ORIGINAL ARTICLES

Haemorrhagic shock encephalopathy syndrome in the British Isles

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Abstract

The aetiopathogenesis of haemorrhagic shock encephalopathy syndrome (HSES) remains unclear and after concern that a novel environmental agent was the cause, the British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre in 1983 initiated surveillance of this condition in the British Isles. After 1986 cases were ascertained via the British Paediatric Surveillance Unit 'active' reporting scheme; this report presents the findings for 1985-8.

Sixty five patients were reported, of whom 52 satisfied the criteria for inclusion. Of those whose outcome was known, 24 (46%) died, 18 had severe neurological damage, and six survived apparently intact. Epidemiological features of note were: the median age of 15 weeks (range 3-140); statistically significant clustering of admission times suggesting a peak onset period at night; lack of geographic clusters, of secular trends and, except for a slight excess in winter months, of seasonality.

Clinical and pathological features followed a highly consistent pattern, suggesting that HSES is an individual clinical entity distinguishable from conditions with similar presentations, such as septicaemia and Reye's syndrome.

There was no microbiological or epidemiological evidence to support the emergence of a novel environmental agent. Many of the features of HSES were, however, the same as those described in heat stroke and we suggest that the two conditions are the same even though there is usually no history of overt overheating.

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Haemorrhagic shock encephalopathy syndrome (HSES) is a rare but devastating disorder of young children. It was first presented as a clinical entity under this name by Levin *et al* who in 1983 described 10 cases in the UK,¹ although series from France and England describing patients with a similar constellation of clinical features had appeared earlier.²⁻³ Subsequently, over a hundred cases of HSES have been reported in the world literature: from the Netherlands,⁴ Spain,⁵ Belgium,⁶ France,⁷ Germany,⁸⁻⁹ Portugal,¹⁰ New Zealand,¹¹ Israel,¹² the United States,¹³⁻¹⁸ the Far East,¹⁹⁻²⁰ and further cases in the UK.²¹⁻²⁶

After concerns that HSES might be a new disease caused by a novel environmental agent,¹

the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC) and the British Paediatric Association (BPA) set up a joint surveillance scheme in the British Isles. The results for 1982-4 have been reported²⁶ and we now present the findings for 1985-8, after which surveillance was discontinued. During this second period information was collected in greater detail so that the features of HSES could be delineated more fully, with the object of assisting the diagnosis and elucidating the aetiopathogenesis.

Methods

CASE DEFINITION

Clinicians were given the following guidelines but were asked to report even if all nine criteria were not met. A child had to be under 16 years of age with acute onset of: (1) encephalopathy, (2) shock, (3) disseminated intravascular coagulation, (4) diarrhoea (may be bloody), (5) falling haemoglobin concentration and platelet counts, (6) acidosis, (7) raised hepatocellular enzymes, (8) renal function impairment, and (9) negative cultures of blood and cerebrospinal fluid.

The criterion that plasma ammonia concentration should be normal, used in the 1982-4 reports, had proved inconsistent²⁶ so was discontinued for 1985-8.

For the analysis, patients were allocated to one of three groups:

(A) *Definite HSES*: all nine criteria satisfied.

(B) *Probable HSES*: either: (i) eight criteria satisfied but one not met or (ii) at least seven criteria satisfied but no information on the remainder.

(C) *Indeterminate/not HSES*: either: (i) insufficient information, or (ii) another diagnosis more likely, or (iii) presence of a preceding event which may have distorted the clinical course.

CASE ASCERTAINMENT AND DATA COLLECTION

Between January 1985 and May 1986, cases were ascertained through 'passive' reporting by paediatricians throughout the British Isles as described previously.²⁶ From June 1986 to December 1988, reporting changed to the 'active' system of the British Paediatric Surveillance Unit (BPSU).²⁷ The initial report generated a request to review case notes both from the first hospital and, where appropriate, from the referral centre. Epidemiological, clinical, and laboratory data were transcribed on to a standard proforma.

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Results

A total of 65 patients was reported. Thirty two were classified as group A (definite HSES) and 20 as group B (probable HSES). The remaining 13 (group C) consisted of: (i) insufficient information (two cases); (ii) alternative diagnosis (three cases: septicaemia, toxic shock syndrome, valproate toxicity) and (iii) preceding event (eight cases: head injury, severe dehydration, laparotomy, adenotonsillectomy, severe hypoglycaemia, respiratory arrest, cardiac arrest (two cases)).

The following analyses include only the 52 group A and B cases.

EPIDEMIOLOGICAL FEATURES

The secular trends were unremarkable: there were 11 cases in 1985 (some of whom were described in another series²⁴); seven in 1986, 18 in 1987, and 16 in 1988. The annual totals for the preceding three years had been 13, 22, and nine.²⁶ Small numbers hamper interpretation of seasonality, but there were no clear trends either within each year or taking the period as a whole. However 29/52 (56%) of the cases occurred in the winter quarters (the same proportion as in the 1982-4 cases) with the highest numbers occurring in January and February (eight and nine respectively).

