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Hemolytic Uremic Syndrome Complicating Invasive *Streptococcus pneumoniae* Infections: Tunisian Experience

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Abstract

Hemolytic uremic syndrome (HUS), characterized by the triad of micro-angiopathic hemolytic anemia, thrombocytopenia, and acute renal insufficiency, is a common cause of acute renal failure in children. It usually follows an episode of gastroenteritis with enterotoxigenic *Escherichia coli* and is termed typical HUS. However, HUS is also a complication of invasive pneumococcal infection. Reasons for not diagnosing this condition include the absence of a specific laboratory test, the lack of consistent case definitions, unfamiliarity, a misdiagnosis of disseminated intravascular coagulation (DIC), and cases with micro-angiopathic hemolytic anemia and only mild renal injury.

The aim of our study is to describe the epidemiology, the treatment and the evolution of HUS after invasive pneumococcal infections in Tunisia. Cases were identified between 2008 and 2016. Infection with *S. pneumoniae* was confirmed with culture of cerebrospinal fluid, pleural fluid, or blood. Eight children fulfilled our criteria for inclusion in the study. Primary patterns were fever, respiratory signs, neurological signs and uncommon patterns. Pneumonia was a presenting feature in 6 of 8 cases (75%), two patients had confirmed pneumococcal meningitis. Pneumococcal invasive infection was confirmed by positive yield for *S. pneumoniae* by culture in pleural levy or drainage in two cases, cerebrospinal fluid in two cases and blood in four cases. The mean duration of hospitalization was 23.5 days. Antibiotic therapy was initiated in all patients. Six patients from eight required dialysis for a median 27.8 days. No patients received plasma exchange therapy. Two patients died and. One patient with pneumococcal pneumatocele and presented a sepsis complicated with a nosocomial infection following a prolonged stay in the intensive care unit. One patient had bronchiectasis leading to recurrent broncho-pulmonary infections. One patient who was dialysis dependent at discharge died 4 months later.

Keywords: Infection; *S. pneumonia*; Hemolytic uremic syndrome; Renal failure; Dialysis

Introduction

Hemolytic uremic syndrome (HUS), characterized by the triad of micro-angiopathic hemolytic anemia, thrombocytopenia, and acute renal insufficiency, is a common cause of acute renal failure in children. It usually follows an episode of gastroenteritis with enterotoxigenic *Escherichia coli* and is termed typical HUS. However, HUS is also a complication of invasive pneumococcal infection. Early reports implied that this was a rare condition with a poor clinical outcome.

The incidence of HUS after invasive pneumococcal infections is as low but it is possible that pneumococcal HUS is underdiagnosed. Reasons for not diagnosing this condition include the absence of a specific laboratory test, the lack of consistent case definitions, unfamiliarity, a misdiagnosis of disseminated intravascular coagulation (DIC), and cases with micro-angiopathic hemolytic anemia and only mild renal injury.

The aim of our study is to describe the epidemiology, the treatment and the evolution of HUS after invasive pneumococcal infections in Tunisia.

Material and Methods

Cases were defined as those presenting with micro-angiopathic hemolytic anemia (Hb less than 10 g/dl with fragmented RBCs), thrombocytopenia (platelet count less than 130×10^9/l), and acute renal impairment with oliguria and elevated plasma creatinine for age associated with confirmed or suspected pneumococcal infection.

Cases were identified between 2008 and 2016. Infection with *S. pneumoniae* was confirmed with culture of cerebrospinal fluid, pleural fluid, or blood. Outcome data were collected and included hypertension (blood pressure 90 percentile for age and height), Proteinuria (quantitative proteinuria or urine dipstick analysis), and plasma creatinine level (umol/l) at the most recent clinic review.

Glomerular filtration rate (GFR) was calculated with the Schwartz Haycock formula. Disseminated intravenous coagulation was excluded. Complications resulting from pneumococcal infection were also identified.

