Heterogeneity of atypical haemolytic uraemic syndromes

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Abstract

Atypical, non-diarrhoea associated haemolytic uraemic syndrome (D-HUS) is a heterogeneous disorder with a generally poor outcome, although this view has now been questioned. The clinical and laboratory features of 23 children with D-HUS, representing a third of all patients with HUS seen during the last 26 years, were examined. The median age was 4.9 years (range 3 days–13.8 years). Twenty one children (91%) survived the initial phase. All patients except six infants aged <18 months required dialysis (74%). Hypertension (43%), cardiomyopathy (43%), and cerebral convulsions (48%) were common. Nineteen (83%) children were followed up for a median period of 5.5 years (range 0.5–23.4). Only five (26%) patients, among them four infants, recovered completely. Six (32%) patients had one to 10 recurrences, including two siblings with neonatal onset, and eight (42%) developed end stage renal failure. Five children underwent cadaveric renal transplantation, with recurrence and subsequent graft failure in two. Four children died, resulting in an overall mortality of 26%. Atypical HUS is heterogeneous with regard to epidemiology, pathophysiology, and outcome. Children with a recurrent, familial, or neonatal course have worse outcomes; in contrast, infants not requiring dialysis in the acute phase have a better prognosis.

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Gasser *et al* first used the term 'haemolytic uraemic syndromes' (HUSs) in 1955.¹ They reported five children from our institute with microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal failure. Two of their patients had prodromal diarrhoea and two had pleuropneumonia; one patient had no prodrome. The plural form of HUS ('Syndrome' in German) was deliberately used in anticipation of the epidemiological, clinical, and pathophysiological heterogeneity of the disease. The current concept divides the HUSs into two major types: one is associated with a prodromal diarrhoea (D+HUS) and the other without diarrhoea (D-HUS).^{2–5}

Most paediatric cases are D+HUS, affecting mostly younger children and generally having a good prognosis.^{3–13} D-HUS or atypical HUS is less common and is itself heterogeneous¹⁴:

some are familial,¹⁵ some are recurring,¹⁶ some have a neonatal onset,¹⁷ and some are related to neuraminidase producing microbes.¹⁸ D-HUS is generally associated with a greater morbidity and mortality than D+HUS.^{3–10 13} So far, only two studies have been confined to D-HUS: one from London confirmed the worse outcome in D-HUS,¹⁹ whereas the other from Utah, USA, reported that children with D-HUS had a milder nephropathy and did not have poorer outcomes.²⁰

Between 1970 and 1995 inclusive, 66 children with HUS were referred to our institute; 43 (65%) had prodromal diarrhoea and 23 (35%) did not. This paper reports the large clinical heterogeneity of patients with D-HUS, ranging from mild acute nephropathy with subsequent complete recovery to a familial, recurring course with neonatal onset and fatal outcome.

Patients and methods

The HUS was defined as the simultaneous and acute occurrence of microangiopathic haemolytic anaemia, thrombocytopenia, and renal failure. In children with D+HUS, verocytotoxin producing *Escherichia coli* (VTEC) have been examined in stool specimens since 1990²¹; eight of 20 samples were positive. Peritoneal dialysis or haemodialysis was performed in oliguric children unresponsive to diuretics or in the presence of severe electrolyte or acid-base disturbances. Plasma exchange, using the filtration technique, has been administered to all patients with D-HUS since 1992. The volume exchanged was 40 ml/kg body weight; a purified protein fraction was used and an infusion of fresh frozen plasma was given at the end of the treatment if plasma fibrinogen was <1 g/l. Cardiomyopathy was defined as heart failure requiring the use of inotropes. A short course of immunosuppressive or cytotoxic drugs was given to two patients (azathioprine/prednisone and vincristine, respectively). Histological examination of renal tissue was available during the acute phase in eight children.

