Pediatr Nephrol (2001) 16:362–365

ORIGINAL ARTICLE

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Prognosis of *Streptococcus pneumoniae*-induced hemolytic uremic syndrome

Received: 27 July 2000 / Revised: 18 December 2000 / Accepted: 19 December 2000

Abstract *Streptococcus pneumoniae*-induced hemolytic uremic syndrome (HUS) is known to be a severe acute disease leading to death in one-third of cases, but data regarding the long-term follow-up are lacking. A new series of 11 patients with *Streptococcus pneumoniae*-induced HUS associated with meningitis and pneumonia constituted a multi-center review. Among 9 patients with a severe acute infectious disease, 3 died from meningitis and 1 from neurological sequelae after a partial recovery of renal function. The mean duration of dialysis was 32 days in patients with acute renal failure who survived the acute infectious period. Cortical necrosis was documented in five of six kidney specimens. Among the 7 surviving patients, 5 developed end-stage renal failure 4–17 years later.

Keywords Hemolytic uremic syndrome · *Streptococcus pneumoniae* · Meningitis · End-stage renal failure · Dialysis

Introduction

Hemolytic uremic syndrome (HUS) is the clinical hallmark of renal endothelial injury. It is characterized by microangiopathic hemolytic anemia that is associated with renal failure [1]. HUS may follow a chronic or relapsing course, as seen in factor H deficiency, methylmalonic aciduria and homocystinuria due to intracellular vitamin B_{12} deficiency, hereditary and unknown origins, or it may have an acute onset preceded by an infectious disease, such as verotoxigenic *Shigella* or *Escherichia coli* colitis, or invasive *Streptococcus pneumoniae* infection. In the latter, endothelial damage is due to streptococcal neuraminidase activity and exposure of crypted Thomsen-Friedenreich antigen leading to the adsorption of natural circulating agglutinins.

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The clinical description of the primary period of both types of acute HUS is well known [2, 3]. Renal sequelae due to nephron reduction can be observed in patients with verotoxigenic *E.coli*-induced HUS [2], but no data exist regarding the long-term renal function of patients with *S. pneumoniae*-induced HUS [4, 5]. The aim of this work was to study a new series of patients with *S. pneumoniae*-induced HUS with special attention to the long-term follow-up.

Materials and methods

A questionnaire was sent to the general pediatrics and pediatric nephrology units involved in the French Society for Pediatric Nephrology in order to record cases of *S. pneumoniae*-induced HUS. HUS cases were included in the series when *S. pneumoniae* was either isolated from blood or cerebrospinal fluid culture or evidenced by soluble antigens. The questionnaire asked (1) the criteria for HUS: acute onset, anemia with erythrocyte fragmentation (schistocytes), thrombocytopenia, and renal injury evidenced by increased plasma creatinine; (2) dialysis duration and characteristics of blood transfusion. The characteristics of histological examination were recorded when renal samples could be obtained. Liver, pancreas, or brain involvement during the early phase was also recorded. Long-term renal impairment was evaluated by measurement of blood pressure, proteinuria, and plasma creatinine at the last follow-up. The questionnaire also asked for neurological or lung sequelae.

Results

Eleven patients with *S. pneumoniae*-induced HUS were registered over a period of 23 years (1975–1998) in 11 of the 36 pediatric units (11 general units and 25 nephrology units) that sent back the questionnaire. Age at presentation ranged from 1.5 to 39 months (mean 13 months) with a male/female ratio of 4:7. The type of acute infectious disease is presented in Table 1. *S. pneumoniae* was isolated from cerebrospinal fluid in 8 patients, 3 of whom also had a positive blood culture. Two patients had only a positive blood culture and the last patient had positive plasma soluble antigen. None of the isolated strains was resistant to β-lactam.

