hMLH1, $p16^{INK}$, TIMP3 and TPEF/HPP1 were methylated in 15.8% (13/82), 42.7% (35/82), 51.2% (42/82) and 85.4% (70/82) of the cases, respectively. The mean methylation level for each gene was 3.3±10.6%, 6.6±12.6%, 11.7±17.8% and 28±14.8%, respectively. Tumors were divided into CIMP-negative (92.7% (76/82)) when absence or methylation of up to 2 genes was found, and CIMP-positive (7.3% (6/82)) when 3 or more genes were methylated.

Presence of microsatellite instability was positively associated with proximal tumor location (proximal to splenic flexure) and mucin production, while CIMP(+) tumors were associated with mucin production only. No other clinio-pathological associations were found (Table 1. Clinico-pathological associations with MSI and CIMP-status).

From the 82 followed up patients 56% (46/82) were alive and the remaining 44% (36/82) were deceased. The average survival was 39.2±20.2 months (range 1–72 months). 5-FU based adjuvant chemotherapy was performed in 62% (51/82) of the patients while surgical treatment alone was found curative for the remaining 38% (31/82) of them.

According to our results survival of patients is highly dependent on TNM stage ($p<0.001$, Kaplan-Meier test) – Fig.1 (Survival according to patients` TNM stage). No statistical difference in the survival between MSI-high and MSS tumors was found (p=0.69, Kaplan-Meier test) – Fig.2 (Survival according to MSI). Patients whose tumors were MSI and no methylation was found showed a trend towards a better survival (49±15.1 months) versus MSS tumors (39.7±19.6 months) but statistical significance was not reached (p=0.22, Kaplan-Meier test). Cases with MSI and methylated hMLH1 have worse prognosis than those with MSI and no methylation: the mean survival was 22.6±23.6 months and 49±15.1 months, respectively (p=0.028, Kaplan-Meier test) – Fig.3 (Survival according to MSI and methylation of hMLH1). Similar results were found for patients with CIMP-positive versus CIMP-negative tumors – mean survival 26.5±9.5 months vs 53.9±3.0 months (p=0.035, Kaplan-Meier test) – Fig.4 (Survival according to CIMP-status). Patients with MSS tumors showed a better survival if they were subjected to adjuvant chemotherapy compared to those who were treated with surgery alone – 44.2±16.3 versus 33.2±22.4 months (p=0.046, Kaplan-Meier test) – Fig.5 (Survival according to MSI and chemotherapy). In contrast, MSI-high patients have a similar survival irrespectively of whether they have undergone adjuvant chemotherapy or not: mean survival 44.2±16.3 months with chemotherapy vs 33.2±22.4 months without (p=0.78, Kaplan-Meier test).

We observed 5 cases (6.1%) with metachronous CRC formed on the average of 15.9±4.5 months postoperatively. Its rate was significantly higher in MSI-high patients -20% (3/15) than in MSS ones – 3% (2/67). The difference was statistically significant – p=0.04, $\chi 2$-test (OR=8.1, 95% CI 1.2–53.9) – Fig.6 (MSI as a risk factor for metachronous CRC).

Discussion

There is a large body of evidence in literature supporting the diverse nature of colorectal carcinogenesis. Therefore it seems plausible that different pathways may have different prognosis and response to surgery and adjuvant chemotherapy. In the present study we aimed to assess the role of MSI and promoter methylation of DNA as factors affecting prognosis and the risk for development of metachronous colorectal cancer.

Data from previous studies have proven a better prognosis for patients whose tumors are mismatch-repair deficient (20,8). A thorough explanation on why MSI confers a better prognosis is still lacking. A study from Rosty et al showed that only 1.8% of metastatic CRC showed presence of MSI suggesting that the majority of such tumors do not progress to advanced stages (22). Allelic loss and mutations of DCC, K-RAS and TP53 are associated with

worse prognosis, and these are rarely found in MSI cancers (25). In vitro experiments proved that cell lines from mismatch-repair deficient colorectal cancers show a weak response to 5-FU compared to mismatch-repair proficient ones (2). Nevertheless, some authors find a strong correlation between survival and MSI colorectal cancers that have undergone postoperative chemotherapy (7). In contrast to these results we failed to show a statistically significant difference in the survival between MSI and MSS patients (p=0.69). The observed survival advantage of MSI cancers due to mutations of the mismatch-repair genes versus MSS tumors did not reach statistical significance as well. A possible explanation for this discrepancy could be the low number of the patients included in the study and hence the lack of statistical power. We have observed, however, a better survival of MSS patients who have undergone postoperative chemotherapy compared to those who were treated with surgery only (p=0.046), e.g. the benefit of adjuvant chemotherapy is preserved only for MSS colorectal cancers.

According to Bertagnolli et al MMR-dysfunction can predict a better response to adjuvant chemotherapy with irinotecan, fluoruracil and leucovorin than with 5-FU based one (3). This could be due to the fact that microsatellite-repair deficient tumors are more susceptible to irinotecan than microsatellite-repair proficient cancers. Irinotecan inhibits the catalytic activity of topoizomeraze-I stabilizing covalent complexes between the enzyme and DNA. This leads to single- and double-strand fragmentation of DNA which is lethal if a repair system that corrects damages prior to mitosis is missing. Therefore, every process that blocks the functioning of mismatch-repair system including loss of mismatch-repair proteins potentiates tumor cell death (10). An interesting idea could be to study the response of different chemotherapy regimens according to the MSI status. An individualized treatment approach according to the molecular profile of the tumor is a possible option in the near future.

Our results showed a worse prognosis of patients with CIMP-positive tumors. Data from literature reveal opposite results: some of them support our findings (16) while others consider CIMP as a marker for better prognosis (18). The exact reasons why CIMP-positive patients have a worse outcome remain so far elusive. There is a strong relation between DNA methylation and folate metabolism (5), therefore it seems possible that CIMP-positive tumors have major disturbances in the metabolism of folate and methyl groups. They could diminish the susceptibility of tumors to anti-folate substances as are 5-FU and leucovorin. Another possibility could be the spreading out of methylation on a large extent of DNA encompassing numerous genes including for example hMLH1, which leads to MSI. The latter is associated with primary resistance to 5-FU based chemotherapy.

According to our results MSI tumors are statistically significantly associated with metachronous CRCs than MSS cancers – 20% versus 3% (p=0.04, χ2-test). One of the hallmarks of Lynch syndrome, in which the majority of the cases arise through MSI and inherited mutations of MMR-genes, is the elevated risk for metachronous cancers (6). Lawes et al have shown that MSI is a predictor for metachronous cancer among the normal population (15), which supports our results. One possible question is whether patients with epigenetic inactivation of hMLH1 are at higher risk for metachronous cancer. We cannot draw reliable conclusions due to the small number of the studied patients but methylation of hMLH1 was found in 33% of the cases. Velayos et al also support the notion that metachronous cancers are more often associated with mutations of MMR-genes (24). This could be due to the fact that mutations are present in virtually every cell while DNA methylation is associated with ageing of large bowel mucosa (11) and represents a „field defect"(13), e.g. certain areas of large bowel mucosa are prone to methylation while others are not.

In conclusion, our study shows that MSI and CIMP could modify their treatment plan and prognosis in patients with CRC. However, more studies with larger patients` numbers are needed to confirm these results in the Bulgarian population.

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ESOPHAGEAL pH MONITORING: EVALUATION AND TREATMENT OF GERD IN INFANTS AND CHILDREN

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Мониториране на езофагеалното pH – диагноза и лечение на ГЕРБ при кърмачета и малки деца

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РЕЗЮМЕ

Гастро-езофагеалната рефлуксна болест (ГЕРБ) представлява съвкупността от патологични симптоми, възникнали в резултат на рефлукса на стомашното съдържимо в хранопровода. Ралични диагностични методи се използвт за оценка на клиничните изяви на заболяването.

Цел: Целта на изследването е да уточни ролята на 24-часовото pH-мониториране в комплекса от диагностични методи, използвани за оценка на ГЕРБ при малки деца.

Материали и методи: За периода от 15 години сме лекували 185 деца, на възраст от 2 месеца до 4 години, със съмнение за ГЕРБ. Използваха се следните диагностични методи – подробна анамнеза, рентгенографии, езофагоскопия, сцинтиграфия и pH-метрия.

Резултати: Езофагеалното pH-мониториране е най-информативният скринингов метод за разграничаване на физиологичен от патологичен рефлукс, особено за откриване на деца с висок риск от рефлуксна болест и оценяване на патологич-

ABSTRACT

Gastro-esophageal reflux disease (GERD) can be defined as any symptomatic clinical condition that results from the return of stomach contents into the esophagus. Several investigations are used for evaluating the different clinical presentation of the disease.

Aim: The purpose of this study is to reveal the role of the 24-hour pH monitoring in the complex of diagnostic methods for evaluating GERD in young children.

Material and methods: For a period of 15 years we treated **185** infants aged 2 months – 4 years with suspected GERD. A detailed history, X-rays, esophagoscopy, scintigraphy and pH monitoring was used.

Results: Esophageal pH monitoring has been the most informative screening method for distinguishing physiological from pathological reflux, particularly revealing children with a high risk of reflux disease and evaluating pathological GER (gastro -esophageal reflux) by children with related clinical symptoms.

ния ГЕР (гастро-езофагеален рефлукс) при децата с клинични симтоми в следствие на рефлукса.

Ключови думи: ГЕР, ГЕРБ, pH –мониторинг, рефлукс-езофагит, пептична стриктура, хиатална херния

Key words: GER, GERD, pH monitoring, reflux-esophagitis, peptic stricture, hiatus hernia

INTRODUCTION

Gastroesophageal reflux (GER) is a common esophageal disorder in infants that usually resolves by 6 to 12 months of age. Gastroesophageal reflux disease (GERD) is a serious pathologic process that required diagnostic evaluation and multifarious treatment. GER is defined as passage of gastric contents into the esophagus, and GERD is defined as complex of the complications resulting from GER. [6, 8].