As in the previous years, cases were reported throughout the British Isles with no obvious clustering in place or time. Eighteen of the 52 patients were referred to a tertiary care centre. The remainder were managed in their local district general hospitals.

The age range was 6 to 140 weeks (median 14.5) for group A and 3 to 86 (median 16) for group B. The mean age (SD) of the 52 cases as a whole was 19.8 (21.1) weeks and the median and mode 15 weeks and 13 weeks respectively. Fifty (96%) patients were under 1 year of age. The male:female ratio was 14:18 for group A and 13:7 for group B.

CLINICAL FEATURES (TABLE 1)

The 52 patients in groups A and B were clinically very similar and are considered together except where specified. Seven (13%) had pre-existing developmental anomalies and other problems: of these, two aged 13 and 17 weeks, had had repairs of cleft lip and palate,

Time of admission to first hospital in HSES (n=51, one baby not known).

Table 1 Clinical features. Results are number (%)

	Group A (n=32)	Group B (n=20)	Combined (n=52)
Abrupt onset	32 (100)	20 (100)	52 (100)
Prodromal illness	19 (59)	12 (60)	31 (60)
Admission temperature >40°C	18 (56)	9 (45)	27 (52)
Circulatory collapse	32 (100)	20 (100)	52 (100)
Coma	24 (75)	15 (75)	39 (75)
Convulsions	32 (100)	18 (90)	50 (96)
Respiratory disturbance	30 (94)	18 (90)	48 (92)
Vomiting	7 (22)	5 (25)	12 (23)
Loose stools	32 (100)	17 (85)	49 (94)
Oliguria/anuria	27 (84)	15 (75)	42 (81)
Manifest bleeding tendency	27 (84)*	15 (75)*	42 (81)*
Liver enlargement	22 (69)	13 (65)	35 (67)
Outcome:			
Full recovery	4 (13)	2 (10)	13 (2)
Death	13 (41)	11 (55)	24 (46)
Neurological damage	14 (44)	4 (20)	18 (35)
Uncertain	1 (3)	3 (15)	4 (8)

*Five further cases in group A and two in group B had abnormal coagulation tests.

while a third aged 13 weeks had had a repair of a meningomyelocele; two others aged 48 and 36 weeks had spasticity and two aged 140 and 28 weeks had generalised delay. The mean (SD) age of the latter four babies was 63 (52) compared with 16 (12) weeks for the other 48 patients.

Thirty one patients had a mild prodromal illness with respiratory (n=19) or gastrointestinal (n=12) symptoms. The remainder had been well, although five had had recent contact with infection.

Three babies were each one of twins. In two of these cases (reported in detail elsewhere²⁵) the other twin was found dead at the same time, the deaths being attributed to sudden infant death syndrome (SIDS).

The onset of the main illness was invariably abrupt and catastrophic. Although all the babies had been well or only mildly unwell when last seen (usually the previous night) most were found extremely ill in their cots first thing next morning; this characteristic timing was reflected in the clustering of admissions between 8 am and 11 am (figure); this clustering was unlikely to have occurred by chance ($\chi^2=75.24$, 5 df $p<0.001$).

All 20 babies whose condition when first found by the parents was recorded, were described as unusually hot or sweaty. The first recorded temperatures, taken at varying intervals after admission (methods varied and were inconsistently reported), indicated that most babies (42/49 with this information) were febrile. The modal temperature was 40-41°C and seven patients had a temperature $\geq 42^\circ\text{C}$. Six had subnormal temperatures, one as low as 27°C, but all had been stripped for some time before the recording. One baby had a normal temperature.

No patient was reported to have a rash. Conscious level on admission was recorded in 51 cases: 39 were comatose, 24 dying without regaining consciousness. The other 12 were semiconscious or poorly responsive. Fifty babies had convulsions of whom 35 (67%) were fitting on admission and 10 more began to fit within a few hours. Convulsions were usually generalised or multifocal and difficult to control, especially if they had started early. Of the two babies in

whom no fits were recorded, one died soon after admission and the other had been promptly paralysed for ventilation.

Vomiting was not a major feature; it occurred in only 12 cases and was not copious. Loose stools were noted in all cases except three, either at admission or within the next 10 hours; usually profuse, they were also bloody in 19 cases (37%). Twenty one babies (40%) were assessed as dehydrated on admission, one severely so. Circulatory collapse ('shock') was present in all cases. The mean systolic blood pressure on admission, measured in 32 cases, was 58 mm Hg (range 0-99 mm Hg) and the mean pulse rate, 177/minute (range 110-250/minute). Progressive hepatomegaly, defined as a liver edge more than 2 cm below the costal margin, was recorded in two thirds of cases, reaching a maximum at about 24 hours, with the liver extending usually about 4 cm, but in one case 9 cm, below the costal margin.

Forty two babies (81%) had anuria or oliguria. When urine was passed it usually contained protein and red blood cells. Three babies were dialysed and six others died anuric. In the 10 cases where oliguria was not documented the blood urea concentration was nevertheless raised.