Table 1 Summary of recorded patients (*RBC* red blood cells, *TMA* thrombotic microangiopathy, *CRF* chronic renal failure, *ESRF* end-stage renal failure, *NA* not applicable, *ND* not determined)

	Age (months)	Year	Sex	Disease	Blood culture	Blood transfusion	Duration of dialysis (days)	Kidney biopsy	Outcome	Follow-up (years)
1	39	1998	F	Pneumonia	+	Unwashed RBC	30		CRF (serum creatinine 100 µmol/l)	0.75
2	21	1994	F	Pneumonia	ND	Unwashed RBC	0		Recovery	4
3	10	1975	F	Meningitis	+	ND	10	TMA	Died day 10	NA
4	8	1986	M	Meningitis	ND	Washed RBC	2		Died day 2	NA
5	8	1991	M	Meningitis	ND	Unwashed RBC	30	TMA, cortical necrosis	Died 3 months	NA
6	7	1994	F	Meningitis	+	Unwashed RBC	23	TMA, cortical necrosis	ESRF 4 years	4
7	6	1982	F	Pneumonia, meningitis	ND	Unwashed RBC	44	TMA, cortical necrosis	ESRF 11 years	17
8	7	1994	M	Meningitis	ND	Unwashed RBC	41	TMA, cortical necrosis	ESRF 4 years	4
9	9	1976	M	Meningitis	+	ND	0		Recovery	0.5
10	1.5	1996	F	Meningitis	ND	Unwashed RBC	10	TMA, cortical necrosis	Died day 10	NA
11	27	1999	F	Pneumonia	+	Washed RBC	25		CRF (serum) creatinine 130µmol/l	2

All patients had erythrocyte fragmentation with severe hemolytic anemia (mean hemoglobin 5 g/dl, range 2.5–7.7 g/dl) and schistocytosis (mean 5.4%, range 2.5%–10%). Blood transfusions were performed in the 11 patients using washed red blood cells in 2 patients, unwashed red blood cells in 7, and undefined in 2. Of the 11 children, 9 had severe acute renal failure and required peritoneal dialysis or hemodialysis. The 6 patients who survived the initial period were dialyzed between 23 and 44 days (mean 32 days). Six biopsy specimens showed thrombotic microangiopathy, which was associated with cortical necrosis in 5.

Five patients developed chronic renal failure and 3 progressed to end-stage renal failure 4–11 years after the acute episode. Of these 3 patients, 2 had cortical necrosis on renal biopsy. One patient has been grafted for 6 years and currently has normal renal function. Two patients easily recovered from a mild early phase and had neither renal (blood hypertension or proteinuria) nor neurological sequelae at 4 months and 4 years of follow-up.

Three patients died after 2–10 days of dialysis from meningitis. One patient suffering from hypertension, proteinuria, and renal failure died 3 months after the acute infectious disease from neurological sequelae. One additional patient developed hydrocephaly. No pulmonary sequelae were observed in the 4 patients with pneumonia. Extrarenal HUS complications were observed in 2 patients with hepatitis; 1 of them developed pancreatitis.

Discussion

Antigens of the endothelial surface are made of complex carbohydrate residues substituted and hidden by neuraminic acid (sialic acid). Thomsen-Friedenreich (TF) antigen is a dissacharide that is masked by sialic acid and is a cryptic component of the erythrocyte group MN tetrasaccharides [6]. All serotypes of *S. pneumoniae* can have neuraminidase activity able to unmask the TF antigen. Patients with *S. pneumoniae*-induced HUS have detectable serum neuraminidase activity, while patients with pneumococcal infection without HUS features do not have detectable activity [7]. The presence of natural antibodies against the TF antigen is seen in humans beginning in infancy [4]. These circulating agglutinins are adsorbed on unmasked TF antigens exposed on endothelial cells, platelets, and erythrocytes, and induce hemolysis and endothelial damage [4, 5, 6, 7, 8]. The severity of meningitis is also probably related to the exposure of TF antigen within the central nervous system [9].

We report a series of 11 patients with *S. pneumoniae*-induced HUS. Although our cases were not diagnosed by direct evidence of TF antigen on red blood cells, the association between hemolytic anemia due to erythrocyte fragmentation, acute renal failure, and bacteriological evidence of pneumococcal infection is sufficient for the diagnosis of *S. pneumoniae*-induced HUS [10]. In addition, thrombotic microangiopathy, which is the histologi-

cal hallmark of HUS, was observed in six of the six kidney biopsies in our patients.

