Early detection of Cognitive and Behavioral Sequelae in Children Survivors of Bacterial Meningitis

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Abstract:

Cognitive deficiencies after bacterial meningitis in children (predominantly persistent difficulties in learning, deficits in short term memory, behavioral problems and poor academic performance) have been described.

Aim:

Assess early cognitive and behavioral sequelae in children survived of bacterial meningitis and detection of subtle deficits with relevant contribution to rehabilitation strategies, either by identifying deficits that can be addressed or capacities that can be used to facilitate functional recovery.

Methodology:

This Case control study included 30 child aged (6- 18) years of both sexes infected with bacterial meningitis confirmed by lumber puncture. Thirty healthy subjects without a medical history of neurological disease matched the age, gender, length of school education and social class of the study population served as a control group. Psychiatric assessment in both groups carried out using Stanford-Binet Intelligence Scale and Child Behavior Check-List Parents form (CBCL/6- 18). Also Familial Socioeconomic Status Scale was conducted to match both groups.

Results:

Results showed highly significant difference in compsite IQ measures between case& control group with mean ±SD (87.97±20.09 vs. 104.1±14.19 p= 0.0007) respectively with also affection to all IQ subscales, the highest statistical significance was in short term memory subscale (p = 0.0024). While there was statistically significance difference in CBCL only in two subscales, Rule-break problem& Aggression (p= 0.0166& 0.0013) respectively. There was no statistical significance as regard Anxious/Depressed, withdrawn, Somatic complains, social problems, thought problems, Attention problem and other problem scales.

Conclusion:

In Children with bacterial meningitis as regard Stanford-Binet Intelligence testing, showed highly significant difference in compsite IQ measures between case& control group with also affection to all IQ subscales, the highest statistical significance was in short term memory subscale and also parent report (CBCL) identified patients with bacterial meningitis disease as having more behavior problems.

Key Words:

Behavioral problems, cognitive function and meningitis.

Introduction:

Meningitis is a serious public health problem demanding early diagnosis, effective treatment, prevention and control. It is a major cause of morbidity and mortality among infants and children[1]. In Egypt, case-fatality rate ranged from (8.5- 55)%[2].

Apart from endemicity, a violent epidemic disease occurs every (6- 12) years in the African meningitis belt[3]. Meningitis is considered as an endemic disease in Egypt[4].

There are three main organisms that account for over 90% of the world's cases of meningitis in children which are Neisseria meningitidis, Streptococcus pneumonia and Haemophilus influenza type b[5].

The complications of meningitis can be divided into early complications which occur during the first 24 hours and may be the immediate cause of death and late complications (those usually recognized after several days or later). The early complications are cerebral edema, septic shock, disseminated intravascular coagulation, myocarditis, hyponatremia with water intoxication, and convulsions. Sensorineural deafness is also an early complication but may not be detected until later[6].

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Cognitive difficulties are a recognized consequence of brain insults. Bacterial meningitis can cause widespread damage including impaired verbal learning and memory, loss of attention/concentration, impaired speed of thinking and executive functions (e.g. concept formation and abstraction)[8].

The morbid consequences of central nervous system (CNS) infections are often overlooked in the face of high mortality rates. However, neurological impairments not only affect the child's development and future prospects but also place an economic and social burden on communities and countries that often have few resources to deal with such problems[8].

It is not unusual for children to display changes in behavior after meningitis. Although child has made a full medical recovery, it sounds like he is experiencing these behavioral after effects. Going back into school and routine activities can be very helpful, provided of course that child is ready to meet the demands of school. These behaviors should be temporary, but can last for a number of weeks or months; they are commonly still apparent three months following hospital admission and normally improve over the year following admission[9].

Cognitive deficiencies after bacterial meningitis in children (predominantly persistent difficulties in learning, deficits in short term memory, behavioral problems and poor academic performance) have been described[10].Short term memory is the domain which is affected most frequently and most severely after bacterial meningitis[11].

Several studies have evaluated the intelligence quotient (IQ) of survivors of bacterial meningitis compared to their siblings or other control children.[12] Although not all of the studies found a difference in the mean IQ compared to controls (usually siblings), a greater proportion of children who had meningitis had IQ less than 70[13].

