Chapter

Delirium in Children after Cardiac Surgery: Brain Resuscitation

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Abstract

This chapter presents the current data on delirium in children in the postoperative period with the correction of congenital heart defects. The analysis of the causes of delirium, according to the literature data, pathophysiology, clinical signs, and methods of diagnosis of postoperative delirium, is shown. In addition, methods for the prevention of delirium in children during cardiac surgery are presented.

Keywords: postoperative delirium, children, cardiac surgery, cardiopulmonary bypass

1. Introduction

Today, the problem of postoperative delirium (POD) in children is rapidly gaining relevance along with the increase in the number of anesthetic treatments in the world. Preparations for general anesthesia are constantly being improved, new, safer types appear, and outdated ones are losing popularity. The properties of all anesthetics currently used in medicine are being continuously studied. However, based on the mechanism of their action, there is no need to wait for complete safety for the brain, since the purpose of any anesthetic is to influence the functional activity of brain neurons. For children, this effect on the brain is especially dangerous. This is due to the fact that, at the age of up to 1 year, there is active development and change in the structure of the child's brain. First, an excess part of neuroblasts undergo apoptosis, and the rest of them must form dendrites and axons of neurons. Secondly, there is a process of neuronal differentiation and synaptogenesis, which underlies the cognitive development of the child. The effect of anesthetics can disrupt the fine mechanisms of regulation of the described processes and lead to impairments in the cognitive sphere in the immediate or late postoperative period [1–3]. In children, the clinical manifestation of such disorders is primarily postoperative cognitive dysfunction (POCD) and POD. POCD occurs noticeably more often—up to 80% (and even up to 100% in patients with ketamine anesthesia) [4] compared to POD, which occurs in 27–50% of patients [5, 6]. However, identifying POCD is a laborious process. Based on the classic definition given by L.S. Rasmussen et al. back in 2001, this is a cognitive disorder that develops in the early and persists in the late postoperative periods, clinically manifested in the form of impaired memory and other higher cortical functions (thinking, speech, etc.), confirmed by neuropsychological testing data in the form of a decrease in indicators testing in the postoperative period by at least 10% of the preoperative level [7]. In the realities of surgical practice, preoperative neuropsychological testing of children, despite the battery of tests available for almost all age groups, is extremely rare. This fact sharply reduces the frequency of detection of POCD in pediatric patients.

2. Delirium

The issue of the development of POD in children is completely different. Due to the pronounced clinical picture and the absence of the need for preoperative testing, the detection of this complication is much easier compared to POCD. Moreover, according to the studies of N. Sikich and J. Lerman, AML in children in most cases proceeds in an active form with severe symptoms [8]. This distinguishes it from POD in adults, in which up to 75% are hypoactive and mixed, and therefore hidden from diagnosis, forms, which is confirmed by their detectability, which is only 40% [9].

The current definitions of POD are presented in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [10] and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [11], according to which the definition of POD sounds like "acute emerging disorder of consciousness with impairment of the functions of attention and understanding." The timing of its occurrence is limited to 5 days of the postoperative period. Previously, delirium was perceived not as a separate syndrome, but as an inevitable symptom, necessarily accompanying a critical state. In the literature, one can find various terms regarding POD, such as critical illness encephalopathy or ICU psychosis [12, 13]. However, for several years now, the term "postoperative delirium" has been approved, and the European Society of Anesthesiologists (ESA) even released a guideline on this condition [9], so this is the term we will use. Of particular value to us is the presence in this manual of a section devoted to the peculiarities of AML in children, even though the definition of delirium in childhood is not given there. After all, neither the DSM-5 nor the ICD-10 contains the child population. Nevertheless, this was an important step in the study of delirium in children, given that there have always been difficulties in the study of delirium in the pediatric population.