In some patients, GER can be diagnosed from the history alone [9]. Several investigations are needed in suspected GERD in order to asses the different manifestations of the disease. Esophageal pH monitoring is shown to be the most informative method for screening pathological reflux [1, 10, 11].

The aim of our clinical study is to reveal the role of the 24-hour pH monitoring in the complex of diagnostic methods for evaluating the various clinical presentation of GERD in young children.

CLINICAL MATERIAL

For a period of 15 years **185** infants and children aged 2 months – 4 years with suspected GER underwent 24-hour pH monitoring at the Department of Pediatric Surgery at Hospital „Pirogov“ and the University Paediatric Hospital – Sofia. The patients are divided into six clinical groups:

1. Physiological GER (n = 35)
2. Children with high risk of reflux disease (n = 22)
3. Cow‘s milk allergy (n = 8)
4. GERD with respiratory or pseudoneurological symptoms (n = 45)
5. GERD with underlying surgical complications n = 63
6. Neurologically impaired children n = 12

METHODS

Clinical tests were performed according to each individual indication:

Upper GI examination was used in 171 children (92,4 %) in order to identify anatomic abnormalities of the esophago-gastric junction, presence of esophageal stricture, hiatus hernia and the degree of spontaneous regurgitation.

Endoscopic investigation was performed in 148 children (80 %). Changes of the esophageal mucosa were confirmed according to the *Savary and Miller's* classification with a grading from I to IV degree.

Ninety-four 24-hours esophageal pH-monitoring (**EpHM**) studies were performed in 78 infants with software program by *S.T.Innovators, Bulgaria.*

For the present study following criteria were studied:

1. Reflux index (RI) in % = percentage of reflux time with pH under 4,0.
2. Number of reflux episodes for 24 hours (RE).
3. Number of reflux episodes lasting more than 5 min (RE^5).
4. Duration of the longest reflux episode (min) and the timing of appearance (DRE).

Tc 99 scintigraphy was used by 29 patients (15,7 %) as a functional test for evaluating gastric emptying and pulmonary aspiration.

RESULTS

1. Physiologic GER (N = 3 5 Age 2–5 months)

Clinical features: scanty postprandial or nocturnal vomiting, regurgitation.

Clinical investigations: no respiratory or neurological symptoms, no infection of the urogenital tract, no cow's milk allergy or metabolic disorders.

X-ray findings: incompetence of the cardia, insignificant reflux.

Fibroesophagoscopy: gaping of the cardia, no esophagitis.

EpHM: RI: 5.2 +/– 2,2 % RE: 17 +/– 9 RE^5: 3 DRE: 7 min during sleep

Treatment: Positional therapy, milk-thickening, prokinetiks agents.

2. Children with high risk of reflux disease (N=22 Age 4- 8 m)

Clinical features: Regurgitation during sleep, excessive vomiting.

Clinical investigations: no respiratory or neurological disorders, no infection of the urogenital tract, no cow's milk allergy. *X-ray findings:* wide cardia, obtuse angle of Hiss, marked reflux. *Endoscopy:* esophagitis I–II degree.

EpHM: RI: 16 +/– 3,7 %; RE: 27 +/– 11 RE^5: 7 DRE:12 min during sleep

Treatment: positional therapy, prokinetic agents, proton pump inhibitors.

Results: Relief of symptoms, weight gain. Two infants were referred to surgery 4 months after unsuccessful treatment.

3. Cow's milk allergy (n = 8 Age 5–8 m)

Clinical features: vomiting, insignificant growth retardation. *X-ray findings:* wide cardia, no significant reflux. *EpHM*: RI: 9,1 +/– 2,6 %; RE: 9 +/– 7 RE^5: 1 DRE: 9 postprandial. *Treatment:* exclusion of milk proteins, prokinetic agents.

4. GERD and associated symptoms (n = 45 Age: 2 mo – 2 y)

a) Respiratory symptoms and asthma-like conditions (n = 17)
Clinical features: insignificant regurgitation, negligible weight loss, chronic cough, recurrent bronchial obstructive syndrome. *EpHM:* manifested reflux RI: 28,6 +/– 6.1; RE: 13 +/– 7 RE^5: 8 DRE: 17 during sleep. *Tc 99 scintigraphy:* delayed gastric emptying, poor esophageal clearance, and accumulation of the radionucleide in the lung after 24 h. *Treatment:* positional therapy, fractionated diet, PPI and prokinetics. Four infants were referred to surgery.

b) Pseudoneurological symptoms (N = 21)
- Hyperirritable children (N = 11 Age 3–5 m)
  Clinical features: irregular vomiting, uncoordinated head movement, crying
  X-ray findings, endoscopy: normal. *pH data:* low-grade reflux (RI = 6,1 +/– 3,2). *Treatment:* milk-thickening, prokinetics agents, anti-colic agents, tranquillisation drugs.
- Apnoea (N = 7 Age 2–4 m)
  Clinical features: cyanosis and apnoea, no significant vomiting. Normal neurological status. *EpHM:* extreme reflux RI: 34,4 +/– 7,1; RE: 17 +/– 3 RE^5: 11 DRE: 19 during sleep. *Treatment:* positional therapy, prokinetics agents, H_2 blockers. *Results:* Relief of symptoms, markedly decrease of reflux.
- Sandifer syndrome (n = 3)
  In these children with established reflux disease the so called „torticolis“ resolved after antireflux therapy (n=1) or surgery (n=2).

5. GERD with underlying surgical complications (N=63 Age 8 m–4 y)

Clinical features: vomiting, failure to thrive, respiratory infection, anemia, dysphagia. *X-ray findings:* high grade barium reflux, obtuse angle of Hiss, hiatus hernia (n=13), esophageal stricture (n=35), secondary short esophagus (n = 15). *EpHM:* a) excessive reflux (n = 38) RI: 43.4 +/– 9.2 RE: 21 +/– 4 RE^5: 18 DRE: 22 +/– during sleep and postprandial b) inaccurate data due to esophageal stricture (n = 25) *Endoscopy:* Grade III–IV esophagitis, peptic or fibrous stricture. *Treatment:* Nissen fundoplication and gastrostomy (n=9); without gastrostomy (n = 43); Thal fundopexy procedure (n = 11)

6. Neurologically impaired children (N = 12 Age 2–4 y)

a) CNS damage (N = 8)
Clinical features: vomiting, regurgitation, dysphagia, weigth loss.

EpHM: various results – from marked acid reflux (RI over 30 %) to insignificant changes (RI 5.6 +/– 2.4) *X-ray finding:* incompetence of the cardia, marked barium reflux. *Treatment:* Nissen fundoplication (n = 12)

b) Neglected children (N = 4)
Clinical features: Restricted growth due to rumination and vomiting.
Diagnosis is made by clinical observation. No marked abnormalities detected by fluoroscopy or esophagoscopy. *Treatment*: positive emotional stimuli led to weight gain (n = 1). *Surgery* was necessary in 3 cases.

DISCUSSION

In normal infants GER can be physiological due to the immaturity of the lower esophageal sphincter. Another cause for regurgitation or vomiting is the psychosocial factor – mother negligence, overfeeding or inappropriate feeding, and psychical distress. Physiological GER can be diagnosed from the history alone and it is not necessary to perform EpHM in asymptomatic reflux [8, 9].

Thickened feeds and elevation of the head of the bed are helpful in reducing the symptoms of GER by young infants and no specific treatment is required. Cisapride and later Domperidone are useful in reducing the frequency of vomiting [6, 8].

Important groups represent children with a high risk of reflux disease. GER may be a transitory problem but if untreated, it can result in serious complications: anaemia, respiratory distress, apnea, failure to thrive, esophagitis and stricture. The EpHM is the most appropriate test for evaluating the risk group. In many cases GER may resolve after medication with Cisapride and/or PPI [4, 8, 10].

Cow's milk allergy is a transitory and accompanying factor leading to vomiting rather than an etiological factor for GER. Our investigations revealed considerable clinical improvement after milk protein exclusion and a trial of a hypoallergenic formula feed [7].

A primary high-grade acid reflux is frequently associated with respiratory tract damage. It can take a subclinical course with „innocent regurgitation" or negligible vomiting. The prolonged duration of reflux episodes during sleep correlated with the evidence of acute or chronic respiratory symptoms. The pulmonary complication may often be a primary manifestation of the illness. There is a high prevalence of pathologic gastro-esophageal reflux in asthmatic children, contributing to asthma severity. Cyanosis and apnoea are also signs of excessive acid reflux related to respiratory dysfunction. Patients with chronic cough, recurrent pneumonia and asthma should be investigated by means of EpHM for the possibility of GER and treated accordingly the clinical manifestations [3, 5]. Antireflux surgery should be also considered in management [2, 8, 11].

The association between GER and neurologically impaired children is well described. The injured afferent input results in esophageal motor disturbances, abnormalities in the swallowing mechanism and incompetence of the cardia. In neglected children rumination is due to lack of love and attention to the child. The surgical procedure must be performed earlier because of risk of growth retardation.

GER with underlying surgical complications forms the most important group which is associated with prolonged exposure of the esophagus to acid juice and further developing of esophagitis and stricture. The upper GI series are not specific for the diagnosis of reflux, but is useful for evaluation the presence of anatomic abnormalities, such as hiatus hernia and esophageal stricture. Endoscopy and biopsy can determine severity of esophagitis [4]. In most cases EpHM is very contributive to the diagnosis.

There are further indications for surgery such as ineffective conservative treatment of GER or the presence of hiatus hernia. The Nissen fundoplication is the most preferred antireflux procedure which results in significant clinical improvement [2, 8, 10].