Most babies had disturbed breathing patterns when first seen, respiration usually being rapid and shallow (n=36) or sometimes very irregular (n=12). There was no evidence of major pulmonary disorder and the respiratory disturbances appeared to be central. Thirty nine babies (75%) required assisted ventilation, which was initiated sometimes for respiratory support and sometimes to control seizures and raised intracranial pressure. Ventilation was continued in some cases for up to seven days.

Forty two (81%) babies demonstrated a bleeding tendency within the first 24 hours of admission, usually from the gastrointestinal tract, venepuncture sites, or an endotracheal tube. Among the remaining 10 patients, clotting tests were abnormal in the seven in whom they were performed.

OUTCOME

Twenty four babies died (46%, 13 boys and 11 girls), 13 (41%) in group A and 11 (55%) in group B. Some died within a few hours of admission and 19 (37%) had succumbed by the

fourth day of the illness. Death within 48 hours was more common in group B (eight cases compared with two in group A) possibly because it prevented the emergence of all the diagnostic criteria. Outcome was related to severity of encephalopathy at presentation: babies with intractable convulsions and deep coma were likely to die, while those with less depressed consciousness and less frequent fits usually survived.

Of the 28 survivors, 18 had severe neurological damage, typically manifested by a fall-off in head growth, developmental regression, spasticity, cortical visual impairment, and seizures. In four babies the neurological outcome was uncertain, while six were deemed to have recovered. The mean duration of admission among survivors (excluding one child who stayed in hospital for seven months partly for social reasons) was 23 days (range 8-80 days). Early readmissions because of seizures were common.

HAEMATOLOGICAL FEATURES (TABLE 2)

Haemoglobin concentrations were normal at presentation in all patients, but in 47 of the 48 cases where successive measurements were made, fell by a mean of 36 g/l (range 17-83 g/l) over the next 12-48 hours. Eighteen babies received a blood transfusion. Platelet counts were initially always normal or raised, but fell to a mean of approximately $54 \times 10^9/l$ (minimum $16 \times 10^9/l$) over a similar period. The initial white cell count was raised in every case except one, with a mean value of $23 \times 10^9/l$ (range $7.3-67.3 \times 10^9/l$). Either neutrophils or lymphocytes were reported to predominate, and in some cases neutrophils were immature. Coagulation tests, a wide variety of which were performed in all except four patients, were always abnormal, with an initially moderate disturbance becoming more severe by 24 hours.

BIOCHEMICAL FEATURES (TABLE 2)

All patients except two were initially hypernatraemic, with a mean serum sodium concentration of 145 mmol/l and a highest value of 156 mmol/l. All were acidotic, the mean serum bicarbonate being 11.5 mmol/l (minimum 6.9 mmol/l) and the mean arterial or capillary pH being 7.16 (minimum 6.80). Acidosis was often hard to correct. Blood urea was usually slightly raised on admission and always rose higher over the next 48 hours to a mean maximum concentration of 17.0 mmol/l, the highest level being 29.7 mmol/l.

A progressive rise in hepatocellular enzymes was invariable, activities being moderately raised where assays were done early and grossly raised by 48-72 hours. Hypoglycaemia (blood glucose <2 mmol/l) was a common early feature, being recorded in 36 (75%) of the 48 cases in whom the blood glucose was measured (this includes some measurements by reagent strips as well as laboratory assays). Hypoglycaemia was either present on admission (14 cases, 29%) or developed over the next few hours (22 cases, 46%). It was often profound, with recordings of

Table 2 Laboratory results

	Group A (n=32)	No of cases investigated	Group B (n=20)	No of cases investigated
	Mean (SD)		Mean (SD)	
Fall in haemoglobin (g/l)	35.0 (16)	32	33.0 (11.0)	16
Lowest platelet count ($\times 10^9/l$)	53.00 (24.7)	32	56.00 (26.00)	12
Initial white cell count ($\times 10^9/l$)	22.90 (11.1)	31	24.50 (12.40)	20
Initial sodium (mmol/l)	145.00 (4.9)	31	146.00 (5.50)*	18
Initial bicarbonate (mmol/l)	11.50 (2.5)	31	11.40 (2.70)	17
Initial pH	7.16 (0.14)	26	7.12 (0.16)	15
Maximum blood urea (mmol/l)	17.00 (4.9)	32	16.20 (4.40)	16
	No of cases		No of cases	
Blood glucose <2 mmol/l	23	29	13	19
Hepatic transaminases: abnormal	32	32	18	18
α_1 -Antitrypsin <20 μ mol/l	5	12	1	7
Ammonia ≥ 100 μ mol/l	9	29	5	16

*Excluding one concentration of 122 mmol/l.

zero in 14 cases, and difficult to correct by dextrose infusion. No insulin assays were performed.

Plasma ammonia concentrations were measured at least once in 45 children, 29 in group A and 16 in group B. Thirteen patients had concentrations below 50 µmol/l, 18 between 50 and 99 µmol/l, and 14 had concentrations of 100 µmol/l or more, the highest being 328 µmol/l. In eight of the cases where the ammonia was 100 µmol/l or more, the sample had been taken within an hour of admission; in each of these eight the concentration had fallen below 100 µmol/l within 24 hours. In five cases the timing of the raised concentration was not recorded; in one case it was recorded as normal on admission, but as 124 µmol/l 36 hours later.