The widespread and systematic introduction of protocols for screening patients for delirium in the intensive care and intensive care units made it possible to study this issue in detail in the adult population and identify its absolute relevance. High numbers of delirium prevalence were obtained, as well as many consequences of delirium for the patient and medical organizations were revealed: dementia persisting for up to 15 months after surgery and more [14], increased mortality and morbidity in the immediate and late postoperative periods, prolongation of the period of stay patient in intensive care units, the development of dependence on the ventilator and an even higher probability of infectious complications, although the mechanism of the relationship between these complications and cognitive impairments has not yet been elucidated [15, 16]. Thus, the studied characteristics of delirium in the adult population stimulated researchers to study POD in children. However, such works are still few in number, and it is very difficult to carry out them and obtain objective data. Very revealing is a study that surveyed pediatric intensive care and intensive care units around the world about whether they routinely screen for delirium? And 75% of the respondents answered that they do not use it [17]. This is due, of course, not so much to the reluctance to carry out such screening, as the difficulties in its implementation. There is always a difference in the cognitive status, psychomotor and psycho-speech development, characteristics for each age period of the child [18, 19]. We must not forget that many diseases significantly affect the preoperative cognitive abilities of children, as happens in children with congenital heart disease (CHD). And then their cognitive potential can be strikingly different due to the variability of cerebral perfusion and oxygenation, starting from birth [20]. This implies the need for a large number of different test systems for screening for delirium. The number of scientific works devoted to the pediatric population, especially in the last 10 years, has increased dramatically, according to how the delirium assessment scales in children appear and are validated, which are clearly insufficient [21]. In recent years, data on the epidemiology and clinical features of POD in children are only beginning to accumulate.

Based on the data that are found in the world literature, the prevalence of POD in children can be represented only in the range from 2 to 80% [22–24]. The breadth of this range can be explained by the fact that research on delirium in children is carried out in different age groups, with various pathologies and types of surgical correction, so there is no one average indicator and cannot be. Against this background, it seems interesting that a large study in 2003 with the participation of 521 children, demonstrating the frequency of occurrence of delirium in different areas of surgery [25]. So, the leading position was taken by otorhinolaryngology with an indicator of 26%. At the same time, urology and orthopedics have more modest figures—15%, and abdominal surgery—13%. Quite strange data, given the absolutely different volumes of surgical intervention in the presented surgical profiles, but the authors of the article themselves could not explain this dependence. This study did not affect young patients with CHD after their surgical correction. There are two explanations for this: firstly, surgery to correct CHD is most often carried out in conditions of artificial circulation, which immediately presupposes a large set of pathological factors, which we will discuss later. Secondly, all congenital heart diseases differ greatly in their hemodynamics and, consequently, in the level of hypoxemia and blood supply to the brain, which affects the child's cognitive abilities both before and after surgery [20]. However, there are works on a group of pediatric patients undergoing cardiac surgery. For example, a study by A. Patel et al. Deserves attention, in which patients were observed from birth to 21 years after correction of various CHD [26]. Based on its results, the frequency of POD development was revealed—49%. Interestingly, in addition to the prevalence of delirium, it also revealed an increase in the number of bed days for such patients in intensive care, which coincides with the adult population. Additionally, the risk factors for the development of POD in children after this type of surgery were also considered, but this will be discussed a little later. The only drawback of this study was that it included children with a RACHS score (scale for assessing the severity and risk of CHD correction) from 1 to 6 points. In other words, a mixed assessment was carried out for all children with a wide variety of hemodynamic and cerebral oxygenation options, which, of course, cannot but affect the results [20]. Similar data are available in another study of a cohort of patients with the same type of surgery, after which the incidence of delirium was 57% [27]. Thus, the world literature does not provide data on the assessment of children with a ranking by the types of CHD and their correction, which indicates the prospects of studying this issue.