Nineteen children with D-HUS were regularly followed up either by us or by the local paediatrician. Re-evaluation included any signs of clinical and laboratory evidence of recurrence, renal function (as assessed by plasma creatinine), blood pressure,²² and urine analysis (haematuria, normal <10 erythrocytes/ μ l; and proteinuria, normal <1+ on albusix and/or protein:creatinine ratio <20 g/mol). Normal plasma creatinine (μ mol/l) was defined according to age: <40 ($\leq$ 4 years), <50 (>4–6 years), <60 (>6–10 years), <70 (>10–12 years), and <90 (>12 years). Complete recovery was

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Table 1 Clinical characteristics of 23 patients with D-HUS

Age at presentation	No of patients	Acute dialysis	Long term follow up	Complete recovery	ESRF* (initial episode)	Death (initial episode)	Recurrence	Familial
< 1 month (neonates)	3	2	3	1	2 (0)	1 (0)	2	2
1-18 months (infants)	6	1	4	3	0	0	0	0
> 18 months	14	14	12	1	6 (5)	5 (2)	4	0
Overall	23	17	19	5	8	6	6	2

* ESRF = end stage renal failure.

defined as the absence of recurrence and normal findings of plasma creatinine, blood pressure (without drugs), and urine analysis. Sequelae were defined as mild (normal plasma creatinine in the presence of hypertension or abnormal urine analysis, or both), moderate (increased plasma creatinine), or severe (end stage renal failure).

STATISTICAL ANALYSIS

Data between two groups were compared with the unpaired Student's *t* test or Mann-Whitney test, where appropriate. Fisher's exact test was used to compare categorical variables.

Results

ACUTE PHASE (≤3 MONTHS)

The median age of the 23 children with D-HUS (12 girls) was 4.9 years (range 3 days–13.8 years). All presented at admission with renal failure (median plasma creatinine 566 µmol/l) and anaemia (packed cell volume 0.18); 22 were thrombocytopenic ($46 \times 10^9/l$). The urine samples showed haematuria and proteinuria in 20 patients; three were anuric at admission. Twenty one of 23 children (91%) survived the acute phase. Seventeen patients (74%) were dialysed: 10 (including the two children who died) had temporary dialysis for 5–122 days (median 28 days) and seven (30%) subsequently required long term dialysis. Six children, all infants aged <18 months, required no dialysis (table 1). Seven patients, all requiring dialysis, underwent plasma exchange: only one recovered completely; two had moderate sequelae and four developed end stage renal failure.

Ten children (43%) were hypertensive. Cerebral convulsions occurred in 11 (48%); six were also hypertensive and their median plasma sodium concentration was 132 mmol/l (range 119–144), which was slightly lower than in those without convulsions (median 135 mmol/l, not statistically significant). At discharge, 19 of the 21 surviving children had a normal neurological assessment, but two children with severe convulsions had developed spastic tetraparesis. Cardiomyopathy was present in 10 (43%) children. One patient developed transient diabetes mellitus requiring insulin treatment for one week. Both children with an early fatal course had convulsions and cardiomyopathy.

Infections were present in 11 children (48%). Neuraminidase producing *Streptococcus pneumoniae* was the causative organism in two (one with meningitis, one with pneumonia). A female neonate aged 12 days had HUS associated with (non-verocytotoxin producing) *E*

coli. Cultures of cerebrospinal fluid and blood were positive, whereas urine and stool cultures remained negative. Infections probably not related to the HUS were present in eight patients, upper respiratory tract infection in seven, and florid chickenpox in one.

LONG TERM OUTCOME

Nineteen (91%) of the 21 surviving children were regularly followed up for a median period of 5.5 years (range 0.5–23.4). Only two infants not requiring dialysis could not be located; at discharge their plasma creatinine had almost returned to normal. Five children (26%) recovered completely, including three infants and one neonate who had not received acute dialysis. Of the eight children who had required acute dialysis, only one showed complete recovery, five had moderate sequelae (three were also hypertensive), and two boys died, one during the third episode of HUS and one of end stage renal failure six months after a *S pneumoniae* meningitis.

End stage renal failure

Eight children (42%) developed end stage renal failure, five after the initial attack and two siblings after a recurrent course. Of the seven children undergoing long term renal replacement treatment, two died, resulting in an overall mortality of 26% (six of 23; table 1). Five children had cadaveric renal transplantation.

