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Systemic capillary leak syndrome due to systemic inflammatory response syndrome in infants: a report on 31 patients

Case Report

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Abstract: The aim of this study was to describe the clinical features, management strategies and outcomes of 31 infants with systemic capillary leak syndrome (SCLS) secondary to sepsis or systemic inflammatory response syndrome. There were 23 boys and 8 girls, with an average age 9.6 ± 2.1 days (range, 3.1 to 20 days). The primary disease was pneumonia in 11 patients and sepsis in other 20. Within 72 hrs of admission, all had progressive skin and mucosal edema, septic shock, respiratory distress, oliguria and severe hypoalbuminemia (10-20g/L). Other complications were pulmonary edema or hemorrhage, disseminated intravascular coagulopathy, heart failure, renal or liver dysfunction. All patients were treated with mechanical ventilation with a mean mechanical ventilation time of 19.7± 3.5 days. Intravenous hydroxyethyl starch was also applied at an early stage for 4-12 days, together with broad spectrum antibiotics, plasma and albumin infusion. Twenty one patients (67.0%) were discharged from the neonatal intensive care unit after a median stay of 29 days, and 7 died (37.0%) in the hospital. During a 6.3-month follow-up, 4 patients had hydrocephalus and another 4 had muscle spasm or rigidity in the lower-limbs. We conclude that SCLS is a serious complication of neonatal sepsis with a high rate of in-hospital mortality and post-discharge disability.

Keywords: *Infants • Sepsis • Systemic inflammatory response syndrome • Capillary leak syndrome • Mortality*

1. Introduction

The systemic capillary leak syndrome (SCLS) refers to a clinical condition characterised by reversible plasma extravasation and vascular collapse [1]. Clinically, it is often accompanied by hemo-concentration, hypoalbuminemia, shock and massive edema [1-3]. SCLS may be caused by transient endothelial dysfunction due to endothelial contraction, apoptosis, injury, or a combination [1-3]. The diagnosis is made clinically and by exclusion of other diseases that cause similar symptoms and signs, most notably sepsis, anaphylaxis, and angioedema [1,2]. Most of the reported cases of SCLS were in adults [1], although there have been several reports on SCLS in young children following operations for congenital heart diseases [4,5]. SCLS in infants has not been reported. Systemic inflammatory response syndrome (SIRS) is a serious condition related to systemic inflammation, organ dysfunction, and organ failure [6]. SIRS is the result of sudden and significant release of proinflammatory cytokines [6]. SIRS is closely related to sepsis, in which patients satisfy criteria for SIRS and have a suspected or proven infection. In this report we described the clinical features and outcomes of 31 infants who were managed at our neonatal intensive care unit.

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2. Case reports

This was a retrospective analysis that was approved by the Institutional Review Board of Liaocheng People's Hospital. Between January 2009 and October 2012, 31 patients with SIRS were admitted to the neonatal intensive care unit of our hospital for treatment. There were 23 boys and 8 girls, with an average age 9.6 ± 2.1 days (range, 3.1 to 20 days). The gestational age of the patients varied from 30.5 to 40.1 weeks, and 23 were born preterm. Their weight on admission varied from 3.6 to 12.1 kg. Eight patients were delivered by vaginal birth and 23 were delivered by cesarean section.

Majority of the patients had complications during pregnancy or at birth. These complications included fetal distress (n=10), premature rupture of membrane (n=9), placental abruption (n=3), meconium inhalation (n= 6), anoxia after birth (n=6), gestational hypertension (n=10). On admission, 11 patients had pneumonia and 20 had sepsis. All patients had at least two of the following diagnostic criteria of systemic inflammatory response syndrome (6,7): a) body temperature >38°C or <36°C; b)heart rate>160 beats/min; c) respiration rate >60 beats/min or partial pressure of carbon dioxide <32mmHg; d) white blood cell count > 15 × 109/L or <4 ×109/L; e) C-reactive protein> 8mg/L.

Within 3 days of admission, all patients had extensive skin and mucosal edema, hypoalbuminemia (10-20g/L), dyspnea, and oliguria (hourly urine output <0.5ml/kg). As shown in Table 1, all patients had septic shock, which was defined as mottling skin, peripheral cyanosis and coldness, and capillary refilling time of more than 3 seconds. The other conditions were respiratory distress, pulmonary hemorrhage, disseminated intravascular coagulopathy, renal and hepatic dysfunction and heart failure (Table 1).