α₁-Antitrypsin concentrations were available in 19 patients and were reduced (<20 µmol/l) in six, including all three in whom samples were taken in the first 12 hours. Only three recordings of immunoreactive trypsin were available, all taken after 24 hours: two were normal and one appreciably raised (>400 mg/ml). Pi phenotyping was available on four surviving babies; three were Pi MM and one Pi MZ. Creatine phosphokinase was raised (1886, 1921, and 4185 IU/l) in three of the four cases in whom it was assayed, the samples being taken between

24 and 72 hours after admission. Amylase was assayed in five cases (all within 24 hours of admission); it was raised in one (240 IU/l) and normal in the remainder (68, 78, 131, and 163 IU/l).

MICROBIOLOGICAL FINDINGS (TABLE 3)

Microbiological findings were inconsistent and of uncertain clinical relevance. The organisms grown from blood and cerebrospinal fluid (CSF) (15 cases and two cases respectively) were all regarded as contaminants by the clinicians concerned. No pleocytosis accompanied the two positive CSF cultures. However, in six other samples of CSF there was a small excess of lymphocytes, 7–16 cells being counted per mm³. In 12 CSF samples the protein content was slightly raised, with a mean value (SD) of 79 (41) g/l.

Stool specimens were cultured in 51 cases, of which six yielded possible pathogens. No significant infection was found in the 46 patients whose urine was cultured.

RADIOLOGICAL FINDINGS

Chest x ray films were taken on 44 babies, usually after intubation. Abnormalities were seen in 15: collapse of an upper lobe (10 cases), streaky shadowing (two cases), underinflation of one lung (one case), aspiration (one case), and unspecified changes (one case). These appearances were thought by the relevant clinicians to be secondary rather than causative features of the illness.

NEUROLOGICAL INVESTIGATIONS (TABLE 4)

Electroencephalographic abnormalities of various kinds were found, focal or multifocal spike activity being the most common. Recordings made in the first 72 hours were abnormal in 22 of 23 patients; when 12 of these 22 were re-examined after an interval of a week or more, nine remained abnormal. Cranial ultrasonography was abnormal in 10 of the 24 patients investigated, with initial diminution of ventricular volume and subsequent asymmetry or atrophy of cerebral tissue. Computed tomography often showed diminution of ventricular volume initially and cerebral atrophy later; low density areas in the cortex were seen at all stages.

Table 3 Microbiological findings

	Group A (n=32)	Group B (n=20)	Combined (n=52)
Blood culture			
Performed	32	18	50
Positive	7	8	15*
CSF culture			
Performed	32	16	48
Positive	2	0	2†
Stool culture (bacterial)			
Performed	32	19	51
Positive	4	2	6‡
Viral studies (culture or serology)			
Performed	23	12	35
Positive	5	1	6§

*Staphylococcus coagulase negative (n=10), Staphylococcus coagulase positive (n=2), Streptococcus faecalis (n=1), Streptococcus viridans (n=1), Moraxella catarrhalis (n=1).

†Staphylococcus coagulase negative (n=1), Staphylococcus coagulase positive (on enrichment) (n=1).

‡Clostridium difficile (n=3); pathogenic Escherichia coli (n=2); Gram positive cocci (n=1).

§Enterovirus (three including one coxsackie B5); adenovirus (n=1); rotavirus (n=1); parainfluenzae type 3 (n=1).

Table 4 Neurological investigations

<i>Time after presentation</i>	<i>Electroencephalography</i>		<i>Cranial ultrasonography</i>		<i>Cranial computed tomography</i>	
Total patients investigated		23		17	10	
0–72 hours	Focal/multifocal spikes	14	Diminished ventricles	7	Diminished ventricles	6
	Low amplitude activity	4	Normal	10	Low density areas	3
	Slow waves	3			Normal	3
	Flat	3				
	Unspecified abnormalities	5				
	Normal	1				
Total patients investigated		6		4		2
3–7 days	Low amplitude activity	2	Asymmetrical ventricles	1	Diminished ventricles	1
	Flat	1	Normal	3	Low density areas	1
	Unspecified abnormalities	3				
Total patients investigated		12		3		7
8–120 days	Focal/multifocal spikes	5	Asymmetrical ventricles	1	Low density areas	3
	Slow waves	1	Cerebral atrophy	1	Cerebral atrophy	4
	Hypsarrhythmia	1	Normal	1		
	Unspecified abnormalities	2				
	Normal	3				

