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Haemolytic–uraemic syndrome in Western Australia, 1980 to 1994

Carol Cameron, Michael Gracey and Andrew G. Penman
Health Department of Western Australia, Perth

Abstract: A retrospective, population-based study of patients hospitalised with the haemolytic–uraemic syndrome in Western Australia from 1980 to 1994 was undertaken to describe the epidemiology of the disease in this state. We identified 41 patients. Episodes were commonest in children under five years of age (63.4 per cent) and were more frequent in females (58.5 per cent) than in males; only one Aboriginal patient was detected. More than 90 per cent of episodes had a gastrointestinal prodrome lasting from one to 22 days; in 47.6 per cent of these episodes patients had bloody diarrhoea. The average hospital stay was 26 days, and 63.4 per cent of patients required dialysis (mean 10 days). More than 20 per cent of patients developed chronic renal failure, 9.7 per cent died, two patients developed hypertension and one child became epileptic; three of the 10 patients over 16 years of age (30 per cent) died. The haemolytic–uraemic syndrome is potentially fatal, affects mostly young children, and is usually preceded by a gastrointestinal illness. Episodes can occur in common-source outbreaks but, with the exceptions of related cases in families, that appears not to have been so in Western Australia since 1980. There is a need for increased awareness of the haemolytic–uraemic syndrome to enhance prospects for earlier detection and better clinical outcomes. Improved public health surveillance is also needed to reduce the risks of the syndrome in the community. (*Aust N Z J Public Health* 1996; 20: 462–6)

THE haemolytic–uraemic syndrome comprises a triad of concurrent features: microangiopathic haemolytic anaemia, thrombocytopaenia and acute renal failure,[1–4] and may have infectious and noninfectious causes.[3] In 1983 Karmali et al. isolated a verocytotoxin-producing strain of *Escherichia coli* from patients with the haemolytic–uraemic syndrome in Canada.[5] Since then, epidemiological studies in many countries have investigated a possible link between the verocytotoxin-producing strain (which produces a Shiga-like toxin[1]) and haemorrhagic colitis and the haemolytic–uraemic syndrome, and found such a link.[6–16] Outbreaks of the haemolytic–uraemic syndrome have been recorded in the United Kingdom (UK),[11] United States (US)[4,6–9,12–15] Canada[5] and Australia.[16]

In January 1995, an outbreak of the haemolytic–uraemic syndrome associated with a verocytotoxin-producing *E. coli* was reported in South Australia;[16] coincidentally, a similar outbreak

Correspondence to Dr Michael Gracey, Principal Medical Adviser, Office of Aboriginal Health, Health Department of Western Australia, 189 Royal Street, East Perth, WA 6004. Fax (09) 222 4113.

occurred in the US.[17] Both were related to the consumption of small goods: mettwurst and salami. Overseas outbreaks have been predominantly related to verocytotoxin-producing *E. coli* serotype O157:H7, but in Australia serotypes other than this have caused haemorrhagic colitis and/or the haemolytic–uraemic syndrome.[16,18] The South Australian outbreak in 1995 was caused by *E. coli* O111 and the American outbreak was associated with *E. coli* O157:H7.[16,17]

No point-source outbreak of the haemolytic–uraemic syndrome has yet been identified in Western Australia (WA) and epidemiological data are sparse. This retrospective, population-based study was undertaken to describe the epidemiological features of episodes of the haemolytic–uraemic syndrome in WA that led to hospitalisation. It also aimed to provide baseline data from which to develop public health measures to increase awareness of the disease, its presentation and transmission in order to enhance prospects for its more successful control and clinical management.

Methods

The data used in this study were derived from the WA Hospital Morbidity Data System, maintained by the State Health Purchasing Authority's Health Statistics Branch. We identified the medical records of all patients admitted in WA from 1980 to 1994 to acute-stay public hospitals with a primary or secondary discharge diagnosis of haemolytic–uraemic syndrome (ICD-9 CM code 283.1).[19] These records were then reviewed individually and demographic characteristics, medical history and disease source and outcome were abstracted using a standardised form and analysed with SPSS. Because of the time lapse from the onset of the disease to the commencement of this study (in some cases 15 years) and the likelihood of recall bias, no attempt was made to interview patients or their families. Follow-up varied from six months to many years depending on both the outcome of the illness and the year of diagnosis (that is, patients diagnosed in 1994 had less follow-up time than those diagnosed in 1980; those with no complications made fewer return visits to the hospital).

An episode was defined as haemolytic–uraemic syndrome only if the primary or secondary discharge diagnosis stated that it was and if there was evidence of microangiopathic haemolytic anaemia (<10 g/dL), thrombocytopaenia (<150 000 cells/mm^3) and renal impairment (blood urea nitrogen >30 mg/dL). Evidence of microangiopathic anaemia was accepted only if verified by positive blood film and/or renal biopsy.

