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Transfusion-associated necrotizing enterocolitis (TANEC) – early post-transfusion complication in neonates with extremely low birth weight (ELBW) or one of the risk factor necrotizing enterocolitis (NEC)? One centre's experience

Potransfuzyjne martwicze zapalenie jelit (TANEC) – wczesne powikłanie poprzetoczeniowe u noworodków ze skrajnie niską masą urodzeniową (ELBW) czy jeden z czynników ryzyka martwiczego zapalenia jelit (NEC)? Doświadczenie jednego ośrodka

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Keywords

TANEC, NEC, neonates, extremely low birth weight, early post-transfusion complication

Słowa kluczowe

TANEC, NEC, noworodek, skrajnie niska masa urodzeniowa, wczesne powikłanie poprzetoczeniowe

Summary

Introduction. Necrotising enterocolitis (NEC) is a disease developing in neonates. In extreme cases, the septic necrosis of the intestine wall can cover the entire thickness of its wall and result in intestine perforation and, in consequence, to peritonitis. Transfusion of packed red blood cells (RBCs) is indicated as a NEC onset predisposing factor, possibly resulting in development of the disease unit referred to as TANEC (transfusion-associated NEC) in 48 hours upon transfusion. The noted TANEC cases caused a more serious course than in case of NEC and in most cases they required a lifesaving surgical intervention and were connected with high death rate. Neonates with TANEC are more probable to undergo a lifesaving surgical intervention than neonates with NEC in whom no RBCs were transfused.

Aim. Gathering data from the literature and our own experience associated with NEC and analysis, whether TANEC can be considered as a new early post-transfusion complications that occurs in premature infants with ELBW.

Material and methods. The analysis covered medical documentation and laboratory test results in order to explain the reasons for post-transfusion complications in a 3-months old female neonate.

Results. Based on the data from literature and upon analysis of the described case, one can pose the following question: can TANEC be deemed the new early post-transfusion reaction in preemies with ELBW?

Conclusions. TANEC can be deemed the new early post-transfusion reaction in preemies with ELBW. Determination of such a cause and effect relation requires performance of further research and clinical analysis on a greater number of patients.

Streszczenie

Wstęp. Martwicze zapalenie jelit (ang. *necrotizing enterocolitis* – NEC) jest jednostką chorobową noworodków. W szczególności dotyczy noworodków z niską masą urodzeniową (ang. *extremely low birth weight* – ELBW) oraz 5% noworodków urodzonych przedwcześnie. W krańcowych przypadkach septyczna martwica ściany jelita może obejmować pełną grubość jego ściany i prowadzić do perforacji jelita, a w konsekwencji do zapalenia otrzewnej. Jako czynnik predysponujący do wystąpienia NEC wymienia się transfuzję koncentratu krwinek czerwonych (KKCz), która może być powodem rozwoju w ciągu 48 godzin po transfuzji jednostki chorobowej zwanej TANEC (ang. *transfusion-associated*

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ted NEC). Odnotowane przypadki TANEC były powodem poważniejszego od NEC przebiegu i w większości wymagały interwencji chirurgicznej ratującej życie oraz były związane z wysoką śmiertelnością.

Cel pracy. Zebranie danych z piśmiennictwa oraz doświadczeń własnych związanych z NEC i analiza, czy TANEC można uznać za nowy wczesny odczyn poprzetoczeniowy występujący u wcześniaków z ELBW.

Materiał i metody. Analizie poddano dokumentację medyczną oraz wyniki badań laboratoryjnych, które wpłynęły do Pracowni Konsultacyjnej Regionalnego Centrum Krwiotwórczości i Krwiolécznictwa w Katowicach (PK RCKiK Katowice), celem wyjaśnienia przyczyn powikłania poprzetoczeniowego u 3-miesięcznego noworodka płci żeńskiej.

