

Mankovskyi D. S. Leading morphological dominants of stroke as a basis for the morbid psychotype in cardiosurgical patients with postoperative hypoxic-ischemic injuries. *Journal of Education, Health and Sport*. 2021;11(10):423-434. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2021.11.10.039>
<https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2021.11.10.039>
<https://zenodo.org/record/6604031>

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.
© The Authors 2021;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike.
(<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.
The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 30.09.2021. Revised: 12.10.2021. Accepted: 29.10.2021.

LEADING MORPHOLOGICAL DOMINANTS OF STROKE AS A BASIS FOR THE MORBID PSYCHOTYPE IN CARDIOSURGICAL PATIENTS WITH POSTOPERATIVE HYPOXIC-ISCHEMIC INJURIES

D. S. Mankovskyi

State Institution “Heart Institute of the Ministry of Health of Ukraine”

Abstract

The study of the structural dominants of stroke as a valid element of the evidence base of the morbid psychotype in cardiosurgical patients with postoperative hypoxic-ischemic injuries is currently a priority. It is mostly due to the actual issues of unresolved problems of patient-oriented strategy of neurological support of cardiosurgical patients, endless contradictions in the tactics of management of this category of patients, frequency and clinical polymorphism of postoperative complications (strokes, encephalopathies, dysfunction, neurosis etc.). Preoperative preparation of patients, transoperative management of patients; issues of premedication, anesthesia; prevention of complications and persistent disabilities, prognosis of efficiency and further quality of life, sometimes social psychoadaptation – all of this require specialists having a deep and comprehensive understanding of the leading components of the nosological prototype, the basic criteria of morphological patterns of the disease. Taking into account the latter, the role and the importance of morphological diagnosis of clinical manifestations is clearly growing among a fairly wide range of complications in cardiac surgery.

Aim of research: was to investigate the leading morphological dominants of stroke as a basis for the morbid psychotype in cardiosurgery patients with postoperative hypoxic-ischemic injuries.

Material and research methods. Morphological analysis (histological examination) was performed on pieces of brain (gray and white matter), 0.5 cubic cm in size of healthy individuals (infection control, IC, n = 12) and those who belonged to the group of clinical observation, CO, n = 18 (also including thanatological follow-up data from own retrospective annals and archives. The author of the work pays tribute to the bright memory of Professor, Doctor of Medical Sciences A. F. Yakovtsova – Honorary Professor of the Department of Pathological Anatomy, Kharkiv National Medical University, Ministry of Health of Ukraine – for professional consultations during the implementation of this fragment of the dissertation research). The sectional material was carefully removed, pieces with sections of cortical and cerebral matter were separated, and then washed in running water. Fixation was performed for at least 24 hours in 12% formalin solution on phosphate buffer (pH = 7.0-7.2), at $t^0=18-20^0\text{ C}^0$ in a glass-ceramic vessel. Dehydration of the material took place through a system of ethyl alcohols solutions from 30⁰ to absolute, poured into resin (paraffin / celloidin according to the needs of the study). From the obtained blocks, using the resources of the microtome “MK-25”, we made a series of histological sections with a thickness of 5-10 μm (in one of three mutually perpendicular planes: frontal, horizontal, sagittal). The obtained sections were stained depending on the research tasks, its strategy, taking into account the type of tissue (hematoxylin-eosin, according to Van Gieson). Histological examination of gray and white matter of the brain was performed by stages.

Microscopic analysis of the material was performed using a light optical system of the Lieca microscope (Germany) (x 100; x 300). The cortical and cerebral substances of the cerebral hemispheres and areas of the penumbra were examined. Comparison of control samples with the clinical version was carried out in a comparative aspect.

Results. Morphological analysis of native brain preparations samples of healthy individuals, IC (cases of sudden death for the reasons unrelated to pathology of the central and peripheral nervous system) showed in favor of a complete correlation of structural and functional changes with sex-age parameters of postnatal ontogenesis. Gray and white substances are contrast, clearly differentiated, their layers are well marked, they did not contain any signs of foci of inflammation, destructive-degenerative processes, heart attacks and necrosis.

