Necrotizing enterocolitis in children with low birth-weight induced with mucormycose strains

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Submitted: 2008-11-01 Accepted: 2008-11-18 Published online: 2008-12-29

Key words: **enterocolitis; children; mucormycose strains**

Neuroendocrinol Lett 2008; **29**(6):1021–1025 **PMID:** 19112402 NEL290608C02

Abstract

BACKGROUND: The nosocomial occurrence of mycotic infections negatively affects results of the neonatal care in newborns in the sense of their increased mortality and morbidity.
AIM: The communication presented here is focused on an analysis of predisposing factors and clinical patterns of infections induced with mucormycosis strains.
The authors provided an analysis of six case reports concerning newborns that died in association with nosocomial infections, where mucormycosis strains were microbiologically and microscopically detected in autopsy.
RESULTS: The newborns in the group considered died due to general metabolic breakdown induced by peritonitis based on the large intestine perforation – enterocolitis. The predisposing factors include low birth-weight, asphyxia after the delivery, catheterization of umbilical veins and v. cava inferior and introduction of the endotracheal ventilation. Nosocomial nature of the infection propagation is suggested by a delayed onset of manifestations after the delivery.
CONCLUSION: The authors point out the possibility of the origination of nosocomial infection induced with mucormycotic strains. Thus, they recommend adhering to a strict anti-epidemic regimen at neonatal departments with a particular emphasis put on consequent prohibiting of the storage and use of food at the departments. They emphasize the fact that the most frequent clinical pattern induced with mucormycotic strains in newborns with low birth-weight is necrotizing enterocolitis. They also stress the fact that the final diagnosis of the infection is most typically established based on the histological examination only.

ORIGINAL ARTICLE

INTRODUCTION

The neonatal mortality including newborns with low birth-weight is being continuously reduced. The occurrence of nosocomial infections is also decreasing. Staphylococcus and streptococcus stains were the first infectious agents. Thereafter, Gram-negative opportunistic bacteria (e.g. coliform, pseudomonad and clebsiella species) became important. Due to the recent development of the intensive care, the importance of mycotic opportunistic strains has recently increased. One type of these strains considered in the work presented here are the mucormycotic ones.

The purpose of the communication presented here was to analyze six case reports of newborns that died in association with the mucormycotic infection, which complicated the issues of the neonatal care and negatively affected the final outcome in these newborns.

CASE REPORTS – SIX CASES

1. M. A. Delivery in the 26th week of pregnancy; birth-weight 850 g, birth-length 36 cm, female, 2nd pregnancy. Eighty hours after the membrane rupture and a loss of amniotic fluid, Oracef was administered. A condition of spontaneous, preterm delivery, vertex presentation now existed. After delivery, the child was asphyxial and had an Apgar score of 6. After 5 hours, the child was transferred to the Intensive Care Unit for Pathological Neonates in České Budějovice. While receiving care at the complex intensive care, a fluctuating blood pressure, as measured directly in the umbilical artery, was observed. A catheter was therefore inserted into the umbilical vein for a period of 6 days. The neonate developed anuresis, which was treated with peritoneal dialysis for 3 days. After a temporary improvement and the removal of catheters, on the third day a retrogression was observed which included abdominal bloating, a stool flow, and a clinical picture of paralytic ileus. Then a new metabolic breakdown occurred and the child died 10 days after birth. The post mortem examination revealed blood in the ventricles of the brain and subarachnoid space of the meninges, and massive aspiration of amniotic fluid into the air sacs. Mucormycosis of the peritoneum and intestine was spreading into the blood vessels of the abdominal cavity where it induced a thrombosis. Mucormycosis was also found in the spleen and the kidneys. The placenta was without pathological findings.

2. V. P. The female child is from a high risk pregnancy, delivered in the 30th week spontaneously. The birth-weight was 1100 g, birth-length 43 cm. After birth, the child was diagnosed as highly premature with a high IRDS, and accepted for complex intensive care. After seven days the condition stabilized. The child was icteric and catheter was not introduced. On the 8th day, there was an acute deterioration, and bilateral pneumonia occurred. Fortum and Tobramycin were replaced by Rocephin. The left hip and left lower-limb became livid, afterwards, the lower-limb at first turned blue then black and cold. Proctorrhagia then occurred and the abdomen became swollen to ileotic (with symptoms of ileus). Medication used: streptasis, heparin and sandoglobulin. The child died with a clinical picture of haemorrhagic shock and paralytic ileus. A post-mortem examination was requested with a diagnosis of the syndrome of vena cava inferior, thrombophlebitis of lower extremities, ileus, sepsis, and IRDS. Exitus lethalis occurred 10 days after birth. From the post-mortem report, the following can be extracted: a low degree of hypoxic encephalopathy diagnosed by way of microscopic examination of the brain. There was a small subependymal haematoma of the left lateral ventricle and mucormycosis of the intestine with rectosigmoideal gangrene. Mucormycetes had grown through the blood vessels of the rectal wall, the vessels of the lesser pelvis, from where they continued to the renal vessels and the blood vessels of the spleen.