3. Source of problems

The best defense is an attack, and in our case, the best fight against delirium is to prevent the factors that lead to it. Many studies do not ignore these factors. Among them, one can single out those that are relevant for any surgical interventions, and those that are found only in cardiac surgery. The first group of factors is very diverse, and it is interesting that they exist even before the start of the operation. Among them, there are obvious ones, such as the administration of anticholinergic drugs or benzodiazepines for the purpose of premedication, which has long become by no means a positive tradition for many medical institutions [28, 29]. A less obvious factor that is rarely paid attention to is the increased level of preoperative anxiety in the child, which significantly increases the risk of developing POD in the postoperative period [30, 31]. If we talk about the characteristic features of children in the older age group, then it makes sense to single out the social predictors of POD: this is the male gender and the low level of education. It is also known that belonging to the white race reduces the likelihood of AML [32]. Age plays an important role in the pathophysiology of POD development. It's all about the active transformation of the child's brain—the development of neurons and interneuronal connections at the age of up to 1 year. That is why most researchers consider this age to be the most dangerous for operations in terms of the development of cognitive impairment [1–3], although there are studies on the basis of which the FDA recommends extending this age interval to 3 years. According to the same recommendations, the duration of anesthesia over 3 h is associated with an increased risk of developing POD [33]. The frequency of anesthesia, of course, also has a negative impact [34]. Regarding the anesthetic management itself, it must be remembered that inadequate analgesia can lead to the appearance of delirium, and pain is important not only from the surgery itself but also from concomitant manipulations, such as tracheal intubation or placement of a central venous catheter [9, 35, 36]. Given that the brain is a finely organized structure with special needs, metabolic imbalances in the body, such as episodes of intraoperative hypoxia or hypoglycemia at any time of the operation, are also a risk factor for the development of POD [37]. Often, such hypoxia can occur due to blood loss and acute anemia (which is very typical for cardiac surgery), in which case transfusion of erythrocyte mass and fresh frozen plasma is used. But, as recent studies show, such correction may increase the risk of postoperative cognitive impairment. The reason for this is the systemic inflammatory response (SIR) [38, 39], and we will return to it later.

More narrowly specialized is a group of factors in cardiac surgery. Such interventions are often accompanied by hemodynamic changes and infusion of sympathomimetic drugs, which is especially typical for surgical interventions in children with CHD and adversely affects cerebral perfusion and, consequently, the child's cognitive status [40, 41]. However, the widest range of factors provoking the development of postoperative cognitive disorders is cardiopulmonary bypass [42]. This is the contact of the patient's blood with the surface of the circuit of the heart-lung machine, initiating SIR [43], hemolysis due to mechanical injury of erythrocytes from the operation of roller pumps, and contact of blood with the air [44], hemodilution, which causes a decrease in the patient's hematocrit and oncotic blood pressure [26, 45]. The consequence of hemodilution and hemolysis, and not only large blood loss, explains such a frequent need for transfusion during cardiac surgery. The components of donor blood, carrying foreign material for the body, always incline it to the progression of SIR, affecting the brain [38, 46]. In a recent study, it was found that children who received at least one transfusion were twice as likely to develop POD as compared to children without a history of transfusions. Moreover, the following relationship was observed: every 10 ml of RBC transfusion per kilogram of body weight increased the likelihood of developing delirium by 90% [39].

With the introduction of the latest devices for registering microemboli in the circuit of the heart-lung machine, the problem of their influence on the cerebral vessels and cerebral ischemia that occurs, in this case, has gained relevance [47, 48]. Changes in the patient's blood temperature during cardiopulmonary bypass are also directly related to it. The whole point is in mixing the venous blood flowing into the cardiotomy reservoir (the temperature of which is always lower) and the arterial blood flowing out of the oxygenator (most often having a temperature that is familiar to humans—about 37°C). With this mixing, air bubbles are formed from the liquid part of the blood, which can get to the patient, causing air microembolism [49]. Temperature control is also important to avoid cerebral hyperthermia, which can negatively affect the brain [50].

