Acute neurology and neurophysiology of haemolytic–uraemic syndrome

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Abstract

Involvement of the central nervous system (CNS) is found in around 30% of children with haemolytic–uraemic syndrome (HUS). This complication is the single most common cause of mortality and also a major contributor to the morbidity associated with HUS. We reviewed 22 children with HUS and acute CNS involvement. Both global and focal derangements occurred, and in survivors, early regional EEG abnormalities—especially those in the occipital and temporal areas—were prognostically useful.

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Haemolytic–uraemic syndrome (HUS) is the commonest cause of acute renal failure in children in the UK. Most cases are infectious in origin (for example, *Escherichia coli* O157:H7, or *Shigella*), although sporadic, non-infectious causes (resulting from idiopathic, familial, or autoimmune diseases, drugs, or tumours) also occur. Annually, the incidence of HUS is about 1.5 per 100 000 in children younger than 15 years of age.¹

Neurological involvement in the acute phase of HUS occurs in 17–52% of children; the most common acute problem is generalised or partial seizure activity in more than half of those with neurological signs.^{2–5} Early CNS involvement is also a major contributor to chronic neurological morbidity.⁶ We have therefore undertaken a review of the clinical and neurophysiological features of CNS involvement during HUS in 22 children. Our purpose was to evaluate early features possibly predictive of chronic neurological sequelae.

Methods and findings

The records of 22 children treated between 1985 and 1992 at Great Ormond Street Hospital for Children, London, for clinical symptoms and laboratory findings consistent with the diagnosis of HUS were reviewed. All 22 patients had prodromal gastrointestinal symptoms, with positive stool cultures in five patients (*E coli* O157:H7 in three, rotavirus in one, and *Shigella* in one). There were 11 boys and 11 girls aged 0.1–13.3 years (mean 3.3 years). All patients had experienced some neurological involvement during the acute phase of HUS and had undergone neurophysiological investigations. A total of 81 electroencephalographic (EEG) and 30 evoked potential recordings were reviewed. The type of acute

neurological derangement and long term neurological outcome were also reviewed. The mean time of follow up was 4.4 years (range 0.2–7.1 years).

ACUTE NEUROLOGY AND OUTCOME

Five of 22 (23%; 95% confidence interval (CI) 8 to 45%) children died during the acute phase of HUS. The mean time from onset of symptoms was eight days (range 3–13 days). The form of acute neurological involvement seen in these patients was: acute seizures in 14 children; coma or irritability in six; and focal neurology with either hemiparesis or aphasia in the remaining two. Ten of the 22 patients had some focal ictal or motor neurology. On follow up, seven of the 18 surviving children had neurological sequelae: two cases each with complex partial seizures, cognitive deficits, or cortical visual defects; and one child with both hemiparesis and dysphasia. In 10 patients there were no long term neurological problems, although in two of these cases some deficits (homonymous hemianopia and delayed speech development) were transient for up to a year after the illness (table 1).

With regard to factors potentially predictive of outcome, seizures, alone or as part of neurological involvement, were associated with mortality or long term neurological sequelae (Kendall tau b -0.4 , $p < 0.05$). For example, six of the eight children with partial or secondarily generalised seizures had neurological sequelae. When only generalised seizures were present, sequelae occurred in four of six cases. When seizures were absent, only two of eight children experienced any neurological sequelae.

EARLY NEUROPHYSIOLOGY AND NEUROLOGY

During the acute phase of HUS a variety of generalised and focal EEG features were evident in these children (table 1). In survivors, early generalised slowing in EEG activity as the sole abnormality was not associated with any long term neurological sequelae. Periodic EEG findings—intermittent activity not associated with drugs or immaturity—were associated with either death (three cases) or multiple neurological impairments (two cases). Slowing of EEG activity which was lateralised to one hemisphere was seen in four patients, one of whom developed a moderately severe cognitive deficit while another was left with hemiparesis and dysphasia. Focal discharges, emanating from the temporal region, were seen in two patients. Both subsequently developed epilepsy with complex partial seizures. Visual evoked potential studies showed reduced amplitudes in three patients, two of whom were left with visual impairments.

