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# CT and MRI in haemolytic uraemic syndrome with central nervous system involvement: distribution of lesions and prognostic value of imaging findings

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**Abstract** *Background*: Central nervous system (CNS) involvement is a common complication in haemolytic uraemic syndrome (HUS). Various imaging findings have been described, mostly as case reports. Although there are a few retrospective studies on larger patient groups there is no report that focuses on MRI. *Objective*: To analyse the CT and MRI studies of patients with neurological complications of HUS, to describe the typical imaging findings, and to evaluate their predictive character with regard to follow-up examinations and clinical outcome. *Materials and methods*: Of 57 patients with clinically proven HUS who were referred to our hospital between 1995 and 2003, 17 had signs of serious CNS involvement and 10 underwent neuroimaging. Nine MRI and seven CT studies were performed in the acute phase and five MRI and two CT studies were done for follow-up. *Results*: In six patients, pathological imaging findings were seen on CT or MRI performed in the acute phase of the disease whereas CT and MRI scans were completely normal in four patients. All patients with positive imaging findings had pathological changes within the basal ganglia. Additional findings were seen in the thalami ($n=2$), cerebellum ($n=2$) and brain stem ($n=1$). On follow-up imaging performed in five cases, the pathological imaging findings had resolved completely in two and partially in three patients. All patients had a good neurological outcome. Comparing the various MRI findings, a haemorrhagic component within an acute lesion was the most reliable parameter predicting residual pathologic findings on follow-up imaging. *Conclusions*: Basal ganglia involvement is a typical finding in patients with neurological complications of HUS. Even in patients with severe CNS involvement on acute imaging studies, prognosis was favourable for clinical outcome and resolution of pathological imaging findings.

**Keywords** Brain · Haemolytic uraemic syndrome · MRI · CT · Children

## Introduction

Haemolytic uraemic syndrome (HUS) is a multisystem disease which is characterized by uraemia, thrombocytopenia and haemolytic anaemia. It is the most common cause of acute renal failure in children and is primarily seen in small children between 1 and 4 years of age. The disease typically starts after a gastrointestinal infection with diarrhoea (D+ type), but can also occur sporadically (D− type). In about 90% of the typical D+ cases, enterohaemorrhagic strains of *Escherichia coli* can be found in stool cultures. Histological studies have shown

that verotoxin produced by the bacteria binds to the endothelium of small organ vessels and leads to thrombotic vessel occlusion [1–3].

Besides the kidneys, the central nervous system (CNS) is involved in 20–50% of cases. Common signs of severe CNS involvement are seizures, alteration of consciousness, hemiparesis, visual disturbances and brain stem symptoms [1, 3, 4]. The pathogenesis of CNS involvement is not yet fully understood; however, a toxin-mediated vasculopathy involving the small intracerebral vessels similar to the pathological process occurring in the kidneys is thought to be the most probable mechanism [5, 6]. It is, however, known that severe fluid and electrolyte disturbances and hypertension can also be responsible for encephalopathy in HUS patients [1, 4].

There are several reports in the literature about CT and MR findings in patients with HUS and CNS involvement [7–15]. Various imaging findings have been described and the prognostic value of imaging has been discussed [9, 10]. The purpose of our retrospective study was to analyse the CT and MRI findings in patients with HUS and serious CNS involvement. Using mainly MRI, including diffusion-weighted imaging in the most recent cases, we tried to evaluate the predictive character of various imaging signs with regard to diagnostic and clinical outcome.

## Materials and methods

From 1995 to 2003, 57 children with HUS were referred to the department of paediatrics at our hospital because of acute renal insufficiency. A total of 17 patients (29.8%) had clinical signs of CNS involvement. Two children died from hypovolaemic shock before imaging could be performed. In a further five children, the neurologic symptoms resolved after initial therapy so that imaging was no longer necessary. Ten children (six girls, four boys; age 17 months–7 years, mean 3 years 1 month) underwent neuroimaging. The laboratory and clinical data, including the neurological symptoms leading to neuroimaging, are summarized in Table 1.