Of great importance is not only the fact of cardiopulmonary bypass but also its duration, as well as the time of clamping of the aorta (actually ischemia of the heart myocardium) [37]. All of these factors, in addition to their direct destructive effect on the brain, ultimately initiate and enhance the development of SIR [43, 51]. The combination of such a variety of factors determines the entire complex of the pathophysiology of brain damage.

However, the problem is also that the onset of delirium is influenced not only by intraoperative but also by many factors of the immediate postoperative period. For cardiac surgery (especially in children), this period is always difficult due to the volume of interventions. Often, a long stay in the intensive care unit is required, due to which patients experience stress caused by medical manipulations, noise and disturbance of circadian rhythms, pain syndrome, and many other factors [52, 53]. In an attempt to neutralize at least some of these factors, benzodiazepines are often used (especially in patients on mechanical ventilation). But such an aspiration does not always benefit the patient and, based on recent studies, increases not only the incidence of POD, but also the length of stay in the intensive care unit [54, 55]. It is also interesting that the harmful effect of benzodiazepines can be enhanced by the administration of anticholinergic drugs [56]. Often, patients require prolonged mechanical ventilation, which is directly related to the risk of delirium. A recent study shows that any form of respiratory support can lead to the development of delirium. Of course, invasive artificial ventilation of the lungs with the presence of an endotracheal tube in a child has the greatest effect on him; nevertheless, attention is drawn to the fact that even the use of nasal cannulas for oxygen therapy can increase the risk of developing AML [26].

4. A bit of pathophysiology and clarity

The brain has a special type of structure and interaction of cells, and SIR (which was given great attention in the previous section) manifests itself in it as a neuroinflammatory response, which determines all the disorders that are clinically manifested in a patient [57]. If we want to understand the essence of this process, then we need to look at the theory of the neurovascular unit of the brain (NVU).

The fact is that regulatory processes in the brain are a special type of cell interaction that requires the creation of an isolated microenvironment. For this purpose, there is the blood-brain barrier (BBB) and its components, the functional unit of which is NVU. NVU consists of microvessels that are associated with astrocytes, which in turn are associated with neurons and their axons. The BBB contains special carrier proteins for the selective transport of substances from blood plasma to neurons. All this in combination ensures the coordinated work of the brain through intercellular communications and metabolic coupling of cells of the central nervous system [58]. Cerebral injury leads to the activation of microglia and astrocytes and the sequential production of inflammatory mediators in the brain [59]. Mediators damage the BBB and further stimulate cell death and gliosis [60]. Moreover, when the integrity of the BBB is violated, the NVU can be influenced not only by local but also by systemic cytokines (recall the notorious SIR). They stimulate the expression of adhesion molecules, potentiate the adhesion and extravasation of neutrophils and monocytes into ischemic tissues [61]. Local production of chemokines enhances leukocyte extravasation in these tissues [62]. All of these processes occur within the NVU, producing certain pathological changes in the tissues of the brain, followed by its dysfunction. Summarizing the above, we can conclude that not only destructive factors such as hypoxia have a damaging effect on the brain, but also any other factors that can cause SIR [63, 64]. In addition, one should not forget about the physiological features of children, because the first year of life in them is characterized by increased permeability of the vascular wall and hydrophilicity of the interstitial space, which, of course, further contributes to the accumulation of excess fluid in it and increased SIR [65].

As you may have noticed, almost all etiological factors realized by such complex pathophysiological mechanisms are modifiable, and they can and should be combated! However, in some cases, even after making every effort, you will still encounter delirium after the operation. But you still need to be able to recognize it.