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Table 1 Clinical and EEG characteristics of 22 children with haemolytic-uraemic syndrome

Generalised encephalopathy					
	Sex	Age	Other neurology	Early EEG	Neurological sequelae
Coma					
1.	M	10 mth	None	Slow (1–2/s)	None
2.	M	3 mth	None	Slow (1–2/s)	None
3.	F	2 y 2 mth	None	Slow (1–2/s)	None
4.	M	2 y 8 mth	None	Slow (1–2/s)	None
5.	F	13 y 3 mth	None	Slow (right)	None
6.	M	2 y 9 mth	None	Slow (1–4/s)	Died
Seizures					
7.	F	1 y 3 mth	None	Slow (1–2/s, occipital)	None
8.	F	1 y 10 mth	None	Slow (~2/s, posterior)	None
9.	M	1 y 4 mth	Left hemiparesis	Slow (1–3/s)	None (transient speech delay)
10.	M	3 y 2 mth	None	Slow (1–2/s)	None (transient visual deficit)
11.	M	10 days	Partial seizures, coma	Periodic, multifocal discharges	Visual and developmental problems
12.	M	6 y 3 mth	Coma	Periodic, left temporal discharges	Epilepsy (complex partial seizures); visual, cognitive and motor problems
13.	F	1 y 8 mth	Left hemiparesis	Periodic	Died
14.	M	2 y 1 mth	None	Slow (1–3/s)	Died
15.	F	3 y 6 mth	Left hemiparesis	Periodic, multifocal discharges	Died
16.	F	8 y 6 mth	Deep coma	Periodic, multifocal discharges	Died
Focal derangements					
	Sex	Age	Clinical features	Early EEG	Neurological sequelae
Motor					
17.	M	3 mth	Left hemiparesis	Slow (2–6/s)	None
18.	M	3 y 3 mth	Right hemiparesis, aphasia	Slow (left)	Right hemiparesis and dysphasia
Seizures					
19.	F	8 mth	Left sided	Slow (1–2/s, right)	None
20.	F	2 y 7 mth	Right sided	Slow (1–4/s)	None
21.	F	5 y 9 mth	Left sided with right	Slow (~1/s), right temporal discharges	Epilepsy (complex partial seizures); homonymous hemianopia
22.	F	8 y 4 mth	Left sided seizures, coma	Slow (2–3/s, right)	Cognitive deficit (moderately severe)

Discussion

In this review of HUS we found that during the acute phase of illness CNS involvement consisted of both generalised and focal impairments. Coma or an ictal cause of more generalised encephalopathy was confirmed by the presence of diffuse slowing of EEG activity. Focal derangements—motor, visual, or ictal—suggestive of more regional or specific cerebral processes were highlighted by focal alterations in EEG activity or by the presence of focal epileptiform discharges. In survivors, early regional EEG abnormalities, especially those in the occipital and temporal areas, were potentially useful in identifying those who would subsequently develop visual problems and epilepsy.

The pathophysiology of CNS derangement in HUS could be metabolic in origin, given the apparently diffuse nature of insults such as uraemia, hyponatraemia, or hypocalcaemia.⁷ Equally, focal toxin mediated mechanisms resulting in focal vascular endothelial injury or multifocal thrombotic pathology may occur.⁸ Clinically differentiating between these evolving general and focal processes is difficult. In this regard, five previous neurophysiological studies of HUS have described the acute findings in 36 children.^{2–5,9} In common with these studies we have also found in our study of 22 children that diffuse encephalopathy with irregular generalised slow delta activity is most frequently seen. However, in this review, we found a significant number of additional focal abnormalities suggesting an added focal pathophysiological process. Importantly, a unique association between repetitive discharges in the temporal region and the subsequent development of temporal lobe epilepsy was noted.

Such a focal predilection is reminiscent of the temporal lobe vulnerability seen in herpes simplex encephalitis.¹⁰

In the course of managing children with HUS, we believe that it is important to consider whether there has been any CNS involvement. Much can be established from the clinical history and examination. However, early neurophysiological investigation adds to this by confirming the presence and nature of background or focal features which may be of long term neurological importance, particularly when these are localised to the occipital or temporal regions.

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