Nine MRI and seven CT studies were performed in the acute phase of CNS disease. Follow-up imaging was available in seven patients using MRI in five and CT in two cases. Image interpretation was performed by two radiologists specialized in paediatric neuroradiology on a consensus basis. The CT and MR images were evaluated for pathological changes at different anatomical sites, and these were graded from 0 (no change) to 3 (severe changes). The lesions were further characterized regarding signs of haemorrhage, contrast enhancement and restricted water diffusion. The imaging findings on the acute and follow-up examinations were compared and correlated with clinical data.

## Results

In four patients with HUS and clinical signs of CNS involvement the CT and MRI studies performed in the acute phase of the disease were normal (patients 7–10). Two of these patients had follow-up examinations. In one patient MRI showed mild enlargement of the inner and outer CSF spaces, most probably due to therapeutic effects. In the other patient follow-up CT was normal. In all four patients neurological symptoms resolved completely.

In six patients (patients 1–6) neuroimaging studies performed in the acute phase demonstrated pathological imaging findings (Table 2). All six patients had abnormalities of the basal ganglia with the dorsolateral portion of the lentiform nucleus being most commonly affected. In addition, abnormalities were seen in the thalami ($n=2$), cerebellum ($n=2$) and brain stem ($n=1$).

**Table 1** Clinical data of patients ($n=10$) with haemolytic uraemic syndrome and central nervous system involvement requiring neuroimaging studies

| Patient no. (type) | 1 (D+) | 2 (D+) | 3 (D+) | 4 (D+) | 5 (D+) | 6 (D+) | 7 (D+) | 8 (D−) | 9 (D+) | 10 (D+) |
|---|---|---|---|---|---|---|---|---|---|---|
| Neurological symptoms | Seizures, stupor | Seizures, coma, hemiparesis | Hemiparesis, altered mental state | Seizures, hemiparesis | Seizures, altered mental state | | Seizures, altered mental state | Seizures, altered mental state | Seizures, altered mental state | Tremor |
| EEG | ++ | ++ | +++ | ++ | + | | + | ++ | ++ | + |
| BP | + | + | + | – | + | | + | + | + | + |
| Sodium | + | – | – | – | – | | – | ++ | ++ | ? |
| CT | A | A | A | A | | A, F | A, F | A | | |
| MRI | A | A, F | A, F | A, F | A, F | | A | A | A | A, F |

EEG: + minor generalized changes; ++ distinct generalized changes; +++ severe generalized changes
BP: – normal; + systolic blood pressure above 95th percentile
Sodium: – normal; + Na 130–135 mmol/l; ++ Na < 130 mmol/l
CT/MRI: *A* cross-sectional imaging in acute phase; *F* cross-sectional imaging at follow-up

**Table 2** Distribution and extent of pathological imaging findings on acute and follow-up CT and MRI

| Patient no. | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CT | MRI | CT | MRI | CT | MRI | CT | MRI | CT | MRI | CT | MRI |
| Basal ganglia | | | | | | | | | | | | |
| Acute | 0 | 2D | 3C | 3HC | 0 | 2D | 0 | 1 | | 2HC | 3 | |
| Follow-up | | | | 2 | | 1H | | 0 | | 1 | 2 | |
| Thalami | | | | | | | | | | | | |
| Acute | 0 | 1D | 0 | 0 | 3 | 3DH | 0 | 0 | | 0 | 0 | |
| Follow-up | | | | 0 | | 1H | | 0 | | 0 | 0 | |
| Cerebellum | | | | | | | | | | | | |
| Acute | 0 | 0 | 0 | 3H | 0 | 0 | 0 | 0 | | 1 | 0 | |
| Follow-up | | | | 2 | | 0 | | 0 | | 0 | 0 | |
| Brain stem | | | | | | | | | | | | |
| Acute | 0 | 0 | 0 | 0 | 2 | 2D | 0 | 0 | | 0 | 0 | |
| Follow-up | | | | 0 | | 1 | | 0 | | 0 | 0 | |
| Outcome | Complete recovery | | Weakness in minute motor activity | | Weakness of right leg | | Complete recovery | | Complete recovery | | No information | |

*0* no changes, *1* minor changes, *2* distinct changes, *3* severe changes, *H* plus haemorrhage, *C* contrast enhancement, *D* restricted diffusion

In four patients, the signal changes of the basal ganglia and thalami extended into the surrounding white-matter tracts of the internal and external capsules (Fig. 1). As expected, the extent and distribution of lesions were seen much better on MRI than on CT.