Results

Clinical presentation

Eight children fulfilled our criteria for inclusion in the study. The median age at presentation was 16.6 months (range from 7 to 44 months). There were four boys and four girls (sex-ratio=1). Patients were all previously healthy and no one received anti-pneumococcal vaccination. Primary pattern was fever in 5 cases, respiratory signs in 5 cases, neurological signs in 2 cases and uncommon patterns (purpura, vomiting and abdominal pain). Median delay between primary signs onset and HUS was 8 days (range from four to twelve days)

Pneumonia was a presenting feature in 6 of 8 cases (75%), two patients had confirmed pneumococcal meningitis (Figure 1). T-antigen testing was not performed in all cases. However, in 7 cases pneumococcal infection was confirmed

(Table 1).

Figure 1: Site of Invasive Pneumococcal Disease
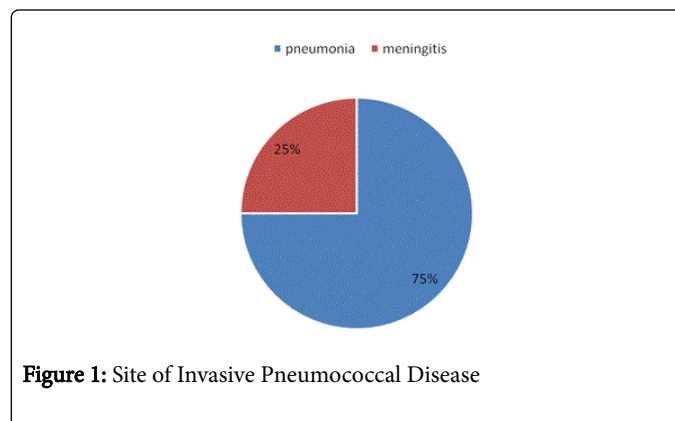
Patient No. (P)	Age Mo	Anti-Sp vaccina-tion	Gender	Peak SCr, Umol/l	Dialysis	Duration of Dialysis, d	Plasma therapy	Response	Hospital Duration, d	Death	Discharge SCr, Umol/l	Delay until remission	Outcome
1	10	No	Male	106	Yes	3	No	-	8	No	73	7 d	2mo, no CKD Baseline SCr 23 umol/l, Uprot =
2	18	No	Male	132	Yes	20	No	-	42	No	39	40 d	1y, peritonitis, baseline SCr 24 umol/l Uprot = 0
3	44	No	Female	103	Yes	13	No	-	26	No	37	14 d	3y, bronchiectasis, baseline, SCr 39 umol/l, Uprot =0
4	24	No	Female	87	No	-	No	-	18	No	18	5 d	NA
5	11	No	Male	242	No	-	No	-		No			3y, pneumatocele, nosocomial infection, psychomotor retardation, baseline SCr 34 umol/l
6	8	No	Female	280	Yes		No	-		Yes	-	-	-
7	7	No	Female	360	Yes	120	No	-		Yes	-	-	-
8	11	No	Male	346	Yes	11	No			No		12	4mo, no CKD baseline SCr38 umol/l ,subdural hematoma hemiparesia

Table 1: Clinical presentation.

The median maximum creatinine level (pre-dialysis) was 207 umol/l (range 87-346 umol/l). The median minimum hemoglobin level was 5.23 g/dl (range, 2.8-7.2 g/dl). Median minimum platelet count was 43 109/l. Coombs test was positive in four cases and blood smear showed schizocytes in all cases ranging from 1.5 to 5% (Table 2).

Patient No.	Hb nadir	Transfusion	Platelets nadir	Coombs test result	Blood smear % schizocytes
1	2.8	2	14000	+ IgG / C3d	1.5

2	6	1	15000	+ C3d	4
3	4.1	2	41000	Negative	5
4	6.2	1	75000	Negative	5
5	5.6	3	18000	Positive	yes
6	7.2	-	90000	Negative	yes
7	4	2	75000	Negative	yes
8	6	1	23000	Positive	yes

Table 2: Hematological signs.

