Received:
13 November 2017

Revised:
14 December 2017

Accepted:
20 December 2017

<https://doi.org/10.1259/bjr.20170861>

Cite this article as:

Sanz D, D'Arco F, Robles CA, Brierley J. Incidence and pattern of brain lesions in paediatric septic shock patients. *Br J Radiol* 2018; **91**: 20170861.

SHORT COMMUNICATION

Incidence and pattern of brain lesions in paediatric septic shock patients

¹DEBORA SANZ, MD, ²FELICE D'ARCO, MD, ²CARLOS ANDRES ROBLES, MD and ¹JOE BRIERLEY, MD

¹Paediatric Intensive Care Unit, Great Ormond Street Hospital for Children NHS Trust, London, UK

²Department of Neuroradiology, Great Ormond Street Hospital for Children NHS Trust, London, UK

Address correspondence to: Dr Debora Sanz

E-mail: Debora_sanz@hotmail.com

Objective: Brain injury is frequently observed during septic shock and may be primarily related to the direct effects of the septic insult on the brain or to secondary/indirect injuries (e.g. hypotension, hypoxaemia and hyperglycaemia). We sought to assess incidence and pattern of brain lesions diagnosed by neuroimaging in paediatric septic shock patients.

Methods: Retrospective descriptive hospital-based study included paediatric patients with a single episode of septic shock admitted to our tertiary paediatric intensive care unit from January 2010 to December 2013.

Results: 49 of 193 septic shock patients had a neuroimaging examination [CT only 22 (45%), MRI only 14 (29%) and both 13 (27%)]. Neuroimaging was normal

in 16 patients (33%) and showed acute lesions in 20 patients (40%). The most frequent findings were: cerebral infarcts/hypoxic ischaemic injury in 8 (16%) and cerebritis in 7 (14%). The incidence of acute brain lesion in our septic shock cohort was 10% (20 of 193).

Conclusion: The diagnosis of brain dysfunction in septic shock patients relies essentially on neurological examination and neurological tests, such as electroencephalography and neuroimaging. Neuroimaging can reveal acute intracerebral structural lesions and their reversibility, helping with management and prognosis.

Advances in knowledge: Ischaemic lesions and cerebritis are the most common brain anomalies complicating paediatric septic shock.

INTRODUCTION

Brain dysfunction is a frequent and occasionally severe complication of septic shock. Its presence has been shown to be an independent determinant of poor prognosis in patients with sepsis.¹ Current literature suggests that up to 70% of adult patients diagnosed with sepsis exhibit symptoms of encephalopathy;^{2,3} however the incidence of septic encephalopathy has not been clearly demonstrated in children.

The brain abnormalities reported on imaging in children with severe sepsis can vary in nature and location and can involve different regions of the brain, consequently the potential pathophysiology may also be also variable.⁴

The aim of this study was to review all the cases of sepsis in a tertiary paediatric UK centre, in order to assess the incidence and pattern of brain lesions diagnosed on brain MRI and/or CT and the usefulness of neuroimaging in management of such complex patients.

METHODS AND MATERIALS

Patients and data collection

This is a retrospective descriptive study including paediatric patients with one episode of septic shock, admitted to our tertiary paediatric intensive care unit (PICU) from January 2010 to December 2013 who underwent neuroimaging as part of routine clinical care. Patients were excluded if they have more than one episode of septic shock during the study period, because of the difficult correlation between imaging and clinical status, or if they did not undergo neuroimaging. Septic shock was defined using contemporary international consensus definitions.⁵ Relevant demographic and clinical data were collected from electronic medical records.

Neuroimaging data

CT scans of the head with or without contrast (depending on the clinical indication) were performed on a dual source CT scanner (Somatom Force; Siemens Healthcare, Erlangen, Germany). MRI scans of the brain were performed on a 1.5 Tesla scanner (Symphony; Siemens Healthcare, Erlangen, Germany) or on a 3 Tesla scanner (Prisma; Siemens

Healthcare, Erlangen, Germany). Standard brain protocol included: Axial T_1 and T_2 weighted images (WI), coronal fluid-attenuated inversion-recovery sequence, axial echoplanar imaging diffusion-weighted imaging sequence and axial, coronal and sagittal postcontrast T_1 weighted images when clinically indicated (e.g. clinical signs of active infection). When clinical suspicion of stroke and/or venous sinus thrombosis was present, magnetic resonance angiographic and magnetic resonance venographic (MRV) sequences were acquired.

MRI and CT scans, performed during patient's admission on PICU for septic shock, were analysed together with follow-up MRI in the following 8 weeks after discharge from PICU when available.