The results of the study of the material, from persons belonging to the clinical observation group (ischemic stroke as one of the prototypes of hypoxic-ischemic complications in cardiosurgery patients), showed the presence of ischemic injuries. The latter were characterized by a phased nature, which to some extent depended on the timing of the onset of the stroke phenomenon, the depth of organic damage, microtopography, the volume of areas of destructive and degenerative changes. The foci of edema being inflammatory phenomena and the result of ischemia attracted the attention. The substance of the brain in these loci and adjacent areas is “softened”, brittle, flabby, in a state of dyschromatosis, it is not elastic enough. Some histological preparations observed in the near-term period contained areas of necrosis, with elements of generalizations of ischemic phenomena. Neighboring with damaged areas the fragments of the substance are saturated with leukocyte infiltrates, which are more contrast. Heart attacks (morphologically they are trivial focal necrosis) were the leading diagnostic features of ischemic genesis.

Conclusion. The pathogenetic scenario of stroke has a number of phases. Its primary leading morphological dominants (as a component of the morbid psychotype of cardiosurgery patients with postoperative hypoxic-ischemic disorders) include the occurrence of focal cerebral infarctions (white, red, mixed). The latter by their nature are necrosis and are caused by ischemia, due to the development of vascular disorders (stasis, thrombosis), lack of blood supply / trophism of the relevant areas of the brain. The final stages of the morphological strategy of stroke are characterized by the appearance of foci of proliferation, astrocytes, collagen fibers, the formation of gliomesodermal, connective tissue scars, cysts.

Key words: cardiac surgery patients; morbid psychotype; hypoxic-ischemic disorders; stroke; morphological dominants; stasis; thrombosis; cerebral infarction; astrocytes

**ВЕДУЩИЕ МОРФОЛОГИЧЕСКИЕ ДОМИНАНТЫ
ИНСУЛЬТА КАК ОСНОВА МОРБИДНОГО ПСИХОТИПА
КАРДИОХИРУРГИЧЕСКИХ БОЛЬНЫХ С ПОСЛЕОПЕРАЦИОННЫМИ
ГИПОКСИЧЕСКИ-ИШЕМИЧЕСКИМИ РАССТРОЙСТВАМИ**

Д. С. Маньковский

Государственное учреждение «Институт сердца Минздрава Украины»

Резюме

Изучение структурных доминант инсульта как основательного элемента доказательной базы морбидного психотипа кардиохирургических больных с послеоперационными гипоксически-ишемическими расстройствами имеет теперь приоритетное значение. Последнему во многом способствует живая проблематика нерешенных вопросов пациент-ориентированной стратегии неврологического сопровождения кардиохирургических больных, стойкие противоречия тактики ведения упомянутой категории пациентов, частота и клинический полиморфизм послеоперационных осложнений (инсульты, энцефалопатии, невроты, невриты, тяжелые формы, т.д.). Дооперационная подготовка больных; трансоперационное ведение пациентов; вопросы премедикации, обезболивания; профилактика осложнений и устойчивых инвалидаций, прогноз работоспособности и дальнейшего качества жизни, иногда социальная психоадаптация – все это требует от специалистов глубокого и всестороннего осознания ведущих составляющих нозологического прототипа, базовых критериев морфологических паттернов заболевания. Учитывая последнее, понятным образом растет роль и значение морфологической диагностики клинических проявлений среди широкого спектра осложнений кардиохирургической практики.

Цель исследования: изучить ведущие морфологические доминанты инсульта как основание морбидного психотипа кардиохирургических больных с послеоперационными гипоксически-ишемическими расстройствами.

Материал и методы исследования. Гистологическому исследованию подвергали кусочки головного мозга, 0,5 куб. Секционный материал удаляли, промывали в проточной воде, фиксировали в 12% растворе формалина на фосфатном буфере (рН=7,0-7,2), обезвоживали в батарее спиртов возрастающей концентрации, заливали в смолы (парафин/целлоидин). Из блоков изготавливали гистологические срезы

(5-10 мкм), которые окрашивали гематоксилин-эозин, по Ван-Гизону. Анализ проводили, применяя оптическую систему микроскопа Lieca (Германия) (x 100; x 300). Сопоставление контрольных образцов с клинической версией проводилось в сравнительном аспекте.

