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ผลการอัลตราซาวด์กะโหลกศีรษะในผู้ป่วยแรกเกิดและทารกที่วินิจฉัยโรคเยื่อหุ้มสมองอักเสบเฉียบพลัน

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Spectrum of Cranial Sonographic Findings of Acute Bacterial Meningitis in Neonates and Infants

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หลักการและวัตถุประสงค์: โรคเยื่อหุ้มสมองอักเสบจากเชื้อแบคทีเรียในเด็กแรกเกิดและทารกเป็นการติดเชื้อที่รุนแรงและมีอัตราการเสียชีวิตสูง การวินิจฉัยอาศัยการตรวจร่างกาย ผลตรวจน้ำไขสันหลังและภาพวินิจฉัยประกอบกัน การตรวจอัลตราซาวด์กะโหลกศีรษะเป็นการตรวจแรกที่ใช้ในการประเมินรอยโรคในสมองในเด็กทารกโดยเฉพาะในหอผู้ป่วยวิกฤต ดังนั้นการศึกษานี้จึงมีวัตถุประสงค์เพื่อศึกษาลักษณะของภาพอัตราซาวด์กะโหลกศีรษะในผู้ป่วยแรกเกิดและทารกที่วินิจฉัยโรคเยื่อหุ้มสมองเฉียบพลัน

วิธีการศึกษา: ข้อมูลผู้ป่วย ผลการตรวจน้ำไขสันหลัง และผลการตรวจอัลตราซาวด์กะโหลกศีรษะ ของผู้ป่วยเด็กแรกเกิดและทารกที่อายุน้อยกว่า 1 ปี ที่ถูกวินิจฉัยโรคเยื่อหุ้มสมองอักเสบที่โรงพยาบาลศรีนครินทร์ ระหว่างเดือนกุมภาพันธ์ พ.ศ. 2552 ถึงเดือนพฤษภาคม พ.ศ. 2561 ได้รับการเก็บข้อมูลย้อนหลัง

ผลการศึกษา: ผู้ป่วยทั้งหมด 39 รายที่วินิจฉัยภาวะเยื่อหุ้มสมองอักเสบ พบว่าส่วนใหญ่อายุน้อยกว่า 1 เดือน (20/39, ร้อยละ 51.3) โดยเชื้อที่พบส่วนใหญ่ได้แก่ group B *Streptococcus* (GBS) (5/16, ร้อยละ 31.3) ซึ่งร้อยละ 80 ของเชื้อพบในเด็กอายุน้อยกว่า 1 เดือน จากผู้ป่วยเยื่อหุ้มสมองอักเสบทั้งหมด 39 ราย พบว่า มีผู้ป่วย 18 ราย (ร้อยละ 46.2) มีผลอัลตราซาวด์กะโหลกศีรษะปกติ ในขณะที่ 21 ราย (ร้อยละ 53.8) พบลักษณะผิดปกติ ได้แก่ เยื่อหุ้มสมองหนามากกว่าปกติ (18, ร้อยละ 46.2) โพรงสมองโตขึ้น (6, ร้อยละ 15.4) โพรงสมองอักเสบ (8, ร้อยละ 20.5) มีน้ำในช่องนอกเนื้อสมอง (12, ร้อยละ 30.8) เนื้อสมองมีความผิดปกติ (5, ร้อยละ 12.8) และลิ่มเลือดในหลอดเลือดดำในสมอง (2, ร้อยละ 5.1)

สรุป: ลักษณะของภาวะเยื่อหุ้มสมองอักเสบในอัลตราซาวด์พบได้ทั้งไม่มีความผิดปกติ และมีความผิดปกติ โดยเยื่อหุ้มสมองหนามากกว่าปกติพบได้บ่อยที่สุด การที่แพทย์คุ้นเคยกับลักษณะเหล่านี้จะช่วยให้วินิจฉัยโรคได้รวดเร็วและให้การรักษาโรคได้เหมาะสม

Background and Objective: Bacterial meningitis is one of the most serious infections in neonates and infants with high morbidity and mortality. A combination of physical examination, cerebrospinal fluid (CSF) analysis, and imaging modality is essential for diagnosis. Cranial sonography (CRS) is an initial examination for intracranial evaluation in critically ill neonates and infants. This study aimed to evaluate the spectrum of cranial sonographic findings of acute bacterial meningitis in neonates and infants.