Statistical analysis

Continuous variables not normally distributed were summarized as a median with interquartile range, with group comparison performed using the Mann-Whitney test. Categorical data were compared using χ^2 or Fisher exact test as indicated. All p values of less than 0.05 were considered statistically significant. SPSS v. 23 (IBM, Chicago, IL) was used for all statistical analysis.

RESULTS

From January 2010 to December 2013, a total of 197 children with septic shock were admitted to our PICU, 4 were excluded from the study because they had more than 1 episode of septic shock during the study period. Of the remaining 193 patients 144 did not undergo neuroimaging leaving 49 children (25%)

who underwent neuroimaging examination. Demographic and clinical data are summarized in [Tables 1 and 2](#).

Neuroimaging performed during the study period were: brain CT alone in 22 (45%) patients, brain MRI alone in 14 (29%) patients and both brain CT and MRI in 13 (27%) patients.

Neuroimaging results were normal in 16 (33%) patients. 13 (27%) patients in the study group with neuroimaging performed during the shock septic episode had previous neuroimaging abnormalities, including brain tumour, basilar arterial thrombosis and pontocerebellar infarctions, leukodystrophy, periventricular leukomalacia, polymicrogyria, cerebral atrophy, generalized reduction of white matter bulk and basal ganglia calcifications, and they did not present any acute change on the neuroimaging performed during the shock.

The remaining 20 (41%) patients presented acute abnormal findings on the scan. Cerebral infarct or diffuse hypoxic ischaemic injury in 8 (40%) patients ([Figure 1](#)), cerebritis in 7 (35%) patients, combination of ischaemia and cerebritis in 1 (5%) patient, intracranial haemorrhage in 2 (10%) patients ([Figure 2](#)), posterior reversible encephalopathy syndrome (PRES) in 1 (5%) patient and sinus venous thrombosis in 1 (5%) patient ([Figure 3](#)). The total incidence of acute brain lesion in our septic shock cohort was 10.3% (20 of 193). Results are summarized in [Figure 4](#).

Blood culture was positive in 16 (47%) patients with septic shock and abnormal neuroimaging investigation. Group B streptococcus

Table 1. Patients' characteristics

Characteristic	Total ($n = 193$)	Neuroimaging ($n = 49$)	p
Patient demographics			
Age (months), median (IQR)	12.63 (1.45–65.98)	32.47 (2.83–131.75)	0.32708
Age category, n (%)			
0–28 days	37 (19)	7 (14)	0.535883
29 days–1 year	59 (31)	12 (24)	0.483706
1–5 years	47 (24)	9 (18)	0.450613
5–10 years	19 (10)	7 (14)	0.437024
>10 years	31 (16)	14 (29)	0.06253
Male, n (%)	126 (65)	30 (61)	0.61855
Paediatric Index of Mortality score, median (IQR)	9% (5–15%)	7% (3–14%)	0.79486
Paediatric Index of Mortality score-2, median (IQR)	8% (4–15%)	6% (3–14%)	0.79486
EEG, n (%)	74 (38)	33 (67)	0.000347
Max. 48 h vasoactive-inotropic score, median (IQR)	32 (13.25–81.88) ^a	32 (20–50) ^c	0.8493
Length of mechanical ventilation (days), median (IQR)	3 (2–10) ^b	6.5 (3–14)	0.00544
Length of stay in ICU (days), median (IQR)	5 (2–12.5)	9 (4–18)	0.0041
Mortality, n (%)	55 (28)	11 (22)	0.474274

EEG, electroencephalography; ICU, intensive care unit; IQR, interquartile range.

^aNine missing data.

^bOne missing data.

^cTwo missing data.