CONCLUSIONS

GER in infants can result in serious consequences. In the first year of life most of the children have a positive response to the conservative treatment. The clinical manifestation of GERD such as vomiting, anaemia, apnoea, respiratory distress, failure to thrive and esophagitis should be investigated thoroughly. The 24-hour pH monitoring is the most appropriate screening method for locating the group of children with a high risk of acid reflux disease and children with associated complications. It is a valid and reliable test for evaluating acid reflux. Surgical treatment should be considered when therapy failed and underlying surgical complications are present.

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Deontological Problems of Clinical Toxicology in Bulgaria during the Decade 2000–2010

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Деонтологични проблеми на клиничната токсикология през десетилетието 2000–2010 година

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РЕЗЮМЕ

Специфичните особености на клиничната токсикология винаги са пораждали много деонтологични въпроси и правни проблеми, свързани главно с динамичните взаимоотношения между лекаря и пациента, способността на интоксикирания болен да възприема и обработва адекватно поднесената информация за неговото състояние и необходимост от лечение,респективно- да се съгласява или да отказва медицинска помощ, да позволява или отказва разгласяване на данни за неговото отравяне и др. През декадата 2000–2010, след въвеждането на здравно-осигурителната система и влизането на България в Европейския съюз, бяха направени редица важни промени в здравното законодателство, подзаконови нормативни актове, приеха се етичните кодекси на лекарите и другите медицински професии. В тези документи частично се разрешават някои от старите клинично-токсикологични проблеми. Новите условия породиха и някои нови проблеми, свързани с автономията на пациента и правото му на конфиденциалност, достъпа до медицинска помощ, отношенията на токсиколога с родните на пациента, работодателя му, застрахователя му, другите му лекуващи лекари; влиянието на финансовите и здравно-осигурителни фактори и т.н. Авторите считат, че е необходим текущ анализ и обсъждане на деонтологично-правните въпроси и трудности, свързани с клиничната токсикология, като важна част от съвременната клинична медицина в България.

Ключови думи: дентология, клинична токсикология, съзнание, информация, автономия, достъп, принуда, закон

ABSTRACT

The specificity of the clinical toxicology has always aroused many deontological questions and legal problems, mainly connected with the dynamic interrelation between the doctor and the patient, the ability of the intoxicated patient to perceive and process the received information about his state and necessity of treatment, respectively- to agree or refuse medical help, to permit announcing some data about his case of intoxication, etc. During the decade 2000–2010 after Bulgaria became a member of EU and after the establishment of the Health Insurance System a number of changes in the health laws and minor decrees have been done, the new codes of Bulgarian physicians and of other medical professions have been approved. Some of the old clinical toxicological problems have been partially solved in these documents. However, the new conditions aroused new problems, connected with the patient's autonomy, his right to confidentiality, access to medical help, relations of the doctor with the patient's family, patient's employer, patient's insurance agent and patient's treating doctor for other diseases; the influence of financial and health insurance factors, etc. The authors consider that as the clinical toxicology is an important part of the clinical medicine in Bulgaria nowadays, a current analysis and discussion of the deontological and legal questions and difficulties of this discipline is necessary.

Key words: deontology, clinical toxicology, patient, consciousness, information, autonomy, duress, access, law

Introduction

The specificity of the clinical toxicology often creates complex deontological problems. [2, 3, 6, 8, 10, 11].The main factors that can lead to deontological and legal problems in this discipline are: 1. High relative part of patients with temporary or constantly changed consciousness because of toxic encephalopathy, psychosis, stress, etc. Difficult or impossible perception and processing of the information as a consequence of the changed consciousness. Frequent cases of temporary restricted patient's autonomy in the process of management of an intoxicated patient. Quick negative or positive dynamics in the mental status. 2. Initially intentional auto aggression: high percentage of patients with suicidal attempts or different type of auto aggressive behavior. Frequent initial refusal of medical help. 3. Very high relative part of emergency toxicological cases, which require urgent admittance in hospital, quick diagnosis and treatment. 4. Medical procedures and manipulations which can be rejected by the patient as non pleasant or humiliating- stomach lavage, urethral catheterization, enema, extracorporeal detoxification of the blood, fixation or isolation of the patient and etc. 5. Frequent total or partial lack of information about the case at the beginning; unclear or distorted history, simulation, dissimulation or aggravation. 7. High relative part of socially poor patients, patients with serious psychic acute or chronic diseases or with serious somatic co morbidity. 8. Expensive and long management and treatment of the severe intoxications. 9. Lack of enough information about the nature of the acute and chronic intoxications in society, including the patient's relatives, employers, media, and etc. 10. The health laws, decrees and orders do not reflect fully the specificity of the toxicological patients.

During the decade from 2000 to 2010 year, some important social, political and economic changes have taken place in Bulgaria. They had a significant reflection on the whole health care system and in particular-the clinical toxicology. The changes with the greatest direct impact on the health care system are the establishment of the Health Insurance System and the beginning and dynamic development of the health reform in Bulgaria. [4, 5, 7]. The entering of Bulgaria in EU in 2007 also had important influence on the tasks of the healthcare system because of the great potential expansion of the contingent of patients. The European regulations about social and healthcare insurance and the Helsinki declaration about the ethical principles are valid in Bulgaria since 2007 year. The laws and decrees concerning toxicological medical help have some differences in different European countries. Changes have been made in Bulgarian Health law and some of them are especially

important for clinical toxicologists. During the last decade new ethical medical codex was approved and the rules of the good medical practice generally accepted.

All these changes during the last decade have led to progress in some deontological and legal toxicological problems, left unsolved others and created new serious ones.

Aim:

Review of some of the most important contemporary deontological problems of the clinical toxicology in the light of the changes during the decade 2000–2010 year.

Discussion

One of the most important goals of the contemporary deontology is the increased significance of the informed consent of the patient about his treatment at any stage of the diagnostic and treatment process. [1, 4, 11, 13, 14] In the law of Health from 2009 it is fixed in section II-Rights and obligations of the patient, in art. 84. (2), art. 86, 87, 88, 89, 90, 91.As often the main problem of a toxicological patient is the state of consciousness, often with quantitative or qualitative toxic changes at different stages of severity or other kind of mental disorders, the key problem is the total or partial inability of this patient to perceive, get and process the information and therefore- to give an informed consent and especially-an informed refusal of treatment. Partially this problem is solved in art. 87. (1), (4), art. 89. (2), art. 90. (4), (5):

Art. 89. (2) the activities of para 1 can be implemented in favour of the health of the patient without written informed consent only when his life is immediately threatened and:

1. his physical or psychic status does not allow expressing of informed consent;
2. it is impossible to be achieved informed consent by parent, guardian or trustee or by the person of art. 162, para 3 in the cases the law requires it.

Art.90. (4) In the cases when under para 1 there is refusal by a parent, guardian or trustee and the life of the patient is threatened, the chief of the medical establishment can take decision for implementing life saving treatment.

It should be discussed an uniform scale of defining the consciousness changes. Nowadays many physicians use Glasgow coma scale (GCS), but it is too rough and in broad outline when it comes to minimal changes at the beginning of an intoxication. The Reed scale is more suitable but is not enough popular among doctors- non- toxicologists.[9]. Another open to criticism point is art. 90. (2)-that the refusal of treatment shall be certified in the medical documentation with the signature of the person. A patient who is inadequate because of minimal or medium severe toxic changes of the central nervous system can make a simple signature without realizing what really has been done. The well known quick dynamics of the acute intoxications leads to additional complications of the process of receiving of an informed consent from a toxicological patient. The following suggestions would help the doctor to start the treatment of such patient in optimal time: 1. The new revisions of the Law of Health give more freedom to the doctor-specialist to take decision for implementing life saving treatment.[7]. In every such case he must explain his motives to the patient and his relatives. It is not very clear who should help to realize the compulsory measures in these cases- medical staff, police or special guards. If the doctor decides to accept the patient's refusal of treatment he should insist on the presence of the family and once again inform about the possible risks. The informed refusal of treatment should be made either by hand written whole sentence by the patient himself or by filling special formulary of refusal. 2. The presence of patient's family at the admission and the discharge from hospital is not compulsory, but has great common sense. Most of hospital orders include it. 3. When the patient refuses only part or stage of the treatment or single diagnostic or therapeutic procedure, the conduct should be the same. 4. With the progression of the management of an intoxication we expect improvement of the CNS toxic symptoms and the ability of the patient to process information and take adequate decisions, so a dynamic communication between the patient and his treating doctor and medical team is necessary. Unfortunately the shortage of medical personnel and the increasing volume of work in some hospitals nowadays make this dynamic communication insufficient.

Special attention should be kept on the cases of psycho motor agitation and inadequacy that need restriction. Physical restriction is always a shocking procedure for the patient and his family. The doctor should explain the motive for this procedure and that it is temporary. Art. 150 (1) discuss in detail the measures for temporary physical restriction and the rules of their application.[4].

As a whole during the last decade the access of the toxicological patients to qualified medical health has been unlimited and sufficient. However some groups of patients have higher potential risk of delayed or obstructed access to toxicological help: people from small and distant villages, people without telephones, social outsiders, patients with severe addictions, patients-children or mentally ill, who are neglected by their relatives. A new group can be added: working people with occupational accident, who are afraid of losing their job and seek toxicological help late or do not seek it at all. It is probable that such cases will increase in the situation of economic crisis.

