Pattern of sepsis and meningitis in a University Hospital

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ABSTRACT

الهدف: تحديد الأعراض السريرية و معايير السائل النخاعي(CSF) و التي تؤسس معايير التشخيص السريع لتعفن الدم و الالتهاب السحائي.

الطريقة: تم اختيار الحالات من خلال الفحص المبدئي لألف طفل أعمارهم من يوم ١ ــ ١٣ سنة و لديهم أعراض القيء الحاد ، الحمى التشنج و الإسهال.في الفترة من يناير ١٩٩٧ إلى ديسمبر ٢٠٠٠م و ذلك بقسم الأطفال – مستشفى جامعة الملك عبد العزيز بجدة. وقد تم فحص الحالات المختارة سريرياً، تسجيل التاريخ المرضي و إجراء فحوصات كاملة للدم و السائل النخاعي(CSF) وقد قسم المرض إلى مجموعتين: أ– تعفن الدم (٩٤) حالة. ب– الالتهاب السحائي (٢٦) حالة.

النتائج: وجد أن معظم الحالات التي تعرضت لسحب عينات السائل النخاعي من حديثي الولادة (٣٥,٨٪) و كانت حالات تعفن الدم أكثر عدداً (٧٨,٣٪) مقارنة بالالتهاب السحائي (٢١,٧٪) وثبت أن حديثي الولادة أكثر عرضة لهذه الإصابات و كان القيء أهم الأعراض المصاحبة لجميع الحالات .تميزت حالات الالتهاب السحائي بانخفاض مستوى خضاب الدم و كريات الدم البيضاء و كريات الدم عديدة النوى ، و تركيز الكلوريد في السائل النخاعي مقارنة بحالات تعفن الدم .وتميز الالتهاب السحائي أيضاً بوجود ارتباط موجب بين نسبة الجلوكوز في الدم ، وكذلك بين كريات الدم البيضاء في السائل النخاعي و نسبة البروتين فيه .بينما تميز تعفن الدم بوجود ارتباط ايجابي بين كريات الدم الليمفاوية وكريات الدم الحمراء في السائل النخاعي (جميع الارتباطات معنوية إحصائيا) .

خاتمة: كانت حالات تعفن الدم أكثر من حالات الالتهاب السحائي بين الحالات التي تم تنويمها بقسم الأطفال والمحولة من قسم الطوارئ و قد كان أكثر المرضى الذين احتاجوا لفحص السائل النخاعي من حديثي الولادة ، و كان القيء الحاد أهم الأعراض المشتركة ، توصي الدراسة بضرورة الفحص الدقيق للأطفال الذين يعانون من القيء و التشنج بالرغم من كون السائل النخاعي سلبياً و ينبغي ملاحظتهم جيداً و أجراء فحوصات البول و الدم وإعادة تقييم الحالات بواسطة أخصائي الأطفال.

Objectives: To define the clinical and cerebrospinal fluid (CSF) criteria that establishes a diagnosis of sepsis and meningitis immediately on admission.

Methods: One thousand children, aged one day to 13 years, presenting with acute onset of vomiting, fever, convulsion, and diarrhea to the Pediatrics Department, King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia from January 1997 to December 2000 were evaluated. Cases were subjected to history, clinical examination, and lumbar puncture (LP). On admission, chemical, cytological, and bacteriological examinations of blood and CSF were carried out. Patients were divided into sepsis (n=94) and meningitis (n=26) groups.

Results: The most common age liable for LP was in the neonatal period (35.8%). Septic cases were more than meningitis (78.3% versus 21.7%). Neonates were the most commonly affected age in sepsis and meningitis; and the predominant symptom in all groups was vomiting. In meningitis, hemoglobin was less (p<0.05) while, blood white blood cell counts (WBCs) (p<0.05), blood neutrophils (p<0.05), CSF-chloride (p<0.000) and CSF-WBCs (p<0.001) were more than sepsis. In meningitis, a positive correlation was found between CSF-glucose with WBCs (r=0.52, p<0.05), neutrophils (r=0.49, p<0.05), and blood-glucose (r=0.56, p<0.01); and between CSF-WBCs and CSF-protein (r=0.55, p<0.01). In sepsis, a positive correlation was found between CSF-lymphocyte and CSF-red blood cell count (r=0.37, p<0.001).

