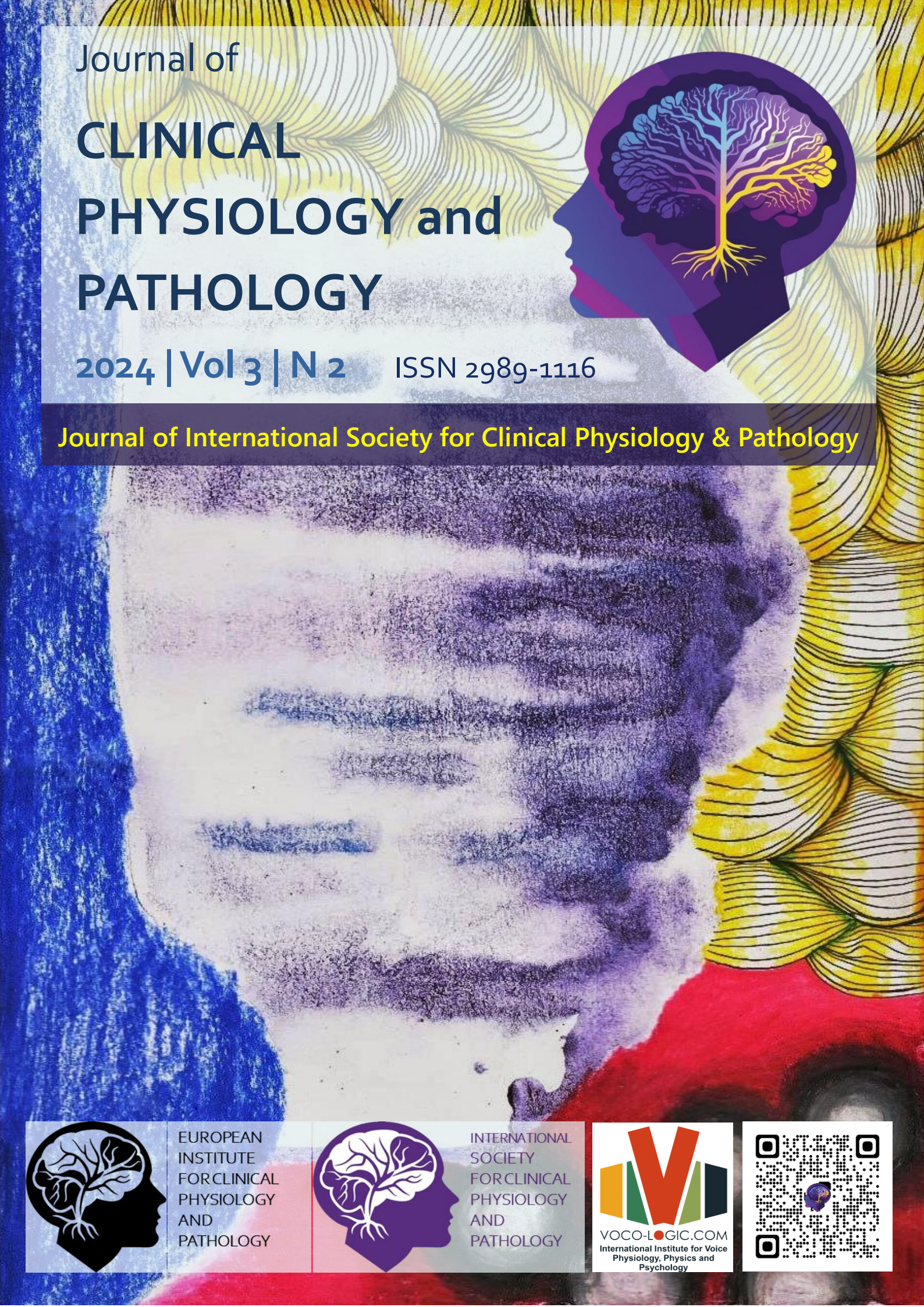
Journal of

CLINICAL PHYSIOLOGY and PATHOLOGY

2024 | Vol 3 | N 2 ISSN 2989-1116

Journal of International Society for Clinical Physiology & Pathology



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Journal of CLINICAL PHYSIOLOGY and PATHOLOGY

2024 | Vol 3 | N 2 ISSN 2989-1116 (Online)

Journal of International Society for Clinical Physiology & Pathology

Medical & biological reviewed journal

The authors declare that they have no competing interests

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Founder and Publisher: **International Society for Clinical Physiology & Pathology**

ISSN 2989-1116 = Journal of Clinical Physiology and Pathology (Online)

COBISS.CG-ID 25476356

Website of ISCPP: https://iscpp.eu/

Website of JISCPP: https://journal.iscpp.eu/

Editor office address: 85347 Norveska, 5, Igalo, Herceg Novi, Montenegro

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Contents

Article

The Comparison of Searching Strategies for Genes Related to Ischemic Stroke: Case-control Human and Model Animal Studies

Gennady Khvorykh[1*], Andrey Khrunin[1], Ivan Filippenkov[1], Lyudmila Dergunova[1], Svetlana Limborska[1]

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Abstract: The genetic basis of ischemic stroke (IS) remains unexplored. In this research we compared the lists of candidate genes obtained with three approaches: classical genome-wide association studies (GWAS), cluster-based GWAS and transfer of transcriptome data from rat to human subjects. The risk genes of IS downloaded from three online repositories were also included into consideration. Human orthologues of rat genes demonstrated good presence in public repositories thus pointing the potentials of rat data transfer approach. Different search strategies resulted in almost unique sets of candidate-genes. We assumed the approaches considered complement each other. The studies of genetic basis of multifactorial diseases can benefit from multiple research strategies.

Keywords: ischemic stroke, genome-wide association studies, animal models, genes

Citation: Khvorykh G., Khrunin A., Filippenkov I., Dergunova L., Limborska S. The Comparison of Searching Strategies for Genes Related to Ischemic Stroke: Case-control Human and Model Animal Studies. Journal of Clinical Physiology and Pathology (JISCPP) 2024; 3 (2): 4-7.

https://doi.org/10.59315.JISCPP.2024-3-2.4-7

Academic Editor: Igor Kastyro

Received: 15.04.24
Revised: 07.05.24
Accepted: 30.05.24
Published: 28.06.24

1. Introduction

Ischemic stroke (IS) is a multifactorial disorder with heritability reaching up to 40% depending on its subtypes [1]. About 80 genes are found to be associated with IS [2] but its genetic basis remains underexplored [3]. The key approaches to identify risk genes are linkage analysis, candidate gene studies and genome-wide association studies (GWAS), among which the last one was the most productive. Nevertheless, it has some limitations, which consequences are incomplete set of genetic markers and low reproducibility. Previously we introduced two promising extensions of GWAS and candidate gene approaches. Firstly, we demonstrated that statistical tests of individual single nucleotide polymorphisms (SNPs) can be elaborated with clustering approaches resulting in blocks of linked SNPs [4]. Secondly, we proposed and applied the protocol for the translation of the results obtained from rat models of IS into humans [5-8]. Here we present the results of comparative analysis of genes obtained with traditional and cluster-based GWAS and with transcriptome analysis of rat brains under ischemic conditions (Figure 1). Risk genes retrieved from three public repositories were also included into comparisons.

