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Author(s)	So, CC; Leung, YY; Yip, SF; Chan, SY; Lam, CCK; Chan, GCF; Chim, S; Chan, LC
Citation	Hong Kong Medical Journal, 2011, v. 17 n. 3, p. 237-241
Issued Date	2011
URL	http://hdl.handle.net/10722/139915
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Common association of haemolytic uraemic syndrome with invasive *Streptococcus pneumoniae* infection in five Chinese paediatric patients

CC So 蘇志釗
YY Leung 梁毓恩
SF Yip 葉仕輝
SY Chan 陳樹仁
Clarence CK Lam 林俊傑
Godfrey CF Chan 陳志峰
Stella Chim 詹愷怡
LC Chan 陳立昌

Haemolytic uraemic syndrome is an important cause of acute renal impairment in childhood. We review the incidence, and clinical and laboratory features of haemolytic uraemic syndrome in a Chinese population. Five patients were identified from 2006 to 2008. All patients were young children with associated invasive *Streptococcus pneumoniae* pulmonary infection. Serotypes 3, 14, and 19A were confirmed in four patients. The classical post-diarrhoeal form associated with *Escherichia coli* (O157:H7) infection was not seen. One patient died of acute respiratory failure. *Streptococcus pneumoniae* infection, as an associated condition in haemolytic uraemic syndrome, is important and relatively common in Chinese patients, especially among children. The acute clinical picture is similar to that reported in the western literature, except for an uncommon association with meningitis. The medium-term renal outcome of the Chinese population appears to be more favourable than the Caucasians. Widespread vaccination against *Streptococcus pneumoniae* may have resulted in changes in bacterial epidemiology and clinicians should be continuously aware of this severe disease. The use of washed blood components for transfusion in the acute stage requires further study.

Introduction

Haemolytic uraemic syndrome (HUS) classically presents as a post-diarrhoeal disease, and is often associated with *Escherichia coli* (O157:H7) infection. However, the relative incidence of HUS associated with invasive pneumococcal infection may be underestimated due to lack of awareness,¹ and the incidence may be increasing.² Pneumococcal HUS is characterised by T-antigen activation, whereby the enzyme neuraminidase produced by the bacteria cleaves N-acetylneuraminic acid from the glycoproteins on the cell membrane of the red blood cells (RBCs) and glomeruli and exposes the Thomsen-Friedenreich antigen (T-antigen). This desialylation of glycoprotein is thought to be important in the pathogenesis of HUS.³ Pneumococcal HUS is associated with significant mortality and morbidity in Caucasians.² This report is of a retrospective review of all patients with a diagnosis of HUS made between January 2006 and December 2008 at the Haematology Division, Department of Pathology, Queen Mary Hospital, Hong Kong. Data on clinical manifestations, laboratory findings and follow-up status were collected from the patients' medical records and compared with reports in the literature.

Haemolytic uraemic syndrome was defined by a triad of microangiopathic haemolysis, thrombocytopenia, and acute renal impairment. Acute disseminated intravascular coagulation was excluded by the absence of a significantly raised D-dimer level (<8 mg/L). Acute renal impairment was determined by a serum creatinine level above the age-specific reference range in a patient with no known history of renal disease. Neurological signs should be absent unless there was documented evidence of central nervous system infection. T-antigen activation on RBCs was documented by *Arachis hypogaea* (peanut) lectin agglutination.

Case report

Five patients with HUS were identified, and all were children with invasive *Streptococcus pneumoniae* respiratory infection (Table). There were two boys and three girls. Their median age was 3 years (range, 2-4 years). Haemolytic uraemic syndrome was diagnosed between 3 days and 11 days after the onset of febrile illness for all patients. Bacteriology was confirmed by positive blood and/or pleural fluid culture (Table). Only one of the isolates was sensitive to penicillin. Serotyping results were available for four patients: type 14 (n=2), type 3 (n=1), type 19A (n=1). Four of the five patients developed empyema requiring decortication. Two patients received ventilatory support. None of the patients

Key words
Haemolytic-uraemic syndrome;
Pneumococcal infections; Serotyping;
Streptococcus pneumoniae; Vaccination

Hong Kong Med J 2011;17:237-41

Li Ka Shing Faculty of Medicine, The
University of Hong Kong, Hong Kong;
Department of Pathology

CC So, MB, BS, FRCPath
YY Leung, MB, BS, FRCPath
SF Yip, MB, BS, FRCPath
CCK Lam, MB, BS, FRCPath
LC Chan, MB, BS, FRCPath
Department of Paediatrics and
Adolescent Medicine
SY Chan, MB, BS, MRCPCH
GCF Chan, MD, FRCPath
S Chim, MB, BS, MRCPCH