Conclusion: More septic cases were admitted to the Pediatric Department through Emergency than meningitis cases. The most common pediatric patients liable to LP were neonates, and the most common presenting symptom was vomiting. Children with vomiting and convulsion and no organism in CSF must be carefully examined, and urine and blood culture must be collected. These children must be closely observed in hospital and re-evaluated by a pediatrician.

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The use of lumbar puncture (LP) in the diagnosis of CNS infection in children is controversial.[1] Lumbar puncture use began to decline after concerns were expressed that the procedure may be precipitating brainstem herniation and death in some patients, although the causal association between LP and cerebral herniation remains unproven.[2] Lumbar puncture might also provide false reassurances, with delay in diagnosing meningitis when initial CSF is normal.[3] Infection of the subarachnoid space and meninges results in CSF pleocytosis and the characteristic symptom triad with headache, fever, and meningitis. Implicit in the definition of meningitis is the absence of additional CNS involvement, such as encephalitis and myelitis.[4] Despite the advent of new antimicrobial drugs and intensive care unit (ICU) charge, mortality and morbidity remains high.[5] Because there were few studies on the clinical and pathological features found in infants with this disease,[6] and because without definite CSF or blood-culture results, or both, initial CSF features may result in possible over-diagnosis of acute bacterial meningitis.[7] Febrile convulsions occur predominantly in children under 3 years of age,[8] and are a common cause of morbidity in the tropics.[9] Convulsions occur in 25-30% of children with bacterial meningitis, which in 30-40% of cases, especially those under 2 years of age, may not show meningeal signs.[10] The American Academy of Pediatrics recommends that after the first seizure with fever in infants younger than 12 months of age, a CSF examination be strongly considered.[11] In the clinical setting, rapid diagnosis of sepsis and meningitis has many advantages, such as avoidance of unnecessary extensive diagnostic work-up and over treatment, shortened hospitalization, and reduced costs of medical care. This retrospective study aimed to evaluate various clinical and CSF values in 120 children with an established diagnosis of sepsis and meningitis, and to find predicators that could be used as guidance in routine practice for this potentially fatal CNS infection.

Methods. This retrospective study was carried out from January 1997 to December 2000 and included 1000 cases with suspicion of CNS infection or meningococcal septicemia admitted to the Pediatric Department, King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia. All patients received a spinal tap on the day of admission. According too clinical and laboratory findings, the patients were divided into sepsis (n=94) and meningitis (n=26). Their age ranged from one day to 13 years. Exclusion criteria for participation in this study were traumatic lumber puncture (>500 x 10^6 erythrocytes or >500 erythrocytes/mm^3 in CSF cell count), prematurity, concomitant neurological diseases affected CSF biochemistry, neurosurgical before onset of meningitis or sepsis, or presence of immunodeficiency disease. Information obtained from records included patients age and sex, complete history, and clinical symptoms and signs on admission. Complete blood count, blood glucose, and blood culture, urinalysis, or urine culture, CSF biochemical analysis, and culture were also collected and analyzed. Specimens of CSF were designated normal on initial examination if no organisms were seen on a Gram stained film, if white blood cell count was <5/mm,[12] if glucose concentration was ≥3 mmol/l, and if protein concentration was <0.4 g/l. Patients were considered as "septic"[13] when at least 4 of the following symptoms were present: 1. Alternation of consciousness, 2. Tachypnea, tachycardia (>90 percentile for age), 3. Inadequate peripheral circulation, 4. Instability of temperature and blood pressure, 5. Skin rashes, 6. Sudden changes in leukocyte count (up and down), 7. Drop in platelets count, 8. Hypoglycemia, hypocalcemia. Diagnosis of bacterial meningitis was based on the presence of a bacterial pathogen identified by Gram stain, culture of CSF, or both.[9] A presumed diagnosis of bacterial meningitis was made in children with no bacterial pathogen identified in CSF, but with pleocytosis (mainly polymorphs, >5 WBCs/m^3)[14] and typical biochemical changes in CSF. Local ethics committee approval was obtained prior to commencement of the study.

A statistical analysis was performed using SPSS software version 12 to compare the clinical and laboratory findings of sepsis and meningitis. Statistical analysis was based on unpaired student t tests. Correlation between different clinical and laboratory findings was performed using Spearman correlation. A *p*-value less than 0.05 was considered significant.