Materials and methods: Patients under 1 year of age with the diagnosis of acute bacterial meningitis who underwent CRS in Srinagarind Hospital between February 2009 and May 2018 were enrolled. Demographic data, CSF profiles, and CRS findings were retrospectively reviewed.

Results: The study comprised 39 acute bacterial meningitis cases with cranial sonography identified from 89 diagnosed cases. Most of which were less than 1 month (20/39, 51.3%). Group B *Streptococcus* (GBS) was the most common organism (5 out of 16, 31.3%), which was almost isolated in the first month of age (4 out of 5, 80.0%). Eighteen out of 39 cases (46.2%) showed normal CRS, whereas 21 cases (53.8%) showed abnormal CRS including echogenic sulci (18, 46.2%), ventriculomegaly (6, 15.4%), ventriculitis (8, 20.5%), accumulation of extra-axial fluid (12, 30.8%), parenchymal change (5, 12.8%) and venous sinus thrombosis (2, 5.1%).

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คำสำคัญ: อัลตราซาวด์กะโหลกศีรษะ; ภาวะเยื่อหุ้มสมองอักเสบ; เด็กแรกเกิด; ทารก

Conclusion: Sonographic findings in acute bacterial meningitis revealed both normal and a large number of abnormalities which most frequent abnormality was echogenic sulci. Therefore, it is important to familiar with these findings in order to make a prompt diagnosis and provide appropriate treatment.

Keywords: cranial sonography; bacterial meningitis; neonates; infants

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Introduction

Bacterial meningitis is one of the most serious infections in children with high mortality and morbidity[1]. The incidence of bacterial meningitis in Thailand is 24.6 per 100,000 for children under five years[2], which is similar to other countries[3]. Amongst the pediatric population, neonates and young infants have the highest incidence, particularly at the age of fewer than 2 months[4].

Early diagnosis of primary infection and its complications leads to prompt treatment which is essential for a favorable outcome[5]. Identifying intracranial infection in neonates and infants could be a clinical challenge due to atypical manifestations, and non-specific signs and symptoms[1,6]. Therefore, a combination of physical examination, laboratory test, and imaging examination is helpful for the diagnosis.

Cranial sonography (CRS) is usually used as the initial imaging examination for intracranial evaluation in neonates and infants because of its portability, no need for sedation, real-time, non-ionizing radiation, and reproducibility. Abnormalities in CRS are depicted in approximately 65% of infants with acute bacterial meningitis and could be up to 100% in patients with severe neurological symptoms[7]. A wide spectrum of abnormalities had been categorized depending on the locations; including on the surface of the brain, in the ventricular system, and brain tissue[8]. Some sonographic findings are more common in some pathogens[7,9,10], which the common pathogens causing meningitis in each country differ due to different immunization programs[2,4,11,12]. Therefore, this study aimed to review the spectrum of CRS findings in neonates and infants with acute bacterial meningitis in our hospital in the last 10 years. We also evaluated CRS findings in each causative pathogen.

Materials and Methods

Patient and Imaging Selection

This study was approved by the Ethics Committee for Human Research, Khon Kaen University (HE621330). Informed consent from patients and their families was waived given the retrospective nature.

All patients under 1 year of age with a diagnosis of acute bacterial meningitis who underwent CRS at Srinagarind Hospital, Khon Kaen University between February 2009 and May 2018 were enrolled. Patients with unavailable clinical/laboratory/imaging data, pre-existing neurological abnormality, or brain anomaly/malformation were excluded. A total of 39 out of 89 patients were eligible. Twenty-one patients had follow-up sonography and all studies were retrospectively reviewed.

Clinical and laboratory data were collected from an online database of our hospital using PRAXIS Total Information and Collaboration (PRAXTICOL) and Health Object (HO) programs. The imaging studies were reviewed via Picture Archiving and Communication System (PACS). Demographic data comprised age, sex, prematurity, and treatment. Laboratory data comprised cerebrospinal fluid (CSF) profiles and CSF pathogens. All data were managed using Research Electronic Data Capture (REDCap) hosted at Khon Kaen University[13].