Correspondence to: Dr CC So
Email: scc@pathology.hku.hk

五名患有溶血性尿毒綜合徵的華籍兒童中常見併發的入侵性肺炎鏈球菌感染

溶血性尿毒綜合徵是幼年期急性腎衰竭的主因之一。本文回顧華人溶血性尿毒綜合徵的發病率、其臨床和實驗室檢查特徵。2006至2008年期間，五名受入侵性肺炎鏈球菌感染的病童中，四人確診為血清3型、14型和19A型。所有患者並未出現與上述綜合徵相關的腹瀉和大腸桿菌O157:H7感染。一名病童因急性呼吸衰竭死亡。與溶血性尿毒綜合徵息息相關的肺炎鏈球菌感染尤其多發生在華籍兒童，不可忽視。這種疾病的急性臨床症狀與西方文獻相若。雖然華籍患者較大機會感染不常見的腦膜炎，但其腎功能的中期康復進度似乎較西方患者理想。針對肺炎鏈球菌的廣泛疫苗接種或會改變細菌的流行病學，醫生應持續監察這種嚴重疾病。至於在急性發病期間以血液洗滌方式輸血的做法，還需作進一步研究。

had evidence of meningitis.

All patients had impaired renal function as evidenced by a raised serum creatinine level (range, 101-756 $\mu\text{mol/L}$ [reference range, 10-60 $\mu\text{mol/L}$]). Two patients developed oliguria, one of whom required dialysis for 2 weeks for anuria, fluid retention, and rapidly deteriorating renal function. Profound anaemia and thrombocytopenia were consistent findings. Peripheral blood smear examination revealed RBC fragmentation in all patients, which provided the first clue to the diagnosis (Fig). None of the patients had significant bleeding. The mean nadir haemoglobin level and platelet count was 41 g/L (range, 13-55 g/L [reference range, 95-165 g/L]) and $7 \times 10^9/\text{L}$ (range, $4-9 \times 10^9/\text{L}$ [reference range,

150-400 $\times 10^9/\text{L}$), respectively. The clotting profile was deranged in all patients, as reflected by prolonged activated partial thromboplastin time (range, 56.5-109.0 seconds [reference range, 25.9-33.7 seconds]) and normal-to-mildly prolonged prothrombin time (range, 11.5-20.4 seconds [reference range, 11.3-13.5 seconds]). Fibrinogen was elevated in all patients (range, 4.14-7.66 g/L [reference range, 1.46-3.38 g/L]), partially masking the coagulation defects. In keeping with the clinical picture, evidence of frank disseminated intravascular coagulation was not detected with D-dimer assay at presentation ($<8 \text{ mg/L}$ in all patients).

T-antigen activation on RBCs was documented in all patients. Direct antiglobulin test was positive for complement with or without immunoglobulin in four patients. All patients received RBC transfusion. Four patients received platelet transfusion for prophylaxis or to cover invasive procedures. Washed RBCs and plasma-reduced platelet concentrates were transfused, except for one patient who was transfused before a diagnosis of HUS was made. This patient had respiratory failure requiring cardiopulmonary resuscitation soon after admission, with an associated rapid drop in haemoglobin level and platelet count. She received urgent transfusion with unwashed RBCs and ordinary platelet concentrates. She developed disseminated intravascular coagulation and died of refractory septicaemic shock and multi-organ failure a few hours later. This patient had previously received one dose of pneumococcal vaccine. The other four patients had not been vaccinated against pneumococcus.

TABLE. Clinical features, laboratory findings and outcomes of patients with haemolytic uraemic syndrome (HUS)

Patient No.	Sex/age (years)	Onset* (days)	Respiratory disease	Respiratory intervention	Peak serum creatinine ($\mu\text{mol/L}$) [†]	Dialysis	Nadir haemoglobin (g/L) [‡]	Nadir platelet count ($\times 10^9/\text{L}$) [§]	T-antigen activation
1	M/4	10	Pneumonia, empyema, pleural effusion	Decortication	268	No	13	9	Yes
2	F/2	11	Pneumonia, pleural effusion	Nil	756	Continuous ambulatory peritoneal dialysis for 2 weeks	55	4	Yes
3	F/3	3	Pneumonia, empyema	Decortication, mechanical ventilation	368	No	44	9	Yes
4	M/3	10	Pneumonia, empyema, pleural effusion	Decortication	101	No	49	8	Yes
5	F/3	5	Pneumonia, empyema, pleural effusion	Mechanical ventilation	130	No	46	6	Yes

* Onset of pneumococcal HUS after initial febrile illness

[†] Reference paediatric range (10-60 $\mu\text{mol/L}$)

[‡] Reference paediatric range (95-165 g/L)

[§] Reference paediatric range (150-400 $\times 10^9/\text{L}$)

[¶] All patients received washed red blood cells and plasma-reduced platelet concentrates after the diagnosis of pneumococcal HUS

All four surviving patients had normal serum creatinine (<60 mmol/L), haemoglobin (>100 g/L), and platelet (>150 x 10⁹ /L) levels, and no hypertension, proteinuria, or haematuria during a median follow-up of 31 months (range, 24–48 months).