Another serious and relatively new problem of clinical toxicology is connected with the intoxicated patients without a health insurance. [5]. It is known that many of the non-health insured people have different medical, social or psychic problems that lead to acute or chronic intoxications: addictions, high rate of depression and suicidal behavior, significant co morbidity, inadequate feeding, numerous hospitalizations, lack of relatives to take care after the discharge from hospital. Often these intoxications require a complex, long and expensive treatment and create a heavy financial burden on the toxicology clinics and departments and their hospitals. According to the Law of Health, art. 84. (1), art. 85, 99 and art. 100. (2) non-insured patients receive adequate and quick medical help as emergency patients.[4]. Nowadays there is not clear judicial and administrative decision about those non-insured patients who need long lasting or repeating treatment.

Another constant source of deontological problems is the problem of doctor's secret in clinical toxicology. The information about the patient is strictly confidential. At the same time in many cases it is inevitably to inform the family about the patient's problem, often against his will (suicidal attempt, depressive reaction, misuse of drug or addiction, etc.). As a principle it should be announced only to the closest family members, better after informing the patient. The disclosure of patient's data to his employer or colleagues is undesirable without permission from the patient. When the confidential information is wanted from the court or other judicial way it is not necessary to get the permission of the patient. Strict confidentiality should be kept when patient's information is used for scientific articles, medical discussions and especially-in contacts with media. Some socially important cases can be announced in media without details and disclosure of personality of the patient. During the last 10 years this problem has growing actuality.

Inseparable part of toxicologist's work is the communication with the family of the patient. In case of toxic change of the consciousness or chronic mental disorder of the patient the information about the necessity of treatment should be given to a family partner, close relative, caretaker, or close friend. The information should be only for the purpose of the management and optimally confidential. The doctor does not take side in family arguments but can give an advice for whole family psychological help. In case of family violence the competent organs should be informed. When the patient is

a child the information is given to his parents but it is good to inform the child also in easy to understand way about the necessary treatment.

One of the important factors of the successful treatment in clinical toxicology is the good interrelation between the doctor and patient. In many toxicological cases the temporary or constant change of consciousness makes this interrelation difficult or impossible. However when it is possible it has a positive effect on the diagnostic ant treatment process because the patient is involved as an active participant in it. Even the partial including of the intoxicated patient as a partner in his management gives positive results. The doctor-toxicologist should respect the right of his patient to be informed and if possible- actively involved in discussing the diagnostic and treatment plan.

Conclusions:

Clinical toxicology is a discipline rich of deontological and judicial problems. During the last decade some progress has been made in health care legislation which affects in particular toxicology. However a lot of unsolved old problems have remained and new ones appeared. This increases the individual responsibility of the doctor- toxicologist in every single case. Current reports and discussion of contemporary deontological problems in toxicology would help the better solutions.

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Physical Factors (natural and reformed) in the Treatment of Metabolic Syndrome

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Физикални фактори (естествени и преформирани) при лечението на метаболитния синдром

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РЕЗЮМЕ

Метаболитният синдром (МС) е мултикомпонентен сърдечносъдов рисков фактор. Международната диабетна федерация (IDF) през 2005 г. създаде глобалния консенсус за диагностика на МС:

1. Централно затлъстяване – обиколка на талията > 94 см за мъже и >80 см за жени от европеидната раса

В съчетание с две от следните нарушения:

2. Повишени триглицериди >1,7 mmol/l
3. Понижен HDL холестерол <1,03 mmol/l за мъже и <1,29 mmol/l за жени
4. Повишено артериално налягане >130/85 mmHg или лечение на хипертония
5. Повишена плазмена глюкоза на гладно >5,5 mmol/l или диагностициран диабет тип 2 или НГТ

Глобалният кардиометаболитен риск се налага от факта, че сърдечно-съдовите рискови фактори не съществуват изолирано, а

ABSTRACT

Metabolic Syndrome (MS) is a multi-component cardio-vascular risk factor. International Diabetes Federation (IDF) in 2005 created global consensus for the diagnosis of MS:

1. Central obesity – waist circumference > 94 cm for men and > 80 cm for women

In combination with two of the following violations:

2. Elevated triglycerides >1,7 mmol/l
3. Decreased HDL cholesterol < 1,03 mmol/l for men and < 1,29 mmol/l for women
4. Increased blood pressure > 130/80 mmHg or treatment of hypertension
5. Increased fasting plasma glucose >5,5 mmol/l or diagnosed type 2 diabetes

The global cardiometabolic risk is imposed by the fact that cardio-vascular risk factors do not exist separately but are expressed together in one and the same individual.

There are two main strategies for MS treatment (remedial algorithm):

се изявяват съвместно в един и същи индивид.

Две са основните стратегии за лечение на МС (лечебен алгоритъм):

- Немедикаментозна интервенция – тук се включват средствата на физикалната и рехабилитационна медицина за лечение и превенция на метаболитния дисбаланс;
- Директно медикаментозно третиране на метаболитните рискови фактори

Всичко това ни даде основание да направим обзор на физикалните фактори (естествени и преформирани) за оказване на положително въздействие при метаболитен дисбаланс.

Ключови думи: метаболитен синдром, физикални фактори, липолиза, обезитас

- Non-medicamentous intervention – which includes the remedies of physical and rehabilitation medicine for treatment and prevention of metabolic imbalance;
- Direct medicamentous treatment of metabolic risk factors

All of the above gave us the reason to make an overview of the physical factors (natural and reformed) for exerting positive influence on the metabolic imbalance.

Key words: metabolic syndrome, physical factors, lipolysis, obesity

The information in the Bulgarian and foreign literature regarding the application of physical factors for the purpose of prophylaxis and treatment of Metabolic Syndrome (MS) is rather scarce.

According to I. Angelov /2005, 2006/ balneo-water treatment prophylaxis includes alkaline mineral waters /Ilientsi, Kurilo, Mihalkovo/, sulphite waters /Shipkovo/ and mostly slightly mineralized waters /Gorna Banya, Hisar, Velingrad, Varshets, etc./, 200–300 ml before meals, three times a day for a period of 20–30 days. Two courses are conducted per year. According to the author this stimulates glycogenesis, improves the exchange of fats, carbohydrates and purines. The resorption of fats is impeded and they have anti-toxic and choleric activity.

Balneo-water treatment prophylaxis helps release of bile and some remains of food; it has a laxative effect and improves dyslipidemia, arterial hypertonia.

Solar and air baths and UV radiation.

Solar and air baths are conducted under conditions of physiologically cool weather, with duration of up to two hours after obtaining pigmentation, 12–14 procedures, two courses a year. In the first 5–6 days until getting pigmentation, their duration is about 15–30 minutes. This is done in the morning hours /8–10am/ and around lunch time they should not last longer than 10–12 minutes.

I. Angelov /2006/ advices extended duration after pigmentation – 60–120 minutes in the absence of overheating or cooling out.

In the winter months UV radiation is used in suberythemal doses – one course.

I. Angelov /2005/ expresses an opinion that sun bathes in a sub-comfort zone improve glucose absorption; the oxidation of the free fatty acids is improved which reduces their ability to re-esterify into triglycerides. The oxidation processes and the protective strengths of the organism are activated.

It is important that sun baths have a relaxing impact when used after kinesitherapeutic procedures.

On the issues of MS prophylaxis there is also some information provided by P. Raven /1990/, M. Hanefeld /1995/, I. Koleva et al. /2002/, A. Tsaneva /2005/.

Sauna, climate – therapy and SPA

Relaxing procedures are quoted – juniper bath, shower, underwater jet massage, sauna. Their efficiency on the restoration of patients after continuous kinesitherapeutic procedures is reported /I. Angelov, 2006/.

I. Topuzov /2006/ reports considerably good results after the application of rehabilitation of gynoid obesity (differs from the abdominal, but often combined with it), including kinesitherapy with locally acting physical procedures in the area of female basin – electrotherapy with cellutron and laser therapy.

Our studies /T. Troev, candidate-dissert., 1993, St. Gatev, 1988/, conducted two times with respect to the influence of sauna-therapy on the body weight, fatty exchange, blood sugar and blood pressure, prove lack of changes in the fat exchange after one-month application of sauna, three times a week /p> 0,05/. Despite the changes, statistically significant in body weight, they are most probably due only to transient loss of liquids /p< 0,05/.

It was concluded that changes in body weight after sauna procedures do not lead to considerable modifications of fat exchange – total cholesterol, β- lipoproteins. This is why we recommend that sauna can take part in body weight regulation only when it is accompanied by observation of a hypocaloric diet and is combined with a specific nutrition regime.

Changes in blood sugar are within the physiological range; they do not lead to metabolic modifications or pathological disturbances / p>0,05/. This is why in diabetics treated only with a diet or having diabetes type 2, additional correction of their daily medicamentous programme is not necessary. However the situation is different when it refers to diabetes type 1 – sauna increases insulin resorption from the subcutaneous depot – an intake of additional quantity of food or correction of the insulin doses are recommended along with sauna treatment.

We found out that after a one-month application of sauna, a reduction of the systolic and diastolic arterial pressure and pulse frequency is observed – /p<0,05/, which is preserved for up to 2–3 months after the treatment /T. Troev, 1993/. This means that conditions for „economic“ work of the heart are created. This is why we pay attention to the possible increase in the cardio-depressive effect of β-blockers / Obsidan, Sectral, Visken/ and Ca-antagonists from the verapamil group /Verapamil, Dilzem/ in their combination with sauna therapy in patients with MS.

Finally we have to note that sauna treatment improves the albumin-synthesizing function of the hepatocytes /ASAT, ALAT/ and has a positive effect on the indices of activity of the inflammatory process – ESR, leucocytes, fibrinogen, N-acetylneuraminic acid, /p<0,05/, /T. Troev, candidate-dissert., 1993., The availability of non-alcoholic steatosis in MS is not contraindication for its application.

In 2006 I. Angelov confirmed our observations – sauna can be used as a remedial procedure for patients with MS /availability of diabetes type 2, arterial hypertonia/, but with shorter duration – up to 10 minutes, without occurrence of hyperthermia or dehydration.