More subtle adverse outcomes, such as cognitive academic and behavioral problems are present in 20% of bacterial meningitis survivals. But these more subtle problems often remain undetected until the child starts school which may be several years after he/ she has been cured of meningitis[14].

Methodology:

The present study is carried out at Abbassia Fever Hospital during the time interval from October 2010 to September 2011. It was performed as a Case control study in children aged (6- 18) years of both sexes infected with bacterial meningitis. It included 30 patients and 30 healthy children as control group well matched as regard age, sex, school attendance duration& socioeconomic level.

Patients were eligible for the inclusion in this study if they had received a lumbar puncture and satisfied laboratory eligibility "confirmed bacterial meningitis" according to the World Health Organization criteria[15] by the presence of one of the following criteria: CSF gram stain positive for gram negative bacilli, gram positive cocci or gram negative cocci and CSF cell count> 10/ml. OR CSF culture positive for Streptococcus Pneumonia or Neisseria meningitidis or Haemophilus infeluanzae. OR CSF white cell count> 100/ml, polymorphneuclears> 50% and CSF/ blood glucose ratio less than 0.5. OR CSF white cell count> 100/ml, polymorphneuclears> 50% and CSF glucose less than 30 mg/dl. OR CSF white cell count> 1000/ml and polymorphneuclears> 50%.

- Inclusion criteria were: Patients diagnosed as bacterial meningitis, Age ranges from (6- 18) years, both sexes and No history of preexisting neuropsychological deficits.
- Exclusion criteria were: Children aged 5 years or younger, Pre-existing neurosurgical conditions, Seizure disorders, cerebral palsy, degenerative neurological disorders, Cranial fractures, Known immunodeficiency states, symptomatic AID, Active viral infections, Cyanotic congenital heart disease, Inaccessibility for follow-up and Known deafness barrier to admission.

The study protocol was approved by the Ethical Commity Ain Shams University. Written consent was obtained from guardians of every patient enrolled in the study after explaining the nature of the study.

All the children in the bacterial meningitis group were subjected to the following:

1. History Taking.
2. Clinical Examination.
3. Investigations:
4. CSF samples were examined for: Total and differential cell count, Glucose and protein determination, direct gram stain film& Culture on chocolate and sheep blood agar plates.
5. Psychometric evaluation: Intellectual development was assessed by appropriate Stanford-Binet Intelligence Scale fourth edition. It tests intelligence across four areas, which are verbal reasoning, quantitative reasoning, abstract/ visual reasoning and short term memory Total testing time is around (45- 60) minutes. Raw scores are based on the number of items answered and are converted into a standard age score corresponding to age group, similar to an IQ measure[16].
6. Also behavioral problems were assessed by appropriate Child Behavior Check-List Parents form (CBCL/6- 18) which is a widely used instrument that assesses behavioral problems. The CBCL version for ages (6- 18) years is orally administered to a parent, who rates the presence and frequency of certain behaviors on a 3-point scale (0= not true, 1= somewhat or sometimes true, and 2= very true or often true[17].
7. Familial Socioeconomic Status Scale[18]: This scale had been proved to be reliable and valid. It can help the user to determine the socioeconomic level for the Egyptian family. It depends mainly on the monthly income per person within the family, father's occupation, and father's education[18].

Results:

Of the 37 case patients with meningitis who were enrolled in the study, 2 died, the guardians of one patient refused enrollment, one proved to be TB meningitis, and 2 were referred to other hospitals for neurosurgical intervention. At follow-up after (3- 4) weeks after discharge from hospital, an additional one case patient could not be located; thus, 30 case patients were available for analysis& 30 in control group.

Case and control subjects enrolled in the study were well matched with respect to age and gender and socioeconomic features Table 1.

Table (1) Distribution of Age, Gender& socioeconomic status in both Groups

		Case	Control	P Value
Age		11.23±3.7	10.83±4.1	0.518
Gender	Male	21 (70%)	21 (70%)	
	Female	9 (30%)	9 (30%)	
Socioeconomic		100.34±48.87	105±37.85	0.074

The study included 30 cases their age ranged from (6- 18) years old with a mean of 11.23±3.7 SD. Out of the 30 cases; 21 (70%) were males and 9 (30%) were females, as in table (2)& figure (1).