Результаты. Морфологический анализ образцов нативных препаратов головного мозга здоровых лиц (случаи внезапной смерти по причинам, не связанным с патологией центральной и периферической нервной системы) свидетельствовал в пользу полного соотношения структурно-функциональных изменений половозрастным параметрам нормы постнатального онтогенеза. Серые и белые вещества контрастны, четко дифференцированы, их слои хорошо обозначены, не содержали никаких признаков наличия очагов воспалений, деструктивно-дегенеративных процессов, инфарктов и некрозов. Результаты изучения материала от лиц, относившихся к клинической группе наблюдения (ишемический инсульт как один из прототипов гипоксически-ишемических осложнений у кардиохирургических больных), продемонстрировали наличие характерных для ишемии расстройств. Последние отличались фазным характером, в определенной степени зависевшим от сроков дебюта инсультного феномена, глубины органических повреждений, микротопографии, объема участков деструктивно-дегенеративных изменений. Привлекали внимание очаги отека, воспалительных явлений, обозначенной вследствие этого ишемии. Вещество головного мозга в локусах повреждений и приближенных к ним зонах «размягчено», хрупкое, мелочное, в состоянии дисхроматоза, снижением упругости. Отдельные гистологические препараты по наблюдениям в отсроченный период содержали участки некроза, с элементами генерализаций ишемических явлений. Соседствующие поврежденным зонам фрагменты вещества насыщены лейкоцитарными инфильтратами, более контрастны. Ведущим диагностическим признаком ишемического генеза были инфаркты (по морфологической сущности – тривиальные очаговые некрозы).

Вывод. Патогенетический сценарий инсульта отличает фазный характер. К числу его первичных ведущих морфологических доминант (в качестве составляющей морбидного психотипа кардиохирургических больных с послеоперационными гипоксически-ишемическими расстройствами) следует отнести факты появления очаговых инфарктов мозга (белых, красных, смешанных). Последние по своей природе представляют некрозы и вызываются ишемией, вследствие развития сосудистых расстройств (стаз, тромбоз), недостатка кровоснабжения/трофики соответствующих

участков вещества головного мозга. Финальные стадии морфологической стратегии инсульта обозначает организация очагов пролиферации, появление астроцитов, коллагеновых волокон, формирование глиомезодермальных, совмещенных тканей рубцов, кист.

Ключевые слова: кардиохирургические больные; морбидный психотип; гипоксически-ишемические расстройства; инсульт; морфологические доминанты; стазы; тромбозы; инфаркты мозга; астроциты

Introduction

The study of the structural dominants of stroke as a valid element of the evidence base of the morbid psychotype in cardiosurgical patients with postoperative hypoxic-ischemic injuries is currently a priority [1, 2, 3]. It is mostly due to the actual issues of unresolved problems of patient-oriented strategy of neurological support of cardiosurgical patients, endless contradictions in the tactics of management of this category of patients, frequency and clinical polymorphism of postoperative complications (strokes, encephalopathies, dysfunction, neurosis etc.) [4, 5]. Preoperative preparation of patients, transoperative management of patients; issues of premedication, anesthesia; prevention of complications and persistent disabilities, prognosis of efficiency and further quality of life, sometimes social psychoadaptation – all of this problems require specialists having a deep and comprehensive understanding of the leading components of the nosological prototype, the basic criteria of morphological patterns of the disease. Taking into account the latter, the role and the importance of morphological diagnosis of clinical manifestations is clearly growing among a fairly wide range of complications in cardiac surgery. One of them is a stroke. Its current socio-medical characteristics include the predominance in the pathomorphosis of neurotic disorders of somatized versions, which result in a prolonged course of the disease; resistance to the most proven treatments; development of both temporary and permanent disability. Somatic suffering is an influential psycho-traumatic factor, the potentiated secondary neurotic disorders make negative influence on the somatic matrix of the body, creating the basis for the development of mutual encumbrance syndrome [6]. Thus, a thorough solution to this problem lies in the field of basic research of the structural and functional profile of stroke, its morphological design, determination of current macromicroscopic dominants, which are promising criteria for diagnostic systems / algorithms of complications in cardiosurgery patients with hypoxic-ischemic injuries.

Taking into account all mentioned above, the feasibility of the study is beyond doubt.

