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Original Article

Use of Transcranial Doppler for Management of Central Nervous System Infections in Critically Ill Children

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ABSTRACT

BACKGROUND: The primary objective of this study was to characterize changes in cerebral blood flow measured using transcranial Doppler in children with central nervous system infections. We hypothesized that children with central nervous system infections have abnormal cerebral blood flow, associated with a greater frequency of complications and poor neurological outcome. **METHODS:** We conducted a single-center, retrospective study of children admitted to the neonatal or pediatric intensive care unit with central nervous system infection and undergoing transcranial Doppler as part of routine care between March 2011 and July 2015. **RESULTS:** A total of 20 children with central nervous system infection underwent 35 transcranial Dopplers. The mean age was 8.2 ± 6.3 years, including 12 boys and eight girls. The most common infection was meningitis (n = 11, 55%), with the remainder comprising encephalitis (15%), meningoencephalitis (20%), and abscess or empyema (10%). Bacterial (n = 10, 50%) and viral (n = 6) sources were common with only one (5%) fungal infection and three (15%) unknown but presumed viral etiology. The patients underwent transcranial Doppler 4 ± 9 days after intensive care unit admission. Mean cerebral blood flow velocities were overall increased compared with reference values for age (healthy children and critically ill children) mostly because of hyperemia (n = 21, 60%) and vasospasm (6%). Hypoperfusion (cerebral blood flow velocity <1 S.D. of normal value) in at least one vessel was associated with morbidity (intubation, vasoactive medications, neurosurgery, cardiac arrest) ($P = 0.04$) and mortality ($P = 0.03$). Two patients had increased intracranial pressure and hyperventilation was safely achieved with transcranial Doppler monitoring to avoid ischemia. Serial transcranial Dopplers were used to guide blood pressure management. **CONCLUSIONS:** Transcranial Doppler can be used in children with central nervous system infection as a tool to assess cerebral blood flow. In this retrospective study, cerebral hypoperfusion was associated with increased morbidity and mortality. If transcranial Doppler is to guide medical therapy and management of cerebral blood flow in children with central nervous system infections, these results will need to be validated in prospective studies with a more homogenous population of children with encephalitis or meningitis.

Keywords: transcranial Doppler, cerebral blood flow, vasospasm, central nervous system infection, pediatric intensive care unit

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Introduction

Central nervous system (CNS) infections are life-threatening diseases associated with significant morbidity and mortality.[1] In adults with meningitis, variable patterns of cerebral blood flow (CBF) have been described, including an increase correlating to the type of bacterial pathogen,[2] hyperemia in patients with reassuring clinical state, decrease

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caused by cerebral edema,[3] and vasospasm.[4] Altered CBF related to cerebral edema and arterial narrowing is associated with poor outcome in adults with meningitis.[3,4] Little is known about changes in CBF in children with CNS infections. Hyperemia in the acute phase of the infection[5] and cerebral edema with decreased CBF[6] have been reported.

Transcranial Doppler (TCD) ultrasonography permits dynamic monitoring of blood flow velocities in major intracerebral arteries and is a surrogate for CBF.[7] TCDs are part of the clinical standard of care for children with sickle cell disease,[8] but there is limited published experience with its use in acquired brain injuries in children. Clinical applications of TCD in the pediatric intensive care unit (ICU) have been proposed: noninvasive assessment of CBF, intracranial pressure (ICP), and vasospasm in children with traumatic brain injury, evaluation of cerebral autoregulation, identification of microemboli in patients at risk for stroke, diagnosis of cerebral circulatory arrest, and monitoring of ICP and vasospasm in patients with CNS infection.[9]

We hypothesized that CBF is abnormal in children with CNS infections, including hyperemia, hypoperfusion, and vasospasm, and that these patterns are associated with a greater frequency of complications related to the disease and to worse outcome.

Material and Methods

Study design and patient population

This was a single-center, retrospective, descriptive study of all pediatric patients aged up to 18 years with CNS infections who underwent TCD at Lurie Children's Hospital of Chicago pediatric or neonatal ICU from March 2011 to July 2015. The local institutional review board approved this study.

Data sources

Patients were identified from the neurocritical care database of our institution. Children with a diagnosis of CNS infection (meningitis, encephalitis, meningoencephalitis, abscess, and empyema) and who underwent TCD studies during their ICU stay were included. All patients identified underwent a medical chart review to obtain pertinent medical information and imaging data.