Discussion

Haemolytic uraemic syndrome in Chinese patients is commonly associated with invasive *S pneumoniae* infection. This complication appears to be restricted to the paediatric age-group and is uncommon in adults, probably because T-antigen activation usually occurs in the paediatric age-group. Indeed, all five patients with HUS in this report were young and had severe pulmonary *S pneumoniae* infection. Observation of microangiopathic haemolysis at peripheral blood smear examination and demonstration of T-antigen activation on RBCs provide strong support for the diagnosis of HUS. The acute clinical and laboratory findings in terms of disease onset, pulmonary, renal and haematological manifestations of the patients in this report were similar to pneumococcal HUS reported in both Chinese and Caucasian series,^{2,4} with the exception of an uncommon association with meningitis in Chinese patients. A study of 43 patients from the UK reported an acute mortality rate of 9%, with three of four deaths related to central nervous system involvement.²

No documented case of *E coli* (O157:H7) infection and associated HUS has been seen at Queen Mary Hospital from 2003 to 2008. This confirms findings from other reports of Chinese patients,^{4,5} but contrasts with reports from western

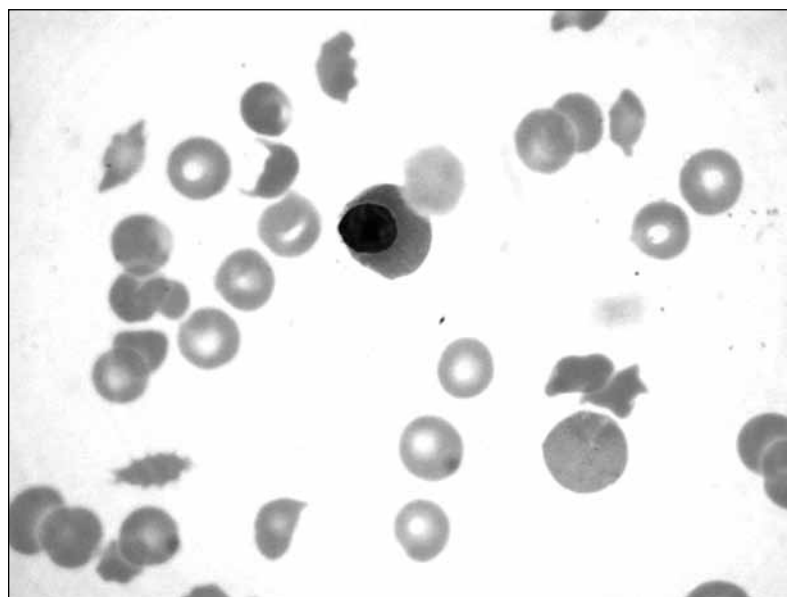


FIG. Peripheral blood smear of patient 5 showing red blood cell fragments and absence of platelets. A nucleated red cell is depicted in the centre of the picture (Wright stain; original magnification, x 100)

countries where pneumococcal HUS constitutes 5% or less of all HUS,^{6–8} although an increasing trend has been observed.² The marked difference in relative prevalence of *E coli*- and *S pneumoniae*-induced HUS among different ethnic groups is intriguing, and may point to underlying genetic and/or environmental factors affecting disease susceptibility.

In the largest reported series of pneumococcal HUS, renal morbidity at a median follow-up of 9

Transfusion [†] (units transfused)	Follow-up duration (months)	Serum creatinine and blood cell counts at last follow-up	Pneumococcal vaccination history	<i>Streptococcus pneumoniae</i> serotype	Bacterial culture from blood	Bacterial culture from pleural fluid	Antibiotic sensitivity
Red blood cells (7)	36	Normal	Nil	Not tested	Positive	Negative	Resistant to penicillin, sensitive to ceftriaxone
Red blood cells (4), platelets (1)	27	Normal	Nil	3	Positive	Negative	Sensitive to penicillin, cefotaxime
Red blood cells (3), platelets (3)	18	Normal	Nil	19A	Positive	Positive	Resistant to penicillin, sensitive to ceftriaxone, vancomycin
Red blood cells (3), platelets (1)	18	Normal	Nil	14	Negative	Positive	Moderately sensitive to penicillin, sensitive to cefotaxime, vancomycin
Red blood cells (3), platelets (3)	Died 1 day after admission	Not applicable	Prevenar (one dose)	14	Positive	Positive	Moderately resistant to penicillin, sensitive to cefotaxime, vancomycin