3. L. M. Male, birth-weight 1900 g, birth-length 43 cm. Child was from a 4th pregnancy. The mother was admitted to the Gynaecology Department due to developing eclampsia. Baby was delivered by caesarean section due to a diagnosis of intrauterine hypoxia. Apgar score 3/5/5. After birth, resuscitation was necessary, respiratory failure appeared, and the child was transferred to the Intensive Care Unit for complex intensive therapy. After six days of intensive care his condition became stabilised. On the 7th day, food intolerance and symptoms of ileus occurred, and an X-ray showed retroperitoneum. On the 8th day, an exploratory surgery of the abdominal cavity was performed, which revealed perforation of the sigmoideum. Following the operation, the condition of ileus worsened and the child died with symptoms of peritonitis. The clinical diagnosis was as follows: perinatal asphyxia, IRDS, secondary peritonitis, and necrotizing enterocolitis. From the post-mortem report can be extracted: intestinal mucormycosis with infected blood vessels, induced thrombosis of the portal vein and the lienal artery. A necrosis of the sigmoideum, perforated on the 8th day after birth, treated by sigmoideostomy. There was abundant haemorrhagic infarction of almost the entire intestine.

4. V. Š. Delivered in the 27th week of pregnancy with a birth-weight of 960 g, birth-length 37 cm, and a male from a first pregnancy. Immediately after birth, complex intensive care was introduced. After 12 hours, a serious cardiac arrhythmia appeared causing repeated shock to the circulatory system. The child did not respond to conservative therapy. There were high elevations of potassium in the serum and peritoneal dialysis was started. Following the introduction of the dialysis, the circular disorders improved and the condition

stabilised. On the 3rd day, the child became anaemic with symptoms of bleeding into the ventricles of the brain. Peritoneal dialysis was terminated. On the 5th day, the child was able to urinate and the blood pressure measured was normal and stabilised. On the 8th day of life, haematoma in the abdominal wall occurred; both lower extremities were pale, ischaemic and cold and later became livid with a clinical picture of gangrene. The exploratory surgery of the abdominal cavity reveals haemoperitoneum. The child died on the 15th day. Based on post-mortem report, the following can be extracted: a heavy perinatal asphyxia caused by bleeding and premature detachment of the placenta and extreme prematurity. Deterioration of the intrinsic environment requiring peritoneal dialysis. Mucormycosis of the large intestine spreading into the vessels of the abdominal cavity, followed by thrombosis and a metastasis dissemination in part of the body and both lower extremities due to thrombosis of the aorta induced by mucormycetes.

5. V. J. was delivered spontaneously on the 26th week of pregnancy with a birth-weight of 780 g and birth-length 38 cm. The child displayed signs of respiratory disorders, asphyxial with a Silverman score of 8 points, and respiratory and metabolic acidosis. An umbilical catheter was inserted into the vein and artery. On the 4th day the child stabilized, breathing became spontaneous and the child was taken off the ventilator. An ultrasound of the head showed intraventricular haemorrhage inside the CNS of the 2nd-3rd degree. On the 5th day, the child had developed a swollen abdomen and had blood in the faeces. An X-ray of the abdomen showed signs of blockage. During the examination of the abdominal cavity, peritonitis and an intestinal perforation were found. A resection on part of the intestine was performed and colostomy was introduced. The condition, however, worsened and the child died a few hours after the operation. From the post mortem report, the following can be extracted: mucormycosis was found in the area of the sigmoideum, inside the mesenteric arteries and on the peritoneum.