Bacteriology

Pneumococcal invasive infection was confirmed by positive yield for *S. pneumoniae* by culture in pleural levy or drainage in two cases, cerebrospinal fluid in two cases and blood in four cases [Table 3]. All 7 isolates were fully susceptible to penicillin, cephalosporin, vancomycine and erythromycin. Serotype determination was not undertaken in all cases (Figure 2).

| Patient No.	Primary patterns	Onset	Primary Infection	Positive Culture*Site (s)	Antibiotherapy	DIC	Classification
1	Dyspnea	7 d	Pneumonia	Pleural levy	Penicillin A	NA	Proven
2	Fever seizures	10 d	Meningitis	CSF	3GC+Vancomycine	no	Proven
3	Dyspnea	12 d	Pneumonia	NA	3GC+Vancomycine+clarid	no	Probable
4	Fever abdominal pain	NA	Pneumonia	Pleural drainage	3GC then Penicillin A	no	Proven
5	Vomiting dyspnea prupura	4 d	Pneumonia	Blood	3GC	no	Proven
6	Fever productive cough	7 d	Pneumonia	Blood	3GC+vancomycine	no	Proven
7	Fever irritability	12 d	Pneumonia	Blood	3GC+Vancomycine	no	Proven
8	Fever dyspnea	7 d	Meningitis	Blood / CSF	3GC+vancomycine	no	Proven

Table 3: Bacteriological data.
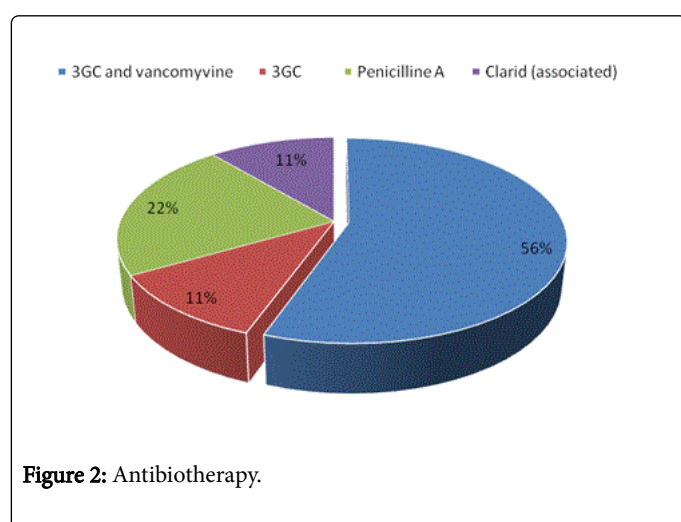
Figure 2: Antibiotherapy.

Treatment

The mean duration of hospitalization was 23.5 days. Antibiotic therapy was initiated in all patients. Five Patients were treated with the association Cefotaxime and vancomycine, one patient received only 3GC and two patient received penicillin A. Macrolids were associated once. Six patients from eight required dialysis for a median 27.8 days (range, 3-120 days).

No patients received plasma exchange therapy.

7 cases required transfusion at least once, four patients required two or more iterative transfusions. Of the patients who underwent transfusion, five of eight received leukocyte-depleted red blood cells. Whole blood transfusion was avoided in all patients.

None received platelets transfusion.

Renal biopsy was performed in one case. It showed thrombotic microangiopathy associated with extensive cortical necrosis (Masson's trichome stain).

Morbidity and mortality

Two patients died and. One patient with pneumococcal pneumatocele and presented a sepsis complicated with a nosocomial infection following a prolonged stay in the intensive care unit. One patient had bronchiectasis leading to recurrent broncho-pulmonary infections. One patient who was dialysis dependent at discharge died 4 months later.

Renal outcome

Mean discharge of serum creatinine median was 41 umol/l (range from 18 to 73 umol/l) and for patients whose evolution was favourable, median delay until remission was 15.6 days.

The median duration of follow-up was 18 months (range, 2-36 months). Estimated GFR was calculated for 5 patients. No patients had either hypertension or proteinuria on follow up and have chronic kidney disease on follow-up (Figure 3).
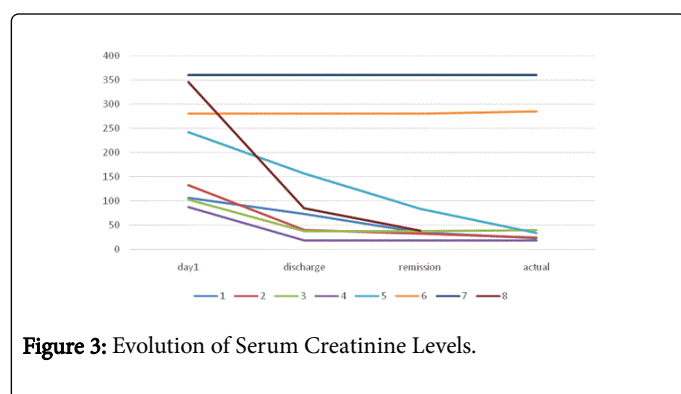

Figure 3: Evolution of Serum Creatinine Levels.