Imaging protocol

CRS was performed using a 7.5-10 MHz linear transducer approaching through the anterior fontanelle. Six coronal images and five sagittal images were taken according to standard planes[14].

Additional views such as mastoid view, posterior fontanelle/foramen magnum, and trans-temporal view might be performed for specific purposes[15]. Color Doppler sonography was applied for ruling out venous

sinus thrombosis in all cases and for additional characterization of certain gray-scale findings[8].

Imaging analysis

Two pediatric radiologists (N.T., with 5 years of experience, and T.R., with 2 years of experience) retrospectively reviewed sonographic findings by consensus and were blinded to the clinical and laboratory data. The sonograms were reviewed for the presence of echogenic sulci, ventriculomegaly and its degree including mild, moderate, severe, ventriculitis, parenchymal changes [either focal (abscess, infarction, hemorrhage) or diffuse (cerebritis)], accumulation of extra-axial fluid including subdural effusion and empyema, and venous sinus thrombosis[8,12,16].

Statistical analysis

All statistical analyses were performed using STATA Version 10. Descriptive statistics were used for describing patient demographic data. Categorical data were presented as numbers and percentages. Correlation between detection of pathogens in CSF and abnormalities in CRS was evaluated using Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Results

Patients

A total of 39 (43.8%) out of 89 patients diagnosed with acute bacterial meningitis during the study period were enrolled. Of which, there were 24 males (61.5%) and 15 females (38.5%). The median age of patients was 40 days (range 3-300 days). There were 22 patients under 2 months of age, most of which were less than 1 month (20/39, 51.3%). In terms of maturity of the patients, there were 21 term (21/35, 61.8%) and 13 preterm (13/35, 38.2%) infants. The patients' maturity data were not available in 5 patients.

Four out of 39 cases (10.3%) referred from other hospitals had no CSF profiles documented in the hospital data. Therefore, there were 35 cases (89.7%) with available and abnormal CSF profiles which approximately half of them (19 out of 35, 54.3%) showed negative bacterial organisms in CSF culture. Group B *Streptococcus* (GBS) was the most common organism (5 out of 16, 31.3%), which was almost isolated in the first month of age (4 out of 5, 80.0%), while the other occurred in a 2-month-old infant. The second and third most common organisms were *Haemophilus influenzae* (*H. influenzae*) (4 out of 16, 25.0%) and *Salmonella* (3 out of 16, 18.8%), respectively. The latter was found isolated in 5-7-month-old infants.

Sonographic findings

Out of 39 included cases, 18 cases (46.2%) showed normal CRS, whereas 21 cases (53.8%) found abnormal sonographic findings including 18 (46.2%) echogenic sulci (Fig. 1), 12 (30.8%) accumulation of extra-axial fluid (Fig. 1), 8 (20.5%) ventriculitis (Fig. 2), 6 (15.4%) ventriculomegaly (Fig. 2 and 3), 5 (12.8%) parenchymal changes (Fig. 3 and 4) and 2 (5.1%) venous sinus thrombosis (Fig. 4).

Of six cases with ventriculomegaly, 5 (83.3%) patients had severe dilatation whereas 1 (16.7%) patient had mild dilatation. Most of which (4/6, 66.7%) found symmetrical ventricular dilatation.

Four out of 5 cases (80.0%) with parenchymal changes found diffusely increased parenchymal echogenicity, and a case showed focal parenchymal lesions. A 7-month-old term male infant with *Salmonella* meningitis showed diffusely increased echogenicity of brain parenchyma, bilaterally and well-demarcated hypoechoic areas at the right frontal lobe and bilateral thalami; representing cerebral infarction at right MCA territory and bilateral thalami (Fig. 3). Two complicated cases with venous sinus