6. J. E. Spontaneous delivery. First pregnancy, birth-weight: 980, birth-length: 39 cm. Delivery by caesarean section. After the delivery, the child was asphyxial, with difficult breathing. It was intubated with introducing the controlled ventilation. The umbilical catheter was furthermore introduced. On the sixth day, disorders in supplying limbs with the blood occurred. The child started vomiting and exerted bloated abdomen. Secondary respiratory disorders were encountered. Clinical pattern of paralytic ileus. The child died on the eighth day after the delivery with symptoms of failure of all organs. In autopsy, mucormycotic strains were found in the mesenterium, vessel walls, large intestine and spleen. The finding in the brain tissue was negative.

DISCUSSION

Nosocomial mycotic infections are relatively widespread, but their clinical aspects are varied and can occur from thrush to candidiosis and mycotic sepsis. Strains of mucormycosis (zygomycosis) are opportunistic mycotic strains. Among the most common pathogens occurring in humans are those belonging to Rhizopus, Absidia, and Mucor. These strains may grow on a number of substrates in the laboratory but also can appear on food items. They thrive at 37°C. When stained, the clinical samples show thick-walled cells of irregular shapes, nonseptate hyphae which branch perpendicularly (Agarwal 2006; Miler 2001; Sugar 2000). These pathogens are ubiquitous and found on fruit and other crops which grow in soil. They cause infections characterized by invasion of the blood vessels, followed by thrombosis and necrosis of the mucous membranes. In our case, we did not cultivate the pathogens affecting our newborns, as we did not consider this at the time of diagnosis. In any case, cultivation from fixed material is extremely difficult. The infection was acquired from the nursing staff. It can be transmitted through spores in the air or through hand-contact, directly or indirectly. In our case the infection was most likely contracted through hand-contact. The infection may have entered through the gastrointestinal tract, both upper and lower airways, or the skin. In this case, the infection entered through the mouth. In our case, all the newborns were extremely premature and have developed immunodepression due to severe prenatal and postnatal asphyxia (Oh and Notrica 2002; Ryan 1982; Siu and Lee 2004).

Clinical forms of mucormycosis can be extremely varied. In general, there is a rhinocerebral form where mycetes spread around the mucous membrane of the nose, the orbit, and further to the brain (Lewis 1990; Miller 1980). Then there is a skin form characterized by the development of dead tissue scarring and a gastrointestinal form connected with the development of necrotic nidi, and may result in perforation of the intestine and peritonitis. An abdominal form affects the intestine, spleen and liver. Thrombosis of the renal vessels, as observed in our newborn, has not yet been described in any available literature. It is therefore important to test for mucormycosis in all newborns with signs of a paralytic ileus or spontaneous perforation of the intestine. This is an important point, as even foreign literature does not describe mucormycosis as a cause of perforation of the intestine (Dhingra 2008; Nichol 2004; Siu and Lee 2004; Zhang 2005). The skin type of mucormycosis has been ascribed to the use of plasters (Linder 1998; Oh and Notrica 2002; Ryan 1982). The literature describes successful therapy using amphotericin (Agarwal 2006; Lewis 1990). We have not tried that type of therapy ourselves. However, we did not consider such a diagnosis.

The clinical symptoms of mucormycosis in our newborns included development of gangrene of the extrem-

Table 1. Summary of data about six newborns with diagnosis of mucormycosis

Newborn	1	2	3	4	5	6
Parity	2	2	4	1	2	1
Week of pregnancy	26	30	33	27	27	28
Way of delivery	pprom sp	spont	SC	spont	spont	SC
Condition after delivery	pathol	asphyxia	asphyxia	asphyxia	asphyxia	asphyxia
Gender	f	f	f	m	f	m
Birth-length (cm)	36	43	43	37	38	39
Birth-weight (grams)	850	1100	1900	960	780	980
Intubation and ventilation	yes	yes	yes	yes	yes	yes
Catheterization of umbilical vessels	yes	yes	yes	yes	yes	yes
Day of symptoms onset after birth	immed	8	7	3	5	6
Day of exitus	10	10	9	15	8	8
Blood supply disorders in limbs	no	yes	yes	yes	yes	yes
Symptoms from abdominal cavity	ileus	ileus	ileus	ileus	ileus	ileus
Secondary respiratory disorders	yes	yes	yes	yes	yes	yes
Symptoms from CNS	no	yes	no	yes	yes	no
Renal failure – peritoneal dialysis	yes	no	no	yes	no	no