Results

Selection of episodes

According to the WA Health Department Hospital Morbidity Data collection for 1980–1994, there were 117 records with a primary or secondary discharge diagnosis of haemolytic–uraemic syndrome; 16 of these records could not be located. As 11 of those patients were admitted to nonpaediatric hospitals

Figure 1: Distribution of the population in Western Australia. Populations: metropolitan area 1 221 243 (72.8%), central 53 180 (3.2%), northern 67 108 (4.0%), southern 224 320 (13.4%), western 110 569 (6.6%)

and were aged over 69 years, it is unlikely, based on the findings of this study, that any would have met the case definition (only 14.7 per cent of adults diagnosed as having the haemolytic–uraemic syndrome met the case definition and only two were over 58 years of age). The other five missing records were from Princess Margaret Hospital for Children and were presumed burned in a fire in the early 1980s.

Of the 101 records examined, 58 had an episode of haemolytic anaemia but failed to meet the selection criteria, as blood tests showed an absence of renal failure and/or microangiopathic anaemia. In most of these patients, anaemia occurred as a result of reactions to drugs or prosthetic heart valves. Two patients had a discharge code of haemolytic–uraemic syndrome but were diagnosed prior to 1980.

All of the 41 records which met the criteria for selection were located in five metropolitan hospitals, with 13 of the patients having been transferred from country locations. Because of the dispersal of WA's nonmetropolitan population in areas that are sometimes very remote from the city, seriously ill patients are usually referred quickly to teaching hospitals in the metropolitan area and are commonly evacuated by air (Figure 1). Princess Margaret Hospital is the only children's hospital and receives sick children from all over the state, and, in this case, took 65 per cent of admissions.

Demographic data

The overall incidence rate was 0.19 per 100 000 but this differed for males (0.15 per 100 000) and females (0.24 per 100 000). Non-Aboriginal children under five years of age had a slightly higher incidence rate than Aboriginal children under five years (1.41 and 1.23 per 100 000). The ages of the patients ranged from the first month of life to 76 years (Figure 2). Twenty-six patients (63.4 per cent of all

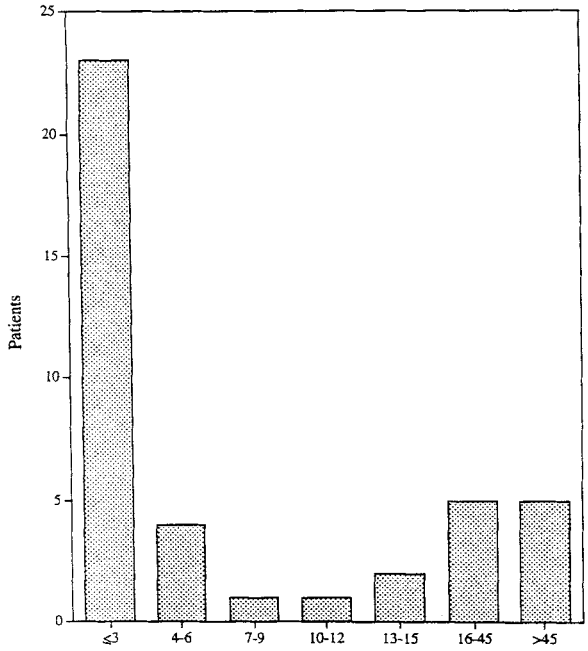

Figure 2: Number of patients with the haemolytic–uraemic syndrome in each age group in Western Australia, 1980 to 1994

patients) were under five years of age, with the median age in this group being three years; 75.6 per cent of patients were under 16 years (range: neonate to 15 years) with the mean age of this subset being 3.1 years.

Clinical course and treatment

The average length of stay in hospital was 25.8 days (range 5 to 74 days), and although 42 per cent of episodes occurred in late summer or early autumn, a chi-squared test showed no significant differences between seasons (χ^2=2.60, 3 df, P>0.05). No geographical clustering of episodes was detected and the annual frequency varied from two to five cases over the 15-year period.

Clinical features of patients prior to admission are listed in Table 1. Data about symptoms of family members were poorly recorded. In eight instances, at least one family member developed diarrhoea and two sets of sisters went on to develop the haemolytic–uraemic syndrome.

In more than 90 per cent of episodes there was a gastrointestinal prodrome, including 46.3 per cent with bloody diarrhoea. Three preterm neonates (two sibling twins and one other) developed the haemolytic–uraemic syndrome with no recognised prodromal symptoms. Two other patients had upper respiratory tract infections with fever but without gastrointestinal symptoms and one 76-year-old man died on the day of admission, with minimal data recorded. Of the two patients with upper respiratory tract infections, the sputum from the adult male grew *Mycoplasma* but that of the child was negative.