Wyniki. W oparciu o dane z piśmiennictwa oraz po przeanalizowaniu opisanego przypadku, można postawić pytanie: czy TANEC można uznać za nowy wczesny odczyn poprzetoczeniowy występujący u wcześniaków z ELBW?

Wnioski. TANEC można uznać za nowy wczesny odczyn poprzetoczeniowy występujący u wcześniaków z ELBW. Ustalenie takiego związku przyczynowego wymaga przeprowadzenia dalszych badań i analizy klinicznej na większej liczbie pacjentów.

INTRODUCTION

Necrotising enterocolitis (NEC) is a disease developing in neonates. In particular, it affects neonates with extremely low birth weight (ELBW) and 5% of prematurely born neonates. The incidence of NEC is particularly high in neonates whose body mass does not exceed 1000 g and is up to 42.4%. In preemies weighing from 1001 to 1500 g it is also high, as it amounts to 39%. The risk for neonates with body mass from 1501 to 2000 g is lower (3.8%), and above 2000 g it is 0.11% (1).

NEC is a syndrome of clinical symptoms connected with occurrence of ischaemic and necrotic changes located in the small and/or large intestine. In extreme cases, the septic necrosis of the intestine wall can cover the entire thickness of its wall and result in intestine perforation and, in consequence, to peritonitis. Necrotising enterocolitis can be accompanied by an inflammatory condition of other sections of the digestive tract, respiratory and circulatory system failure, posing a serious hazard to the child's life (2).

Due to the immaturity of organs and systems necessary to live in the extrauterine environment, most neonates suffering from ELBW requires intensive neonatological care. An additional factor determining the multi-organ failure condition in a neonate affected by ELBW is perinatal asphyxia. This causes the onset of mechanisms typical for shock. The production of catecholamines is increased, resulting to centralisation of circulation which, in consequence, leads to significant limitation or complete cutting off blood circulation through the abdominal cavity organs, including the intestines. The most severe damage is, however, inflicted during reperfusion, when a great amount of free oxygen radicals is released, damaging the cells of the intestine mucous membranes. Air and gas present in the lumen of the intestine can penetrate through the damaged mucous membrane to the wall, causing its stratification. The damaged mucous membrane is permeable for microorganisms: bacteria, fungi and viruses which, in consequence, leads to NEC onset (3).

The scope of pathological changes caused by the microorganisms depends to a great extent on the ma-

turity of the topical defensive mechanisms such as: T and B lymphocyte count in the digestive tract as well as intensity of the necrotic processes in the intestine epithelium. Necrosis of enterocytes results in failure to form a proper mucous membrane barrier of the intestine, including, among other things, secretive immunoglobulin A (sIgA), secreted from the 2nd-3rd week of life, as well as lymphocytes, macrophages, lactoferrin and acetylhydrolase. Acetylhydrolase reduces the concentration of the platelet activating factor (PAF) considered an important NEC risk factor (3, 4).

The immunological mechanisms in a neonate with ELBW are also impaired due to the lack of passive acquired immunological agents in the digestive tract, mostly immunoglobulins provided with the mother's milk in normal conditions (5, 6).

NEC can be difficult to diagnose. Its early symptoms can have the course and be similar to symptoms resulting from respiratory problems, preserved arterial duct or infection: frequent apnoea and bradycardia, temperature instability, excessive somnolence. Other symptoms may indicate problems with digestion, but they are often the same as symptoms of food intolerance resulting from preterm birth: vomiting, depositing of the digesta in the stomach, cyanosis of the abdominal walls, slightly flatulent belly, tenderness of the abdominal cavity, diarrhoea, bloody stools and sometimes invisible blood in the stool, detected by guaiac test (7).

Diagnosis of the necrotising enterocolitis is based on clinical symptoms, laboratory tests, radiological and ultrasound image as well as surgical examination. High, abnormal values of the laboratory test results reflect the severity of the disease process. The abdominal X-rays show bloated intestine loops with thickened oedematous walls. Dilated intestines with poor or absent peristalsis are predominant in the ultrasound test. In order to determine the final diagnosis, surgical consultation is conducted (8).