5. You need to know the enemy by sight, or how not to pass by delirium

Aggression, sometimes with self-damaging actions (attempts to remove drainage tubes, venous catheters, etc.), agitation, insomnia, disturbance of circadian rhythms, depression, disorientation, uncontrolled speech, short-term memory disturbances, hallucinations, impaired perception, decreased attention level, disturbances consciousness [66]. All this is a description of various manifestations of POD in children. Of course, there is nothing new in it, and almost every doctor who works with children in the postoperative period has encountered such manifestations. The question is: how to distinguish such a clinical picture from the normal behavior of a child who is simply experiencing a feeling of fear and anxiety and wants to be close to his parents as soon as possible? Special scales come to the rescue. There are not so many of them in pediatric practice, but they all have a high diagnostic value. And this value rises sharply in the field of cardiac surgery. First of all, this is due to the fact that most children after cardiac surgery are in the intensive care unit and intensive care, and contact with them is often difficult due to prolonged mechanical ventilation and the presence of an endotracheal tube or tracheostomy cannula. However, in modern scales, such difficulties are taken into account, as are the characteristics of children of all ages [67]. Let us consider a few of them.

As described earlier, POD in children is most often found in a hyperactive form with severe symptoms [8]. Such delirium is commonly referred to in international guidelines as emergence delirium [68]. In this case, it is necessary to carry out a differential diagnosis between the child's agitation after surgery and this type of delirium. Agitation is characterized by anxiety and discomfort in the child. Emergence delirium includes a wider range of symptoms: disorders of the child's consciousness, in particular, disorientation in the outside world, changes in perception, including hypersensitivity to stimuli, and the appearance of hyperactive motor skills during awakening from anesthesia with no success in trying to calm the child [69, 70]. It is easier to carry out such differential diagnosis using The Pediatric Anesthesia Emergence Delirium (PAED) scale. The assessment is carried out quickly, in 5 blocks: the child's eye contact with others, the purposefulness of his actions, his ability to become aware of his surroundings, the general level of anxiety, and the child's reaction to attempts to calm him down. Points are assigned from 0 to 4 for each block [8]. The maximum total score is 20. The result of 10 points or more indicates the presence of emergence delirium with a sensitivity level of 64% and a specificity of 86%, 12 points or more—100% and 94.5%, respectively [71]. Such a high level of sensitivity can be explained by the specialization of the scale specifically from the emergence of delirium with severe symptoms. If we are talking about using it to diagnose all types of delirium, then its sensitivity is not yet clear enough and, according to some researchers, does not exceed 50% [72].

PAED, as already noted, has a very low sensitivity to hypoactive forms of delirium, and a different scale is required for their detection. This role can be played by The Cornell Assessment for Pediatric Delirium (CAPD), which is, in fact, a modified PAED scale (see **Table 1**). The changes consist of the addition of three new assessment units to those already existing in PAED, and they are aimed precisely at the detection of the hypoactive form of delirium [73]. The following areas of assessment have emerged: the need for communication, inadequate level of activity while awake, and delayed response when interacting with the child. Similarly, a score for each block is given from 0 to 4 points, and a result of 9 points or more indicates the presence of POD. Studies showing different levels of sensitivity and specificity depending on the age of the patient cannot be ignored. So, for example, for children over 13 years of age, the specificity is 98%, but the sensitivity reaches only 50%. The situation is mirrored in the group of children under 2 years of age, in which the specificity will already be only 68%, but the sensitivity will be 100% [74, 75]. As for the age at which to start using the PAED and CAPD scales, most studies agree at the age of 1.5 years. The presented scales are a good example of the fact that the assessment of AML in the

Criteria	**Never 4**	**Rarely 3**	**Sometimes 2**	**Often 1**	**Always 0**	**Score**
Does the child make eye contact with the caregiver?						
Are the child's actions purposeful?						
Is the child aware of his/her surroundings?						
Does the child communicate needs and wants?						
	Never 0	Rarely 1	Sometimes 2	Often 3	Always 4	
The child is restless						
Is the child inconsolable?						
Is the child underactive very little movement while awake?						
Does it take the child a long time to respond to interactions?						
Total score						

Table 1.
Cornell assessment of pediatric delirium scale [73].