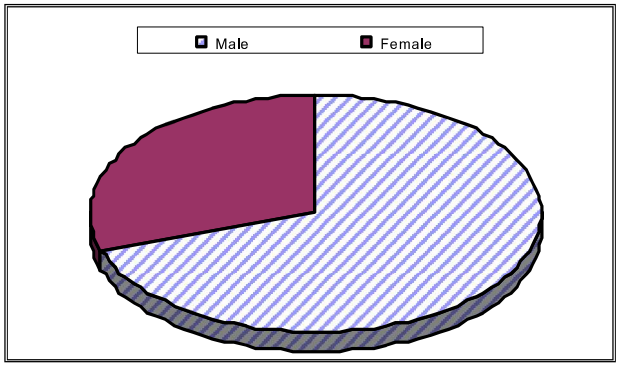

Figure (1) Sex distribution of the studied cases

Table (2) Age and sex distribution of the studied cases

Age	Range	6- 18 Years
	Mean±SD	11.23±3.7
Sex	Male	21 (70%)
	Female	9 (30%)

As regards to the clinical manifestations of the studied 30 cases, all of them (100%) suffered from fever, 19 (63.3%) suffered from headache, 29 (96.7%) had neck rigidity, 17 (56.7%) suffered from vomiting, 10 (33.3%) had seizers, 21 (70%) had altered conscious level, 29 (96.7%) were found to have positive Kernig's or Brudziniski's signs and only two (6.7%) cases had irritability, as in figure (2).

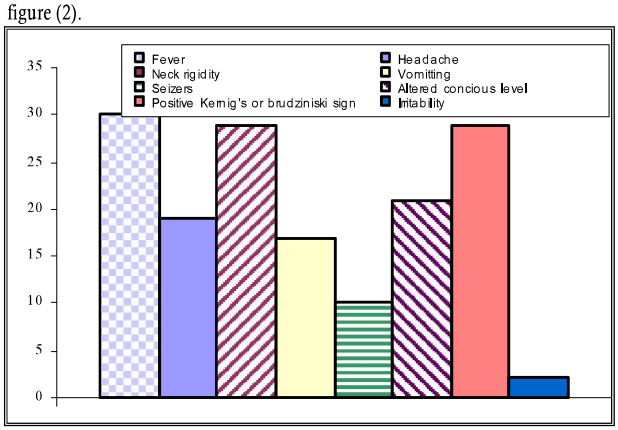

Figure (2) Clinical manifestations of the studied cases

CSF examination of the studied cases was done. The WBC count ranged from (130- 48000) with a mean of 1900±1700 SD. The polymorph count ranged from (60- 100) with a mean of 88.33±10.94 SD. The lymphocyte count ranged from (0- 40) with a mean of 11.67±10.94 SD. The sugar content ranged from (0- 82) with a mean of 38.7±23.56 SD. And the protein level ranged from (37- 1792) with a mean of 120±75 SD, as in table (3).

Table (3) Laboratory investigation of CSF

	Range	Mean ±SD
WBC Count	130- 48000	1900±1700
Polymorph Count	60- 100	88.33±10.94
Lymphocyte Count	0- 40	11.67±10.94
Sugar	0- 82	38.7±23.56
Protein Level	37- 1792	120±75

Stanford-Binet intelligence scale test was done for the studied 30 control and 30 cases. The compsite IQ score of the cases ranged from (36- 118) with a mean of 87.97±20.09 SD, there were four patient having mental retardation (two were moderate and two were mild retardation), while that of the control ranged from (82- 145) with a mean of 104.1±14.19 SD, and the difference between case and control was highly statistically significant ($p \leq 0.0001$), also there was statistical significance difference($p \leq 0.05$) as regard Verbal reasoning, Abstract/visual reasoning, Quantitative reasoning and Short term memory subscales with p value (0.0133, 0.0036, 0.0043&0.0024 respectively) as shown in table (4).