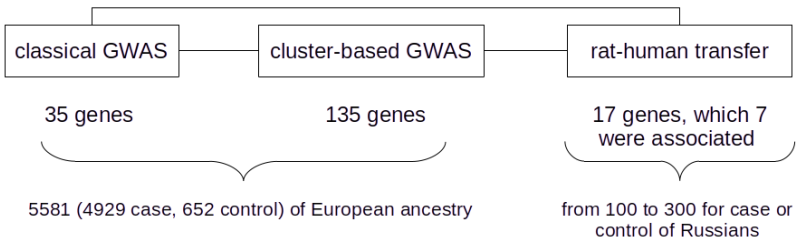

Figure 1. Candidate gene searching strategies

2. Patients and Methods

We explored SNPs in 17 genes obtained by transferring rat genes expressed differentially under tMCAO into human genome, genotyped them by real-time PCR in a cohort of individuals self-identified as Russians [5-8]. Seven of these genes were found to be associated with IS. The classical and cluster based GWAS were made for 5581 individuals with European ancestry (4929 cases and

652 controls). The first one consisted of statistical testing of individual SNPs under different models of inheritance, the second one utilized SNP grouping with density-based spatial clustering algorithms DBSCAN [9] and HDBSCAN [10] followed by haplotype inference and statistical testing [4]. Previously we did not include the intergenic SNPs in downstream analysis. Now all SNPs were annotated and genes thus obtained considered. The annotation was made with snpEff software [11]. We also considered 131 genes associated with IS from Monarch Initiative (monarchinitiative.org, accessed on 13 June 2023) [12], 1159 genes from DisGeNET (disgenet.org, accessed on 7 October 2022) [13], and 400 genes from GWAS Central (gwascentral.org, accessed on 2 April 2023) [14].

3. Results

The classical GWAS revealed 29 SNPs significantly associated with IS, while cluster-based GWAS detected 666 and 892 SNPs from blocks associated significantly for DBSCAN and HDBSCAN, respectively [4]. The p-values in both approaches were ‹ 0.05 after Bonferroni correction. These SNPs can potentially affect 35 (classical GWAS), 1035 (DBSCAN) and 1362 (HDBSCAN) genes. The number of common genes for both algorithms of clusterization consisted of 135. They were further analyzed. This resulted in 13 common genes between classical and cluster-based approaches. The gene RUNX1 detected with classical GWAS and seven genes (USF1, CD34, KIF26B, MSX2, LHFPL3, RUNX1, and LGALS2) identified with cluster-based approach were presented in online repositories. Seventeen genes analyzed within rat-human approach contained 6 genes (CCL23, HSPB1, PTX3, CD14, LGALS3, and TSPO) from DisGeNET and RGS9 from GWAS Central (Figure 2)

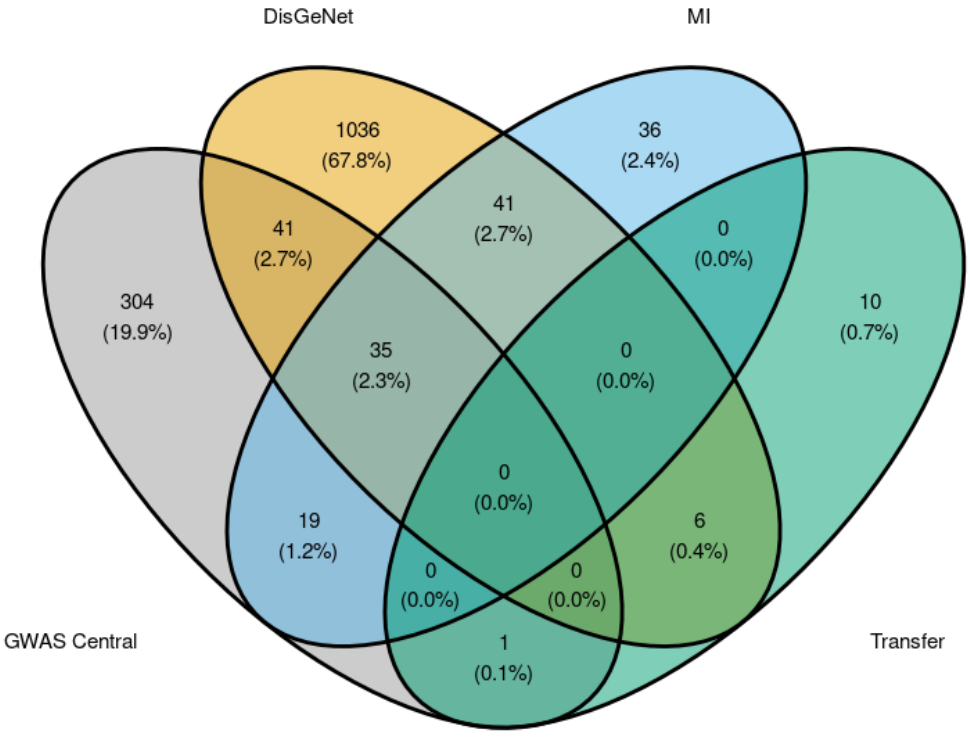

Figure 2 The intersections of candidate genes determined by rat-human transfer ap-proach with known genes in online repositories.

Neither of 7 genes validated by rat-human transfer protocol were presented in the results of classical or cluster-based GWAS. However, two of such genes, LGALS3 and PTX3, were presented in DisGeNET. Among three online resources of genes associated with IS, DisGeNET had the highest number of unique genes, that is 68.6%, while Monarch Initiative has the lowest number (2.4%).

4. Discussion

The number of candidate genes obtained previously for European cohort with cluster-based approach in-creased from 88 to 135 because of inclusion into consideration the intergenic SNPs. Classical and cluster-based GWAS resulted in 13 common genes, thus demonstrating 14% and 78%

of unique genes, respective-ly. We hypothesized cluster-based GWAS detects the genes missed by classical one since it is less influ-enced by multiple testing correction. We saw cluster-based approach resulted in more candidate genes than classical GWAS and it had greater fraction of genes in common with public resources. Therefore, it makes sense to consider the results of both approaches together. Last years, we have elaborated the protocol that allowed transferring the results of transcriptome analysis of rats under model ischemia into human studies. It is interesting to compare the results obtained with human genomic and rat transcriptomic data analysis. Previously we examined 17 human orthologues of rat genes expressed differentially under tMCAO [5-8]. All of these genes except CHRM4 were presented in GWAS data since the SNPs affecting them, according to snpEff, were genotyped and tested. Now we found that seven genes validated with rat-human transfer protocol were not reproduced by classical or cluster-based GWAS. Nine genes that were not verified with rat-human approach were also absent among the significant results of both GWAS approaches. It is clear that this comparison is preliminary, and more genes processed with transfer protocol should be considered. This is supported by the presence of 7 out of 17 genes considered in online repositories as being associated with IS. We believe this indicates a possibility for rat transfer protocol being further applied. For example, other model animals can be analyzed in similar way, allowing new genes associated with IS to be identified.