Table 5 Postmortem findings

Case No	Duration of illness (hours)	Brain		Lungs		Liver		Kidneys		Adrenals	
		Gross	Histology	Gross	Histology	Gross	Histology	Gross	Histology	Gross	Histology
Group A											
1*	102	Soft and swollen, herniation	NA	Congestion, patchy haemorrhage	Focal haemorrhage	Fatty, 'nutmeg' pattern	CLN	Congestion	Some ATN	Normal	Medullary congestion
2	71	Swollen	Zonal hypoxic damage	Congestion	NA	Normal	NA	Congestion	NA	Normal	NA
3	19	Soft and swollen	NA	Congestion	NA	Pale	NA	Normal	NA	Normal	NA
4	65	Swollen	NA	Congestion, patchy collapse	Oedema	Slightly pale and fatty	CLN, some fatty change	Swollen	Normal	Normal	NA
5	51	Soft and swollen	NA	Congestion, patchy haemorrhage	Congestion, intra-alveolar haemorrhage	Enlarged and fatty	CLN	Normal	ATN possible chronic glomerulopathy	Normal	NA
6	52	NA	NA	Congestion	Focal haemorrhage	Not enlarged, mottled red/brown	CLN	Focal pallor	Some ATN	Some haemorrhage	Haemorrhage
7	56	Swollen, herniation	Hypoxic damage	Congestion	Congestion, focal haemorrhage	Enlarged irregular pale areas	Fatty change (micro-vesicular), focal necrosis (not zonal)	Normal	Normal	Normal	Normal
8	76	Swollen, herniation	Oedema	Congestion	Congestion	Normal	Periportal fatty change	Normal	Congestion	Normal	Normal
9	72	Soft	Hypoxic damage	Congestion, focal haemorrhage	Intra-alveolar haemorrhage	Enlarged and fatty	CLN, fatty change	Pale	Fatty infiltration of tubular epithelium	Normal	NA
10	29	Swollen, herniation	NA	Patchy collapse	Some oedema, intra-alveolar haemorrhage	Pale and fatty	Diffuse fatty change (micro-vesicular)	Normal	A few cystic tubules	Normal	Normal
Group B											
1	35	Soft, ?infarction	Haemorrhagic changes	Congestion, haemorrhage	Congestion	Pale, mottled	Inter-sinusoidal haemorrhagic changes	Congestion	NA	Haemorrhage, infarction	Infarction
2	56	Swollen, herniation	NA	Normal	NA	Partly yellow discolouration	NA	Congestion	NA	Normal	NA
3†	7	Normal	NA	Congestion	NA	?Fatty change	NA	Normal	NA	NA	NA
4	8	Congestion, focal haemorrhage	Micro-thrombi, micro-infarction	Focal haemorrhage, ?pneumonitis	Congestion	Congestion	Congestion, no fatty change	Normal	Congestion	Haemorrhage, infarction	Infarction
5	12	Normal	NA	Congestion, haemorrhage	Congestion	Normal	Congestion	Normal	Normal	Congestion	Congestion
6	120	Swollen	Focal lymphocytic infiltration	Patchy broncho-pneumonia	Congestion	Yellow	Centrilobular congestion, cholestasis	Normal	Normal	Swollen, haemorrhage	Normal

*Also pituitary necrosis, †also haemorrhagic colitis.
ATN=acute tubular necrosis, CLN=centrilobular necrosis, NA=not available.

The sequence of changes found in these three investigations suggests an initial and severe generalised cerebral disturbance leading on quickly to cerebral oedema, and then sometimes to infarction and atrophy. Further evidence for an extreme rise in intracranial pressure was provided by a case in which brain tissue was extruded through a monitoring catheter.

POSTMORTEM FINDINGS (TABLE 5)

Necropsy reports were available for 10 of the 13 fatal cases in group A and for six of the 11 fatal cases in group B. A seventh group B patient had an immediate postmortem liver biopsy, but no necropsy.

Small focal haemorrhages in many organs were a common feature. The lungs were usually

congested, and often there was focal intra-alveolar haemorrhage. The kidneys were usually normal, though some degree of acute tubular necrosis was seen in three cases. Adrenal haemorrhage and infarction was noted in four cases, and in one case there was infarction of the pituitary gland.

In 13 cases the brain was soft and/or swollen and in five of these there was cerebellar herniation; the three babies whose brains were not swollen had all died early in the illness.

Changes in the small gut were reported in three cases: in one, a degree of villous blunting, in the second, partial villous atrophy with crypt abscess formation, and in the third, an increase in acute inflammatory cells. In one baby aged 3 weeks, the youngest in the series, the only abnormality was in the macroscopic appear-

ance of the large bowel, which was described as 'consistent with haemorrhagic colitis'. In this patient shock and encephalopathy had preceded bloody diarrhoea and she met the criteria for inclusion in group A.

The hepatic findings are described below in some detail in view of the interest in distinguishing HSES from Reye's syndrome (see discussion).

The macroscopic appearance of the liver was described as normal in only three of the 16 cases. Among the remainder it was 'pale', 'yellow' and/or 'fatty' (n=11); 'congested' (n=1); 'mottled reddish-brown' (n=1). There were abnormalities in all 13 livers examined histologically. In five of these, all group A, fatty changes were described: in one, the fat occurred throughout the lobule, but was reported 'insufficient for Reye's syndrome'; in another it was a diffuse microvesicular infiltration 'in keeping with a Reye-like syndrome'; in the third it was described as an 'extreme degree of fatty change'; in the fourth it was periportal; in the last it was 'widespread with small and medium sized vesicles not displacing hepatocyte nuclei and not typical of Reye's syndrome'. In three of these five cases hepatic cell necrosis was also reported: centrilobular in two, widespread and focal in one.