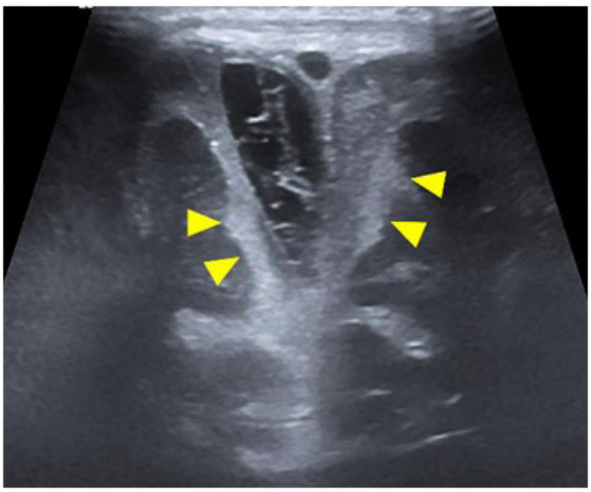

Figure 1 Thickened meninges and subdural empyema. Coronal CRS in a 5-month-old term male infant with *Salmonella* meningitis demonstrated echogenic thickening of leptomeninges (arrowhead) and widening of extra-axial spaces along bilateral parasagittal frontal convexities with internal septation on the right and echogenic content on the left.

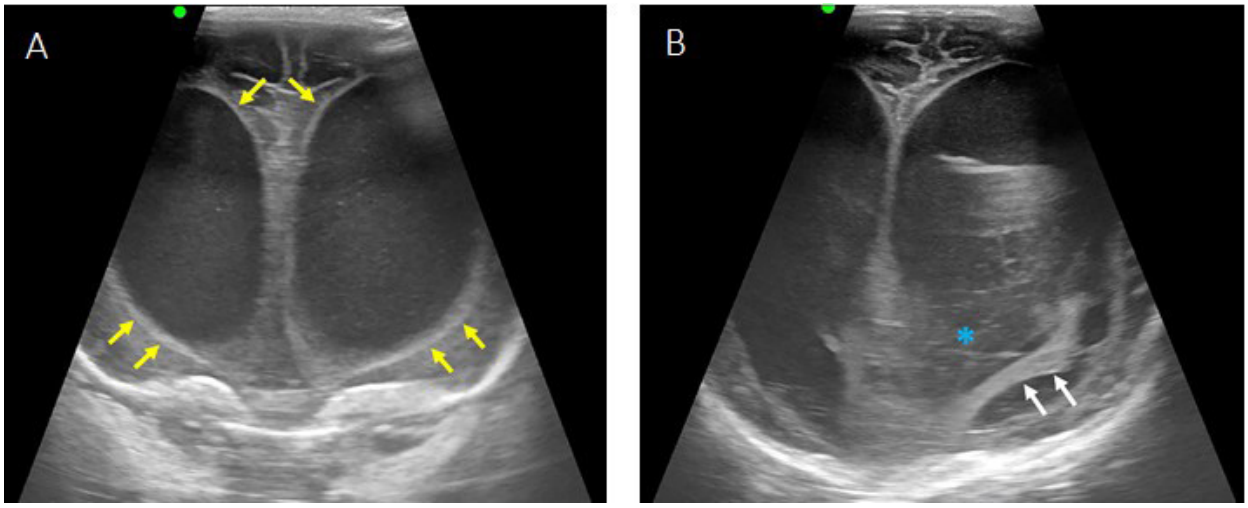

Figure 2 Ventriculitis. Coronal CRS of a 36-day-old term male infant with unidentified pathogen in bacterial meningitis (A) showed severe ventriculomegaly with thickened and echogenic ependymal lining (yellow arrow) of bilateral lateral ventricles. (B) demonstrated intraventricular debris (asterisk) and septation (white arrow).

thrombosis at superior sagittal sinus were proved to be GBS meningitis and one of which had associated parenchymal hematomas at bilateral parasagittal frontal lobes (Fig. 4).