5. Conclusions

The comparison of three strategies for searching the candidate genes of IS on the level of gene lists showed that they complement each other. A combination of these methods can reinforce the studies of genetic underpinnings of ischemic stroke and other multifactorial diseases.

6. Prognosis and Conclusion

The natural history of Moyamoya disease tends to be progressive in children and adults. In studies with long-term follow-up of untreated patients, progression of neurological deficit and poor outcome were reported in 50-66% of cases. Radiographic progression within five years of diagnosis was noted in 36% of children with moyamoya. Vascular pathology is usually aggravated by extensive occlusion of intracranial large arteries and collateral circulation. Patients often suffer from cognitive and neurological decline due to recurrent ischemic stroke or hemorrhage.

Application of artificial intelligence: The review is written without the use of artificial intelligence technologies.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Funding: This research was supported by the Thematic plan of the National Research Centre "Kurchatov Institute" (5f.5.9.) (gene set comparisons) and by the Russian Science Foundation, grant number 23-14-00131 (per-forming classical and cluster-based GWAS).

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Improvement of Pathogenetic Periodontal Treatment through Laser Combined with EHF Irradiation

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Citation: Parfenova S., Kobzeva Yu., Ostrovskaya L., Domenyuk D., Kochkonyan T., Parfenov A., Aslanyan M., Tverskova V., Rashidova F., Gikoshvili M., Galevich A., Tsaturyan D., Ivanyuta O. Improvement of Pathogenetic Periodontal Treatment through Laser Combined with EHF Irradiation. Journal of Clinical Physiology and Pathology (JISCPP) 2024; 3 (2): 8-12.

https://doi.org/10.59315.JISCPP.2024-3-2.8-12

Academic Editor: Igor Kastyro

Received: 22.04.23
Revised: 10.05.24
Accepted: 05.06.24
Published: 28.06.24

Publisher's Note: International Society for Clinical Physiology and Pathology (ISCPP) stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Rationale. Verification of chronic generalized periodontitis is rated among the most promising areas of personalized therapy. Osteodestructive changes will inevitably lead to tooth loss. Correction of microcirculatory disturbances, which constitute one of the factors indicating the hemostasis of periodontal tissues, may help reduce the financial burden faced by the entire healthcare system when offering medical assistance to the respective category of patients.
Aim of study. This study was aimed at determining the role of combined laser and EHF irradition in the pathogenetic therapy offered to cases of chronic generalized periodontitis.
Materials and methods. The whole set of periodontal treatment procedures offered to 40 patients was expanded with a combination of laser and EHF irradiation (MATRIX unit). As the study was carried out, clinical and laboratory values were recorded, as well as an assessment of the indicators for periodontal tissues was done, namely, measures were taken for the pocket depth; the contents of the pocket discharge was identified; the Muhllemann-Cowell index, the papillary-marginal-alveolar index (PMA), the plaque index (PI), and the oral hygiene index (OHI) were evaluated, along with the hemostasis system microcirculatory link studied – the platelet functional activity (adhesion and aggregation), in particular.
Results. The comprehensive treatment of periodontitis, which included combined laser and EHF irradiation, resulted in an improved clinical status: the depth of periodontal pockets revealed a decrease, whereas no suppuration was to be observed. The improvement in the periodontal tissues came along with positive dynamics of the following indices – the PMA index featured a statistically significant decrease; the PI values showed a change to a lesser extent compared to the PMA index, yet also within the statistically significant range; the oral hygiene improved, which manifested itself through an increase in the OHI values. Notable is that the difference in the index values taken prior to the comprehensive treatment and following it, was significant. This change in the indices is related closely to changes in the aggregation and adhesive capacity of platelets.
Conclusion. Given the above, the obtained data point at high efficiency of the combination of laser and EHF exposure introduced into the set of treatment measures offered for periodontal diseases. The clinical and laboratory data are important both as a theoretical expansion to the available knowledge and from the practical stance. Platelet functional activity indicators are important markers of inflammation issues affecting periodontium. The study outcomes allow viewing the combination of laser and EHF irradiation as an effective component of comprehensive treatment for the said pathology, as well as recommend it be introduced into the treatment plan.

Keywords: chronic generalized periodontitis, combined laser and EHF irradiation, disturbed microcirculation, index evaluation for periodontal tissue status.

1. Introduction

Diseases involving periodontium are one of the most complex pathologies faced by dentists, both in the Russian Federation and abroad, while ranking second in prevalence giving way to dental caries. As reported by the World Health Organization (WHO), 95% of the adult population and 80% of children globally, have been diagnosed with various clinical manifestations of inflammatory periodontal diseases (IPD) [1]. The overall medical and social role of IPD, taken as a special section within dentistry, is due to the following factors: high incidence; diverse etiology; tendency to progression; significant issues in arriving at stable remission; mild symptoms through the early stages; an increase in the number of young capable population featuring severe destructive and atrophic periodontal changes; possible loss of intact teeth; chronic infection foci arising due to the development of gingival and periodontal pockets, as well as their role in the occurrence of general somatic pathology [2-10]. The protective and compensatory periodontal mechanisms and the human body status as a whole is a factor that determines the prevalence and intensity degree of the inflammatory process [11-15].

Gingivitis and periodontitis account for the most common pathologies in the structure of periodontal diseases. The two health issues in question rely on inflammation, a typical pathological process based on changes occurring through the effects of periodontal pathogens [16-18].

The clinical picture of chronic generalized periodontitis in its early stages can be described by a low-manifest and latent course, which makes setting diagnosis in due time complicated and, respectively, leads to a later start of proper treatment and rehabilitation measures [19].

Microcirculation disorders associated with increased activity of the vascular-platelet hemostasis link play a key role in the IPD pathogenesis. Patients with chronic generalized periodontitis have disturbances involving both the aggregation-related function of platelets and their adhesive activity, whereas it is the severity of the disease course that is decisive for the degree of such disturbances [20-24]. One of the most significant effects wrought by helium-neon laser radiation is a positive impact it has on microcirculatory issues. There are results of numerous studies available, which confirm a significant decrease in blood viscosity and platelet aggregation activity. An important point about the hypo-coagulation effect of low-intensity laser radiation is the improvement in the kallikrein-kinin system values [25].

One of the mechanisms behind laser radiation effects is the generation of secondary weak radio emission belonging to the EHF band. A certain part of the biological effects of low-intensity laser radiation may be mediated by this endogenous EHF effect [25]. The advantage of such an impact implies high efficiency, non-invasiveness, none of any adverse responses and contraindications to use, low cost, and good compatibility with other methods [26].

Cells are known to produce electromagnetic vibrations of a very wide range through their life cycle. However, the predominantly narrow range of EHF waves is employed by cells to exchange information required to regulate intracellular functions and intercellular interaction [25,26]. An extra piece of proof to this idea is a response appearing on the side of both cells and the body as a whole, to low-intensity, informational influences [27].