Results. One hundred and twenty patients were subdivided into 3 groups, neonates (n=43), infants (n=35), and older children (n=42) according to their age. In all groups, patients were suffering from sepsis. Of neonates and infants, the male numbers were higher than females, while in older children, females were higher than males. In all groups, vomiting was the most common presenting sign. In neonates, vomiting was the most common sign, followed by diarrhea, convulsion, fever, and headache. In infants, vomiting was the most common sign followed by convulsion, diarrhea, fever, and headache. In older children, vomiting was the most common sign followed by fever, convulsions, diarrhea, and headache. The blood culture was positive in one case in neonates, one case in infants, and 3 cases in older children. The CSF stain and culture were negative in all cases (**Table 1**). **Table 2** shows the difference in demographic and clinical characteristics of

Table 1 - Demographic and presenting symptoms and signs of patients.

Items	Neonates (n=43) n (% within type)	Infant (n=35) n (% within type)	Old children (n= 42) n (% within type)	*P*-value
Diagnosis				
Meningitis	8 (18.6)	10 (28.6)	8 (19.0)	$p>0.05$
Sepsis	35 (81.4)	25 (71.4)	34 (81.0)	
Gender				
Males	25 (58.1)	20 (57.1)	19 (45.2)	$p>0.05$
Females	18 (41.9)	15 (42.9)	23 (54.8)	
Vomiting				
Yes	18 (41.9)	18 (51.4)	22 (52.4)	$p>0.05$
No	25 (58.1)	17 (48.6)	20 (47.6)	
Diarrhea				
Yes	10 (23.3)	10 (28.6)	9 (21.4)	$p>0.05$
No	33 (76.7)	25 (71.4)	33 (78.6)	
Headache				
Yes	2 (4.7)	3 (8.6)	8 (19.0)	$p<0.05$
No	41 (95.3)	32 (91.4)	34 (81.0)	
Fever				
36°-37°	37 (86.0)	32 (91.4)	22 (52.4)	$p>0.05$
37.5°-37.9°	6 (14.0)	3 (8.6)	20 (47.6)	
Convulsion				
Yes	8 (18.6)	12 (34.3)	12 (28.6)	$p>0.05$
No	35 (81.4)	23 (65.7)	30 (71.4)	
CSF gram stain				
Positive	-	-	-	$p>0.05$
Negative	43 (100)	35 (100)	42 (100)	
CSF culture				
Positive	-	-	-	$p>0.05$
Negative	43 (100)	35 (100)	42 (100)	
Blood culture				
Positive	1 (2.3)	1 (2.9)	3 (7.1)	$p>0.05$
Negative	42 (97.7)	34 (97.1)	39 (92.9)	

Table 2 - Demographic and cerebrospinal fluid and blood cultures of meningitis and sepsis patients.

Items	Meningitis (n=26) n (% within type)	Sepsis (n=94) n (% within type)	*P*-value
Gender			
Males	12 (46.2)	52 (55.3)	$p>0.05$
Females	14 (54.8)	42 (44.7)	
CSF gram stain			
Positive	-	-	-
Negative	26 (100)	94 (100)	
CSF culture			
Positive	-	-	-
Negative	26 (100)	94 (100)	
Blood culture			
Positive	4 (15.4)	1 (1.1)	$p<0.01$
Negative	22 (84.6)	93 (98.9)	

patients with meningitis and sepsis. The most common age with meningitis was infants, and in sepsis were neonates. In cases of meningitis, only 4 cases showed positive culture. Organisms detected in meningitis were one case of *Staphylococcus Aureus (S. Aureus)*, one case of *Streptococcus Pneumonia (Strep. Pneumonia)*, one case of *Coagulase negative Staphylococci*, and one case of *Haemophilus Influenzae*. Meanwhile, for sepsis, only one case (1.1%) showed *Strep. Pneumonia*. **Table 3** shows routine laboratory parameters measured in peripheral blood and CSF of septic and meningitis patients. Blood hemoglobin was significantly lower in meningitis compared to sepsis ($p<0.05$), while peripheral blood, white blood cell count (WBCs), peripheral blood neutrophils, CSF-WBCs, and CSF-chloride were significantly elevated in meningitis compared to sepsis. Other measured parameters (peripheral blood lymphocytes, peripheral blood platelets, peripheral blood glucose, CSF-RBCs, CSF-lymphocytes, CSF-protein, and CSF-glucose) showed no significant differences between sepsis and meningitis. **Table 4**

Table 3 - Laboratory findings of meningitis and sepsis patients.