Table 2. Comparison between normal and abnormal neuroimaging patients

	Normal neuroimaging (n = 15)	Abnormal neuroimaging (n = 34)	p
Patient characteristics			
Age (months), median (IQR)	66.53 (17.4–133.2)	14.73 (1.03–131.03)	0.13888
Age category, n (%)			
0–28 days	1 (7)	6 (18)	0.41423
29 days–1 year	2 (13)	10 (30)	0.297627
1–5 years	3 (20)	6 (18)	1
5–10 years	4 (27)	3 (9)	0.179383
>10 years	5 (33)	9 (26)	0.734927
Male, n (%)	8 (53)	22 (65)	0.53189
PIM score, median (IQR)	6% (3–12%)	8% (3–15%)	0.72786
PIM-2 score, median (IQR)	6% (3–10%)	7% (4–19%)	0.77948
Max. 48 h VIS, median (IQR)	42.5 (25.75–91.5) ^a	32 (17.5–47.5) ^a	0.09102
Length of mechanical ventilation (days), median (IQR)	4 (2–14)	7.5 (4–15.25)	0.3472
Length of stay in ICU (days), median (IQR)	9 (4–18)	9.5 (4.75–17)	0.674482
Type of neuroimaging, n (%)			
CT only	8 (53)	14 (41)	0.537746
MRI only	5 (33)	9 (26)	0.734927
Both	2 (13)	11 (32)	0.292519
Clinical manifestation, n (%)			
Seizure	4 (27)	11 (32)	0.750074
Low GCS/lethargy	5 (33)	12 (35)	1
Pupil alteration	3 (20)	5 (15)	0.68687
Signs of raised ICP	0 (0)	2 (6)	1
EEG, n (%)	8 (53)	25 (74)	0.197701
EEG result, n (%)			
Normal	1 (13)	1 (4)	0.522959
Background abnormalities	7 (88)	21 (84)	0.363252
Ictal discharges	0 (0)	3 (12)	0.543259
Positive microbiological result, n (%)			
Meningitis, n (%)	0 (0)	5 (15)	0.305695
Immunosuppression, n (%)	5 (33)	9 (26)	0.734927
Cardiac arrest, n (%)	2 (13)	6 (18)	1
Mortality, n (%)	3 (20)	8 (24)	1

EEG, electroencephalography; GCS, Glasgow Coma Scale; ICU, intensive care unit; ICP, intracranial pressure; IQR, interquartile range; PIM, Paediatric Index of Mortality; VIS, vasoactive-inotropic score.

^aOne missing data.

was the most frequent germ isolated (5 patients), followed by *Staphylococcus aureus* (2 patients) and *Streptococcus pyogenes* (2 patients). Other germs isolated were: *Staphylococcus coagulase negative*, *Escherichia coli*, *Streptococcus viridans*, *Neisseria meningitidis* B, *Enterococcus faecalis* and *Magnusiomyces capitatus*. One patient had multiple germ positive blood culture, including *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus*

faecium and *Stenotrophomonas*. Rapid antigen direct tests from nasopharyngeal samples were positive for Influenza B in 1 patient.

Lumbar puncture was performed on 13 (38%) patients with septic shock and abnormal neuroimaging investigation and result was compatible with meningitis in 5 patients. 4 of the 5 meningitis

Figure 1. A 12-year-old male with gastro-intestinal origin sepsis. Axial T_2 weighted image (WI), T_1 WI and T_2 gradient recalled echo sequence (GRE) (left to right, top row), DWI, ADC and T_1 postgadolinium WI (left to right, bottom row) show multifocal primarily cortical-subcortical lesions, some of them in watershed regions, with contrast enhancement and diffusion restriction, suggesting subacute ischaemic lesions. T_1 WI shows spontaneous hyperintense signal in keeping laminar necrosis. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging.

were caused by group B streptococcus in children aged 24–30 days, and the remained meningitis was caused by *Enterococcus faecalis* in a 11-year-old girl.

DISCUSSION

Our observational study showed that, in paediatric septic-shock patients, the most frequent acute brain lesion patterns, found on neuroimaging, were ischaemia and cerebritis (*i.e.*: cerebral oedema/damage in the clinical context of infection), which is similar to those described in previous studies in adults, where

leukoencephalopathy and ischaemic stroke were the most frequent findings.^{4,6}

Reviewing the current literature, few imaging studies have been carried out in septic-shock patients, and very few in children. In most of the cases, brain MRI was performed because of acute neurologic symptoms. The fact that common brain lesions were brain infarcts and/or confluent white matter lesions (leukoencephalopathy), provides insights

Figure 2. Preterm male with neonatal sepsis. Axial T_1 WI, T_2 weighted image (WI) and T_2 gradient recalled echo sequence (GRE) (right to left) show multiple, asymmetric focal lesions in the cerebral white matter with haemorrhagic transformation along the course of the deep medullary veins. There is generalized reduction of the white matter bulk.

Figure 3. A 26-day-old, term male with *Klebsiella* sepsis. Coronal, axial T_2 weighted image (WI) and coronal MRV (phase contrast) show absent flow void within the left sigmoid (T_2 WI) and absent flow signal on MRV, in keeping with thrombosis. No venous infarction or intracranial haemorrhage is demonstrated at this point. Also, a left sided cephalohematoma is noted. MRV, magnetic resonance venography.