Table (4) Stanford-Binet intelligence scale test results of the studied control and cases

		Case	Control	P Value
Verbal Reasoning	Range	39- 135	65- 132	0.0133
	Mean ±Sd	88.37±20.19	99.57±13.02	
Abstract/Visual Reasoning	Range	36- 134	77- 142	0.0036
	Mean ±Sd	89.47±23.43	105.57±17.17	
Quantitative Reasoning	Range	36- 110	76- 142	0.0043
	Mean ±Sd	87.73±16.11	98.73±12.32	
Short Term Memory	Range	36- 129	84- 145	0.0024
	Mean ±Sd	91.87±22.98	106.93±12.15	
Total IQ	Range	36- 118	82- 145	0.0007
	Mean ±SD	87.97±20.09	104.1±14.19	

There was statistically significance difference in CBCL only in 2 scales Rule-break problem& Aggression (p= 0.0166& 0.0013) respectively. There was no statistical significance as regard Anxious/ Depressed, withdrawn, Somatic complains, social problems, thought problems, Attention problem and other problem scales as shown in table (5).

Table (5) Child Behavior Checklist (CBCL) parent report syndromes scores of case and control

		Case	Control	P Value
Anxious/ Depressed	Range	1- 12	3- 15	0.0984
	Mean ±Sd	5.6±2.82	7±3.59	
Withdrawn	Range	0- 30	0- 18	0.4474
	Mean ±Sd	9.7±7.43	8.47±4.73	
Somatic Complains	Range	0- 13	0- 9	0.1462
	Mean ±Sd	3.97±3.8	2.77±2.34	
Social Problems	Range	0- 15	0- 13	0.1856
	Mean ±Sd	6.9±3.95	5.63±3.37	
Thought Problem	Range	0- 11	0- 7	0.4841
	Mean ±Sd	2.63±2.65	2.2±2.04	
Attention Problem	Range	0- 10	1- 8	0.0890
	Mean ±Sd	5.1±3.43	3.83±2.1	
Rule-Break Problem	Range	0- 14	0- 8	0.0166
	Mean ±Sd	4.5±3.71	2.5±2.44	
Aggression	Range	0- 12	0- 6	0.0013
	Mean ±Sd	4.7±3.03	2.53±1.78	
Other Problem	Range	1- 15	0- 31	0.5464
	Mean ±Sd	7.13±3.69	6.4±5.46	

Discussion:

The study employed a prospective, longitudinal design and compared thirty post meningitis children (one month after discharge) to thirty healthy subjects without a medical history of neurological disease selected to match the age, gender and length of school education of the study population (served as a control group).

Clinical manifestations results were analyzed using the entire group to determine the percent. Patient diagnosis decisions would be much easier if everyone with bacterial meningitis presented to the emergency department with classic triad of meningitis (fever, stiff neck, and altered mental status).

In the current study, analysis of clinical picture data showed that fever was the most frequent (30 cases, 100%), neck rigidity and positive Brudziniski's and Kernig's signs (29 cases, 97%), so fever, neck rigidity and positive Kernig's or Brudziniski's signs are the most important signs and earliest to appear. altered level of conscious (21 cases, 70%) headache (11 cases, 37%) vomiting (17.57%) seizures (10 cases, 33%) and irritability (2 cases, 6%).

Unfortunately, large retrospective and prospective studies have revealed that just 44%-66% of patients with this disease will present with the so-called

classic triad of meningitis fever, stiff neck, and altered mental status[19].

Even fever- while a common aspect of the current study; is not present in all patients with meningitis in other studies. However, it is somewhat reassuring to learn that the complete absence of fever, stiff neck, altered mental status, and headache makes the diagnosis of bacterial meningitis very unlikely[20]. In the current study, analysis of laboratory data of CSF showed Gram positive diplococcic in direct gram stain CSF film in 3 samples (10%) one of them was culture negative (additional value of Gram staining for CSF culture-negative pretreated patients).

In a large study from Denmark, CSF Gram staining was the only positive laboratory finding for 4% of 875 patients with bacterial meningitis[21]. In an Indian study of 535 suspected meningitis cases, CSF Gram staining identified the causative organisms for 36 (65%) of 55 pretreated patients, while CSF culture was positive for only 5 (9%) patients(22).Positive Gram stain can detect only bacterial counts higher than 1000 cells per mL in CSF[23].

CSF culture remains the gold standard for the diagnosis of bacterial meningitis, CSF cultures was positive for Streptococcus Pneumonia in 4 samples only (13%). In a study from the United Kingdom including 103 patients with clinically defined meningococcal meningitis, only 13% had positive CSF cultures[24].