Numerous studies have revealed that the best result when dealing with treating inflammatory periodontal diseases can be expected through combined treatment only, which includes etiological, pathogenetic and symptom-bound therapy [27]. Physiotherapeutic effects serve an extremely valuable component of combined treatment offered to cases of inflammatory periodontal diseases. Effective treatment of microcirculatory disorders determines largely the overall treatment in patients with inflammatory periodontal diseases and has a significant effect on the course of the diseases mentioned above [26]. Treating such disorders via non-medication methods, unlike pharmacotherapy, entails no side effects, and given their significant effectiveness, can be recommended as a component of comprehensive treatment for patients suffering from inflammatory periodontal diseases.

Aim of study

The study was aimed at identifying the role that combined laser and EHF irradiation have in the pathogenetic therapy of chronic generalized periodontitis.

2. Materials and Methods

The examination carried out within the study involved 40 patients with periodontitis, whose comprehensive treatment included the combined effects of laser and EHF irradiation (MATRIX device). Through the study, clinical and laboratory parameters were recorded, as well as an assessment carried out for the indicators showing the status of periodontal tissues: measures were taken for the pocket depth; the contents of the pocket discharge was identified; the Muhllemann-Cowell index, the papillary-marginal-alveolar index (PMA), the plaque index (PI), and the oral hygiene index (OHI) were evaluated, along with the hemostasis system microcirculatory link studied, namely, the platelet functional activity (adhesion and aggregation).

Platelet adhesion and aggregation were evaluated by the impedance method, the principle of which implies recording microcurrents flowing in a special electrode unit when it is immersed in a blood sample. During that, the change in the impedance (resistance) of the electrode system is measured. The impedance increase is in a direct proportion to the platelet mass deposited on the electrode unit. The impedance kinetics allows quantifying the kinetics of the aggregation process. The initial contact of the electrodes with the blood sample results in a platelet monolayer developing on them. Then, as agonists are added (ADP, collagen, arachidonic acid, ristocetin, etc.), there is a gradual aggregation of platelets on the electrodes happening, which leads to some typical changes in the electrical properties of the system.

This method also allows taking into account the leukocyte-platelet adhesion phenomenon observed in some patients' samples. The following parameters were used for quantifying aggregation: the degree of aggregation, which is estimated by the maximum aggregatogram amplitude, which corresponds to the maximum increase in the resistance at the electrode following the introduction of the inductor; the aggregation rate, which is estimated by the aggregatogram amplitude 1 minute following the aggregation start; the delay time – estimated by the time in seconds elapsed after the inductor addition and prior to the start of aggregation registration; the area under the aggregation curve – the product of the amplitude and the rate of its development.

The obtained data statistical processing was performed using the EXCEL and STATISTICA 6.0 software package, with the average value and the average error determined based on the Student and Mann-Whitney reliability criteria.

3. Results

An objective examination of the patients with generalized periodontitis undergoing treatment showed a significant decrease or complete disappearance of inflammation affecting the free and attached gums. Respectively, the depth of periodontal pockets featured a decrease (from 5.28±0.17 mm to 4.04± 0.24 mm), whereas their suppuration was no longer to be observed. Apart from the clinical improvement, there was also positive dynamics registered in the indices. The papillary-marginal-alveolar index demonstrated a statistically significant decrease, if compared to the values obtained prior to the treatment (mild chronic generalized periodontitis cases – by 82.76±3.62%; patients with moderate degree – by 81.1±3.29%; severe cases – by 75.35±2.98%) (Table).

Table 1. Changes in the indices due to the effect of laser and EHF irradiation treatment in patients with periodontitis

Index / Group			Oral hygiene index, points	Papillary-marginal-alveolar index, %	Periodontal index, points
Control (n = 20)			1.03(0.9;1.2)	3.21 (1.1;5.3)	0.032(0.012;0.09)
Chronic generalized periodontitis	Mild course (n=20)	Prior to treatment	2.12 (1.8;2.2) Z1=3.71; p1=0.000205	47.75 (40.1;52.4) Z1=5.17; p1=0.000001	3.47 (2.9;4.1) Z1=4.67; p1=0.000003
		Following treatment	1.17 (0.9;1.4) Z1=1.47; p1=0.140895; Z2=3.92; p2=0.000089	8.23 (4.9;12.6) Z1=2.51; p1=0.012093 Z2=4.67; p2=0.000003	1.74 (1.2;3.5) Z1=2.74; p1=0.006190; Z2=2.05; p2=0.040057
	Moderate course (n=20)	Prior to treatment	2.24(2.1;2.4) Z1=4.33; p1=0.000015	65.6 (51.6;76.8) Z1=5.32; p1=0.000001	4.25 (3.9;4.8) Z1=5.07; p1=0.000001
		Following treatment	1.34 (1.2;1.6) Z1=2.43; p1=0.015247; Z2=3.11; p2=0.001866;	12.41 (5.6;17.1) Z1=3.11; p1=0.001866; Z2=5.18; p2=0.000001	2.25 (1.8;2.6) Z1=2.74; p1=0.006190; Z2=4.00; p2=0.000063

	Severe course (n=20)	Prior to treatment	2.62 (2.5;2.9) Z1=4.29; p1=0.000018	84.4 (78.2;87.3) Z1=6.87; p1=0.000001	6.37 (5.9;7.1) Z1=5.87; p1=0.000001

		Following treatment	1.62(1.5; 1.8)
			Z1=2.63;
			p1=0.008443;
			Z2=3.82;
			p2=0.000136;
				20.8 (17.6;24.2)
				Z1=4.58;
				p1=0.000005;
				Z2=6.68;
				p2=0.000001
					4.13 (3.8;4.5)
					Z1=3.11;
					p1=0.001866;
					Z2=4.58;
					p2=0.000005

Note: each case demonstrates the average value, the lower and the upper quartiles (25%;75%); Z1, p1 – compared with the control group; Z2, p2 – compared with the group of patients prior to treatment.

The periodontal index showed a smaller change (in patients with mild chronic generalized periodontitis – by 49.85±2.08%; in cases of moderate degree – by 47.0±2.31%, whereas patients with severe course featured a decrease of 35.16±1.88%), which, however, fell within the statistically significant range ($p \leq 0.05$). This can be accounted for by the treatment eliminates inflammatory phenomena in periodontal tissues only, yet do not eliminate the periodontal pocket. Along with inflammation subsiding, there was an improvement noted in the hygiene status of the oral cavity, which expressed itself through positive dynamics in the oral hygiene index values (Table). A comparison of the indices before and after the treatment made it obvious that the best clinical results were to be observed after treatment with the MATRIX unit, the difference in the indices being significant ($p \leq 0.05$).

The changes in the indices correlate closely with changes in platelet aggregating and adhesive capacity [26]. The identified correlations of clinical and laboratory data are of importance both in view of theoretical understanding and of practical application. From the theoretical stance, the data explain the mechanism behind pathogenetic changes in periodontal tissues in case of inflammatory diseases. As far as practical use is concerned, platelet functional activity indicators constitute important differential and diagnostic criteria for evaluating inflammatory periodontal diseases [27].