In case of suspected NEC, the procedure always begins with conservative treatment. The first step is to discontinue the enteral feeding. There is an open probe left in the stomach in order to drain the deposited

content. Targeted antibiotic therapy is implemented, proper coverage of the calorific demand is provided, administration of fluids, stabilisation of respiration and circulation as well as balancing of electrolyte and haematological disturbances are performed. An absolute and urgent indication of surgical treatment is intestine perforation, indication by the presence of gases in the free peritoneal cavity (pneumoperitoneum), presence of gas bubbles in the intestinal wall (*Pneumatosis intestinalis*). The surgical procedure consists in removal of the necrosis induced changes and perforations of the intestinal section and then in creation of enterostomy-colostomy in case of resection of a part of the large intestine, ileostomy in case of resection of a part of the small intestine (9).

There are still some unknown factors responsible for NEC. In addition to the immaturity of the digestive system, these include: preterm birth, low birth body mass, damage to the intestine tissue resulting from insufficient blood or oxygen supply, disturbances in the mesentery blood flow, intestine infection, blood transfusion as well as presence of undigested food residues in the intestines and artificial hypertonic feeding in large volumes as well as too fast introduction of enteral feeding. The immaturity of the gastric tract in preemies and disturbances of peristalsis can lead to disturbances in absorption of nutrients as well as their abnormal digestion, fermentation and ischaemia of the intestinal mucous membrane (10).

Transfusion of packed red blood cells (RCBs) is indicated as a NEC onset predisposing factor, possibly resulting in development of the disease unit referred to as TANEC (transfusion-associated NEC) in 48 hours upon transfusion. The noted TANEC cases caused a more serious course than in case of NEC and in most cases they required a lifesaving surgical intervention and were connected with high death rate. The TANEC mechanism remains unexplained, but its basic condition for occurrence is ischaemia, blood flow changes in the mesentery, inflammation of the intestine mucous membrane, increased apoptosis of the intestine epithelial cells, immature intestine mucous barrier, possibly enhancing bacterial translocation to the mucous membrane of the intestine and activate the inflammatory mediator cascade. An important role is also attributed to the PAF factor, activating platelets, thromboxanes and cytokines. These factors can aggravate the damage of the intestine mucous membrane (11).

AIM

Gathering data from the literature and our own experience associated with NEC and analysis, whether TANEC can be considered as a new early post-transfusion complications that occurs in premature infants with ELBW.

MATERIAL AND METHODS

The analysis covered medical documentation and laboratory test results provided to the Consultation

Centre of the Regional Blood Donation and Blood Treatment Centre in Katowice in order to explain the reasons for post-transfusion complications in a 3-months old female neonate.

The reaction occurred upon transfusion of 35 ml irradiated leukoreduced packed red blood cells (RCBs), blood type O RhD- negative, which occurred upon 11 hours and 50 minutes from completion of transfusion. Neonate with blood type B RhD- negative, with negative direct antiglobulin test (DAT-negative), born as a preemie with extremely low birth body mass. The mother of the girl, 28 years old female, blood type O RhD+ positive, in whom no immunological alloantibodies directed to red blood cell antigens were detected in the antibody screening test.