Aim of research: was to investigate the leading morphological dominants of stroke as a basis for the morbid psychotype of cardiosurgery patients with postoperative hypoxic-ischemic injuries.

Materials and research methods. Morphological analysis (histological examination) was performed on pieces of brain (gray and white matter), 0.5 cubic cm in size of healthy individuals (infection control, IC, n = 12) and those who belonged to the group of clinical observation, CO, n = 18 (also including thanatological follow-up data from own retrospective annals and archives. The author of the work pays tribute to the bright memory of Professor, Doctor of Medical Sciences A. F. Yakovtsova – Honorary Professor of the Department of Pathological Anatomy, Kharkiv National Medical University, Ministry of Health of Ukraine – for professional consultations during the implementation of this fragment of the dissertation research). The sectional material was carefully removed, pieces with sections of cortical and cerebral matter were separated, and then washed in running water. Fixation was performed for at least 24 hours in 12% formalin solution on phosphate buffer (pH = 7.0-7.2), at $t^0=18-20^0\text{ C}^0$ in a glass-ceramic vessel. Dehydration of the material took place through a system of ethyl alcohols solutions from 30⁰ to absolute, poured into resin (paraffin / celloidin according to the needs of the study). From the obtained blocks, using the resources of the microtome “MK-25”, we made a series of histological sections with a thickness of 5-10 μm (in one of three mutually perpendicular planes: frontal, horizontal, sagittal). The obtained sections were stained depending on the research tasks, its strategy, taking into account the type of tissue (hematoxylin-eosin, according to Van Gieson). Histological examination of gray and white matter of the brain was performed by stages.

Microscopic analysis of the material was performed using a light optical system of the Lieca microscope (Germany) (x 100; x 300). The cortical and cerebral substances of the cerebral hemispheres and areas of the penumbra were examined. Comparison of control samples with the clinical version was carried out in a comparative aspect. Areas with foci of inflammation, hemorrhage, necrosis, heart attack, destructive-degenerative changes, regeneration were subject to close study. The results were fixed in a self-developed research registration card. Evaluation of morphologically identical microscopic features was performed in total. The generalized results were reduced to a unified scheme, according to which conclusions were drawn.

Findings and discussion

Morphological analysis of native brain preparations samples of healthy individuals, IC (cases of sudden death for the reasons unrelated to pathology of the central and peripheral

nervous system) showed in favor of a complete correlation of structural and functional changes with sex-age parameters of postnatal ontogenesis. Gray and white substances are contrast, clearly differentiated, their layers are well marked (regardless of the means of staining: hematoxylin-eosin, Van Gieson), they did not contain any signs of foci of inflammation, destructive-degenerative processes, heart attacks and necrosis. Molecular, outer granular, pyramidal cells are located consistently, well marked on the preparation, regardless of the nature of their color (hematoxylin-eosin, silver impregnation), they did not contain signs of destruction, microtopographic disorganization. The bodies of neurons and associated glial cells were the main structural component of the cortex. Optical magnification allowed their microscopic analysis and concretization. The nuclei of neurons are concentrated within each histological section. The cytoplasm of the latter (in extremely rare cases) remained hypochromic, however, with its own membrane-marked cell boundaries. Light, blue-gray neuropil was characterized by a contrasting color polymorphism (both under the conditions of hematoxylin-eosin and Van Gieson), it made an impression of unstructured substance in some loci of observations. Other areas were well-organized structure that formed the morphological “frame-matrix” of the substance of the brain. Microvessels without signs of wall destruction, development of stasis, and thrombosis were clearly identified on organ sections. The shells had a holistic appearance with the foci of hemorrhage and calcification.

The results of the study of the material, from persons belonging to the clinical observation group, CO (ischemic stroke as one of the prototypes of hypoxic-ischemic complications in cardiosurgery patients), showed the presence of ischemic injuries. The latter were characterized by a phased nature, which to some extent depended on the timing of the onset of the stroke phenomenon, the depth of organic damage, microtopography, the volume of areas of destructive and degenerative changes.