S. pneumoniae-induced HUS is a rare disease, since 25 from the 36 pediatric nephrology units that participated in the study did not record any cases. Only 29 cases are reported in the literature [3, 4, 5, 8, 11, 12], in addition to the 11 cases described in this paper. *S. pneumoniae*-induced HUS is rare compared with verotoxigenic *E.coli*-induced HUS. Of our 11 cases, 8 were primarily observed in France during the period 1975–1998, while the French incidence of verotoxigenic *E.coli*-induced HUS has been measured at a stable level of 100 cases per year between 1992 and 1997 [13]. Our series displayed a mortality rate of 36%, which was quite similar to the 8 fatal causes reported in the 29 patients in the literature (28%). Most of these patients died during the early phase of the disease from severe infections and neurological complications. Thus, HUS is certainly associated with the most-severe forms of pneumococcal disease, as the rate of death following overall invasive pneumococcal disease has been reported to vary between 1% and 8.6% in children from developed countries [14, 15, 16].

Information on long-term follow-up of surviving patients is not available in the literature, except for 2 patients having proteinuria and chronic renal failure 1 and 3 years following the acute disease [4]. Our series showed that a majority of our surviving patients were exposed to the risk of end-stage renal failure. This secondary progression of the renal disease was probably related to a severe nephron reduction due to a widespread initial cortical necrosis. These data have to be compared with the prognosis of verotoxigenic *E.coli*-induced HUS in French series, which is a 1.1% mortality rate [13] and 18% chronic renal failure [2]. End-stage renal failure was observed in 14% and 20% of two pediatric series of *E.coli*-induced HUS with a long-term follow-up of over 10 years after the acute disease [17, 18]. However, under-reporting of mild forms of *S. pneumoniae*-induced HUS could not be discounted in a retrospective study.

Most of our patients were transfused with unwashed red blood cells, which contain uncertain amounts of natural agglutinins against TF antigen and could worsen the disease. The type of blood transfusion is mentioned for 6 patients in the literature [3, 4, 8, 19]. Of these 6, 1 died early despite blood transfusions with washed red blood cells. Seven of our patients received unwashed red blood cells and none was reported to have received fresh-frozen plasma. Patient 2 received only 1 unit and did not exhibit a life-threatening disease or a worsening of hemolytic anemia. No special complication was noticed in the 6 other patients. Despite a theoretical risk, an adverse effect of unwashed blood transfusions containing limited amounts of plasma remains to be demonstrated in *S. pneumoniae*-induced HUS. Conversely, the use of fresh-frozen plasma or plasma products was associated with increased hemolysis [20], and exchange transfusion using a large volume of blood had to be performed with washed blood units [21].

In conclusion, pneumococcal infections are a rare cause of infection-induced HUS compared with verotoxigenic *E.coli*-induced HUS. The early and the late phases of most patients with *S. pneumoniae*-induced HUS have a poor prognosis, which is not similar to the prognosis of verotoxigenic *E.coli*-induced HUS. Paradoxically, a minority of patients develops only a mild disease without long-term consequences. Further work on the long-term prognosis of this disease should utilize a registry, in order to follow prospectively a large number of cases.

Acknowledgements We thank the physicians who devoted time to filling out the medical questionnaire for the 11 patients: E. Berard (Nice, France), A. Bourkia (Casablanca, Morocco), G. Elana (Le Lamentin, Martinique), M. Foulard (Lille, France), M.F. Gagnadoux (Paris, France), J. Gaudelus (Paris, France), G. Landthaller (Rouen, France), C. Loirat (Paris, France), H. Nivet (Tours, France), G. Picon (Marseille, France), W. Proesmans (Leuwen, Belgium).