4. Discussion

Comprehensive treatment employing combined laser and EHF irradiation results in a significantly improved clinical course of inflammatory periodontal diseases. This is to be seen from a statistically reliable improvement in the oral hygiene index, the papillary-marginal-alveolar index, as well as the periodontal index. Combined laser and EHF irradiation with a MATRIX device allows putting to a quick stop inflammation in periodontal tissues and prepare patients for the surgical stage of treatment, also preventing complications [28].

The above means that the obtained data serve proof to a high efficiency of combined laser and EHF exposure if used as a pathogenetic therapy aimed at improving the hemostasis system microcirculatory link.

5. Conclusion

When dealing with patients suffering from chronic generalized periodontitis, there is a need to study the aggregation and adhesive activity of platelets, which is to be done through laser aggregatometry.

Combined laser and EHF exposure has a significantly positive effect on the status of the hemostasis system microcirculatory link in patients with chronic generalized periodontitis. The most pronounced effect can be observed in mild and moderate cases.

The high efficiency obtained through combining the effects of laser and EHF irradiation when treating microcirculation disorders is due to an increase in the adhesive and aggregating capacity of platelets, and this allows proposing the said method to be used as part of the comprehensive treatment administered to patients suffering from the respective pathology.

Application of artificial intelligence:

The article is written without the use of artificial intelligence technologies.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Radiation Methods for Studying the Liver in the Diagnosis of Sinusoidal Obstruction Syndrome in Cancer Patients During Drug Therapy

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Citation: Dunaev A., Bashkov A., Sheikh Zh., Kudryavtseva T., Esin E., Voskanyan S., Shipuleva I., Popov M., Matkevich E., Lazebnaya O. Radiation Methods for Studying the Liver in the Diagnosis of Sinusoidal Obstruction Syndrome in Cancer Patients During Drug Therapy. Journal of Clinical Physiology and Pathology (JISCPP) 2024; 3 (2): 13-15.

https://doi.org/10.59315.JISCPP.2024-3-2.13-15

Academic Editor: Igor Kastyro

Received: 22.04.24
Revised: 07.05.24
Accepted: 03.06.24
Published: 28.06.24

Abstract: Due to the widespread use of drug therapy in the treatment of oncological diseases in the practice of a radiologist, various manifestations of its damaging effects on the liver parenchyma have become more common. One of these side effects is sinusoidal obstruction syndrome, in which a violation of microcirculation develops at the level of the sinuses of the hepatic lobes. Developing pathological changes in the liver parenchyma of a vascular, structural and functional nature can simulate the progression of the oncological process. Also, late diagnosis of drug toxicity can lead to the development of irreversible changes - liver cirrhosis, portal hypertension. Thus, diagnosing sinusoidal obstruction during various medical imaging methods is an urgent task for a radiologist.

Keywords: sinusoidal obstruction syndrome, computed tomography, magnetic resonance imaging, chemotherapy

1. Introduction

Sinusoidal obstruction syndrome (SOS), formerly called veno-occlusive disease, is a life-threatening complication that is associated with high-dose chemotherapy. SOS often develops rapidly and unpredictably. It is important to identify risk factors that will allow timely diagnosis of this complication and initiation of appropriate therapy [1].

It is believed that with SOS there is a toxic effect on the sinusoidal endothelium, endothelial cells, which leads to damage to the sinusoidal barrier [3], giving the liver a bluish tint. This primary damage to the endothelium leads to extravascular release of red blood cells, leukocytes and other blood cells into the space of Disse, which can lead to thrombo-fibrinolytic balance, further dissection of the endothelial lining with embolization and venular occlusion [4]. In the future, hepatorenal hypertension may develop with the development of multiorgan failure.

SOS can manifest itself in acute (1–3 weeks), subacute and chronic phases. Chemotherapy regimens associated with this condition include oxaliplatin, cisplatin, cyclophosphamide and vincristine [2].

Clinically, patients with SOS present with jaundice, hepatomegaly, weight gain, abdominal pain, and encephalopathy [4]. Chronic SOS can progress to liver cirrhosis.

When using instrumental research methods for SOS, hepatosplenomegaly, ascites, edematous thickening of the gallbladder wall, portosystemic shunts and periportal edema are detected. When ascites is detected, it is important to confirm the diagnosis of SOS and carry out a differential diagnosis with malignant ascites associated with the spread of the pathological process through the peritoneum or metastases [7,11]. In surgical patients, the presence of signs of portal hypertension is important because these signs are potentially associated with a worse prognosis for patient survival due to an increased risk of bleeding or liver failure after surgery [6].

2. Diagnostics

Contrast-enhanced CT shows heterogeneous enhancement in the arterial and portal phases of the scan, which is explained by perfusion abnormalities characterized by a "mosaic pattern" or diffuse linear areas of low density resulting from hepatic congestion, which in the delayed phase of scanning may merge with the liver parenchyma [14].

A diffuse reticular pattern in the hepatobiliary phase of contrast-enhanced MRI in patients after chemotherapy is a characteristic feature of TOS [8]. MR images demonstrate a heterogeneous reticular or linear pattern in normal parenchyma, characterized by hypointensity on T1-weighted images and hyperintensity on T2-weighted images. When using a hepatotropic contrast agent, reticular hypointensity of liver tissue on hepatobiliary phase images with a location in the peripheral areas of the liver is highly specific for TOS [12]. This radiological pattern is likely due to decreased penetration of contrast agent into liver tissue due to dysfunctional hepatocyte damage and decreased portal blood flow [13]. In focal SOS, the presence of unclear boundaries, especially on hepatobiliary phase images, as well as the absence of diffusion restriction are important differential diagnostic criteria between toxic manifestations in the liver parenchyma and metastases. Table 1 shows the features of sinusoidal obstruction syndrome [2].

Table 1. Features of sinusoidal obstruction syndrome

Sinusoidal obstruction syndrome occurs when the sinusoidal endothelium of the liver is damaged, usually after administration of oxaliplatin, cyclophosphamide and vincristine. This condition is associated with an increased risk of bleeding and liver failure.	
Radiological findings	**A drug**
Ultrasound: ascites, thickening of the gallbladder wall and hepatosplenomegaly. CT: Ascites, decreased diameter of the right branch of the portal vein (‹0.45 cm), paraesophageal varices, hepatosplenomegaly and recanalization of the umbilical vein. MRI: diffuse hypointense reticular pattern on post-contrast delayed phase hepatobiliary T1-weighted imaging, periportal edema	Oxaliplatin, 6-MP, dacarbazine, azathioprine, cyclophosphamide, fluorouracil and vincristine

3. Results

When conducting oxaliplatin-based chemotherapy, the maximum radiological manifestations of the severity of SOS are determined approximately 4 months after the start of treatment, radiological remission is observed approximately 3 months after cessation of treatment [9]. Cessation of chemotherapy is often accompanied by a decrease in these manifestations, suggesting that SOS, at least in mild to moderate forms, both diffuse and focal, is potentially reversible [10]. Severe forms of SOS can also progress after cessation of therapy, leading to the appearance of regenerative nodules, followed by the formation of cirrhotic changes [15].

4. Conclusions

In conclusion, many chemotherapy drugs can cause various liver lesions in cancer patients, which are becoming more common due to the longer life expectancy of patients. Radiologists must be aware of the imaging features of liver tissue damage during chemotherapy to guide physicians in making therapeutic decisions and, thus, prevent the development of serious complications in patients.