Of thirty-five patients with available CSF culture results, only 16 patients (45.7%) identified etiologies. Four of 15 cases (26.7%) with normal CRS revealed positive pathogens in CSF culture, including 2 GBS, 1 Methicillin-Resistant *Staphylococcus Epidermidis* (MRSE), and 1 *Escherichia Coli* (*E. Coli*). Whereas 12 out of 20 cases (60.0%) with abnormal CRS revealed positive pathogens. Of which, there were 4 (33.3%) *H. Influenzae*, 3 (25.0%) GBS, 3 (25.0%) *Salmonella*, 1 (8.3%) *E. coli*, and 1 (8.3%) *Acinetobacter Baumannii* (*A. Baumannii*) (Table 1). The correlation between detection of pathogens in CSF and abnormalities in CRS was not statistically significant (p = 0.05).

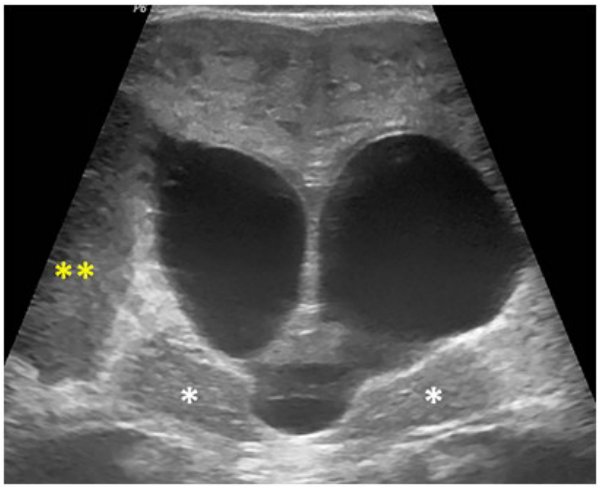

Figure 3 Diffuse parenchymal changes. Coronal CRS of a 7-month-old term male infant with *Salmonella* meningitis showed diffusely increased parenchymal echogenicity with well-demarcated hypoechoic areas at right frontal lobe (yellow asterisk) and bilateral thalami (white asterisk); representing cerebral infarction. Severe ventriculomegaly was found symmetrically.

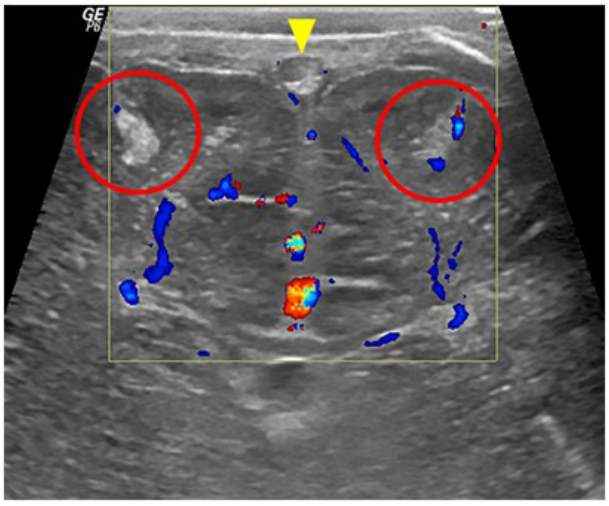

Figure 4 Venous sinus thrombosis and focal parenchymal changes. Coronal CRS of a 12-day-old term male neonate with GBS meningitis showed hyperechogenicity within superior sagittal sinus without intravascular flow, compatible with venous sinus thrombosis (arrowhead). Well-defined hyperechoic lesions at bilateral parasagittal frontal lobes (red circle) were also depicted; representing acute intraparenchymal hematomas.

Discussion

Bacterial meningitis remains a devastating infection with high mortality and severe lifelong disability[17,18]. Children, particularly at the age of less than 2 months, are more vulnerable to meningitis, particularly encapsulated bacteria because of relatively immature immune systems[4,19]. Our study found the highest incidence of acute bacterial

meningitis in the 0-1 month age group patients (51.3%).

The organisms causing bacterial meningitis in children are varied in different countries and different age groups[2,4,11,12]. Unlike the incidence of bacterial meningitis in Thailand of Muangchana et al[2] in 2009, our study found that GBS is the most common pathogens, particularly in the 0-1 month of age group. This might be due to the implementation of conjugated vaccines against bacteria that commonly cause meningitis in the last three decades. The effectiveness of vaccines shows a dramatic decrease in the incidence of *H. Influenzae* type B meningitis worldwide[20].