Patients with meningitis usually followed up only for hearing and vision loss and neurobehavioral squeal usually postponed, which is not correct because developmental deficits have a huge impact not only on the child but also on the entire family and on society. Concerning neurobehavioral sequelae in bacterial meningitis group, in the current study, there were significant differences in Stanford-Binet Intelligence Scale IQ test results between meningitis and control groups ($p < 0.01$) in the five testing domain (verbal reasoning, quantitative reasoning, abstract/ visual reasoning, short term memory and composite IQ) . However, impairments were not generally severe as 87% of meningitis group scores fell within the average normal IQ range and 13% were below normal level (four patient having mental retardation, two were moderate and two were mild retardation). These results agree with the study done by Peter,[25] which showed that there might be a tendency towards lower performance and lower IQ but without being in any way statistically significant compared with controls.

Statistical analysis statistics for bacterial meningitis and control groups via syndromes (anxious or depressed, withdrawn, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior), syndrome groupings (Internalizing and Externalizing), and total problem scores on the Child Behavior Checklist (CBCL) shows that children in bacterial meningitis group were on average rated to have more behavior problems, especially for internalizing behaviors of Anxious/ Depressed and Withdrawn problems, as in bacterial meningitis group, 16 and 14 case (53%- 46%) had Anxious/ Depressed and Withdrawn problems respectively which are significantly different from control group ($p < 0.05$). Also children having behavior problems for internalizing problem scores were more in bacterial meningitis group than in control group (22 and16 case respectively), this difference is statistically significant ($p < 0.05$).

Same results were obtained by Samir et al. (2009)[26] their results showed that 65% (33/51) of the children who survived meningitis had 1 type of impairment (30- 40) days after discharge.

Recommendations:

1. Psychometric evaluation by appropriate Stanford-Binet Intelligence Scale and Child Behavior Check-List (CBCL) is an easy and not expensive way to detect neuropsychological Sequelae after bacterial meningitis in children providing chance for early rehabilitation strategies.
2. Assess late cognitive and behavioral sequelae in children survived of bacterial meningitis and also follow up after several years of early detected neuropsychological sequelae.

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الملخص

الاكتشاف المبكر للمضاعفات المعرفية والسلوكية فى الأطفال الناجون بعدالاصابةبالالتهاب السحائى البكتيري

أجريت هذه الدراسة لتقييم العواقب المعرفية والسلوكية المبكره فى الأطفال على قيد الحياة بعد الاصابه بالالتهاب السحائى البكتيرى. وقد اجريت هذه الدراسه على ثلاثين من الأطفال الذين تم شفائهم من الالتهاب السحائى البكتيرى فى مستشفى الحميات بالعباسية بالمقارنه بمجموعه ضابطه من الأطفال الأصحاء مماثله فى العدد والنوع والسن.

تم عمل التقييم الاكلينيكى (أخذ التاريخ المرضى والفحص الاكلينيكى) وأخذ عينات الدم والسائل النخاعى لعمل التحاليل اللازمه للتشخيص. بالنسبه للسائل النخاعى تم الفحص وتحديد عدد الخلايا الكلى والنوعى ومستوى السكر والبروتين وقد تم عملفحص ميكروسكوبى مباشر بصبغه الجرام وزرع السائل النخاعى على المزارع المناسبه وتم عمل صورة دم كاملة وتحديد مستوى السكر فى الدم.

تم عمل التقييم للعواقب المعرفية والسلوكية للأطفال فى المجموعتان بعمل الاختبارات النفسية التى تقيم صعوبات التعلم وتأخر النمو ومستوى الذكاء وهى مقياس الذكاء ستانفورد بينيه وبالنسبه للمشاكل السلوكيه تم دراستها عن طريق تقيم الآباء لسلوك الطفل(قائمة الآباء لتقييم سلوك الأبناء(CBCL/6-18).

وقد تبين من نتائج الدراسه وجود نقص ملحوظ فى مستوى ذكاء الأطفال الذين تم شفائهم من الالتهاب السحائى البكتيرى وايضا وجود مشاكل سلوكيه اكثر بالمقارنة مع المجموعه الضابطه.