In two of the MR-positive patients where diffusion-weighted sequences were performed (patients 1 and 3), the lesions of the basal ganglia and thalami showed restricted water diffusion with corresponding decrease of apparent diffusion coefficient (ADC) values. Only one patient had follow-up imaging, which showed that most of the areas with restriction of water diffusion on the acute MRI had returned to normal (Fig. 2).

Three patients (patients 2, 3 and 5) had lesions with signs of haemorrhage located in the basal ganglia, thalami or cerebellum on the acute MRI study. All of the haemorrhagic lesions showed residual signal alterations on follow-up imaging. In two patients the basal ganglia lesions also showed contrast enhancement with gadolinium (patients 2 and 5).

Regarding the clinical and neurological outcome in the six patients with positive imaging findings on the acute MRI or CT, three patients had complete resolution of their neurological symptoms within days or weeks. In two patients, minor residual neurological symptoms were present on follow-up (Table 2). Both patients also had residual imaging changes on the follow-up MRI (patients 2 and 3).

## Discussion

CNS disease is the most common extrarenal manifestation in patients with HUS, with an estimated incidence of approximately 20% [1]. Common signs of severe CNS involvement are seizures, alteration of consciousness, hemiparesis, visual disturbances and brain stem symptoms [1]. Although the prognostic value of neurological involvement for long-term outcome is controversial, it is known from several studies that CNS complications are responsible for most of the fatal cases of HUS [1, 16, 17].

The pathogenesis of CNS involvement is debated. Some authors suggest that the encephalopathy is secondary to metabolic changes (hyponatraemia, azotaemia, hydration disorders) or hypertension, whereas the vast majority believe that the neurological damage is directly induced by the verotoxin affecting the endothelium of small brain vessels leading to infarction and bleeding [5, 6, 18]. Various animal models have been used to identify the mechanism of brain injury in HUS. In rabbits, the major abnormalities after injection of verotoxin were microvascular changes with oedema and focal haemorrhage [7]. Whether these changes are due to binding of verotoxin to specific receptors or arise from direct toxin damage combined with a response to localized inflammatory mediators is not clear yet [5, 6].

In patients with HUS and clinical signs of major neurological complications, imaging studies of the brain are performed to document the severity and nature of pathological changes. In most cases, CT has been the initial diagnostic imaging study of choice because of its greater availability compared to MRI. CT is able to document gross infarction, bleeding and generalized oedema, whereas subtle changes are much better demonstrated with MRI. With the advent of newer and faster imaging techniques, MRI is nowadays routinely applied for the evaluation of most non-traumatic CNS disease in children. There are several reports of the MRI findings in patients with HUS and neurological complications [8–15, 19–22]. Although various imaging findings have been described in patients with neurological complications of HUS, most of the studies found