Demographic and clinical data

Demographic information, results of serum bacterial cultures, CSF viral polymerase chain reaction, immunofluorescence and bacterial cultures, respiratory viral polymerase chain reaction, physical examination findings, including signs of increased ICP, medical management, complications, neuroimaging, and TCD characteristics (quantity, timing, indication, and medical management secondary to the results), were abstracted from the electronic medical record.

Outcomes

The primary outcome measures were mean CBF velocities (CBFVs) in the middle cerebral arteries (MCAs) and posterior cerebral arteries (PCAs), pulsatility index (PI), and Lindegaard ratio (LR). To compare children from different age groups, the values were expressed as the percentage of normal values for age. For intubated and sedated patients, values were compared to reference values for critically ill, mechanically ventilated patients.[10] The mean velocities of the PCA were compared with reference values for the basilar artery (BA).[11,12] This analysis made the assumption that the reference values for the PCA and BA are similar, although reference values for velocities in the PCA are not known. The CBFV values obtained for patients who were neither intubated nor sedated were compared to published values for CBFV in healthy and ambulatory children.[11]

TCD studies and definition of abnormal velocities

TCDs were obtained at the discretion of the neurocritical care service. The neuroradiology service used the GE Logiq E9 ultrasound with a M5S transducer. Routinely, TCD scanning in our institution includes imaging of different vessels (anterior cerebral artery, MCA, PCA, and internal carotid artery) and the following parameters are reported: PI, resistive index, and LR. Time-averaged maximum mean velocity (TAMx), peak systolic velocity, and end-diastolic velocity in MCAs and PCAs were recorded. Vasospasm was defined as a TAMx greater than 120 cm/second with an LR greater than 3 or an absolute TAMx greater than 200 cm/second.[13,14] Hyperemia was defined as a TAMx 1 S.D. greater than the normal value for age and sex with an LR less than 3. Hypoperfusion was defined as a TAMx 1 S.D. less than the normal value for age and sex. Side-to-side difference in bilateral MCA and PCA TAMx was calculated ([highest TAMx −; lowest TAMx]/highest TAMx). Studies were classified as normal, hyperemia (≥1 vessel involved), vasospasm (≥1 vessel involved), hypoperfusion (≥1 vessel involved), or a mix of hyperemia, vasospasm, or hypoperfusion. There are no published criteria for these flow patterns in children, and we assigned these definitions to facilitate comparison of results of this study with other populations.

The secondary objectives of this study were to characterize the other factors (demographic, type of infection), which contribute to changes in CBF in children with CNS infection, and to determine whether the presence of abnormal CBF on first TCD was associated with neurological injury (seizures, ischemia on magnetic resonance imaging [MRI]), acquired morbidity in the ICU (intubation, vasoactive medication, need for neurosurgical procedure, cardiac arrest), and mortality. To reduce the confounding effect of the response to medical therapy in patients with multiple TCDs, the results from the first TCD were used in these analyses. Finally, we aimed to report examples of changes in management of these patients made in response to the TCD results.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 20.0 (SPSS Inc, Chicago, IL). Patient characteristics are described using descriptive analysis. The Fisher exact test was used to compare dichotomous variables. The level of significance for all statistical tests was set to $P < 0.05$.

Results

Population characteristics

A total of 20 patients were admitted to the pediatric and neonatal ICU with CNS infection between March 2011 and July 2015 and underwent TCD. During this time period, the neurocritical care service evaluated an additional 28 patients with CNS infection in which TCDs were not obtained. Of the patients for whom no TCDs were obtained, nine presented with seizures, nine had ischemic stroke, and one died. The characteristics of included subjects are summarized in Table 1. The etiology of CNS infections was heterogeneous, including bacterial infection (Streptococcus in five patients, Meningococcus, Rothia mucilaginosa, Mycobacterium tuberculosis, and *Escherichia coli*), viral (enterovirus in two patients, coxsackie, influenza, herpes simplex virus, and West Nile virus), presumed fungal in one patient, and unknown but presumed viral infection in three patients. Some patients had repeated TCDs (n = 9, 45%); 36 studies were attempted, one lacked acoustic windows. Therefore a total of 35 studies were completed. The indications for TCD included assessment for increased ICP (n = 11, 31%), screening for vasospasm in light of an at-risk