Necrosis was also reported in three further group A cases: centrilobular in one; widespread ('therefore not Reye's') in another and as 'massive infarction leaving only periportal cell remnants' in the third.

Overall, of the nine patients who had survived more than 48 hours and whose livers were examined histologically, six showed necrosis, and four had concomitant fatty changes. Of the four who had survived less than 48 hours, none showed necrosis and one showed fatty change.

There was no relationship between plasma ammonia concentrations and hepatic fatty changes.

Electron microscopy of liver tissue was available for only one patient and showed poor cellular preservation, 'blown' mitochondria, lysosomes containing dense areas, but no other distinctive features.

Discussion

This series of cases of HSES, ascertained by routine surveillance, had certain advantages over series reported from referral centres: it enabled epidemiological trends to be assessed; it represented a wider spectrum of the condition because it was not limited to cases severe enough to merit referral; and it allowed the evolution of a rapidly developing illness to be described from its outset.

The data confirmed other reports that most patients with HSES are aged between 3 and 4 months.^{1 4-25} It has been proposed by Chaves Carballo *et al* that HSES should not be diagnosed beyond the age of 1 year.¹⁷ However, two of the patients, one in each group, were aged nearly 2 and nearly 3 years respectively, and older cases have also been described by others.^{5 7 15 24 26 28}

The overall male excess and higher mortality among females in the previous survey²⁶ was not

seen among the 1985-8 cases. As in the earlier series, however, there was neither a distinct seasonal pattern (apart from a slight excess of cases in the winter months) nor any obvious place-time clusters.

The high rate (13%) of previously existing developmental anomalies and problems in these patients was also observed in the 1982-4 series²⁶ and by Levin *et al*, who noted such disorders in seven of their 25 patients, including two with Down's syndrome.²⁴ Furthermore, four of the oldest five infants in the 1985-8 survey had neurodevelopmental problems. These observations are unexplained, but may represent reduced ability to respond to a harmful stimulus because of impairment either of intrinsic mechanisms or of protective behavioural responses.

A mild prodromal illness was frequently but not invariably reported. Information was incomplete, but at least three babies who had no prodrome had been immunised in the preceding 72 hours. Given the frequency with which such symptoms and events occur in infants, however, their significance in the pathogenesis of HSES is uncertain. Despite extensive investigation, no microbiological aetiological agents, including 'exotic' viruses, have been consistently isolated from patients with HSES.^{1 24} Positive microbiological findings in the current series were varied and were considered to be either non-contributory or contaminants.

As in previous descriptions,^{1 4-25} a high temperature was initially observed in most (86%) of the patients reported to this survey, 14% having an admission temperature over 42°C. By contrast some babies had subnormal temperatures, but all of these had been stripped for some time. One baby was described as 'very, very hot to the touch' when found by her parent and the temperature was 41.6°C on admission, but had fallen to 32°C 10 hours later. A similar decline in temperature from high pyrexia on arrival at a casualty department to hypothermia after transfer to an intensive care unit some hours later, has been observed by others.¹⁶ These observations suggest that temperature control may be impaired in HSES (perhaps because of preceding pyrexial insult to the hypothalamus) and illustrate how a normal or low admission temperature could be compatible with preceding fever.

Reports from tertiary referral centres have described death or brain damage as the usual outcome of HSES.^{17 24} Among the 52 cases in this unselected series, six (12%) were reported to have survived intact, though there is still the possibility that sequelae may have emerged after longer follow up.

It has been questioned whether HSES is a distinct clinicopathological entity in its own right, or whether it represents the final common pathway of several disorders with similar features.²⁹ Although there is no single clinical or pathological factor that is pathognomonic for HSES, the pattern of features found in the present series (the largest yet described) and in others⁴⁻²⁶ is markedly consistent.

HSES can therefore, we believe, be distinguished from other conditions that share some of its features. The main differential diagnoses

are septicaemia, overwhelming viraemia, Reye's syndrome, haemolytic uraemic syndrome, staphylococcal toxic shock syndrome, and various inherited disorders.

The presenting features of high fever, shock, and leucocytosis usually (and reasonably) prompt a presumptive diagnosis of septicaemia. If blood cultures are not taken before antibiotic treatment is begun, it is then difficult to exclude this diagnosis as many of the features of HSES, such as disseminated intravascular coagulation and renal failure, could be attributed to it. HSES may, therefore, be misdiagnosed as septicaemia, through either failure to take cultures before treatment or disregard of negative reports. While tropical viruses such as dengue might cause confusion with HSES, no viral infection of temperate climates, however severe and overwhelming, causes the same constellation of features.

The combination of cerebral and hepatic disorder, especially when accompanied by hypoglycaemia and hyperammonaemia, inevitably suggests Reye's syndrome. Indeed some authors have suggested that HSES should not be diagnosed if one or both of these biochemical abnormalities are present.^{17 24} However, Reye's syndrome differs from HSES in a number of clinical and pathological details.