In 2008 in our publication /T. Troev, H. Milanova/ we confirmed the statements expressed by I. Angelov /2005/ on the simultaneous use of physical prophylactic means and diet in patients with MS – the patients' quality of life is improved /the so called social satisfaction/ and new healthy habits are created.

In an independent publication of K. Dimitrova /2005/ attention is paid to the influence of moderate altitude /1500–2500m/ on the indices of people with MS. The study of World Health Report /2002/ consists of 72 men with MS /either working or retired/ who have been randomly divided into two groups with identical stay at moderate /1700m/ or low /300m/ altitude. It is reported that the three-month vacation at 1700m is born well, without leading to pathological deviations in their health status. It reduces the values of arterial pressure, leads to reduction of the body weight index,

improves glycemic control and increases HDL cholesterol. Erythropoiesis is stimulated without increasing the vascular endothelial growth factor /VEGF/.

The stay of the participants at both altitudes lasted for three weeks and included identical nutrition and motive regime. Exercises with moderate physical pressure and continuous walks were used. Due to the slow adaptation upon climbing moderate altitude, short-term stays /less than one week/ are not recommended.

Seven weeks after the end of the holiday, the favourable effects as regard to most MS indices were maintained. This discovery is absolutely up-to-date. Until present no studies have been conducted with such duration /usually up to 14 days/ and not at such altitude. Last, but not least, K. Dimitrova /2005/ reports /quoting World Health Report/ that the psychosocial stress as a leading factor for development of MS has also been influenced, and from there – the development of ischaemic cardiac disease with all consequences.

The entire study is part of the project „Austrian Moderate Altitude Study 2000“ /AMAS 2000/ on the study of the influence of the moderate altitude /1700m/ on the cardio-vascular system, the metabolic status, hemopoiesis, the neuro-psychic condition of patients with overweight and reduced physical activity.

In Bulgaria similar studies have been carried out by I. Angelov /1971, 1986/ but the use of altitude above 1600–1700m is not recommended due to expressed pathophysiological effects: decrease in oxygen saturation, increase in breathing frequency and activation of the sympathetic nervous system. Our opinion with regard to the physiological activity of moderate heights /1500–2000m/ is that they can cause modifications in the cognitive functions, sleep and mood. The same heights are also important for the increase in the physical endurance of professional sportsmen.

K. Dimitrova /2005/ reports the influence of MS indices on the use of balneotherapy and dosed physical pressure in Austria – factors already reported and used in Bulgaria.

I. Angelov /1993/ reports the effect of extreme impact on the energetic substrates and hormonal regulators of energetic metabolism. Energy reserves of healthy individuals with normal weight are approximately the following: carbohydrates – 1200 kCal; fats – 150 000 kCal; protein – 32 000–40 000 kCal. Having in mind that walking on a plain terrain with speed 4.5–5km/h uses up around 300 kCal, it means that for only 3.5 hours all carbohydrate supplies of the organism can be exhausted. The main energetic reserves are accumulated by the fats /I. Angelov, 1993/.

According to N. Boule et al. /2001/ the type of substrate to be used – either carbohydrates or fats – depends on the continuation and intensity of the work performed. The more glycogen is accumulated in the muscles and the slowly it is exhausted during work, the more efficiently and extendedly a person is able to work /R. Ovcharov, V. Georgieva, 1985/.

According to I. Angelov /1986/, V. Goranova /1989/ in healthy individuals and diabetics type 2 performing moderate physical work with duration up to 150 minutes in a sub-comfort zone, hypoglycemia appears extremely rarely. The meteorological environment is able to modify the effects of physical activity on the basic energetic substrates.

The best absorption of glucose and stimulation of lipolysis is achieved when physical activities are performed in a sub-comfort zone / physiologically cool/. The same refers to fat mobilization – it is better stimulated in trained individuals and in physical activity in the area of sub-comfort. In physical activities under conditions of heat, stress exhaustion of the catecholamine supplies in the organism occurs which leads to loss of the possibilities for efficient adaptation.

With a view to the faster restoration and utilization of the accumulated lactate after physical activities, some relaxing procedures are considered appropriate, such as underwater jet massage, sauna, negative air-ionization or sun-air exposures in the area of sub-comfort /I. Angelov, 1993/. Physical burdening, performed in the area of over-comfort – overheating, leads to stimulation of the production of ketone bodies.

In conclusion it should be noted that the reviewed problem on the adaptation of energetic metabolism in physical activity and meteorological impacts has priority. It should not be disregarded that in diabetics the activity of glyconeogenesis is better expressed both when insulin is lacking and under unfavourable meteorological conditions.

Upon physical burdening hyperglycemic reactions may occur.

In conclusion – physical factors /natural and reformed/ can be used for treatment and prophylaxis of the main markers of MS. Physical means are widely accessible and comparatively cheap. They can be applied to a certain extent through self-control and training of the patients themselves. They are also applied for outpatient treatment. They influence the social status of the patients and have a positive effect on the psycho-social stress. They do not solve the main problems in the MS treatment but combined with dietary nutrition, physical activity, medicamentous treatment /if necessary/, prevention of patients with diabetes type 2, of hypercholesterolinemia, body weight, cardiovascular diseases and of the main risk factors can be achieved.

Our statement coincides with that of the deeply honoured I. Angelov, that future belongs to preventive physical therapy through active positive impact on the prophylaxis and treatment of people with MS.

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Long term survival in five rare cases with multiple primary neuroblastoma

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Дългосрочна преживяемост при пет редки случая с първичен множествен невробластом

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РЕЗЮМЕ

Цел: Първичният множествен невробластом се среща много рядко – около 1 % от всички деца с невробластом. Те могат да възникнат едновременно от двете надбъбречни жлези или от различни структури на симтатикусовата нервна система. Целта на изследването е да представи 5 случая с първичен множествен невробластом.

Клиничен материал: Всички 5 деца са момчета, на възраст от 2 месеца до 4 години в момента на диагностициране, при които успешно е проведено радикално хирургично лечение. 4 от децата допълнително са провеждали химиотерапия с Vincristine, Cyclophosphamide и Epirubicin, а едно от тях е провело и лъчелечение. Всички 5 пациента са живи и без данни за туморен процес за период на проследяване от 14 до 32 години.

Заключение: Отличната прогноза при тези редки случаи с първичен множествен невробластом повдига въпроси, засягащи биологичното поведение на туморите и ролята на контрола на имунната система върху факторите, отговорни за клетъчната диференциация, туморния растеж и дисеминация

ABSTRACT

Purpose: Multiple primary neuroblastoma is a very rare entity – about 1% of all children with neuroblastomas. They may arise simultaneously in both adrenal glands or in different parts of the sympathetic nervous system. The purpose of this study is to present 5 cases with multiple primary neuroblastomas.

Clinical Material: All 5 patients were boys aged 2 months to 4 years at the time of diagnosis, which were treated successfully with radical surgery. Additionally, 4 children underwent chemotherapy with vincristine, cyclophosphamide and epirubicin; one of them received postoperative radiotherapy as well. All 5 patients are alive and disease-free for a follow-up period of 14 to 32 years.

Conclusion: The excellent prognosis of those rare cases with multiple primary neuroblastomas arises questions concerning the tumour biological behaviour and the role of the immune system control on factors affecting cell differentiation, tumour growth and dissemination.

Ключови думи: първичен множествен невробластом, ганглионевробластом, оперативно лечение, лъчетерапия, химиотерапия, дългосрочна преживяемост

Key words: multiple primary neuroblastoma, ganglioneuroblastoma, surgery, radiotherapy, chemotherapy, long-term survival

Introduction

Neuroblastoma remains one of the most frequent embryonic tumors in childhood [1]. As with most similar tumors, it is diagnosed before the age of 5, mainly before the second year of life. The improved diagnostic possibilities and the development of a variety of chemotherapeutic protocols have led to minor improvement of the therapeutic results.

Almost two thirds of the patients are being diagnosed in advanced disease stages and only one third of them have a chance to be cured [1,2]. The great diversity of tumor localization presumes the various clinical presentations of the disease.

The simultaneous appearance of multiple neuroblastomas is a rare entity (3). There are few reports in the literature concerning primary neuroblastomas in both adrenal glands [3,4,5] and other multiple tumors of various maturity stages localized in different regions of the sympathetic nervous system [6,7,8,9].

The purpose of this report is to present 5 new cases with multiple primary neuroblastomas and to discuss the various possibilities for the biological behavior of the tumor.

Clinical material

For period between 1972 and 1998 years we treated 193 children with neuroblastoma. Only 5 (1.04%) of them had multiple primary tumors. These were all boys aged 2 months to 4 years at the time of diagnosis.

Case No 1

A 13-month-old boy was admitted with simultaneously located tumors in the left adrenal gland and the mediastinum (August 1979). A typical triad of ptosis, miosis and enophthalmus was found on the right. A thoracotomy and complete excision of 2 well-encapsulated tumors in the posterior mediastinum was performed. Subsequently the other primary tumor in the left adrenal gland was excised by laparotomy. Histological examination from the 3 tumor lesions revealed neuroblastoma. Postoperatively, the child was treated monthly for a year with vincristine and cyclophosphamide.

Case 2

An abdominal tumour was diadnosed by a routine clinical examination in a 3.5-year-old boy (December 1985). Diagnostic workup showed tumors simultaneously located in the abdominal retroperitoneum and the mediastinum. A transcutaneous needle biopsy of the abdominal mass revealed the cytological characteristic of neuroblastoma. Two courses chemotherapy with vincristine, cyclophosphamide and epirubicin were applied. At the thoracotomy a total excision of the mediastinal tumor was accomplished. Subsequently at laparotomy a subtotal excision of the retroperitoneal tumor, arising from the left paravertebral sympathetic chain was carried out. Histological examination revealed mediastinal ganglioneuroblastoma and retroperitoneal neuroblastoma. Postoperatively, the child was treated with radiotherapy in the abdomen with total radiation dose 30 Gy (daily fraction dose 1,5 GY), and chemotherapy with monthly vincristine, cyclophosphamide and epirubicin for 1.5 years.