Application of artificial intelligence: The review is written without the use of artificial intelligence technologies.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Gender Features of Autonomic Regulation of Cardic Activity in Young Athletes

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Citation: Vlasova T., Spirina M., Bezborodova A., Ryzhov A., Tyagusheva E. Gender Features of Autonomic Regulation of Cardic Activity in Young Athletes. Journal of Clinical Physiology and Pathology (JISCPP) 2024; 3 (2): 16-20.

https://doi.org/10.59315.JISCPP.2024-3-2.16-20

Academic Editor: Igor Kastyro

Received: 19.04.23
Revised: 13.05.24
Accepted: 10.06.24
Published: 28.06.24

Abstract: Background. The success of sports activities depends on the level of the athlete's functional state. The study of heart rate variability will help determine the adaptive capabilities and state of cardiac reserves in athletes as they currently are, as well as predict sports results. The purpose of this study is to study gender characteristics of the autonomic regulation of cardiac activity in children involved in sports.
Materials and methods. The study involved 22 children aged 12-18 years. All study participants were divided into two groups: group 1 (n=10) – boys and group 2 (n=12) – girls. Heart rate, systolic and diastolic blood pressure, weight and height were measured non-invasively. Based on the data obtained, adaptation potential, body mass index, and Kerdo index were calculated. When assessing heart rate variability, the autonomic balance index (ABI), autonomic rhythm index (ARI) and tension index (TI) of regulatory systems were calculated. Statistical analysis was performed using t-test, U-test and Chi-square test ($\chi 2$).
Results. In both groups, satisfactory adaptation of the cardiovascular system (CVS) to physical activity was noted (BP <2.6), but the value of this indicator was 7.25% higher in boys ($p < 0.001$), which indirectly indicates that The functional reserve of the cardiovascular system in adaptation to physical activity is better in girls. When calculating the Kerdo index and studying heart rate variability (HRV), it was found that 50% of boys have sympathetic tone and 10% have parasympathetic tone. In the group of girls, an increase in the tone of the sympathetic division of the ANS occurs significantly more often by 8.3%. The RRNN value in the boys group is 15% higher than in the girls group ($p<0.001$). The NN50 and pNN50 values were also higher among boys by 44.87% and 41.17%, respectively ($p<0.05$). SDNN and RMSSD in the girls group are less by 25.5% ($p<0.01$) and 34.5% ($p<0.05$), respectively. The average heart rate is 11.6% higher among girls ($p<0.01$). IVR, VPR and IN were greater in the girls group by 32.8%, 32.9% and 50.8%, respectively ($p<0.01$).
Conclusions. Satisfactory adaptation of the body to physical activity was evident in both gender groups. Linear rhythmogram and column histogram data show that HRV is higher in the boys group, and the stress index is higher in the girls group.

Keywords: heart rate variability and adaptation, child athletes, Kerdo index, adaptive potential, cardiovascular system.

1. Introduction

Current tasks of sports and the high level of sports achievements indicate the need to study the functional capabilities of the cardiovascular system (CVS), which is a key link in the adaptation of the human body to increased physical activity (PE) [1]. The success of sports activities is directly related to the level of the functional state of the body [2, 3]. The main signs characterizing a high level of the functional state of the cardiovascular system include bradycardia, hypotension and physiological hypertrophy of the myocardium. Rational exercise leads to an improvement in the morphological and functional characteristics of the heart and blood vessels. The heart of an athletic person combines economical activity at rest and the achievement of maximum performance during physical activity [1].

The functional activity of the body is regulated through the joint work of the central nervous system (CNS), immune and endocrine systems. The autonomic nervous system (ANS), which provides adaptive regulation, determines the consistency and, ultimately, the effectiveness of the regulatory systems of the athlete's body [4, 5]. The outcome of exposure to stress factors on the body depends on the level of the functional state of the ANS. Economization and mobilization of functions at rest and during exercise determine adaptive changes in regulatory processes, thereby en-

suring variability and variability of regulation under the expected background conditions of activity [6, 7]. The model of heart rate regulation is based on the already studied mechanisms of regulation of the sinoatrial node of the heart. There are autonomous and central regulatory loops. The first of them, autonomous, is formed from the cells of the sinoatrial node themselves with the participation of the parasympathetic division of the ANS. Another circuit, the central one, includes three levels; it provides intrasystem control, hormonal-vegetative homeostasis and interaction of the body as a whole with the external environment [8].

The ANS of adolescent children undergoes a certain transformation due to active hormonal changes. The regulatory functions of the ANS develop unevenly due to the fact that during puberty, significant changes are observed in the ratio both between the severity of sympathetic and parasympathetic, and in the ratio between the segmental and suprasegmental levels of regulation of the activity of the cardiovascular system [9]. During puberty, problems of autonomic nervous regulation arise, such as a decrease in HRV as a consequence of dysregulation of metabolic control [10].

Thus, the autonomic regulation of cardiac activity has gender differences. Assessing the functioning of all regulatory circuits will make it possible to fully determine the adaptive capabilities and state of the athlete's body reserves at the present time and predict the sports result.

2. Patients and Methods

The study was conducted on the basis of the SSOR for cycling in the city of Saransk from September 19, 2022 to October 22, 2022. The study involved 22 children aged 12 to 18 years. All study participants were divided into 2 groups: group 1 (n=10) – boys, group 2 (n=12) – girls. The average age of the participants was 14.9±0.2 years in group 1 and 15.25±0.3 in group 2.

We non-invasively measured heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), body weight, and height. Based on the data obtained, we calculated the adaptation potential (AP) of the CVS using the formula of R. M. Baevsky [11]. Body mass index (BMI) was assessed using SDS tables [12] and centile scales (WHO, 2007). To assess the impact of VNS, the Kerdo index (KI) was used.

Using the BiTronics Lab, a training laboratory for neurotechnology, HRV was assessed using a linear rhythmogram and a column histogram. Short five-minute recordings were used in accordance with the International Standard [13]. The vegetative balance index (ABI), the vegetative rhythm index (VRI) and the tension index of regulatory systems (IN) were calculated.

The distribution of the obtained data corresponds to the law of normal distribution. For indicators for which the differences were not statistically significant, the U test was used. For parametric analysis, t-test and Chi-square test ($\chi 2$) were calculated.

Statistical analysis was performed using the U test and correlation analysis (SPSS Statistics 13) was used.

3. Results and discussion

As part of the study, AP, BMI, KI were calculated, HRV was analyzed and gender differences were identified.

On average, the AP value in group 1 was 1.33±0.016, and in group 2 – 1.24±0.015. In a comparative aspect, the value of this indicator is higher in group 1 by 7.25% ($p<0.001$).

It was found that on average SBP fluctuated within the normal range and amounted to 121.1±0.66 mm Hg in group 1, which is 5.03% more than in group 2 ($p<0.001$). DBP was also normal in both groups and amounted to 78.8±0.37 mm Hg in group 1 and 72±0.57 mm Hg in the 2nd group. In comparative terms, this indicator is higher in group 1 by 9.4% ($p<0.001$). As for KI, its value averaged 30.9±0.99% in group 2, which is 276.1% more than in group 1 (see Table 1). In group 2, increased tone of the sympathetic division of the ANS occurs more often by 8.3% ($p<0.001$).