Ultrafiltration [78, 79]	Maintaining colloidal-oncotic blood pressure by removing excess fluid. An additional effect is the elimination of inflammatory mediators in the composition of the ultrafiltrate
Filtration of the primary filling volume before the start of cardiopulmonary bypass [43]	Removal of various foreign particles that were formed during the assembly of the artificial circulation circuit and can provoke the development of a systemic inflammatory response
Leukocyte filter [80]	A decrease in the number of leukocytes and, as a consequence, a weakening of the reaction of systemic inflammation. Both the patient's own leukocytes and those in transfusion media can be removed
Various technical perfusion solutions (minimization of the cardiopulmonary bypass circuit, biocompatible circuits, limiting the work of cardiotomy aspirators, minimizing the prime) [81–83]	The use of these methods leads to a decrease in the secretion of various proinflammatory cytokines, a weakening of the activation of complement and leukocytes in comparison with the conventional circuitry. There is a significant decrease in red blood cell damage, activation of coagulation cascades, fibrinolytic and pro-inflammatory activity
Aprotinin [84]	Aprotinin inhibits a receptor (protease-activated receptors) expressed on the surface of platelets and endothelial cells, leading to blocking the aggregation process and reducing inflammation
Glucocorticoids [85, 86]	For example, methylprednisolone at a dose of 30 mg per 1 kg of body weight, according to studies, reduces the production of IL-6 and IL-8, but not IL-10 and IL-1ra. These results indicate that one of the mechanisms of the cytoprotective action of methylprednisolone may be the effect on the pro-inflammatory and anti-inflammatory cytokine balance. It should be noted that the effect of systemic glucocorticoids on the development of infection in the postoperative period
Hypothermia [87–89]	Based on the data of modern studies of the use of hypothermia in pediatric cardiac surgery, it can be said that it effectively reduces the metabolic rate, but does not contribute to the proper extent to the prevention or decrease in the severity of the systemic inflammatory response

Table 2.
Prevention and relief of systemic inflammatory response [43, 78–89].

conditions of the intensive care unit does not take much time and effort, but it can bring a lot of new information about the patient. It is only important to do it regularly and, of course, only after assessing the child on a pain scale convenient for a doctor, for example, FLACC, NIPS, or Wong-Baker [76].

There are many works on the effect of POD on clinical outcomes and on the undoubted increase in the duration of hospitalization and even mortality [24]. The question of the impact of POD on the cognitive development of a child in the long term is also important. How much is it possible to compensate for the resulting damage to the brain and further return to normal indicators of its performance? Such questions are just beginning to be investigated and do not yet have a sufficient evidence base [77].

As mentioned above, SIR and neuroinflammation play an important role in the formation of cerebral damage. In the conditions of modern anesthetic technology and perfusion, a considerable amount of information has accumulated on various methods of preventing SIR, which are effective to a greater or lesser extent. We offer an overview of the most commonly used methods for the prevention of SIR (see **Table 2**) [43, 78–89].

Apparently, the future in POD treatment and prevention lies with complex strategies. Even though new drugs are constantly being developed and studies are being carried out on those that have long been used in practice, they will never be able to compare their safety with non-pharmacological measures of influence on the child. Creation in the perioperative period of a calm psycho-emotional environment, as close as possible to a comfortable one for the child, is, along with the elimination of all provoking factors, the key to the prevention of postoperative delirium. An increasing number of researchers are coming to such conclusions. It turns out that even such a simple therapeutic method as massage in the postoperative period can help in the fight against POD [90]. Of course, complex methods of prevention and treatment of delirium are immeasurably more effective. An example is the ADVANCE strategy presented in the above-mentioned ESA guideline [9]. It is interesting that it offers not only the traditional work of the medical staff with the child but also the use of various interactive technologies with the active participation of parents, which is of paramount importance for young patients.

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