A year later, CT and ^{131}I-MIBG scanning showed evidence of a tumor in the right adrenal gland measuring 1x1 cm. The parents refused third operation. The tumor biological behaviour was supposed to be very likely to ganglioneuroma.

After 4 years of follow up there were no signs for tumor progression. In 1999 he had symptoms of hyperthyroidism which were successfully treated. We suppose that there is no relation to the previous anticancer treatment.

Case 3

In 1983, a 10-month-old boy was admitted with a clinically manifest abdominal mass. The tumor was completely resected and the biopsy showed neuroblastoma. The disease was in clinical stage 2. Postoperatively, the child was treated monthly for a year with vincristine, cyclophosphamide and epirubicin. Thirteen years later chest radiograph showed a mediastinal mass. After radical excision the histological examination showed ganglioneuroma

Case 4

In 1995, a 4-year-old boy had a chest radiography done because of a respiratory infection, which showed a mediastinal mass. After thoracotomy, the histological findings showed ganglioblastoma in clinical stage 2. Two months later a CT scan revealed a paravertebral abdominal mass. A radical excision of the tumor was performed with histological characteristic of ganglioneuroma. The child received a total of 6 postoperative courses with vincristine, cyclophosphamide and epirubicin.

Case 5

A male 2-month old boy was admitted with clinical evidence of two abdominal tumors bilaterally (Jule 1998). The CT scan revealed tumors originating from both adrenal glands. A radical resection of both tumors was carried out with histological characteristic of neuroblastomas. The postoperative treatment included only substitution with cortisol.

Discussion

Multiple primary neuroblastoma is a very rare entity – about 1% of all children with neuroblastomas. They may arise simultaneously in both adrenal glands or in different parts of the sympathetic nervous system. In 1978 Ashley collected and analyzed all the published data of multiple primary neuroblastomas (1). We present briefly his review of literature.

In 1938 Wahl and Craig were the first to observe diverse cell differentiation in multiple primary neuroblastomas [5]. The authors described a case with 3 histologically distinct tumors – neuroblastoma, ganglioneuroblastoma and ganglioneuroma. In 1942 Potter and Parrish published a case of a fetus with neuroblastoma, ganglioneuroma and fibroneuroma [8]. In 1959 Gross et al. reported 4 cases out of 217 children with neuroblastoma who had multiple primary tumors [6]. One of these children had 6 tumors originating from different regions of the sympathetic truncus; another child had 3 tumors in both adrenal glands and in the retroperitoneal sympathetic truncus. Chatten and Voorhess in 1967 reported a case with 3 tumors – one in the thoracic sympathetic truncus and 2 in both adrenal glands [7].

Marsden described a case with abdominal neuroblastoma and ganglioneuroma in a hip [9]. In 1966 Knudson and Amorin observed a case with neurofibromatosis and 2 primary tumors-neuroblastoma and ganglioneuroma [7]. Lee et al. report a case of bilateral cystic adrenal neuroblastomas with massive intratumoral haemorrhage [10].

We report 5 cases with multiple primary neuroblastomas with 100% long-term survival. The prognosis of those patients is excellent due to the favorable biological behavior of the primary tumors. There are many reports in literature concerning the phenomenon of spontaneous regression of neuroblastomas in patients under the age of 1 year or in newer reports under the age of 20 months [11, 12, 13]. We suggest that the diverse cell differentiation is a basic precondition for tumor maturation and restricted growth. Radical surgery and appropriate chemotherapy with concomitant radiotherapy when indicated, leads to long-term tumor-free status. Some newer observations sustain our assumptions. In 1994 Suita et al. reported two infants, a girl and a boy, with bilater-

al adrenal neuroblastomas, treated successfully with surgery and chemotherapy [4]. Hiyama et al. (2000) reported 11 cases with multiple primary tumors from a series of 114 neuroblastomas in Japan [6]. All these 11 children had an excellent prognosis after complex treatment and are disease-free for a long-term period.

In the following 14 year period our 5 patients underwent clinical observations and serial investigations. All children are alive and disease-free after a different period of time and have a good quality of life, with no signs of late complications or relapse.

Conclusion

The results of complex treatment in young children with multiple primary neuroblastoma are excellent – 100% long-term survival according to our observation and the relevant literature. The analyzed five rare cases with multiple primary neuroblastomas are interesting in many aspects. They arise questions concerning the biological behaviour of the tumor cells, tumor growth and maturation as well as the role of immune system control on factors affecting cell differentiation.

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По случай на 90 години от рождението на изтъкнатия български учен Проф. д-р Стоян Стоянов (1922–1999) – приноси в областта на клиничната психиатрия и психопатология

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On the 90th Anniversary from the Birth of Prof. Stoyan Stoyanov (1922–1999) – Contribution to Clinical Psychiatry and Psychopathology

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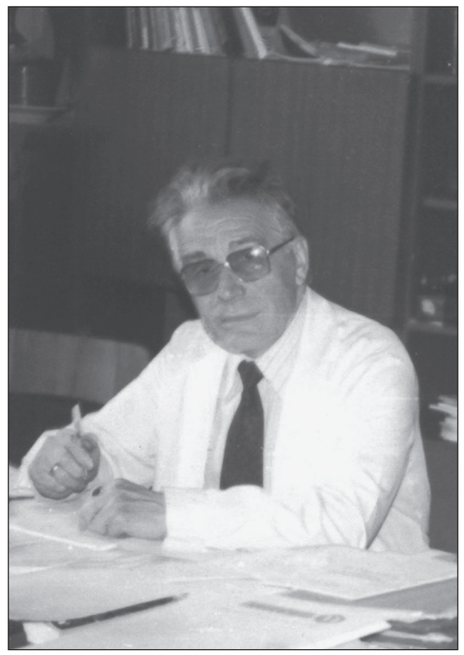


„Човек и добре да живее, умира и друг се ражда.
Нека роденият по-късно, като гледа този надпис,
да си спомня за оногова, който го е направил.“

Търновският надпис на кан Омуртаг,
датиран през 822 г

Стоян Тодоров Стоянов е роден в Разград на 1.07.1922 г. в семейство на земевладелци произхождащи от стар възрожденски род. Завършва медицина в гр. София през 1950 г.

След дипломирането си работи като психиатър във Велико Търново, където участва в основаването на Окръжния психоневрологичен диспансер и става негов първи главен лекар (1951 г.).

През 1954 г печели конкурс за научен сътрудник в Научноизследователския психоневрологичен институт (НИПИ) към Министерство на народното здраве (МНЗ). През 1959 г. придобива специалност по психиатрия. Защитава два дисертационни труда и получава степените кандидат на медицинските науки през 1961 г. на тема „Онейроиден синдром в течението на периодичната шизофрения“ и доктор на медицинските науки през 1980 г. на тема „Парафрения и шизофрения“. През 1972 г. печели конкурс за професор по психиатрия.

Една от последните снимки
на проф. Ст. Стоянов, направена в клиниката
през август 1997

Работил е като главен инспектор в Контролната инспекция на МНЗ през периода 1951–1958 г. и е управлявал една от първите психологични лаборатории в България през 1954 г. През периода 1963–1987 г. е ръководител на мъжко отделение в една от водещите психиатрични клиники в страната, която днес е в рамките на МБАЛНП „Св. Наум“.

Специализирал е в Академията на медицинските науки в Москва, в Университетската болница «Шарите» в Берлин, в Потсдам, във Венеция и в Милано. Бил е консултант е по психиатрия на Университета в Мичиган (САЩ) и експерт към Организацията на обединените нации от 1974 г . Кавалер е на ордена „Кирил и Методий“ първа и втора степен. Председателствал е Консултативния съвет по ендогенни психози и Надзорния съвет на международното научно дружество по проблемите на стреса и адаптацията «Ханс Селие».

През 1999 г. проф. д-р Стоян Стоянов става жертва на автомобилна катастрофа, но обучените от него специалисти психиатри и научното му творчество в областта на невронауките остават трайна следа в психиатрията.

Преди няколко години в статията си „DSM и смъртта на феноменологията в Америка“ Нанси Андреасен алармира за наблюдаван в САЩ към 2005 г. сериозен упадък на внимателното клинично наблюдение и оценка, центрирани върху индивидуалните проблеми на пациента, база за което е доброто познаване на психопатологията (6). За сметка на това обучаващите се старателно запаметяват критериите на диагностичния наръчник, без да се обръщат внимание на изключителната сложност и многообразие в сферата на психопатологията, разкрити от големите автори работили в тази област на психиатрията. Оттук следва, че един от основните начини да се предпазим от тази неблагоприятна тенденция е да се обърнем към класиците, включително и към родните. Несъмнено между тях се нарежда и проф. Стоян Стоянов. Публикациите му се отличават с детайлно описание на болестните състояния, задълбочен психопатологичен анализ, както в напречен, така и в надлъжен срез, установяване на стадиите и закономерностите в развитието на симптоматиката в духа на патокинетичния подход (5).

Като илюстрация на казаното дотук, както и като пример за важния принос на проф. Стоянов в психиатрията може да послужи трудът му „Онейроидният синдром в течението на периодичната шизофрения“, публикуван на руски език (1).