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LITERATURE ABSTRACTS

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High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation

J Am Soc Nephrol (2000) 11:1093–1099

Kidney transplantation corrects most of the metabolic abnormalities that cause renal osteodystrophy. However, many transplanted patients develop osteoporosis and other bone lesions that are related, at least in part, to their immunosuppressive regimen. The precise histologic patterns of bone disease after transplantation are not well defined. In a study designed to investigate this issue, 57 adult posttransplant patients agreed to undergo bone biopsies and blood drawings. There were 32 men and 25 women, mean age 45±2 yr, who had received a kidney transplantation 5.6±0.8 yr before biopsy. History of bone pain, fractures, and avascular necrosis was found in 22, 12, and 7 patients, respectively. Serum creatinine was 1.68±0.1 mg/dl, 21% of patients were hypercalcemic, 63.2% had elevated parathyroid hormone (PTH) (>65 pg/ml), and 91.2% had normal calcitriol levels. Cancellous bone volume/tissue volume was below normal compared to age- and gender-matched control subjects in 56.1% of patients. Bone turnover (activation frequency) was low in 45.6%, normal in 28.1%, and elevated in 26.3% of patients. Bone formation rate/bone surface was low in 59.7%, normal in 35%, and elevated in 5.3% of the patients. Erosion surface/bone surface was high in 21.1% of patients. Mineralization was prolonged in 87.5% of patients, including 9 patients with osteomalacia and 12 patients with focal osteomalacia. Cumulative and maintenance doses of prednisone and time elapsed since transplantation correlated negatively with bone volume and bone turnover (r=–0.32 to –0.59, P<0.05 to 0.01), whereas cumulative doses of cyclosporine or azathioprine, age, gender, or serum PTH levels did not. Regression analysis identified prednisone as the main factor responsible for low bone volume and bone turnover (r=0.54 and r=0.43, P<0.01). No factors were found to predict delayed mineralization. The present study shows that low bone volume, low bone turnover, and generalized or focal osteomalacia are frequent histologic features in transplanted patients. The effects of age, gender, PTH, and cyclosporine on bone volume and bone turnover are apparently overridden by the prominent effects of glucocorticoids. The prevalence of mineralization defect in the presence of normal serum levels of calcidiol and calcitriol suggests vitamin D resistance and deserves further study.

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Clinical and genetic studies of CLCN5 mutations in Japanese families with Dent disease

Kidney Int (2000) 58:520–527

Background Dent disease is an X-linked renal tubular disorder that is characterized by low molecular weight proteinuria, hypercalciuria, nephrolithiasis, and renal failure. The disease is caused by inactivation of a renal chloride channel gene, CLCN5, that encodes a 746-amino acid protein with 12 to 13 transmembrane domains. The Japanese variant of Dent disease has been observed to be less severe, and we have investigated two unrelated Japanese families for CLCN5 mutations.
Methods Six patients from two unrelated families were studied. Leukocyte DNA from probands was used with CLCN5-specific primers for polymerase chain reaction (PCR) amplification of the coding region and exon-intron boundaries, and the DNA sequences of the products were determined to identify abnormalities in the gene. RNA extracted from the kidney, leukocytes, or urine sediments was used to characterize further the effects of the identified mutations.
Results β2-microglobulinuria was detected in five patients, hypercalciuria in two patients, nephrolithiasis in three patients (2 of whom were females), and one 51-year-old man had renal failure. Two novel CLCN5 mutations consisting of an a to g transition at the invariant ag acceptor splice site of intron 5 and an intragenic deletion that encompassed the region between intron 3 and intron 6 were identified. The acceptor splice site mutation led to the utilization of two alternative cryptic splice sites in exon 6 that resulted in a frameshift or skipping of the exon 6. The deletional mutation, which resulted in a loss of exons 4, 5, and 6, is predicted to lead to a loss of domains 1 through 4. Both mutations predict truncated chloride channels that are likely to result in a functional loss.
Conclusions The observations of renal failure in one male and nephrolithiasis in two females represent important new findings in this Japanese variant of Dent disease that is associated with CLCN5 mutations. In addition, our study is the first to demonstrate the use of urinary sediment cells and renal tissue for the detection of CLCN5 transcript abnormalities. These results help to expand the spectrum of CLCN5 mutations associated with Dent disease.