

***Klebsiella pneumoniae* Bacteraemia Complicating Rotavirus Gastroenteritis in Two Infants with Glucocorticoid Deficiency**

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ABSTRACT

Rotavirus gastroenteritis was complicated by *Klebsiella Pneumoniae* bacteraemia in two infants with glucocorticoid deficient conditions who were treated with 'stress dose' hydrocortisone during their illness. Delayed healing in the context of glucocorticoid administration combined with damage from rotavirus infection may result in increased risk of mucosal invasion by gastrointestinal bacteria and subsequent enteric gram-negative bacteraemia.

KEY WORDS

glucocorticoid deficiency, rotavirus, gastroenteritis, enteric gram-negative bacteraemia, corticosteroids, congenital adrenal hyperplasia

INTRODUCTION

Klebsiella pneumoniae bacteraemia complicated rotavirus gastroenteritis in two infants with glucocorticoid deficiency being treated with stress-dose hydrocortisone during their illness. Enteric gram-negative (EGN) bacteraemia is an infrequently recognised complication of rotavirus infection. Rotavirus has not been shown to cause significant gastrointestinal mucosal changes; however, it has been shown to increase epithelial permeability and enhance the ability of bacteria to invade enterocytes¹. Glucocorticoids are thought to cause delay in gastroduodenal healing, most likely due to inhibition of prostaglandin syn-

thesis². There have been no reports of secondary EGN bacteraemia in infants or children with rotavirus infection on corticosteroids. It is hypothesised that high dose glucocorticoids may increase the risk of EGN bacteraemia in rotavirus gastroenteritis.

PATIENT 1

An 8 month-old male infant with congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency was admitted with rotavirus gastroenteritis. His regular medication included oral hydrocortisone (10.5 mg/m²/day) and oral fludrocortisone (100 µg twice daily). He presented with a one-day history of vomiting and watery diarrhoea with no history of fever. Rotavirus infection was confirmed via immunoassay antigen detection (VIKIA[®] Rota-Adeno by bioMerieux). He was commenced on hydrocortisone at a dose of 2 mg/kg intravenously every 6 hours on admission, in addition to intravenous fluids. On admission his C-reactive protein (CRP) was <1.0 mg/L, white blood cell count 19.3 x 10³/mm³ with a neutrophil count of 7.3 x 10³/mm³. His gastroenteritis was complicated by concurrent Norovirus enteric infection. He was hospitalised for six days and then discharged on oral hydrocortisone (triple his oral maintenance dose) after his symptoms settled. However, he required readmission due to recurrence of vomiting and large volume diarrhoea. Previously afebrile, his temperature increased to 39°C 11 days after readmission. Blood cultures revealed a pure growth of *Klebsiella pneumoniae* after 5.9 hours. Haematological testing revealed anaemia, lymphopenia and thrombocytopenia. He was commenced on ceftriaxone and gentamicin, continuing on gentamicin (7.5 mg/kg daily) for seven days after sensitivities were available. Resolution of fever

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occurred within 48 hours of antibiotic commencement with subsequent decline of inflammatory markers, improvement in haematological markers and ultimately full recovery.

PATIENT 2

A male infant aged 8 months with bilateral optic nerve hypoplasia and panhypopituitarism (including ACTH deficiency) was admitted with gastroenteritis. His regular medication included oral hydrocortisone (10.1 mg/m²/day), oral desmopressin (20 µg three times daily) and oral thyroxine (50 µg daily). He had a two-day history of vomiting with no history of diarrhoea. His temperature was 37.8°C on admission. He was commenced on intravenous hydrocortisone at a dose of 2 mg/kg six hourly. An initial blood culture collected at the time of admission was negative. His white cell count on admission was 9.2 x 10³/mm³. He was managed with oral fluids initially. Rotavirus testing on stool (VIKIA® Rota-Adeno by bioMerieux) was positive on day two of admission and culture of stool from the day of admission was negative. He deteriorated clinically on day 3 of his admission with fever up to 39.4°C and signs consistent with sepsis. A blood culture subsequently grew *Klebsiella pneumoniae* after 10 hours. His white cell count was initially normal; however, it became elevated to 24.1 x 10³/mm³ and his CRP peaked at 213 mg/L 32 hours after the initial fever. He also developed anaemia, neutrophilia and thrombocytopenia during the illness. He completed an 11 day course of intravenous antibiotics. He had resolution of fever and improvement in clinical state within 48 hours of starting antibiotics. He subsequently made a complete recovery.

DISCUSSION

Rotavirus is the commonest cause of gastroenteritis worldwide and it has been recognised as the cause of 20% of diarrhoeal deaths in children aged less than 5 years³. Rotavirus infects the enterocytes and it has been demonstrated that rotavirus infection increased enterocyte internalisation and replication of bacteria, including

Listeria monocytogenes, *Yersinia enterocolitica* and *Y. pseudotuberculosis*^{4,5}. These mechanisms are thought to contribute to the pathogenesis of EGN bacteraemia, a recognised complication of rotavirus infection. Secondary EGN bacteraemia complicating rotavirus infection has been described in 12 cases in children ranging in age from two weeks to 18 months⁶⁻¹². Recrudescence of fever in infants with rotavirus infection has been identified as the clinical sign that should raise suspicion of secondary EGN bacteraemia and prompt further assessment and investigation^{6,9,11}.

Unlike other reported cases the patients discussed here both received 'stress dose' glucocorticoid steroids after admission to hospital. Patients with adrenal insufficiency require maintenance glucocorticoid replacement when well. It is recognised that circulating levels of cortisol normally increase during stress, such as illness or surgery; therefore increased doses of glucocorticoids are required in these states and in some cases may need to be administered parenterally¹³. The nature of the effect of high dose corticosteroids on the gastrointestinal tract is controversial and the pathophysiology is not clearly understood. However, studies have shown delayed epithelial healing is most likely due to inhibition of prostaglandin synthesis². Experimental studies have shown that dexamethasone inhibits epidermal growth factor (EGF)-stimulated gastric epithelial cell proliferation and basic fibroblast growth factor^{14,15}, which are essential for mucosal healing via the prostaglandin pathway. These research findings suggest a pathophysiological basis for impaired healing of 'damaged' gastrointestinal mucosa in the setting of glucocorticoid administration. Damage to the gastrointestinal mucosa due to rotavirus infection combined with delayed healing in the context of glucocorticoid administration may increase the risk of invasion of the mucosa by gastrointestinal bacteria. Other potential sources of EGN infection need to be considered, including intravenous catheter infections; however, in both cases discussed here there was no clinical evidence of venous catheter infection.

The first infection with rotavirus is often between 3 and 36 months of age and is more

diarrhoea¹⁶. From 1 July 2007, rotavirus vaccination has been included in the National Immunisation Program in Australia. The two infants described here did not receive the rotavirus vaccine. The impact of rotavirus vaccination on complications such as EGN bacteraemia remains uncertain. There remains a significant population of unvaccinated children within the higher risk age group. Studies have demonstrated that the rotavirus vaccination program provides protection for two years¹⁷. The impact of vaccination after this period for those on high dose glucocorticoids, who are hypothesised to be at increased risk, remains uncertain.

These two cases of ENG bacteraemia complicating rotavirus infection in infants on high dose glucocorticoids for glucocorticoid deficient states raise concern about a potential increased risk for these children. Further research would be beneficial to clarify this possible association and the relevant pathophysiology. The impact of rotavirus vaccination on EGN bacteraemia has yet to be evaluated.

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