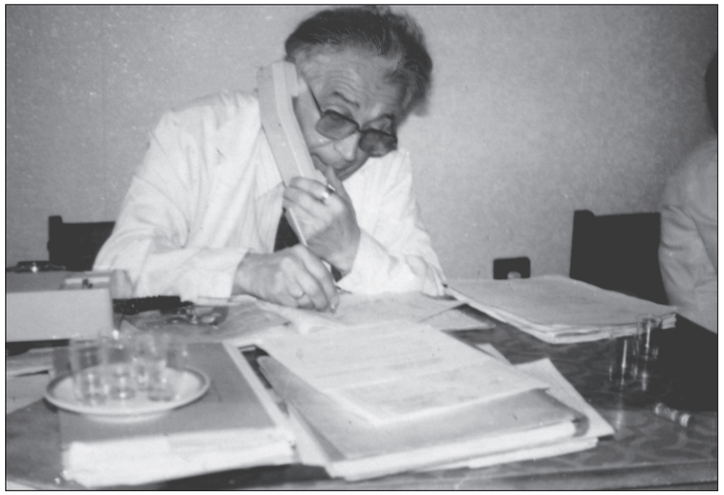
Периодичната шизофрения е една от формите на протичане на шизофренията описана от руската психиатрична школа от втората половина на XX в. наред с пристъпно-прогредиентната и непрекъснато-прогредиентната шизофрения (4). Основните типове пристъпи на периодичната шизофрения, както става ясно и от труда на проф. Стоянов, са онейроидно-кататонни, депресивно-параноидни и афективни (циркулярни). Общото между тях, независимо от различията е, че винаги са налице афективни симптоми, развиват се чувствено-образно налудообразуване и онейроиден синдром, а също в някои случаи и кататонни разстройства. Пристъпите при един и същ болен може да са с различен характер (предимно някой от трите изброени варианта) или да протичат еднообразно, тип „клише“. В много случаи настъпва, макар и не веднага, промяна на личността (редукция на енергетичния потенциал по Конрад). Необходимо е да се изтъкне голямото внимание, което тази школа отделя на типа на протичане, закономерностите, стереотипа на развитие както на болестта, така и на синдромите в нейните рамки. В контекста на тази парадигма проф. Стоянов въз основа на собствени наблюдения, щателно проследяване и документиране на случаи на пациенти с периодична шизофрения установява закономерностите на протичането и особеностите на симптоматиката на онейроидния синдром. Тя е оценена като много важна от гледна точка, както на психопатологията, така на клиниката. В тази връзка Академик Андрей Снежневски подчертава в предговора към книгата от 1968, че трудът на Стоян Стоянов е *„сериозен принос към клиничната психиатрия“*.

Стереотипът на развитие на синдрома се очертава по следния начин. Налице е инициален етап с неспецифични симптоми – например лесна уморяемост, нарушен сън, страшни съновидения, емоционални колебания. Впоследствие се развиват налудности за особено значение и интерметаморфоза (Капгра). Следва развитие на остра фантастна налудност и състояние на т.нар. ориентиран онейроид. Накрая се достига кулминацията на болестта – онейроидното разстройство на съзнанието. В книгата си проф. Стоянов дава детайлно описание на това крайно интересно психопатологично състояние. Отчетливо са очертани афективните нарушения – маниен или депресивен афект (понякога в бърза смяна), като тези нарушения достигат максимума си в кулминацията на психозата. Друга съществена съставна част е помрачението на съзнанието, напомнящо сън с ярки сънища (оттук и oneiroides – съноподобен). Нарушава се психичното отражение на реалността, както по отношение на сетивното, така и на рационалното познание, напълно

се нарушават връзките и отношенията на индивида с околната среда, психичната дейност става напълно субективно обусловена. Нарушението на асоциативния поток е съществено, но все пак се отбелязва тенденция към синтез (за разлика от аменцията), което се счита за добър прогностичен белег. В началните стадии е възможно да са съхранени правилно възприятие и правилна ориентация в околната среда (ориентиран онейроид). По-нататък ориентацията за място се нарушава, грубо се изменя времевата ориентация, налице е понякога и инверсия на циркадните ритми. Собственото „Аз“ претърпява видоизменения и трансформации. Болните са непосредствени участници, дори централни фигури в случващото се в сънноподобното състояние. Сферата на възприятието се доминира от зрителни илюзии и халюцинации. В редица случаи се описват и вербални халюцинации. Налудните идеи са с чувствено-образен характер, фантастни, политематични, често с космическо съдържание, обединени от общия емоционален тон, последователни и взаимосвързани в развитието си. Като друга важна съставна част проф. Стоянов посочва кататонните нарушения – субступор, ступор, възбуда или тяхно бързо редуване. Явления на психичен автоматизъм също влизат в структурата на синдрома, като нерядко го пресичат и подобно на афективните симптоми, понякога се появяват в инициалния период. Прави впечатление несъответствието между бедността на обективните прояви – поведението и външния вид на болния (затормозеност, понякога монотонна възбуда), от една страна и голямото богатство на субективните преживявания, от друга. След оздравяване се наблюдава амнезия за събитията от реалната действителност и собствените действия, но онейроидните преживявания остават до голяма степен съхранени в паметта. Проф. Стоянов отбелязва, че нерядко при болните се среща минала анамнеза за сериозни инфекциозни заболявания, други соматични заболявания, травми на главата (соматогенно изменена почва). На върха на пристъпа отбелязва наличие на феномени напомнящи инфекциозно заболяване. При онейроидната кататония във всички случаи той установява ремитиращо протичане, а онейроидните явления се появяват рано и заемат съществена позиция в клиничната картина на пристъпа заедно с кататонни разстройства с различна тежест, както в посока на ступор, така и на възбуда. При депресивно-параноидния вариант установява отново ремитиращо течение, сериозна изразеност на депресивността, а онейроидните явления се развиват на върха на депресията, сравнително краткотрайни са и в тях се откроява чувствено-образна депресивна фантастна налудност. Наблюденията на автора при циркулярнния вариант установяват, че той протича винаги с манийни или депресивни пристъпи, а онейроидният синдром възниква като закономерен етап в развитието им. След началните неспецифични симптоми следва разгръщане на експанзивна или депресивна симптоматика, често заедно с идеи за особено значение, интерметаморфоза. С нарастване на интензивността на психопатологичната продукция маниакалните и депресивните налудности придобиват експанзивност и преминават във фантастни налудности. При максимума на афективното напрежение се появяват объркаността и дезориентация, ориентиран и впоследствие истински онейроид.

Проф. Стоянов прави съществен научен принос към изучаването на парафренията (5). Неговите изследвания върху този проблем се отличават със същото старателно описание, взискателност и детайлен анализ. Парафренният синдром е бил обект на много дискусии, включително се е стигало до спорове по отношение на това дали парафренията не е отделна нозологична единица – междинно звено между шизофренията и параноята.

Проф. Стоянов отстоява позицията, че се касае по същество за синдром на раз-



Проф. Ст. Стоянов в работния си кабинет в Института по неврология, психиатрия и неврохирургия на Медицинска Академия, около 1985 г. През този период той се занимава с проблемите на парафренния синдром и клиничната патофизиология.

растващо се фантастно налудообразуване, афективни разстройства, сравнително леко изразени промени на личността (2, 3). Към механизмите на интерпретативното или чувствено-образното налудообразуване се включват механизмите на въображението и наличната параноидна симптоматика придобива фантастен характер, като същевременно неизбежно се формират и налудности с мегаломанен или депресивен характер. Парафренията се разглежда в рамките на шизофренията, етап от развитието на болестта и в контекста на споменатите по-горе варианти на протичане. Във всеки от вариантите й може да се открият параноидно-фантастни, афективни, онейроидни и личностови компоненти. При непрекъснатата шизофрения проф. Стоянов описва три вида парафренен синдром – параноидно-парафренен, псевдохалюцинаторно-парафренен и конфабулаторно-парафренен. Разгледани в динамиката на развитието на болестния процес, първите два се формират на базата на вече наличната параноидна или псевдохалюцинаторна симптоматика, както и на настъпила вече личностова промяна. При параноидно-парафренния синдром предшестващата налудна симптоматика се трансформира във фантастно-магаломанна, тя на свой ред се стабилизира, систематизира и като че ли ограничава прогресията на болестния процес. При псевдохалюцинаторно-парафренния синдром фантастно-магаломанните налудности се формират на базата на псевдохалюцинаторни явления, синдром на психичен автоматизъм, но съставките му за разлика от предшестващия не могат да се слеят в единна система. Конфабулаторно-парафренният най-често е следващ, по-дълбок етап, развиващ се на основата на другите два. Същите три варианта на парафренен синдром авторът описва и при пристъпно-прогредиентната шизофрения, на фона на задълбочаваща се стъпалообразна личностова промяна, задължително участие на афективни симптоми, налична възможност за постигане на обратно развитие в ранните етапи и резидуални продуктивни симптоми. По отношение на периодичната шизофрения проф. Стоянов описва онейроидно-афективно-парафренен и онейроидно-кататонно-парафренен вариант. Фантастните мегаломанни налудности се комбинират с налудности за инсценировка, особено значение, понякога и със синдром на психичен автоматизъм. Не се формира съществена промяна на личността. Описва се също постоянно взаимодействие на налудната симптоматика с афективните разстройства присъщи на този вариант на протичане. При кулминацията на пристъ-

па от онейроидно-афективно-парафренен синдромът може да еволюира в онейроидно-кататонно-парафренен.