Table 2. Positive mucormycosis finding in autopsy

Abdominal cavity						
V. cava inferior thrombosis	yes	yes	yes	yes	yes	no
Vessel walls in abdominal cavity	yes	yes	yes	yes	yes	yes
Mesenterium	yes	yes	yes	no	yes	yes
Large intestine	yes	yes	yes	yes	yes	yes
Small intestine	no	no *	no	yes	no	no
Liver, spleen	no	yes	no	yes	no	yes
Vessels in other organs - brain, lungs	yes	no	yes	yes	yes	yes
Brain tissue	bleeding	no	no	no	no	no
Lung tissue	aspir	no	no	yes	yes	no
Skin	no	no	no	no	no	no

*haemorrhagic infarctions

ities and perforation of the intestine; Six babies had indwelling catheters.

Tables 1 and 2 offer a summarization of the most important data resulting from the analysis of particular case reports in our group. Many of them also occur in communications of the other authors (Dhingra 2008). Our experience and also data from the literature emphasize the fact that mucormycoses relatively frequently participate in the origination of enterocolitis with subsequent perforation of intestines and peritonitis. We furthermore compared predisposing factors of the origination of mucormycotic infections in our six case reports and in 18 case reports of 13 authors (Oh and Notrica 2002). In our case reports, there was a 100% abundance of the birth-weight under 1500 g; in literature, this abundance was of 89%. The representation of genders was the same in both cases. In our group, the umbilical catheter was inserted in all the children, in the cases presented in the literature in 50%. All the children in our group died with manifestation of paralytic ileus. The time of the onset of first symptoms was earlier in our group compared with the data from the literature.

Third-generation cephalosporins were administered and all newborns suffered from heavy asphyxia. Four cases belonged to the category of newborns with the lowest birth-weight. All our above-described cases were diagnosed with acute ileus accompanied by perforation of the intestine. The prognosis of the disease was serious, with a 50–80% mortality rate reported in adults and older children. The neonatal mortality rate due to mucormycosis has not yet been evaluated. The recommendations for prevention are within the strict adher-

ence to general rules of hygiene, especially the washing of one's hands (Oh and Notrica 2002; Zhang 2005).

At present, while several hospitals have dealt successfully with incidences of nosocomial infections caused by bacteria, it is important to take into account the possible occurrence of new opportunistic infections caused by viruses and fungi. Our report would like to support this opinion.

REFERENCES

1 Agarwal K, Sharma M, Singh S, Jain M (2006). Antemortem diagnosis of gastrointestinal mucormycosis in neonates: report of two cases and review of literature. Indian J Pathol Microbiol. **49**(3): 430–2.

2 Dhingra KK, Mandal S, Khurana N (2008). Unsuspected intestinal mucormycosis in a neonate presenting as necrotizing enterocolitis (NEC). Eur J Pediatr Surg. **18**(2): 119–20.

3 Lewis LL, Hawkins HK, Edwards MS (1990). Disseminated mucormycosis in an infant with methylmalonicaciduria. Pediatr Infect Dis J. **9**(11): 851–4.

4 Linder N, Keller N, Huri C, Kuint J, Goldshmidt-Reuven A, Barzilai A (1998). Primary cutaneous mucormycosis in a premature infant: case report and review of the literature. Am J Perinatol. **15**(1): 35–8.

5 Miler MJ (2001). Fungal Infections. In: Remington J, Klein J. Infectious diseases of the fetus and newborn infant. 5th ed. Phildelphia: Saunders. p. 828–830

6 Miller RD, Steinkuller PG, Naegele D (1980). Nonfatal maxillocerebral mucormycosis with orbital involvement in a dehydrated infant. Ann Ophthalmol. **12**(9): 1065–8.

7 Nichol PF, Corliss RF, Rajpal S, Helin M, Lund DP (2004). Perforation of the appendix from intestinal mucormycosis in a neonate. J Pediatr Surg. **39**(7): 1133–5.

8 Oh D, Notrica D (2002). Primary cutaneous mucormycosis in infants and neonates: case report and review of the literature. J Pediatr Surg. **37**(11):1607–11.

9 Ryan ME, Ochs D, Ochs J (1982). Primary cutaneous mucormycosis: superficial and gangrenous infections. Pediatr Infect Dis. **1**(2): 110–4.

10 Siu KL, Lee WH (2004). A rare cause of intestinal perforation in an extreme low birth weight infant – gastrointestinal mucormycosis: a case report. J Perinatol. **24**(5): 319–21.