BMI in group 1 averaged 20.58±0.37 kg/m2, and in group 2 – 20.86±0.22. This indicator does not depend on gender ($p>0.05$), however, it was found that in group 1, deviations in BMI in the direction of increasing and decreasing were observed 3.3% more often than in girls (see Table 1).

Table 1. Distribution of the studied indicators in children of different sexes

Index	Interpretation of the indicator	1st group (boys, n=10)	2nd group (girls, n=12)	χ^2,p
Height, m		1,7±0,01	1,63±0,003	–
Weight, kg		62,14±1,73	56,09±0,65	–

Body mass index, kg/m²	Average BMI, kg/m²	20,58±0,37	20,86±0,22	0,65 (p>0,05)
	Body weight deficiency (SDS<-2.0),%	20	16,7	0,94 (p>0,05)
	Normal body weight (SDS±1.0)	60	66,6	
	Excess body weight (+1.0<SDS<+2.0)	20	16,7	
Kerdo index, %	KI medium	11,19±1,91	30,9±0,99	9,16 (p<0,001)
	Parasympathicotonia	10	0	10,6 (p<0,01)
	Normotonia	40	41,7	
	Sympathicotonia	50	58,3	
Adaptive potential		1,33±0,016	1,24±0,015	4,1 (p<0,001)

The indicators used to analyze HRV are presented in Table 2. During the study, we found that RRNN (arithmetic mean of the duration of NN intervals in the analysis epoch) averaged 828±15 ms. in group 1, which is 13% more than in group 2 (p<0.001).

The total number of NN intervals (N) was 183.2±7.25 and 214.5±7.82 among adolescents of the 1st and 2nd groups, respectively. In comparative terms, this indicator is higher by 17.08% in group 1. The number of pairs of studied NN intervals that differ by more than 50 ms. (NN50) in group 1 averaged 48.1±4.4, which is 44.87% more than in group 2 (p<0.05). The proportion of NN50 from the total number of NN intervals (pNN50) in group 1 was 0.24±0.02, and in group 2 it was 0.17±0.018. In comparative terms, this indicator is higher in group 1 by 41.17% (p<0.05). The number of pairs of studied NN intervals that differ by more than 20 ms. (NN20) was also higher in group 1, where this indicator was 82.7±5.64, which is 25.1% more than in group 2 (p<0.05). The standard deviation of mean NN intervals (SDNN) was 149 ± 14 ms. in group 2, which is 25.5% less than in group 1 (p<0.01). The root mean square of successive differences (RMSSD) was 269 ± 20 ms. in group 1 and 200±22 ms. in the 2nd group. In comparative terms, this indicator is higher in group 1 by 34.5% (p<0.05). Heart rate averaged 92.25±1.88 and 103±2.15 for groups 1 and 2, respectively. In comparative terms, the value of this indicator is higher among adolescents of the 2nd group by 11.6% (p<0.01).

In group 2, the average IVR value was 85±4, which is 32.8% more than in group 1 (p<0.01). VPR was also greater in group 2 by 32.9% (p<0.001). The stress index (SI) value was 51.7±0.03.9 and 78.0±5.7 for groups 1 and 2, respectively. Comparing the results obtained, we can conclude that the IN is greater in group 2 by 50.8% (p<0.01).

Table 2. Heart rate variability in children of different sexes

The indicator being studied	1st group (boys, n=10)	2nd group (girls, n=12)	p
RRNN, ms.	828±15	720±10	4,99 (p<0,001)
SDNN, ms.	200±10	149±14	2,96 (p<0,01)
N	183,2±7,25	214,5±7,82	2,94 (p<0,05)
CV, %	30,37±2,09	23,21±2,08	2,43 (p<0,05)
RMSSD, ms.	269±20	200±22	2,32 (p<0,05)

Mo, s.	0,675±0,015	0,597±0,01	4,33 (p<0,001)
AMo, %	0,43±0,019	0,48±0,014	2,12 (p>0,05)
NN50	48,1±4,4	33,2±3,2	2,74 (p<0,05)
pNN50, %	24±2	17±1,8	2,6 (p<0,05)
NN20	82,7±5,64	66,1±5,21	2,16 (p<0,05)
pNN20, %	42±2	36±2,6	1,83 (p>0,05)
ЧСС	92,25±1,88	103±2,15	3,76 (p<0,01)
ИВР	64±3,7	85±4	3,85 (p<0,01)
ВПР	2,28±0,082	3,03±0,147	4,46 (p<0,001)
ИН	51,7±3,9	78±5,7	3,81 (p<0,01)

The results obtained showed that both groups had satisfactory adaptation of the cardiovascular system to physical activity (AP <2.6). Since in 1 the AP value is greater than in 2, this may indirectly indicate a better adaptation of the CVS of girls to physical activity.

An KI value in the range from -10 to +10% is considered normal; positive values of this indicator, beyond this range, indicate the predominance of the influences of the sympathetic nervous system, negative values indicate the predominance of the tone of the parasympathetic nervous system. When analyzing the KI values in both groups, it was found that 50% of adolescents in group 1 are sympathicotonic and 10% are parasympathicotonic. In group 2, we revealed a predominance of sympathicotonics.

Considering the fact that parasympathetic influences reduce heart rate and increase RRNN, we can conclude that children of group 1 have a higher tone of the parasympathetic part of the nervous system than children of group 2. A study by R. Abrarov et al [14] showed in a similar group of children the predominance of the sympathetic link in the autonomic regulation of heart rhythm. However, the authors included healthy children in their study, and we included child athletes, so the differences obtained can be explained by the fact that athletes have higher HRV.

The pNN50 indicator is used to assess the predominance of the parasympathetic component of autonomic regulation (VR) over the sympathetic one. Since the value of this indicator is higher in group 1, we conclude that the parasympathetic type of VR is statistically more common in boys.

The SDNN indicator reflects the total effect of the autonomic regulation of the heart and allows us to conclude that in group 1, the predominance of the autonomic regulation of the heart is observed statistically more often. In a study by M. S. Ishbulatova, SDNN increases in different groups of children aged 9-11 years and on average reaches 93.37 ± 10.08 ms. for boys and 81.35±9.2 ms. for girls [15]. Comparing the results of the author's study with ours, we can conclude that in boys the autonomic regulation of heart rate actually predominates, but in our case the value of the studied indicator turned out to be greater, which probably indicates greater HRV in child athletes.

RMSSD is an indicator that allows you to assess the activity of the parasympathetic part of the ANS. This gives us the right to conclude that in children of group 1, the activity of the parasympathetic component of the ANS is statistically more likely to predominate. The obtained result is comparable to the results of studies by other authors. In the same study by M. S. Ishbulatova, RMSSD among boys 9-11 years old was greater compared to girls of the same age and averaged 111.27 ± 14.03 ms. [15].