Recurrence

Six (32%) of the 19 children followed up had recurrent HUS, two of them after plasma exchange. Two brothers, born 1.9 years apart, had a neonatal onset with the first episode on the third and fourth day of life, respectively. The elder sibling required acute dialysis at the second to fourth attack and developed end stage renal failure after the fifth episode at the age of 6 months. During the next two years he had five further haematological episodes with anaemia and thrombocytopenia. He is currently 6 years old and is maintained on peritoneal dialysis. His younger brother required dialysis for end stage renal failure after the fourth episode at the age of 5 months. He had a further haematological episode within 8 months and died at 13 months of hyperkalaemia. Complement deficiency²³ and methylmalonic acidemia and homocystinuria (CBLC phenotype)²⁴ were excluded.

Two further children had recurrences. One boy (aged 9.7 years) had three episodes within five months, requiring dialysis only during the fatal third episode. The other boy had two episodes within two months. During the initial

Table 2 Published series of D-HUS, including present paper. Values are numbers of patients

Reference	HUS (D+ and D-)	D-HUS (% HUS)	ESRF*	Death	Recurrence	Familial	Complete recovery
Milford <i>et al</i> ⁶	288	15 (5)	4	3	?	1	3/14†
Loirat <i>et al</i> ⁸	161	14 (9)	6	1	6	3	0/13†
Imoberdorf <i>et al</i> ⁷	42	7 (17)	2	2	1	2	?
Tönshoff <i>et al</i> ¹⁰	89	21 (24)	1	10	3	3	?
Kelles <i>et al</i> ¹¹	95	12 (13)	1	2	0	0	3/10†
Wende-Fischer <i>et al</i> ¹³	61	13 (21)	6	4	7	0	?
Fitzpatrick <i>et al</i> ¹⁹	192	20 (12)	4	5	11	1	2/19†
Siegler <i>et al</i> ²⁰	287	22 (8)	2	0	4	2	8/15†
This paper	66	23 (35)	8	6	6	2	5/19†
Overall (%)	1281	147 (11)	34 (23)	33 (22)	38 (26)	14 (10)	21/90† (23)

* ESRF = end stage renal failure.

† Number of patients followed up long term.

episode (aged 12 years) he had acute dialysis and plasma exchange for 10 days. During the second episode, requiring dialysis for two weeks, he began long term plasma exchange, with 53 exchanges during the next 15 months without any further recurrence.

Recurrence in the patients who had a transplantation occurred in two patients, resulting in immediate graft loss in a girl on day 1 and after four years in a boy. The girl is still maintained on haemodialysis, whereas the boy died three years later of heart failure. Neither of them had received cyclosporin.

Renal histology

All eight biopsy samples, taken in the acute phase, showed a thrombotic microangiopathy. Glomerular and arteriolar lesions were present in six patients: three developed end stage renal failure, including two brothers; two had moderate sequelae; and one (a neonate) recovered completely.

COMPARISON WITH D+HUS

All 43 cases of D+HUS were sporadic and there was no outbreak. The median age of D+HUS (19 girls) was significantly lower at 1.1 year (range 0.3–7.4, $p < 0.005$). The initial clinical and laboratory presentation was not significantly different, however. Forty children (93%) survived the acute phase and three died. Thirty one children (72%) required acute dialysis. All patients were in renal failure (median plasma creatinine 382 $\mu\text{mol/l}$) and were anaemic (packed cell volume 0.18); 39 were thrombocytopenic ($49 \times 10^9/\text{l}$) and 11 (26%) were hypertensive. Sixteen (37%) experienced cerebral convulsions, three suffered (fatal) cardiomyopathy (7%, $p < 0.002$) and five (12%) developed intussusception. Thirty four (85%) of the surviving patients were followed up for a median period of 3.5 years (range 0.3–13.9): 56% recovered completely, whereas 12 and 32%, respectively, had mild and moderate sequelae. End stage renal failure, recurrence, or a HUS related death were not observed (all $p < 0.05$). Nine of 10 children without dialysis made a complete recovery, in contrast with only 10 of 24 of the children who underwent dialysis.