Six patients were documented as having been treated with antibiotics during the prodromal period, three with trimethoprim, two with metronidazole, and one with amoxicillin.

All records indicated evidence of microangiopathic anaemia, thrombocytopaenia and renal dysfunction at some time during the patient's clinical course. However, on admission, only 71 per cent were anaemic, 75.6 per cent were thrombocytopaenic and 80.5 per cent had raised urea and/or creatinine levels. Sixty-three per cent had both anaemia and thrombocytopaenia on admission and 48.8 per cent had all three features. Oliguria or anuria lasting more than two days occurred in 70.7 per cent of cases, and 36.5 per cent of patients required dialysis during the acute phase of the illness, for a mean duration of 11.3 days (range 0 to 74 days). Transfusion of packed red blood cells was given in 78 per cent of cases (mean 2.5 units) and platelet transfusion in 39 per cent. A full recovery was made by 60.9 per cent of patients; 22 per cent developed chronic renal failure, 9.7 per cent died, 4.8 per cent developed hypertension requiring medication and one child developed epilepsy. In the under-16-years subset (n=31), one child died and one-third developed chronic renal failure requiring dialysis and/or renal transplantation. Thirty per cent of patients (3 of 10) over 16 years of age died.

Table 1: Clinical features before hospital admission, for episodes of haemolytic uraemic syndrome (n=41), Western Australia, 1980–1994

Symptom	*n*	%
Diarrhoea	30	73.2
Diarrhoea with blood	19	46.3
Vomiting	33	80.4
Abdominal cramps	17	41.5
Fever (>37.2°C)	11	26.8
Upper respiratory tract infection	7	17.1
Headaches, fitting, photophobia or other neurological phenomena	10	24.4

Causative organisms

Only five pathogenic organisms were isolated from stool samples in patients included in this study; two were identified as *E. coli* O111:H2[20] and one as *E. coli* 157:H7. One was identified as an enterohaemorrhagic *E. coli* but was not serotyped, and one isolate grew *Aeromonas hydrophila*. No food vehicle was identified as the source of infection in any episode.

Discussion

This is the first attempt to describe the epidemiology of the haemolytic–uraemic syndrome in WA. As most episodes occur in children under five years of age it is possible that the five unlocated records from the Princess Margaret Hospital for Children were real cases. It is unlikely, however, that the overall findings of the report would be altered substantially by their inclusion. The study is retrospective and involves no reference group, so comparisons of risk are not appropriate.[21] Despite these limitations, findings are similar to population-based studies from other countries which suggest that the disease is more common in females, young children and whites.[4-6,8,9,13,14] The occurrence of more episodes in

the late summer and early autumn appears to be in agreement with studies from the US and Europe, although the sample size in our study was small and the apparent seasonal variation was not statistically significant.[4,5,7,14,19]

In 92 per cent of episodes there was a gastrointestinal prodrome suggestive of infection; however, pathogenic organisms were isolated in only five instances. Four of these isolates[20] were identified by a hospital laboratory[18] and one by the State Health Laboratory Service. One of the isolates was *Aeromonas hydrophila*, and although this microorganism can produce haemolytic cytotoxins,[22] it has not been linked to the haemolytic–uraemic syndrome and may not have been the aetiological agent. As all episodes were sporadic (except in two pairs of two siblings) and as no outbreaks have been reported in WA, this low rate of identification of pathogens was not unexpected. The haemolytic–uraemic syndrome is an uncommon disease, and unless there is a detected clustering of cases it is unlikely that stool samples would be tested for verocytotoxin-producing *E. coli*.[15] Even if such tests were carried out on all patients with bloody diarrhoea, negative results could occur because the standard laboratory test, which uses sorbitol MacConkey's agar to screen for *E. coli* O157:H7, does not identify serotype O111:H- which is considered more common in Australia.[18] Failure to obtain positive stool cultures from individual patients may have resulted from: 1. absence of a pathogenic organism; 2. the initial pathogen no longer being present; or 3. failure of routine laboratory tests to detect the pathogen. Studies of outbreaks of the haemolytic–uraemic syndrome have identified various vehicles of infection, including, most commonly, undercooked minced (ground) meat and, less often, small goods, unpasteurized milk and cider and untreated water.[1,5,6,11,12,14–16,22,23] In WA, where no outbreak has been documented and isolation of causative pathogens from stool samples has been poor, follow-up investigations to identify food vehicles or animal reservoirs of infection have not been carried out.