The neonate, due to anaemia (Hb: 8.3 g/dl) on the 20th day of life, received 50 ml of irradiated leukoreduced packed red blood cells, blood type O RhD- negative. No disturbing post-transfusion symptoms were observed. The condition of the neonate was evaluated as quite good, but due to the persisting anaemia on the 48th day of life, i.e. 28 days upon the first transfusion, further transfusion of 35 ml of irradiated leukoreduced packed red blood cells was performed, blood type O RhD- negative, upon which the occurring post-transfusion reaction was immediate and posed a threat to life. Occurring symptoms: abdominal pains and flatulence, tenderness of abdominal walls, shallow breathing, respiratory failure. The measurement of temperature prior and upon transfusion showed no changes (36.7°C) which was also the case for pulse (165/min) and blood pressure (71/72). The X-ray test showed features of large intestine perforation and lung oedema. The laboratory tests showed: C-reactive protein (CRP) (24.02 mg/l), D-dimers (7.1 µg/ml), antithrombin III (40%), index I: T (0.6), gasometric tests: pH (7.27), pO₂ (41.4), pCO₂ (55). Due to the life hazard, surgical intervention and respiratory support were necessary. Antibiotic therapy was also implemented.

RESULTS

Upon the conducted analyses, in the course of proceedings clarifying the post-transfusion reaction including immuno-hematologic tests of red and white blood cell system as well as bacteriological test, and on the basis of available data, it was impossible to establish the direct relation of the reaction with the transfused blood component.

DISCUSSION

The relation between NEC and transfusion was described for the first time in 1987 (12). However, the first and sparse works regarding the onset of TANEC have appeared in the world literature only recently and they are limited to retrospective test observations. This case description is the first such reference in the Polish literature.

It results from the data provided by world literature that up to 48 hours upon transfusion NEC was developed in 39% of neonates with ELBW. The NEC onset

risk upon transfusion of packed red blood cells (RBCs) is inversely proportionally to the haematocrit (Ht) value from before the transfusion and increases along with the frequency of conducted transfusions prior to the NEC diagnosis by 1.63 times (1.145 to 2.305 times). Neonates with TANEC are more probable to undergo a lifesaving surgical intervention than neonates with NEC in whom no packed red blood cells were transfused. A hypothesis was put forward that TANEC in preemies can be a clinical equivalent of the transfusion-related acute lung injury (TRALI) developing in adults (13-16).

The intestine injury mechanism in a preemie with ELBW, in the course of TANEC, can be a body reaction to the great volume of transfused blood as well as abnormal flow rate in the intestine vessels, coexisting with low blood perfusion. In order to explain the TANEC onset predisposing mechanism, the following hypothesis was set forth: in the course of ischaemia in a preemie, there is insufficient oxygen supply to the intestine tissues. Hypoxia and improper nourishment of the intestine vessels can lead to their narrowing and injury. Observations include abnormal blood flow rate and low oxygen perfusion in the intestinal mesentery vessels. Excessive activation of apoptosis occurs, i.e. programmed death of the intestinal tissue cells, leading to necrosis. Physiological disturbances of the intestine flora are an additional cause for deposition and fermentation of food in the intestines, aggravating the damage of the intestine tissue. Enteral feeding can also be a factor aggravating the inflammatory process. Transfusion of packed red blood cells introduces to the

preemie's body excess of blood, in relation to the abnormal blood flow and low perfusion in the mesentery vessels, which can be an NEC onset predisposing factor within 48 hours from transfusion (17).

Mohamed and Shah showed that preemies with transfused packed red blood cells, within 48 hours from transfusion, are four times more prone to development of NEC as compared to preemies in whom no transfusion of packed red blood cells (RBCs) was performed. In particular, preemies with very low birth body mass (from 528 g), with low pregnancy age index (shorter by 1.5 Hbd) and with preserved arterial duct are prone to TANEC. There was no connection between TANEC and preemies' sex indicated. Neonates with TANEC were almost twice as much prone to death than those who developed NEC and no packed red blood cells were transfused (18).

CONCLUSIONS

The clinical cases described in world literature and the case presented in this paper convince to accept the hypothesis stating that transfusion of packed red blood cells can have a direct impact on the onset of necrotic enterocolitis in preemies with ELBW.

Based on the data from literature and upon analysis of the described case, one can pose the following question: can TANEC be deemed the new early post-transfusion reaction in preemies with ELBW?

Determination of such a cause and effect relation requires performance of further research and clinical analysis on a greater number of patients.

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