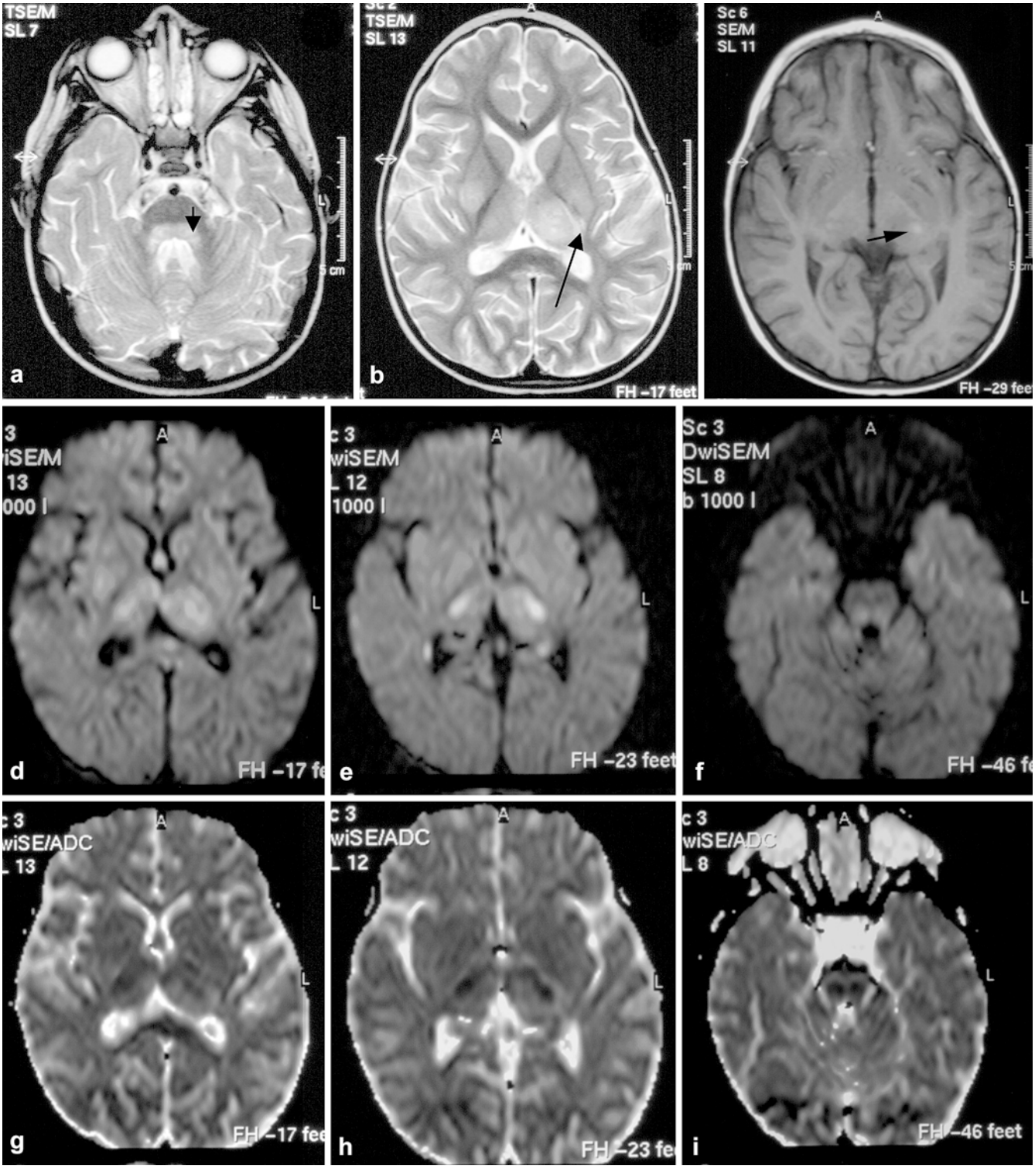


**Fig. 1** A 2-year-old girl with haemolytic uraemic syndrome, progressive alteration of consciousness and right-sided hemiparesis. On the T2-weighted images, there are **a** pathological changes in the dorsal aspect of the brain stem with extension into the cerebellar peduncles (*short arrow*) and **b** bilateral hyperintense lesions in the thalami and dorsolateral lentiform nuclei. On the left side, the posterior limb of the internal capsule is also affected (*arrow*). **c** On the unenhanced T1-weighted image there is hyperintensity in the left thalamus indicating haemorrhage (*arrow*). **d**–**f** The diffusion-weighted sequence demonstrates restricted diffusion in the basal ganglia, thalami and dorsal brain stem with corresponding low-signal intensity on the apparent diffusion coefficient maps (**g**–**i**)