months was considerable,² with 10 of 35 patients showing evidence of renal dysfunction as evidenced by raised serum creatinine level, proteinuria, and/or hypertension. In contrast, the prognosis for renal recovery appears to be favourable for Chinese patients. Two Chinese studies reported complete renal recovery with no evidence of chronic sequelae.^{4,5} The surviving patients in this series also had a normal serum creatinine level with no hypertension or proteinuria at a median follow-up of 31 months. Longer follow-up will confirm whether this renal status remains stable.

Different serotypes of neuraminidase-producing *S pneumoniae* have been implicated in pneumococcal HUS. Serotype 14 is seen in most series but the most prevalent serotype varies among populations.^{2,4,9} Interestingly, the widely used 7-valent pneumococcal conjugate vaccine (serotype 4, 6B, 9V, 14, 18C, 19F, 23F) does not include most of the serotypes isolated in pneumococcal HUS in a recent UK study.² In particular, serotypes 3 and 19A are not covered. Serotype 19A was the most prevalent in the UK study,² reflecting its increasing prevalence in the paediatric age-group since the introduction of the 7-valent vaccine in the US.¹⁰ Serotype 19A is also not covered by the 9- or 11-valent pneumococcal vaccines, and pneumococcal HUS associated with serotype 19A is increasingly being reported.^{11,12} The same epidemiological change in pneumococcal infection has been observed in Chinese populations. A large epidemiological study of serotype distribution of invasive *S pneumoniae* isolates collected from children in Hong Kong between 1995 and 2001 showed that serotypes 6B, 9V, 14, 18C, 19F and 23F together constituted 90% of all isolates.¹³ As serotype 19A was not detected in any isolate, good protection from the 7-valent vaccine could be expected. However, serotype 19A has recently become more prevalent in China in children younger than 5 years.¹⁴ The data from this report showed that serotypes 3 and 19A were present among patients with pneumococcal HUS. A study from Taiwan also detected the occurrence of serotype 3 in patients with pneumococcal HUS.⁹ A pneumococcal vaccination programme using the 7-valent vaccine has been implemented in many countries, including Hong Kong. Post-vaccine surveillance is therefore important to monitor any increase of invasive *S pneumoniae* infection and pneumococcal HUS due to infection by serotypes not covered by the vaccine.

T-antigen activation is demonstrable in all patients with pneumococcal HUS.^{2,9} As anti-T

antibodies are present in the plasma of almost all adult blood donors, washed RBCs and plasma-reduced platelets are routinely used for patients with pneumococcal HUS to reduce the risk of iatrogenic haemolysis caused by antigen-antibody interaction. However, the necessity of these measures has not been studied and remains controversial. It should be noted that anti-T antibody does not fix complement in vitro.¹⁵ There is evidence from animal studies that neuraminidase-treated RBCs have shortened survival, which is independent of anti-T antibody titre.¹⁶ Moreover, although modern ABO typing reagents do not pick up polyagglutination caused by T-antigen activation, haemolytic transfusion reaction due to passive transfer of anti-T antibodies from donors to patients is rarely seen, even among high-risk groups.¹⁷ Anaemia in patients with pneumococcal HUS is also attributed to microangiopathic haemolysis as a result of endothelial damage and disseminated intravascular coagulation. The poorer outcome reported for these patients after urgent unmanipulated blood transfusion may simply reflect a more severe infection. Prospective studies comparing the use of washed versus unwashed RBCs for transfusion in pneumococcal HUS are required, and will have implications for reducing iatrogenic haemolysis and avoiding unnecessary transfusion delays.

This report shows that there is a significant difference in the aetiology of HUS between ethnic groups. Pneumococcal HUS is common in Chinese people, especially in the paediatric population. The acute clinical presentation is similar to that reported in Caucasian patients, except for an uncommon association with meningitis. The medium-term renal outcome appears to be more favourable in Chinese than Caucasian populations. Widespread vaccination against *S pneumoniae* may have resulted in changes in bacterial epidemiology. This calls for close monitoring for any increase in severe infection by previously uncommon serotypes that may necessitate changes in vaccination strategy. Finally, the rationale to use special blood components for transfusion in patients with pneumococcal HUS needs further study.

Acknowledgements

The authors thank the Hong Kong Red Cross Blood Transfusion Services for performing T-antigen activation tests and Dr Samson Wong, Department of Microbiology, Queen Mary Hospital, for providing incidence data on *Escherichia coli* (O157:H7) infection.

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