Neurologic outcome

One of the two patients with meningitis presented due to subdural hematoma during the acute phase of the illness, and leading to sequelar hemiparesia subsequently and the presented an ischemic cerebral stroke leading to transient focal neurological deficit. One patient presented a psychomotor retardation. Other patients had normal neurodevelopmental outcome.

Discussion

HUS complicating invasive pneumococcal infection was first described by Fischer and colleagues in 1971 [1]. Its incidence seems to increase in the last years reaching more than 5% of all HUS [2]. Reason of increasing prevalence is not clear. It affects mainly children under 2 years [3]. No gender predomination was reported [2,4]. In our study only one patient exceeded the age of 24 months. Delay between onset of pneumococcus-related symptoms and the development of HUS have been reported to range of one day to two weeks [5]. In our study it was eight days (range from four to twelve days).

Pneumonia is mostly the initial presentation [6] and meningitis is the second pattern. The diagnosis of HUS in our patients was made on the association of thrombocytopenia, micro-angiopathic anemia, renal insufficiency and blood smear showing schizocytes. Detection of red cell T-antigen activation was not performed in the patients because the tests were not available in Tunisia. Serotype determination was not undertaken in all cases. But concomitant IPD was confirmed in seven cases at least in one site.

Treatment of *S. pneumonia* associated HUS is aimed at supportive care and treatment of underlying infection. Plasmapheresis has been advocated in the guideline. It is meant either to remove neuraminidase and anti-T antibodies or replacement of a deficient host factor [7]. This should be undertaken only in specialized pediatric nephrology centers. Plasma exchange was planned for all our patients but was undertaken in none in one study due to lack of resources. Generally reports indicated that *S. pneumonia* HUS is associated with a poor outcome [1]. In this rare condition patients are more likely to require dialysis (range 75% to 100). Dialysis is the appropriate issue to solve hyperuremia [8].

In the largest series (14 patients) from a single center collected in the pediatric nephrology department in Philadelphia between April 1988 and May 2009: Sixty-four percent of the patients recovered without any long-term sequelae. Three patients developed chronic kidney disease, 1 developed end-stage renal failure, and 1 died in the acute phase [4]. In our study, six patient required dialysis therapy for the management of acute renal failure and the duration was around 3 to 20 days. No one of our patients developed chronic kidney disease and all the survivors recovered totally without any sequelae.

In recent years, the morbidity and mortality rates have declined dramatically .it may be the result of advances in critical care management.

Mortality is higher (12%) than in the typical HUS, as it cumulates both prognosis of HUS and IPD. Other authors report an overall mortality rate of 13% in P-HUS comparing to 1.8% for typical HUS [9].

Death usually occurs during the acute illness and may be caused by complications of severe infection rather than to renal failure directly [10]. Our findings were different: Two patients died; the first presented a sepsis complicated with a nosocomial infection the second was dialysis dependent at discharge.

We reported a higher 25% overall mortality rate due to a reduced number, despite a comparative 7 day delay of management after onset. Literature report a higher mortality in the P-HUS patients due to meningitis subgroup reaching 88%, [11-13] in our series 100% of deaths occurred in patients with pneumonia.

Conclusions

Due to the impossibility of making precised diagnosis, the difficulty of reassembling the necessary criteria and certainly at the lack of specific paraclinical arguments. Authors continue to contribute to create consistent case definition by reassembling an amalgam of a series of an interweaving canon. Otherwise the introduction of the pneumococcal vaccine is surely benefic in reducing pneumococcal HUS among other IPD. We recommend the inclusion of the vaccine in future national immunization schedule as well as using expanded-valence vaccines to prevent this rare but potentially devastating complication.

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