Taking into account the results obtained, namely the values of RRNN, pNN50, SDNN, RMSSD in both groups, we conclude that adolescents of group 1 have higher HRV than adolescents of group 2.

IVR shows the relationship between the activity of the sympathetic and parasympathetic divisions of the ANS. VPR reflects the balance of regulation of the cardiovascular system by the sympathetic and parasympathetic divisions of the ANS. It is known that an increase in these indicators indicates the predominance of the sympathetic link in the regulation of the ANS. The stress index (SI) indicates the degree of influence of the nervous system on the functioning of the heart.

The calculated indices were lower in group 1, on the basis of which we established that parasympathetic influences predominate in this group and this confirms our conclusion that HRV is greater in group 1.

4. Conclusions

1. In both groups, there is satisfactory adaptation of the cardiovascular system to physical activity, but in girls the AP value is 7.25% less than in boys (p<0.001), which may indirectly indicate better adaptive capabilities of the girls' body.

2. The predominance of the tone of the parasympathetic division of the ANS is typical for the group of boys, where 10% of children are parasympathetic; among girls, an increase in the tone of the sympathetic division of the ANS is more common by 8.3% ($p<0.001$).

3. Taking into account the values of RRNN, pNN50, SDNN, RMSSD, heart rate, as well as the results of the stress index, autonomic rhythm index and autonomic balance index, heart rate variability is higher in the group of boys.

Application of artificial intelligence: The article is written without the use of artificial intelligence technologies.

Author Contributions: Conceptualization, T.V. and M.S.; methodology, T.V. and M.S.; formal analysis, A.B.; investigation, A.B. and E.T.; data curation, A.R..; writing—original draft preparation, A.B., and E.T.; writing—review and editing, M.S. and A.R.; supervision, T.V.; project administration, T.V. All authors have read and agreed to the published version of the manuscript."

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Computed and Magnetic Resonance Imaging in the Diagnosis of Focal Nodular Hyperplasia in the Liver in Cancer Patients During Chemotherapy

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Citation: Dunaev A., Bashkov A., Sheikh Zh., Kudryavtseva T., Esin E., Voskanyan S., Shipuleva I., Popov M., Matkevich E., Lazebnaya O. Computed and Magnetic Resonance Imaging in the Diagnosis of Focal Nodular Hyperplasia in the Liver in Cancer Patients During Chemotherapy. Journal of Clinical Physiology and Pathology (JISCPP) 2024; 3 (2): 21-23.

https://doi.org/10.59315.JISCPP.2024-3-2.21-23

Academic Editor: Igor Kastyro

Received: 30.04.24
Revised: 17.05.24
Accepted: 05.06.24
Published: 28.06.24

Abstract: The differential diagnosis of focal changes in the liver remains an urgent task for the radiologist. Focal nodular hyperplasia (FNH), being the second most common benign formation of hepatocellular origin, is formed in cancer patients as a result of vascular disorders during chemotherapy, in particular with the development of sinusoidal obstruction. As a result, the resulting FNH node can simulate metastasis in a cancer patient, especially in cases where the primary tumor has a hypervascular structure. However, radiation semiotics based on computed tomography and magnetic resonance imaging data allows, in most cases, to confidently differentiate the nature of the focal formation and avoid false-positive diagnostic results.

Keywords: FNH-like lesions, computed tomography, magnetic resonance imaging, chemotherapy

1. Introduction

Focal nodular hyperplasia is a benign liver lesion consisting of a proliferation of hyperplastic hepatocytes surrounding a central stellate scar. Any new formation in the liver in a patient with a history of cancer raises serious concerns regarding metastasis. After or during chemotherapy treatment, changes such as steatosis, steatohepatitis, and sinusoidal obstruction syndrome may occur in the liver, which may manifest as focal lesions [2]. In addition to manifestations of hepatopathy, against the background of high doses of chemotherapy, benign regenerative lesions in the form of pseudometastatic nodules are detected in the liver [3]. These lesions are considered a late manifestation of sinusoidal obstruction syndrome (SSO). In adults, focal nodular hyperplasia (FNH) develops in patients with colorectal cancer after oxaliplatin-based chemotherapy [4]. The exact pathogenesis leading to the occurrence of FNH after chemotherapy remains unknown. FNH is a benign hyperplastic lesion that occurs in the setting of a vascular malformation and often occurs with a local increase in pressure in the hepatic arteries [5]. An important side effect of treatment regimens using oxaliplatin is the occurrence of sinusoidal obstruction syndrome (SSO), which has a toxic effect on sinusoidal endothelial cells. SSO reduces oxygen saturation of the liver [6], in-

creases the expression of hypoxia-induced factors and stimulates angiogenesis by activating angiogenic factors [7]. It is hypothesized that SSO and associated liver hypoperfusion may lead to the formation of benign regenerative lesions such as FNH.

New or enlarged FNH-like lesions in the liver in patients under observation with a history of cancer prone to metastasis to the liver may lead to unnecessary invasive procedures if they are mistaken for metastases.

2. Diagnostics

On computed tomography (CT), focal nodular hyperplasia classically appears as a homogeneous, isodense, or slightly hypodense lesion relative to the liver parenchyma. On CT with bolus intravenous contrast, the mass appears as a homogeneous hypervascular lesion; In delayed phases of the scan, accumulation of a central scar can be observed. These pathognomonic signs of FNH should be taken into account in the differential diagnosis of hypervascular metastases in the liver. A differential diagnostic sign that distinguishes FNH from metastases is an irregular shape, unclear contours, hypervascular foci in the hepatobiliary phase of scanning on magnetic resonance imaging (MRI). Metastases often accumulate contrast agent in a ring-like pattern.

Additional MRI features characteristic of FNH are signal isointensity on T1- and T2-weighted images, early contrast enhancement of the lesion, and absence of diffusion restriction on DWI (diffusion-weighted imaging) [8].

Metastatic malignancies that are commonly treated with oxaliplatin regimens are most often hypovascular on MRI. Thus, when hypervascular foci appear in the liver in cancer patients during chemotherapy, one should not immediately write about a metastatic lesion; FNH-like benign lesions should be included in the differential list [9].

Table No. 1 shows the features of sinusoidal obstruction syndrome [8].

Table 1. Features of sinusoidal obstruction syndrome

Focal nodular hyperplasia is thought to result from microvascular changes in the liver and is associated with oxaliplatin use. Oncologists should be aware of this focal lesion because it can be mistaken for hypervascular metastasis. MRI with hepatospecific contrast agent provides important information for the differential diagnosis of focal nodular hyperplasia.	
Radiological findings	**A drug**
MRI: signal isointensity on T1- and T2-weighted images, early contrast enhancement and no diffusion restriction (DWI)	Oxaliplatin-based chemotherapy

3. Conclusions

Although the appearance of FNH-like lesions in the liver during chemotherapy is rAlthough the appearance of FNH-like lesions in the liver during chemotherapy is rare, it is important for physicians to be aware of the occurrence of these benign lesions because they can simulate metastases and prevent overdiagnosis in such cases and prevent unnecessary invasive procedures.

Application of artificial intelligence: The review is written without the use of artificial intelligence technologies.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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