Thus, macromicroscopic examination of brain preparations showed the presence of structural criteria of ischemic stroke. They were organically reflected in the relief of the hemispheres. They were registered *ad oculi*. The foci of edema being inflammatory phenomena and the result of ischemia attracted the attention. The substance of the brain in these loci and adjacent areas is “softened”, brittle, flabby, in a state of dyschromatosis (with changes in color to gray-brown, pale brick), it is not elastic enough. Some histological preparations observed in the near-term period contained areas of necrosis, with elements of generalizations of ischemic phenomena. Neighboring with damaged areas the fragments of the substance are saturated with leukocyte infiltrates, which are more contrast. Heart attacks (morphologically they are trivial focal necrosis) were the leading diagnostic features of

ischemic genesis. The logistics of ischemia, its organic matter and course were accompanied by changes in trophism and triggered processes of cortical disorganization with the formation of reticular structures. The latter became the structural basis for the purposeful formation of zones of destruction with the remains of the cell pool of destroyed hyperchromatophilic neurons. There were no signs of total necrosis, generalization of “softening” foci, appearance of glio-mesodermal scars. However, signs of death of cortical neurons were observed, that indirectly indicated the presence of the phase of incomplete necrosis (compared with clinical patterns of the psychotype of cardiosurgical patients according to medical history, objective observations, complaints, subjective assessments of patients) [2, 6, 7, 8].

Analysis of other series of preparations showed increased infiltration of brain matter by lymphocytes, macrophages, eosinophils. Morphological evidence of the appearance and development of foci of white infarction was found in certain areas of the sections (both gray and white matter of the brain were dispersed). The tissue component in these loci is perforated, powdery, rather brittle, hypochromic. The search for morphological prototypes of mixed heart attacks led to the conclusion of a relatively small number of the latter. Hemorrhagic infarcts were characterized by a tendency to spread, to organize the marked foci, to locate near microvessels or their branches (gray matter). Categorization of cerebral infarctions was focused on the intensity of diapedesis of erythrocytes that migrated to the paravasal space. Thus, the appearance of the hemorrhagic component of edema, necrobiotic changes of glial components, ischemia became expected phenomena. The increase in the permeability of the vascular walls of the microstructure of the mentioned zones led to the accumulation of polymorphic cellular elements (leukocytes, plasma cells, eosinophils) [8, 9].

An interesting point of the mentioned studies (against the background of the formation of a large zone of “softening” of necrotic foci with centered masses of cellular detritus) was the appearance of astrocytes, their proliferating forms. Elimination of detritus, despite the activation of general regenerative activity, occurred exclusively in individual fragments of gray matter of the brain, which contributed, to a large extent, to the preservation of signs of destruction of the latter. In the superficial areas of the cortex (border of destruction with meninges) the formation of structures from fibroblast-like cells (restorative potential of previously damaged meninges) was observed. Accumulation of leukocytes, which were formed as a leukocyte shaft, were observed. In some places, there was a structured boundary between the necrotic focus and adjacent areas of matter.

The proximity of necrosis foci to intact nerve tissue apparently contributed to the appearance of activated astrocytes. The latter distanced themselves, did not have a strict order.

Intact and ischemic areas contained a marked number of vessels of different diameters. Inflammatory foci with evident infiltration progressed around them. Defects in the layers of vascular walls led to the development of thrombosis, caused the appearance of paravasal hemorrhages. Cytoarchitectonics of the cortex in such areas, the differentiation of their cellular components is unclear, with the elements of disorganization. In some preparations there was an active formation of collagen fibers, which inevitably led to the formation of gliomesodermal and connective tissue (small areas of damage) scars, cysts (totalization of destructive loci). The delayed post-stroke process denoted the gradual elimination of cellular detritus against the background of signs of inflammatory reactions in brain tissue. (Infiltration by neutrophils and macrophages became an indicator of the latter. This fact also added a significant contribution to the clinical picture of the morbid pattern of cardiosurgery patients) [2, 8, 9, 10]. Full-fledged cerebrospinal fluid-glial cysts were formed in the areas of former foci of necrosis. The evolution of the latter involved several stages / levels: from primary to almost completely formed one by the glial component of the separated cavities. However, due to histological analysis it was possible to trace the process of shell formation (different stages in different samples of observations) in the planned period. There was an appearance of the glial scar with several layers of astrocytes. Under the conditions of widespread areas of necrosis, the process also concerned subcortical structures, where a significant number of capillaries, connective tissue cells, glial cells were observed at the border of the lesion (mixed glio-connective tissue scar appeared). Diffusely scattered damaged neurons were found at the ischemic boundaries, and disorganization of the cortex (first and second layers) was observed in some places. The glial scar was located between the damaged and preserved areas of the cortex, attaching astrocytes with a consistent layered organization. There was a further development of capillaries. Glial, connective tissue cells (glio-connective tissue scar elements) were concentrated next to them.