Discussion

The current concept divides childhood HUS into postdiarrhoeal D+HUS and non-diarrhoeal or atypical D-HUS.^{2–5} D+HUS

accounts for >80% of paediatric cases, mostly infants and young children,^{3–13} and most cases of D+HUS are caused by VTEC.²⁵ D+HUS is generally associated with a good prognosis.^{3–13} There remains, however, a considerable mortality of up to 10% during the acute phase and the risk of renal failure 15 years later after seemingly cured HUS is not negligible.²⁶

Atypical HUSs, in contrast, comprise a heterogeneous group of various epidemiology, pathophysiology, and outcome.¹⁴ D-HUS is generally associated with a greater morbidity and mortality than D+HUS,^{3–10 13 19} as it was in our series (table 2). Two publications have reported a similar outcome in D-HUS and D+HUS, however.^{11 20} It is noteworthy that the patients from Utah²⁰ had an unusually mild course during the acute phase, with only 21% requiring dialysis, which is far less than in the other series, ranging from 53 to 80%.^{6 8–10 13 19} A full third of our patients with HUS had D-HUS, which is higher than previously quoted,^{3–13 19 20} except for an Italian study (34% D-HUS).²⁷ The absence of D+HUS outbreaks and epidemics in our referral area partly accounts for the high percentage of patients with D-HUS.

A subgroup in our series, seven infants aged <18 months with non-familial HUS, showed a remarkably good outcome: only one required acute dialysis and three of four with long term follow up recovered completely. The age at presentation and benign outcome mimicked the pattern of D+HUS associated with VTEC. VTEC was not routinely searched for in patients with D-HUS and only one child had a documented *E coli* (non-verocytotoxin producing) infection. In fact, the Italian HUS study group has reported that 55% of children with D-HUS were positive for a VTEC infection and that VTEC positivity predicted a good outcome, independent of the presence of diarrhoea.²⁷

Recurrence is common in D-HUS, in particular in association with familial and neonatal cases.^{8 13 15 16 19 20} Familial occurrence accounts for approximately 10% of cases of D-HUS and the prognosis is often poor.^{8 10 15} Neonatal D-HUS represents a rare subgroup^{8 17 28–30} and its familial occurrence is associated with a worse outcome.^{8 28} Rare hereditary, autosomal recessive disorders, excluded in our patients, have been identified in a few families: hypocomplementaemia,^{20 23 31 32} methylmalonic aciduria, and homocystinuria

due to intracellular vitamin B12 deficiency (CBLC phenotype),^{24 33 34} and collagen type III glomerulopathy.³⁵ Recurrence has also been reported in 10 of 11 patients after an apparently successful plasma exchange treatment in the acute phase.¹⁹ Plasma exchange was less successful in our small series of seven patients. Four developed end stage renal failure and two had recurrences.

The risk of recurrence after transplantation in patients with D-HUS (and the role, if any, of cyclosporin) is still a matter of debate. The European Dialysis and Transport Association registry, including D+HUS and D-HUS, quoted a recurrence rate of 10% in children³⁶ and only one study showed a higher recurrence rate.³⁷ No recurrence was reported in two publications on classical D+HUS.^{38 39} A few series of sporadic recurrence of D-HUS after transplantation have been reported, however,^{13 19 20 39} and patients with a recurrent course before transplantation may run a higher risk.^{19 20}

A further distinct subgroup of patients with D-HUS is associated with neuraminidase producing micro-organisms.¹⁸ The poor prognosis may be improved with prompt recognition and appropriate treatment.⁴⁰

The renal biopsy sample findings in our small series were not conclusive with respect to their prognostic implications as arteriolar lesions were shown in children with both subsequent recovery and end stage renal failure. Extensive arteriolar involvement has been shown to be associated with D-HUS and an impaired outcome.³

We conclude that atypical or D-HUSs represent a heterogeneous group of various epidemiology, pathophysiology, and outcome. Children with D-HUS who require dialysis in the acute phase, and in particular children with a recurrent, familial, or neonatal course, have poorer outcomes. A subgroup of (young) patients presenting with a mild nephropathy and not requiring dialysis has a good prognosis, however.

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