Items	Reference range	Meningitis (n=26)	Sepsis (n=94)	Significance
Blood hemoglobin (gram/dl)	12-16	10.42±1.87	12.01±3.13	$p<0.05$
Blood WBCs (K/UL)	5.5-12	14.12±6.05	10.91±5.11	$p<0.05$
Blood neutrophils (%)	-	52.69±26.99	39.59±23.03	$p<0.05$
Blood lymphocytes (%)	30-60	40.67±26.33	38.16±20.59	$p>0.05$
Blood platelets (K/UL)	150-399	310.62±113.13	341.98±257.79	$p>0.05$
Blood glucose (mmol/L)	3.00-5.56	5.73±2.31	4.85±2.88	$p>0.05$
CSF-RBCs (M/UL)	0	271.08±834.42	850.83±4391.69	$p>0.05$
CSF-WBCs (K/UL)	0	156.46±455.07	0.00±0.00	$p<0.001$
CSF-lymphocyte	-	6.50±20.35	21.71±198.06	$p>0.05$
CSF protein (g/L)	0.25-0.4	1.25±2.39	3.60±13.21	$p>0.05$
CSF-glucose (mmol/L)	2-2.2	3.03±1.15	2.95±1.68	$p>0.05$
CSF-chloride (mEq/L)	-	116.82±6.99	95.22±41.97	$p<0.000$

WBC - white blood cells, CSF - cerebrospinal fluid, RBC - red blood cells

Table 4 - Incidence of disturbance in blood and cerebrospinal fluid (CSF) findings among sepsis and meningitis.

Variable	Reference	Meningitis (% within group)	Sepsis (% within group)	Total (% within total)
WBCs (K/UL)				
Normal	5.5-12	14 (53.8)	50 (53.2)	**64 (53.3)**
High	≥ 15	12 (46.2)	34 (36.2)	**46 (38.3)**
Low	0.0-5.49	-	10 (10.6)	**10 (8.3)**
Neutrophils (%)				
Normal	30-60	9 (34.6)	43 (45.7)	**52 (43.3)**
High	>60	10 (38.5)	18 (19.1)	**28 (23.3)**
Low	0-29.99	7 (26.9)	33 (35.1)	**40 (33.3)**
Lymphocytes (%)				
Normal	30-60	8 (30.8)	43 (45.7)	**51 (42.5)**
High	>60	7 (26.9)	18 (19.1)	**25 (20.8)**
Low	0-29.99	11 (42.3)	33 (35.1)	**44 (36.7)**
Platelets (K/UL)				
Normal	150-399	19 (73.1)	63 (67.0)	**82 (68.3)**
High	>400	7 (26.9)	21 (22.3)	**28 (23.3)**
Low	0-149	-	10 (10.6)	**10 (8.3)**
Serum glucose (mmol/L)				
Normal	3-5.56	15 (57.7)	46 (48.9)	**61 (50.8)**
High	>5.6	11 (42.3)	32 (34.0)	**43 (35.8)**
Low	0-2.99	-	16 (17.0)	**16 (13.3)**
CSF-WBCs (K/UL)				
Normal	0-5	3 (11.5)	94 (100)	**97 (80.8)**
High	>6	23 (88.5)	-	**23 (19.2)**
CSF-glucose (mmol/L)				
Normal	2.2-3.9	12 (46.2)	48 (51.1)	**60 (50.0)**
High	>4	5 (19.2)	25 (26.6)	**30 (25.0)**
Low	2-2.1	9 (34.6)	21 (22.3)	**30 (25.0)**
CSF-protein (g/L)				
Normal	0.4-1.2	10 (38.5)	29 (30.9)	**39 (32.5)**
High	>1.2	6 (23.1)	21 (22.3)	**27 (22.5)**
Low	0-0.39	10 (38.5)	44 (46.8)	**54 (45.0)**

illustrates the incidence of disturbance in blood and CSF finding among sepsis and meningitis patients. In meningitis, a positive correlation was found between CSF-glucose with WBCs (r=0.52, p<0.05), neutrophils (r=0.49, p<0.05), and blood glucose (r=0.56, p<0.01), and between CSF-WBCs and CSF-protein (r=0.55, p<0.01). In sepsis, a positive correlation was found between CSF-lymphocyte and CSF-RBCs (r=0.37, *p*<0.001).