In Reye's syndrome the onset of illness is usually slower, with vomiting a prominent feature, while diarrhoea (especially if bloody) and disseminated intravascular coagulation are unusual. Patients with typical Reye's syndrome are considerably older (median age 8–9 years³⁰) than those with HSES; where cases in infancy have been described some may have been confused with HSES.

The hyperammonaemia found in several of the patients in the present series was not as pronounced as that typically found in Reye's syndrome and there was a rapid reversion towards normal concentrations. Hyperammonaemia may be a non-specific accompaniment of severe illness and, moreover, ammonia assays are not always reliable when undertaken by laboratories not performing them regularly. Hypoglycaemia is similarly non-specific: it was a more prominent feature in the 1985–8 cases than in some series^{1 24} but has been reported by others.^{5 7 16 23}

Hepatocellular enzymes are increased to a similar degree in both disorders, but liver histology, with experienced interpretation, should be distinctive. Fatty change is always present in the acute phase of Reye's syndrome, persists for about five days and is typically diffuse, with panlobular microvesicular infiltration of hepatocytes, retention of nuclear position, and no necrosis or inflammatory infiltrates.³⁰ Fatty change was reported in five of the 13 HSES patients whose livers were examined histologically, but in only one of these was it described as consistent with Reye's syndrome. The illness duration was less than five days in all of this group.

Although the hepatic histological changes in Reye's syndrome are also seen in some other conditions, ultrastructural changes appear to be pathognomonic.³⁰ There is little published

information on hepatic ultrastructural changes in HSES.⁷ Electron microscopic examination could be useful in distinguishing it from Reye's syndrome for those cases with fatty livers, but this is best undertaken on antemortem biopsy material, which may limit the feasibility of this approach.

The combination of bloody diarrhoea, renal failure, and disseminated intravascular coagulation may lead to confusion with haemolytic uraemic syndrome. However, in haemolytic uraemic syndrome the onset of the condition is usually less abrupt, diarrhoea precedes rather than accompanies the main illness, encephalopathy, if present, comes late, and liver function is seldom disturbed.

Staphylococcal toxic shock syndrome presents with the same abruptness as HSES and shares the features of high fever, shock, and multisystem involvement. However, there is invariably a rash, not seen in HSES, and a focus of infection is usually evident (the scanty growth of staphylococci in three of our cases was attributed to contamination). Streptococcal toxic shock syndrome is a newly emerging entity which may not always be associated with a rash. It has mostly been described in adults and again there is usually an obvious focus of infection. Group A β haemolytic streptococci were not isolated from any of the patients with HSES.

Various genetic disorders such as malignant hyperpyrexia and inborn errors of metabolism including disorders of ketogenesis, urea cycle disorders, and organic acidurias may present with sudden onset of encephalopathy in infancy or childhood. However, except in malignant hyperpyrexia, high fever is not normally a presenting feature. There may be a suggestive family or personal history, which was not recorded for any of the patients with HSES in the current series (in contrast to the 1982–4 survey²⁶) except the two whose twin died the same night.

The simultaneous occurrence of HSES and SIDS in the pairs of twins in this series supports speculation about a link between the two conditions.^{11 25} Other features supporting such a link are a similar age range, the modal age for HSES coinciding with the second peak of the bimodal distribution for SIDS, and the slight excess in the winter months. Among babies who are classified as having had an 'acute life threatening event' there may be some who have in fact had HSES.

In the absence of an established cause for HSES, explanation of its pathological features remains speculative. We suggest that most (if not all) may best be explained as secondary phenomena following a severe initial insult that affected many tissues.

Various stimuli, not necessarily infective, may cause leucocytosis and also trigger disseminated intravascular coagulation, thereby producing a rapid fall in haemoglobin and platelets. The severe acidosis of HSES is mainly metabolic and may arise initially from poor tissue perfusion and then from renal failure.

Hypoglycaemia was an unexpected and interesting finding; it may have resulted from sudden hepatic dysfunction, but its refractoriness

raises the possibility of hyperinsulinaemia. Unfortunately, no insulin assays were undertaken. Although no pancreatic damage was observed at postmortem examination, the increase of amylase and trypsin is compatible with a leak of pancreatic enzymes.

Hypernatraemia could be explained by sweating; it was found before the onset of diarrhoea, so that intestinal fluid loss is a less likely explanation. The peaking of hepatocellular enzymes at about 48 hours suggests an evolving disorder of hepatic cells that subsequently resolves. Creatine kinase and trypsin were most often found to be raised and α_1 -antitrypsin to be depressed at the onset of the illness and then to revert to normal, suggesting that these were secondary rather than causative features.

Postmortem findings were generally non-specific and were all consistent with reduced blood flow and hypoxia secondary to hypotension. Cerebral oedema may result from a variety of insults, while acute renal tubular necrosis and hepatic centrilobular necrosis may both follow circulatory failure. Widespread petechial haemorrhages are commonly found in babies dying from SIDS and are also often found at post-mortem examination when there has been hypoxic capillary endothelial damage while the circulation continues. Changes in small gut histology similar to those found in four of the cases have been associated with overheating in one report,³ but were regarded as non-specific in another.³¹

Several authors have commented on the close similarity between the clinical and pathological features of HSES and those of heat stroke.^{2 7 10 12 16 17 32 33} The most detailed descriptions of heat stroke are of soldiers in hot climates,^{34 35} but there are also some of babies left in cars in the sun,^{36 37} who appear to be affected in the same way as adults. Such patients present with acute encephalopathy (convulsions, altered consciousness), initial profuse sweating, shock, diarrhoea, renal failure, hypernatraemia, metabolic acidosis, clotting disturbance, thrombocytopenia, and raised hepatic transaminases. Illness severity may be determined not only by the thermal environment but also by individual susceptibility,³⁴ the nature of which is not yet understood.