Information relating to family members, who may also have had gastrointestinal symptoms but did not develop the syndrome, was rarely available in this study. Such information would be valuable in determining risk factors and in identifying vehicles of infection and might be obtained in the future from a case-control study.[15] There is conflicting evidence about the use of antibacterial drugs during the prodrome. Martin et al. found that antimicrobial treatment was associated with a mild clinical course and good outcome (dialysis <10 days, hospital stay <14 days and full recovery).[4] However, others have found an opposite association, especially with the use of sulphonamides and amoxicillin;[7,12,23] the findings of this study support the latter view. The six patients with documented antibiotic treatment during the prodromal period in this study all developed severe disease with a prolonged hospital stay (17 to 74 days) and required red blood cell transfusion and dialysis for longer than 10 days. Two (sisters) proceeded to develop chronic renal failure requiring renal transplantation. However, as complete ascertainment of antibiotic use among patients was not possible and, in the absence of a comparison group, these findings must be considered cautiously.

The haemolytic–uraemic syndrome not associated with diarrhoea is considered rare in children and is more common in adults.[3] One child and one adult in this study developed the syndrome after an upper respiratory tract infection. It is possible that the man with *Mycoplasma* infection may have had septicaemia-associated disseminated intravascular coagulation and not the haemolytic–uraemic syndrome, as the haematological features are similar.[3] Blood clotting times, which are altered in the former but not the latter, were not recorded during this patient's short hospitalisation before his death.

The haemolytic–uraemic syndrome is a rare and serious illness that often requires intensive treatment and prolonged hospitalisation; it carries substantial long-term morbidity and mortality. Its relationship to infection by verocytotoxin-producing *E. coli* is well documented, although the prevalence of these enteropathogens is unknown in Australia. Three important public health issues emerge from the literature and the findings of this study: 1. the need for greater awareness among general medical practitioners (especially those dealing with children) of the existence and presentation of gastroenteritis associated with verocytotoxin-producing *E. coli* and its relationship to the haemolytic–uraemic syndrome; 2. a need for heightened awareness among the general public regarding the severity of the disease and how it can be avoided; 3. the importance of improved surveillance of verocytotoxin-producing strains of *E. coli* by public health professionals and laboratories.

In April of 1995, the haemolytic–uraemic syndrome became a reportable disease in WA and work is under way to inform medical practitioners of disease definition and usual clinical presentations. This will heighten awareness of the disease, although perhaps only in the short term. If an outbreak should occur in the future, an 'Alert' statement issued by health authorities may help curtail the outbreak by increasing awareness among medical and other health professionals and the general public.

Infection by verocytotoxin-producing *E. coli* is considered the most common cause of the haemolytic–uraemic syndrome in North America,[1] and the severity of associated haemorrhagic colitis is being increasingly noted.[1,4,6,7,12,15,22,23,24] The World Health Organization has recognised infection by *E. coli* O157:H7, causing food-borne outbreaks of severe, bloody diarrhoea and renal failure, as a notable new disease of international importance.[25] Some countries have instituted surveillance programs in order to map prevalence and to develop public health policy.[4,6,13,22,23] In Australia, there is as yet no national surveillance program involving the routine culture of stools for verocytotoxin-producing *E. coli*; nor does WA have such a program. It must be appreciated, however, that many serotypes of *E. coli* can be associated with Shiga-like-toxin *E. coli* infections and clinical syndromes (including the haemolytic–

uraemic syndrome), which makes their detection difficult. Early in the clinical course, the numbers of Shiga-like-toxin-producing *E. coli* in faeces may be very high but this can drop very significantly within days.[26]

Conventional microbiological testing of clinical and food samples in WA is based on procedures that involve quantification of coliforms, presumptive then definitive identification of *E. coli*, further definition of *E. coli* serotypes by ELISA and serological testing, followed by in vitro testing using Vero cell lines. In the circumstances outlined above these tests are inadequate. A sensitive Shiga-like-toxin-specific polymerase chain reaction assay has been developed that can detect very small numbers of toxin-producing *E. coli* among other coliforms for screening purposes.[27] Since the outbreak of haemolytic–uraemic syndrome in South Australia early in 1995[16] the Health Department of WA has been conducting intensive surveillance of the State's abattoirs and small-goods processing plants, incorporating screening for verocytotoxin-producing *E. coli* into its small-goods surveillance program, which previously focused only on *Salmonella*. Results are interpreted in relation to clinical, epidemiological and microbiological data and with consultation between those responsible for these different aspects of the case. The National Food Authority had established standards for *E. coli* in uncooked, fermented comminuted meats; the procedures in use in WA are consistent with those standards. Regular and more intensive testing of the food supply should help to ensure that it does not represent a risk to public health. In addition, a system for the electronic transfer of notifiable, infectious disease data directly to the Communicable Disease Control Unit at the Health Department is now being implemented. The matching of information from the small-goods surveillance program and the Communicable Disease Control Unit register will allow a more complete assessment of the presence and prevalence of verocytotoxin-producing strains of *E. coli* in the community. Collation of this information should facilitate a more rapid detection of risk related to food contamination so that future outbreaks of the haemolytic–uraemic syndrome can be averted or contained.

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