Figure 4. Neuroimaging results.

regarding pathophysiology of sepsis-related brain dysfunction. Important factors involved in ischaemic changes seem to be cerebral perfusion impairment and microcirculatory dysfunction, whereas leukoencephalopathy is indicative of a range of pathologic processes including impairment of the blood–brain barrier, axon loss, gliosis, dysfunction in perivascular spaces physiology and ischaemia.^{1,6}

In few previous paediatric case reports of sepsis-associated encephalopathy, neuroimaging also revealed brain oedema, white matter and ischaemic changes;^{7–9} consistent with our findings. In a recent study published by Sandquist et al, authors studied neuroimaging from septic paediatric patients focusing on long term abnormalities rather than acute changes. The most common abnormal finding was volume loss (39%), which could be the final evolution from previous lesions, including ischaemia

or infarcts.¹⁰ Our results are focused on the acute changes detected soon after patients developed septic shock and opposed to Sandquist's study, we separated patients with previous neuroimaging alterations who did not present acute changes on their baseline neuroimaging from the rest of patients to avoid over-estimation of abnormal results. We cannot, of course, exclude subclinical pathophysiological changes in the brains of children who were not imaged and this is a potential area for further research.

Our findings together with evidence from literature show that pathophysiology of the sepsis-related brain damage in children is more likely related to dysfunction in vascular regulation than direct damage from the infective agents; furthermore, it seems that pathogenesis is similar in adults and children. Finally, our study highlights the importance of acquiring brain images immediately when a septic patient presents with neurological symptoms because of the dramatic consequences on the brain and potential change in management strategies if brain injury is confirmed, as well as suggesting need for clinical (neurodevelopmental) follow-up which is not routinely performed in such children at present.¹¹

CONCLUSIONS

This is one of the first studies to assess sepsis-associated encephalopathy and brain injury during septic shock in children. Neuroimaging can reveal acute intracerebral structural lesions and might prove a critical guide to management and to assess prognosis. Longer term outcome studies are required to determine the correlation between CT/MRI findings and outcome of these patients.

REFERENCES

1. Sonnevile R, Verdonk F, Rauturier C, Klein IF, Wolff M, Annane D, et al. Understanding brain dysfunction in sepsis. *Ann Intensive Care* 2013; **3**: 15. doi: <https://doi.org/10.1186/2110-5820-3-15>
2. Yamaguchi H, Tanaka T, Maruyama A, Nagase H. Septic encephalopathy characterized by acute encephalopathy with biphasic seizures and late reduced diffusion and early nonconvulsive status epilepticus. *Case Rep Neurol Med* 2016; **2016**: 1–5. doi: <https://doi.org/10.1155/2016/7528238>
3. Ziaja M. Septic encephalopathy. *Curr Neurol Neurosci Rep* 2013; **13**: 383. doi: <https://doi.org/10.1007/s11910-013-0383-y>
4. Stubbs DJ, Yamamoto AK, Menon DK. Imaging in sepsis-associated encephalopathy--insights and opportunities. *Nat Rev Neurol* 2013; **9**: 551–61. doi: <https://doi.org/10.1038/nrneurol.2013.177>
5. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; **6**: 2–8. doi: <https://doi.org/10.1097/01.PCC.0000149131.72248.E6>
6. Polito A, Eischwald F, Maho AL, Polito A, Azabou E, Annane D, et al. Pattern of brain injury in the acute setting of human septic shock. *Crit Care* 2013; **17**: R204. doi: <https://doi.org/10.1186/cc12899>
7. Kondo A, Sugiyama C, Fujii Y, Inoue T, Maegaki Y, Ohno K. Fulminant sepsis-associated encephalopathy in two children: serial neuroimaging findings and clinical course. *Neuropediatrics* 2009; **40**: 157–61. doi: <https://doi.org/10.1055/s-0029-1243626>
8. Lee SY, Lee KH, Hwang HS, Jeong DC, Chung SY, Kang JH. Septic encephalopathy complicating acute appendicitis. *Pediatr Crit Care Med* 2009; **10**: e11–e13. doi: <https://doi.org/10.1097/PCC.0b013e3181937125>
9. Abe S, Okumura A, Fujii T, Someya T, Tadokoro R, Arai Y, et al. Sepsis associated encephalopathy in an infant with biliary atresia. *Brain Dev* 2008; **30**: 544–7. doi: <https://doi.org/10.1016/j.braindev.2007.12.015>
10. Sandquist MK, Clee MS, Patel SK, Howard KA, Yungler T, Nagaraj UD, et al. High frequency of neuroimaging abnormalities among pediatric patients with sepsis who undergo neuroimaging. *Pediatr Crit Care Med* 2017; **18**: 607–13. doi: <https://doi.org/10.1097/PCC.0000000000001173>
11. Kaur J, Singhi P, Singhi S, Malhi P, Saini AG. Neurodevelopmental and behavioral outcomes in children With sepsis-associated encephalopathy admitted to pediatric intensive care unit: a prospective case control study. *J Child Neurol* 2016; **31**: 683–90. doi: <https://doi.org/10.1177/0883073815610431>