Conclusion. The pathogenetic scenario of stroke has a number of phases. Its primary leading morphological dominants (as a component of the morbid psychotype of cardiosurgery patients with postoperative hypoxic-ischemic disorders) include the occurrence of focal cerebral infarctions (white, red, mixed). The latter by their nature are necrosis and are caused by ischemia, due to the development of vascular disorders (stasis, thrombosis), lack of blood supply / trophism of the relevant areas of the brain. The final stages of the morphological strategy of stroke are characterized by the appearance of foci of proliferation, astrocytes, collagen fibers, the formation of gliomesodermal, connective tissue scars, cysts.

Prospects for further research are to use the leading morphological dominants of stroke as evidence criteria for substantiating the morbid psychotype of cardiosurgery patients with postoperative hypoxic-ischemic injuries in order to improve the patient-oriented strategy of neurological support of the latter.

References

1. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol.* 2016;15(9):913-924. doi:10.1016/S1474-4422(16)30073-4
2. Costa MA, Gauer MF, Gomes RZ, Schafranski MD. Risk factors for perioperative ischemic stroke in cardiac surgery. *Rev Bras Cir Cardiovasc.* 2015;30(3):365-372. doi:10.5935/1678-9741.20150032
3. Demikhov O, Dehtyarova I, Demikhova N, Rud O, Cherkashyna L. Arterial hypertension prevention as an actual medical and social problem. *Bangladesh Journal of Medical Science.* 2020;19(4):722-729. doi:10.3329/bjms.v19i4.46632
4. Mankovsky DS. Tserebralnyi krovoobih ta faktory ryzyku formuvannia hipoksychno-ishemichnykh urazhen holovnoho mozku u kardiokhirurhichnykh patsiientiv pry vykorystanni shtuchnoho krovoobihu [Cerebral circulation and risk factors for the formation of hypoxic-ischemic brain lesions in cardiac surgery patients using artificial circulation]. *Vitshyzniana nauka - perspektyvy ta innovatsii - Domestic science - prospects and innovations: Collection of abstracts of scientific works of the international scientific-practical conference.* Kyiv. «Kyivskyi medychnyi naukovyi tsentr». 2021:22-26. (in Ukrainian).
5. Todurov BM, Kuzmych IM, Tarabrin OO. Porushennia funktsii tsentralnoi nervovoi systemy pislia operatsii zi shtuchnym krovoobihom u patsiientiv z nyzkoiu fraktsiieiu vykydu livoho shlunochka [Dysfunction of the central nervous system after operations with artificial circulation in patients with low left ventricular ejection fraction]. *Klinichna anesteziologia ta intensyvna terapiia - Clinical Anesthesiology and Intensive Care.* 2015; 2:82-90. (in Ukrainian).
6. Rubinshteyn S. *Osnovy obschey psikhologii.* SPb.: Piter, 2019:720. (in Russian).
7. An N. Difficulties in Understanding Postoperative Cognitive Dysfunction. *Journal of Anesthesia & Perioperative Medicine.* 2017;4:87-94.
8. Johnson W, Onuma O, Owolabi M. Stroke: a global response is needed. *Bull. WHO.* 2016;94:634-634. doi: 10.2471/BLT.16.181636.

9. Spoelstra SL, Schueller M, Hilton M, Ridenour K. Interventions combining motivational interviewing and cognitive behaviour to promote medication adherence: a literature review. *J Clin Nurs*. 2015;24(9-10):1163-73.

10. O'Neal J, Billings F, Liu X, Shotwell M, Liang Y, Shah A et al. Risk factors for delirium after cardiac surgery: an historical cohort study outlining the influence of cardiopulmonary bypass. *Can J Anaesth*. 2017;64(11):1129-1137. doi: 10.1007/s12630-017-0938-5.