Table 1. Summary of clinical outcomes of 31 patients with capillary leak syndrome

Type of dysfunction	No. Of Patients	Full recovery	Death
Septic shock	31	21 (67.7)	7 (22.6)
Hypoproteinemia	31	21 (67.7)	7 (22.6)
Respiratory failure	31	21 (67.7)	7 (22.6)
Pulmonary hemorrhage	6	3 (50)	3 (50)
DIC	8	4 (50)	4 (50)
Heart failure	4	2 (50)	2 (50)
Gastrointestinal dysfunction	6	4 (66.7)	2 (33.3)
Delirium	6	3 (50)	3 (50)
Renal injury	3	2 (33.3)	1 (33.3)
Hepatic dysfunction	6	6 (100)	0 (0)
Congenital heart disease	3	0 (0)	3 (100)
21 trisomy syndrome	2	1 (50)	1 (50)

DIC: disseminated intravascular coagulopathy

High blood sugar (random glucose ≥ 11.1 mmol/L) was found in 19 patients. Second degree atrioventricular conduction block was found in 5. Pleural effusion was identified in 10 patients and pericardial effusion was found in 8.

Treatments were mainly broad spectrum antibiotics for infection control, mechanical ventilation to improve oxygenation, nutritional support, and maintenance of homoeostasis. All patients were treated with hydroxyethly starch (10 to 15 ml/kg 8 hurly for 4 to 12 days), alternating plasma and albumin infusion, and diuretics. The mean mechanical ventilation time was 19.7± 3.5 days (range, 7 to 38 days).

Twenty one patients (67.0%) had a full recovery and being discharged from the neonatal intensive care unit. The length of intensive care stay was 23-56 days (median, 29 days). In these patients, septic shock lasted for about 24 to 72 hrs, and the edema subsided between 4 to 18 days following the treatment. After a followed- up of 6 to 9 months (media, 6.5 months), 13 patients were found to have normal development, 4 had hydrocephalus on brain CT, and 4 had significant muscular rigidity/spams in the lower-limbs. The proportion of these patients who had high random blood glucose level (8/8 or 100%) was higher than the other 13 patients who did not have central nervous system complications (1/13 or 7.7%, p =0.02, Fisher's exact test).

Seven patients (23%) died of multiple organ failure at the neonatal intensive care unit. Among these patients, 1 had trisomy 21 syndrome and 3 had severe congenital heart disease.

Autopsy was performed on 3 patients after written informed consent was obtained from the parents. In each of the three patients, there were pulmonary edema, focal pulmonary atelectasis, and peribronchial infiltration of inflammatory cells (Figure 1A). There were large areas of severe necrosis in the liver (Figure 1B). Cerebral softening was found in the brain (Figure 1C).

3. Discussion

Unlike isolated SCLS, the diagnosis of SCLS in patients with septic shock or systemic inflammatory response syndrome can be complex. A common feature in our patients was that extensive skin or mucous edema occurred within 2-3 days after the initial diagnosis of septic shock or systemic inflammatory response syndrome. Edema emerged from lower extremities to the abdominal wall, back, upper limbs, and head.