Pathological features, also described in patients given hyperthermia therapy,³⁸ include cerebral oedema, characteristic changes in the dentate nucleus, Purkinje cells, and Bergmann astrocytes; hepatocellular necrosis and fatty change (both dependent on illness duration); and diffuse multiorgan petechial haemorrhages.

There have also been reports from France,³⁹ India,⁴⁰ and England³ of infants and young children presenting with an illness identical to heat stroke, but lacking a clear cut history of overheating. The authors suggest that heat injury may nevertheless have been the cause if the effects of an initial febrile illness were compounded by excessive insulation (in the European cases) or by very high ambient temperature (in the Indian).

The similarity of these cases and of HSES to classical heat stroke supports the hypothesis that all these disorders may be one and the

same. Biochemical abnormalities reported in HSES, but not in heat stroke, such as raised serum trypsin and reduced α_1 -antitrypsin, may not yet have been sought in the latter condition. It is possible that they are among many epiphenomena that follow an initial global insult. To date there appear to have been no reports in HSES of the specific changes in brain histology noted in heat stroke; it is possible that they, too, have not been sought.

One group has reported finding botryoid nuclei in peripheral white blood cells (said to be specific for heat stroke) in two HSES patients on admission, but not 24 hours later.¹⁰ They were not noted among any of the patients in the present series, but again were probably not specifically sought within the critical time period.

Other authors have expressed scepticism about the relationship between HSES and heat stroke, mainly because of the apparent absence either of a history of overheating or of a very high temperature on admission.^{4 9 24 25 41} Admission temperature is, however, an unreliable indicator of preceding hyperpyrexia and specific details of the infant's home thermal environment are necessary to elicit the possibility of overheating.⁴² These should include the temperature of the infant's bedroom, the insulation provided by the clothing and bedding (preferably estimated in tog values), whether the head was covered, and whether the baby was hot and sweaty when first found.

Other aetiopathogenic theories, for example that HSES results from deficiencies of protease inhibitors,²⁴ abnormalities in stress protein production,²⁵ or bacterial endotoxin leaking through a gut lining damaged by splanchnic ischaemia,¹⁸ are all compatible with the notion that the pathogenic cascade of events culminating in HSES results from a heat induced trigger in a genetically determined, susceptible individual. The rarity of HSES could be compatible with this hypothesis, because an improbable combination of risk factors would have to be present to initiate the cascade. It would also explain the characteristic age range (a time of life when both thermoregulation is immature and maternally derived immunity is waning) and would be compatible with the occasional case occurring in older children—a similar pattern is seen in some of the infection-precipitated Reye-like metabolic disorders. The highly significant clustering of admission times (unlikely to be confounded by administrative factors in such severe illness) also supports this hypothesis—it suggests a peak onset period at night, a time when a baby may be most at risk from heat injury.⁴³ If HSES is, therefore, the result of heat injury, then it is not a new disease. However, recent fashions in bedroom heating and babies' bedding and clothing may pose new risk factors for the condition.

In the absence of a clear understanding of the aetiopathogenesis of HSES, management has to be non-specific and supportive. The current survey did not aim formally to evaluate treatment, which essentially is a salvage operation after the initial catastrophic event preceding presentation. The variety of measures used were

dictated by the course of the illness. It was not possible to demonstrate that any had a consistent beneficial effect, although early vigorous measures to counter cerebral oedema appeared to be associated with improved outcome.

We agree with others, that the term 'haemorrhagic' shock is misleading, because it implies that shock ensues from haemorrhage, whereas in fact it precedes it.⁴⁴ As abrupt onset is invariable, we suggest that if a change of title is contemplated, 'acute shock encephalopathy syndrome' might be more appropriate. Alternatively, if the condition is indeed a form of heat stroke another title is unnecessary.

We propose that the diagnoses of HSES be made on the basis of the features specified in our case definition, plus the exclusion of the similar disorders discussed above. We do not agree that an upper age limit of 1 year should be set or that patients with hypoglycaemia and hyperammonaemia should be excluded. We further suggest that clinical and pathological observations in future series should be reported in relation to the interval after onset, and that there is a need for more detailed and systematic histological and ultrastructural studies, particularly of brain and liver.

In conclusion, the data from this CDSC/BPA surveillance scheme do not suggest that HSES was a major new and increasing public health problem in the British Isles in the 1980s, associated with some novel environmental agent. However, although the disease is uncommon it is so severe that further studies to elucidate its aetiopathogenesis are essential, especially as the possibility of a preventable cause, namely hyperthermia, has been raised.

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