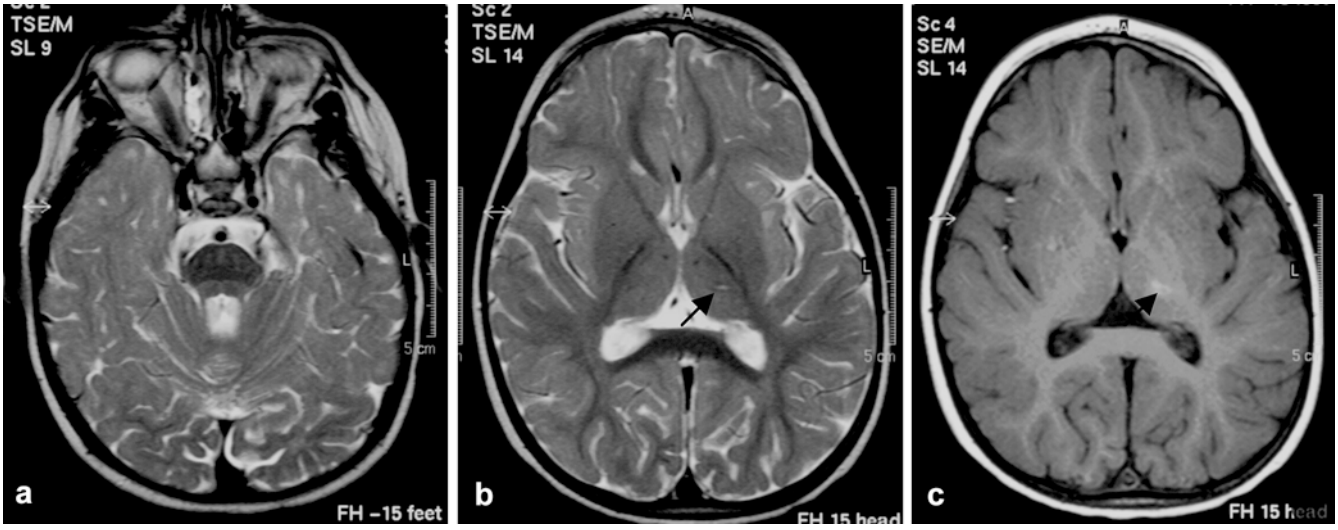


**Fig. 2** Follow-up examination of the same patient as Fig. 1, 4 months later. **a, b** There is almost complete resolution of the signal abnormalities on T2-weighted images. There is a small residual hyperintensity within the left thalamus (*arrow*) with a corresponding hyperintensity (*arrow*) on the T1-weighted sequence representing methaemoglobin (**c**)

basal ganglia lesions to be characteristic [8–11, 13, 14, 21, 22]. Other findings, including territorial infarction or diffuse white-matter changes similar to posterior leucoencephalopathy, which have been described anecdotally, reflect complications rather than specific changes of the disease [12, 15, 19, 20]. Although involvement of the basal ganglia is not specific for HUS and is also seen in various other conditions, including severe hypoxia, intoxication and infectious diseases, it supports the theory of a direct or receptor-mediated verotoxin-induced injury [23]. Our study confirms previous investigations regarding the distribution of pathological changes. We found signal intensity changes in the dorsolateral portion of the lentiform nucleus to be the most characteristic finding. Similar to other reported cases, these signal changes may extend into the surrounding white-matter tracts of the internal and external capsule. Besides the basal ganglia, we found pathological signal intensity changes within the thalamus, the brain stem and the cerebellum. None of our patients had territorial infarction or leucoencephalopathy.

The value of MRI with regard to prognosis of clinical outcome is controversial [9, 10]. We agree with Barnett et al. [10] that involvement of the basal ganglia is frequently associated with good clinical outcome. Even in patients with extensive and multifocal signal abnormalities, most of the initial imaging findings were reversible on follow-up. Analysing the prognostic value of various MRI findings, we found that the most reliable imaging feature indicating the development of a gliotic or cystic remnant on follow-up MRI was the detection of a haemorrhagic component within a lesion. These lesions were associated with at least some minor neurological dysfunction or delayed neurological recovery.

In conclusion, our study confirms that HUS with CNS involvement characteristically involves the basal ganglia. Even in patients with severe imaging findings we found almost complete resolution of disease on follow-up examinations. The positive course of imaging findings correlated well with good clinical outcome in our patients.

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