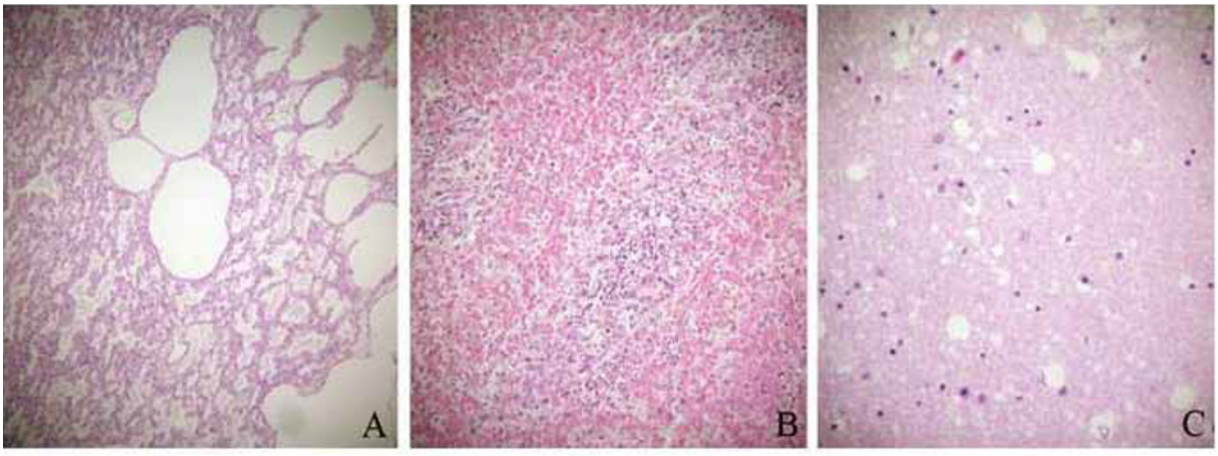

Figure 1. Histopathology in a patient died of capillary leak syndrome (HE staining, ×200). A: lung tissue: emphysema, focal atelectasis, peribronchial inflammatory cell infiltration; B: Liver: a large area of acute severe hepatic necrosis; C: brain: softening of the brain tissues.

The systemic inflammatory response syndrome can lead to capillary endothelial cell damages, increased vascular permeability, and leakage of albumin into the interstitial space. Plasma albumin can be significantly reduced in a short time period, and leading to progressive skin and mucous edema. Pleural and peritoneal exudations are common place. In the present study, all patients had extensive skin and mucous edema, and 10 had pleural effusion on chest X-ray and 8 other had pericardial effusion.

All patients in this report had respiratory failure as a result of pulmonary edema or hemorrhage. Extensive pulmonary edema was evident in the three autopsies. This was consistent with a previous study which showed that septic patients had greater pulmonary capillary permeability, edema, and severity of lung injury than nonseptic patients [8].

In sepsis patients, the pulmonary interstitial exudation leads to impaired gas exchange because of the density of capillary damaging. This results in severe hypoxemia, respiratory distress, and circulatory disorders. Therefore, mechanical ventilation is an essential measure to maintain normal oxygenation [9,10]. In the present study, ventilation support was initiated in all patients, and the mean duration of mechanical ventilation was 19.7 days.

The other important therapeutic measures are crystalloid and colloid to restore the fluid balance in the initial stage of the septic shock. However, a large number of crystalloid fluids will soon spread to the tissue space, resulting in increasing tissue edema [11]. It has been suggested that the initial rescue crystalloid be kept at 20ml/kg, and the subsequent fluid should be colloid, especially hydroxyethly starch [11]. Some data indicated that hydroxyethyl starch has a suitable molecular shape and size to reduce the vascular leakage, and to inhibit the expression of proinflammatory mediators [11-14]. However, a recent meta-analysis showed that hydroxyethyl starch was associated with an increased risk of mortality and acute kidney injury [15], suggesting clinical use of hydroxyethyl starch for acute volume resuscitation needs further investigation. In the present study, all patients received hydroxythly starch for 4-12 days. The effect and the adverse effect of hydroxyethyl starch, however, were difficult to evaluate as this was not a placebo control study.

The in-hospital mortality rate in this cohort of patients was 37%. Three of the 7 deaths were accompanied by complex congenital heart disease, including the case of trisomy 21 syndrome. There was no mortality during the follow-up. However, hydrocephalus and increased muscular tone in the lower limbs were noticed in 8 patients 6 months after discharge. In-hospital hyperglycemia was present in all patients who had post-discharge central nervous system complications, while it was found in only one patient who had a full recovery. Several previous studies showed that hyperglycemia was closely related to the nerve damages and prognosis in patients with sepsis [14,16]. Therefore, optimal management of blood glucose levels at early stages of sepsis may reduce neurological complications.

In conclusion, systemic capillary leak syndrome is a serious complication with a high mortality in infants with severe infection, especially in those with septic shock or systemic inflammatory response syndrome. Mechanical ventilation, fluid resuscitation and early administration to antibiotics and other supportive measures are the treatment of choice.

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Conflict of interest statement

Authors state no conflict of interest.

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