Discussion. Results of the present study revealed that the incidence of sepsis was more prevalent in males than females, while in meningitis females were more than males, however, these differences did not reach significant levels. On the contrary, others[15] reported a higher incidence of meningitis among males. In consistence with others,[15] this study reported that sepsis was most common in the neonatal period, while most meningitis patients were infants. The clinical manifestations of sepsis and meningitis can be quite varied, ranging from transient fever and bacteremia to fulminate disease with death ensuring within hours of the onset of clinical symptoms. The most prominent symptom in our sepsis and meningitis patients was vomiting. This finding is consistent with Abanamy et al,[16] who reported that vomiting was the most common presentation in meningitis, however, a study by Azubuike[15] found it to be fever. In infants, approximately 34.3% of our cases suffered from convulsions, which is higher than that reported by Abanamy et al (18.9%).[16] A single generalized seizure, more complex seizures, signs of increased intracranial pressure and later consciousness developed in approximately 10% of pediatric patients with aseptic meningitis, especially in those over the age of 3 months.[17]

Our patients with meningitis and sepsis showed either normal peripheral WBCs or leukocytosis or leucopenia in sepsis. In patients with meningitis, hemoglobin was significantly low, while WBCs, neutrophils were significantly elevated compared to sepsis. In 1984, Engle and Rosenfeld[18] showed that factors other than sepsis could cause leucopenia in infants with sepsis. Other investigators[19] assessed the utility of peripheral blood WBC count for predicting bacterial illnesses, such as urinary tract infections, bacteremia, sepsis, bacterial meningitis. Generally, these investigators have not relied on peripheral blood WBC count alone, but have used it in conjunction with clinical examination and other tests, such as formal urinalysis and CSF-WBC counts, as part of full sepsis evaluation.[20] Also, our results showed decreased blood glucose levels in approximately 17% of the sepsis patients.

Traditionally, examination of CSF has been advocated as a benchmark investigation in suspected meningococcal meningitis; it is still likely to provide a clinical diagnosis and to yield meningococci for sensitivity testing and further identification.[21] In this study, CSF-WBCs was high in 88.5% of patients with meningitis. The CSF-glucose was low, while CSF-protein was high in patients with meningitis and sepsis. In meningitis, a positive correlation was found between CSF-glucose with WBCs, neutrophils, and blood glucose; between CSF-WBCs and CSF-protein. Meanwhile in sepsis, a positive correlation was found between CSF-lymphocyte and CSF-RBCs.

When confronted with an individual child with meningitis, the clinician must make treatment decisions, based at least partly on CSF evaluation. As bacterial meningitis is usually characterized by a polymorphonuclear (PMN) predominance, many patients with a high percentage of PMNs in CSF are started on antibiotics pending results of bacterial cultures.[21] It is appropriate to initiate antibiotic therapy when the patient seems significantly ill or CSF characteristics are ambiguous. However, Negrini et al[21] suggests that PMN predominance, as a sole criterion, is a poor diagnostic marker of disease type.

In all participating children, CSF culture in 4.2% showed positive culture of organisms. These unexpected results can be explained by either the samples of CSF were not appropriately manipulated, for example, not treated immediately and left out on the bench for a long time, or they were inadequate, or due to treatment of the children with antibiotics, antiviral drugs, or both pending CSF culture results and lack of advanced techniques such as polymerase chain reaction (PCR). In Chang et al's[22] study, *Salmonella species, Streptococcus agalactiae, Escherichia coli (E. coli)*, and *Haemophilus influenzae* were most prevalent, accounting for approximately 59% of pathogens in infantile bacterial meningitis. Gram-negative bacilli, including *Salmonella species, E. coli*, and some rare Gram-negative organisms, accounted for more than 40% of causative pathogens in another study.[22] In this respect, Kotilainen and his colleagues[23] reported that PCR of CSF and blood is most helpful for documenting meningococcal disease in patients with negative culture.

Our study as a retrospect, lacked recording of complications of meningitis. In this respect, it had been reported that bacterial meningitis in infancy has been associated with a high frequency of disability. The cerebrovascular complications of infantile bacterial meningitis cause cerebral ischemia, seizure, focal neurological deficits, and hydrocephalus.[24]

In conclusion, this study emphasizes the importance for physicians to maintain a high index of suspicion for meningitis when confronted with vomiting and convulsions in pediatric patients especially in infants

less than one year. This study recommends that in the absence of validated alternatives and concordant with published guidelines that CSF be obtained from all young infants presenting with repeated vomiting and convulsions. Such a general approach of obtaining CSF analysis will maximize early detection of bacterial meningitis and guide empiric antibiotic treatment. Generally, decisions to perform lumbar puncture that are based solely on current conceptions of total peripheral blood WBC count should be abandoned because they will lead to a significant increase in the number of cases of bacterial meningitis that are missed and false diagnosis of sepsis.

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