Проф. Стоян. Стоянов е и един от пионерите на психофармакологичните изследвания в България. Правил е проучвания върху различни медикаменти от всички психофармакологични класове. През 1977 г. патентова оригинален метод за лечение на негативните форми на шизофренията, признат за изобретение от Института за изобретения и рационализации (понастоящем Патентно ведомство на РБ). В своята същност методът на Стоянов включва в себе си биохимични агенти от цикъла на Кребс, фундаментално звено от енергийната обмяна на невроните. Като друг пример за приносите в областта на психофармакологията може да послужи новаторската му работа в разработването на лечение на никотинова зависимост, а именно проучването на препарата цитизин (Табекс) (7). Това е вероятно един от първите опити за разработване на терапия на зависимост с агонистичен препарат. Описанията на наблюдаваното при проучването се отличават със същата задълбоченост, както описаните дотук психопатологични клинични наблюдения. Този труд не е загубил значението си и до днес. Така в един от миналогодишните броеве на New England Journal of Medicine е публикувано едно проведено от европейски изследователски екип двойно сляпо плацебо-контролирано проучване на ефективността на цитизин, като изводът е, че тя статистически достоверно надхвърля тази на плацебо (8). В тази публикация съвсем закономерно е цитирана и статията на С.Стоянов и М. Яначкова „Treatment of nicotinism with the Bulgarian drug Tabex.“от 1965 г.

Това е чудесна илюстрация на значението на научното наследство оставено от проф. Стоян Стоянов и неговата валидна и в наше време непреходна ценност.

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Изисквания към авторите / Author's guidelines

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

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

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

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

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

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

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

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

exceed one standard typewritten page of 200 words.

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

Title page

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

Text of the article

Titles and subtitles should be standardized.

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

Illustrations

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

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

ци. В същия не се включват резюметата на български и английски, чий-то обем трябва да бъде около 200 думи за всяко (25–30 машинописни реда).

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

Структурата на статиите трябва да отговаря на следните изисквания:

Титулна страница

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

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

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

Основен текст на статията

Заглавията и подзаглавията следва да бъдат уеднаквени и различими.

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

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

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

References

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

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

Examples:

Reference to a journal article:

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

Reference to a book chapter:

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

Submission of manuscripts

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

Илюстрации и таблици

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

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

Използваналитература:

Книгописът се представя на отделен лист. Броят на цитираните източници е препоръчително да не надхвърля 20 (за обзорите до 40), като 70 % от тях да бъдат от последните 5 години. Подреждането става по азбучен ред (първо на латиница, после на кирилица), като след поредния номер се отбелязва фамилното име на първия автор, след това инициалите му; всички останали автори се посочват с инициалите, последвани от фамилното име (в обратен ред) до третия автор, последвани от съкращшениетоет Al. Следва цялото заглавие на цитираната статия, след него названието на списанието (или общоприетото му съкращение), том, година, брой на книжката, началната и

articles accepted for publication will not be returned to the authors.

Peer-review process

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

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

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

Address for sending of manuscripts and other editorial correspondence

1431 Sofia, Zdrave str. 2,
University Hospital for Endicrinology
And the next electronic addresses:
Prof. Dr Philip Kumanov, Editor-in-chief:
phkumanov@lycos.com

With copy for the scientific secretary –
Assoc. Prof. Drozdstoj Stoyanov:
stojanovpisevski@gmail.com

крайната страница. Глави (раздели) от книги се изписват по аналогичен начин, като след автора и заглавието на главата (раздела) се отбелязват пълното заглавие на книгата, имената на редакторите (в скоби), издателството, градът и годината на издаване, началната и крайната страница.

Примери:

Статия от списание:

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

Глава (раздел) от книга:

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

Адрес за кореспонденция с авторите

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

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

Процедура по рецензиране:

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

След положителна рецензия и одобрение на редколегията, авторите на статията дължат заплащане в размер на 10 лв. за всяка стандартна машинописна страница, с

оглед на покриване разноските по ангийска езикова редкация на текста и коректури.

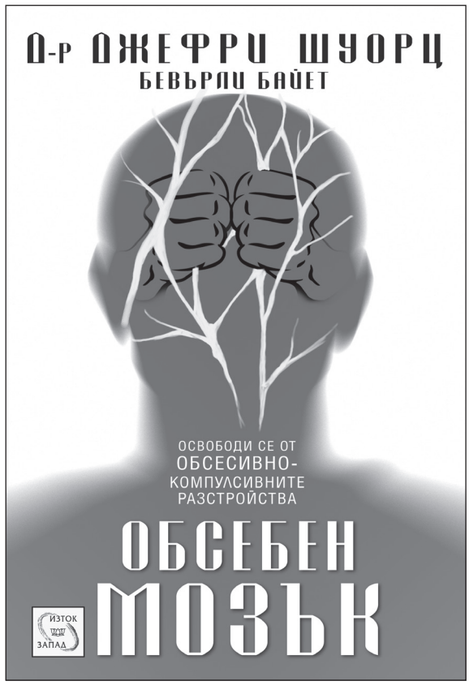
Етически съображения: всички трудове, които отразяват експерименти с хора следва да бъдат съобразени с етическите норми и регулации, въведени от съответния местна или регионална научна комисия и/или с Декларацията от Хелзинки, ревизия от 2000г. Експерименте с животни следва да бъдат също така съобразени със съответните норми и правила.

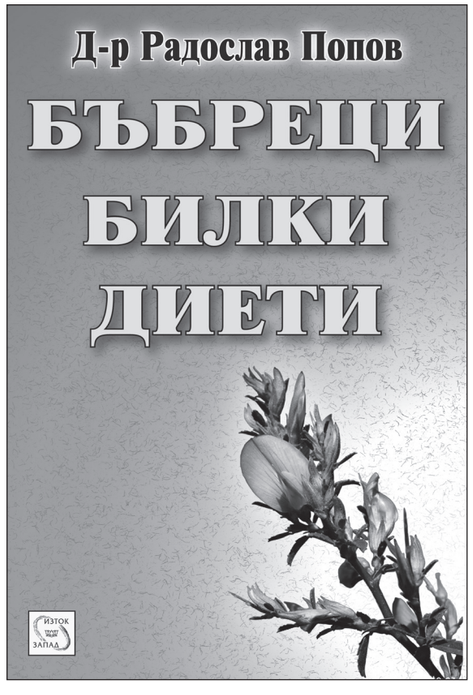
Всички материали за списанието се изпращат на посочения адрес:

Проф. д-р Филип Куманов, дмн, главен редактор,
1431 София, ул. Здраве 2, УСБАЛЕ
или на следния електронен адрес:
phkumanov@lycos.com

С копие до научния секретар –
Доц. Д-р Дроздстой Стоянов:
stojanovpisevski@gmail.com

Experientia docet





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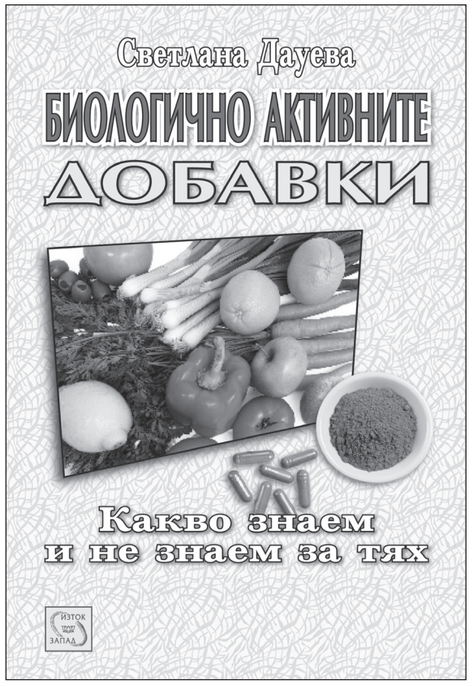

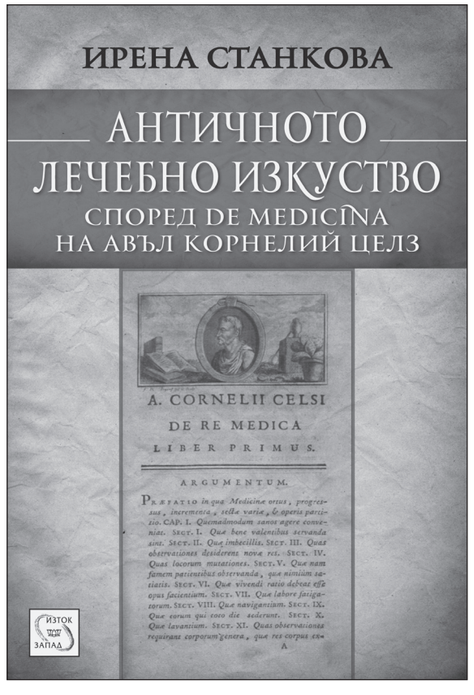

The Royal College of Psychiatrists in Scotland
Philosophy and Psychiatry Special Interest Group
Annual Conference
Friday 5th October 2012
Royal Overseas League, 100 Princes Street, Edinburgh

Programme

FRIDAY 5TH OCTOBER 2012

From 10.00	Arrival, Registration and Coffee

First Session
Chaired by Dr John Callender

10.25 – 10.30	**Welcome** Chair
10.30 – 11.30	**"Situated cognition and neuropsychiatry"** Dr Mark Sprevak, School of Philosophy, Psychology and Language Sciences, University of Edinburgh
11.30 – 12.30	**"Psychiatric disorders and neural mechanisms of understanding"** Dr Peter Gordon, Consultant in Old Age Psychiatry, NHS Forth Valley
12.30 – 13.30	Buffet Lunch served

Afternoon Session
Chaired by Dr Iain Smith

13.30 – 14.30	**"Some Kantian thoughts on free will and grace"** Dr Leslie Stevenson, Honorary Reader in Philosophy, University of St. Andrews
14.30 – 15.30	**"Psychotherapy and the paradox of free will"** Dr John Callender, Royal Cornhill Hospital and University of Aberdeen
15.30 – 16.00	Business Meeting
16.00	Meeting Closes

Please note that this meeting qualifies for 4 hours of CPD points subject to approval by the individual member's Peer Group