A combination of physical examination, CSF analysis, and imaging modality has been used to establish the diagnosis of bacterial meningitis. CSF culture is the gold standard for diagnosis, however, only 30-40% of the confirmed cases were identified causative pathogens[21,22]. Our study reported 45.7%. CRS is imaging of choice for intracranial evaluation, but it may be normal in mild and early meningitis. In the present study, CRS was normal in 46.2%, while it was reported in 30-40% in the previous studies[9,22–24]. The most frequent sonographic abnormality found in the present study was echogenic sulci (18/39 cases, 46.2%) which is similar to published papers[9,22,24]. The echogenic sulci were seen in both cases with identified and unidentified causative pathogen, most notably in *H. Influenzae* meningitis. This is due to the accumulation of inflammatory exudate in subarachnoid space causing increased echogenicity and thickness of the sulci[9,12,24] which is often a transient abnormality[7,8].

We observed an accumulation of extra-axial fluid as a second most common finding (30.8%) which is consistent with Han et al[9]. Nevertheless, other published papers reported other findings: ventriculomegaly in Soni et al[24] and Edwards et al[25], and abnormal parenchymal echoes in Mahajan et al[23]. An extra-axial fluid collection is seen as widening extra-axial fluid space. Subdural effusion represents sterile, reactive fluid which is usually clear fluid. Subdural empyema is rare[9] and appears as a subdural fluid collection with internal echogenic debris or septation. It sometimes has a pressure effect on the adjacent brain parenchyma. It is difficult to distinguish between sterile subdural effusion and early empyema by ultrasound[7], however, the presence of persistent fever, new focal neurological deficits, or seizure raises the suspicion of empyema[7]. The accumulation of extra-axial fluid in this study was most frequently seen in infants with *H. Influenzae* meningitis.

This study found 20.5% of ventriculitis which was seen as thick, irregular, and echogenic appearance of ependyma, presence of intraventricular debris, septation and often associated with ventricular dilatation. Choroid plexitis may be found associated with ventriculitis and appears as increased echogenicity and irregular contour. Ventriculitis was mostly noted in *Salmonella* meningitis in our study.

Ventricular dilatation may be seen in approximately 30%[12] of patients with bacterial meningitis, which was only seen in 15.4% in this study. Ventriculomegaly is often mild and reversible during acute illness. It can progress to moderate or severe dilatation due to obstruction or loss of brain parenchyma[9]. The ventricular dilatation may be either symmetry or asymmetry. Our study observed that most cases with ventriculomegaly were symmetrical and severe dilatation.

We demonstrated a case of *Salmonella* meningitis who had diffusely increased echogenicity of the brain parenchyma and cerebral infarction at right MCA territory and bilateral thalami. Meningitis may result in arterial spasm or direct arteritis which often affects the basal ganglia[26]. However, the larger arteries may be involved resulting in large territory infarctions.

Our study has several limitations. Firstly, as its retrospective design, there were the limited sample size and incomplete laboratory data documentation due to transferring from other hospitals. This affects the power of the study to detect sonographic abnormalities of each pathogen and the correlation between sonographic findings and causative pathogens. Secondly, CRS is highly operator-dependent. Hence, a retrospective review of the images by reviewers might not be as precise as by a real-time operator. Thirdly, we did not have a standardized protocol in our institute of a certain date for the sonographic evaluation of meningitis resulting in a lack of demonstration of early and late signs of the disease. Therefore, we could not advance in the knowledge of the correlation between causative organisms and sonographic changes over time. Finally, this is a single-center study in Thailand. The results may not extrapolate to other countries where the etiology prevalence differs. Since acute bacterial meningitis in neonates and infants is an uncommon disease, a prospective multi-center study in the future

could be beneficial to enhance the understanding of sonographic findings in a certain bacterial organism of meningitis.

Conclusion

In conclusion, spectrum of sonographic findings in acute bacterial meningitis included both normal and a large number of abnormalities. Therefore, recognizing of these findings is essential because a prompt diagnosis and appropriate treatment reduce the risk of acute complications and long-term sequelae.

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