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IgG-INDEX AS EARLY PREDICTOR FOR NEUROLOGICAL MORBIDITY IN EGYPTIAN PATIENTS WITH ACUTE MENINGITIS

By

AFAF ALI MASOUD[1], NADIA ABDELAATY ABDELKADER[1], EMAN MOHAMED BAYIOMY[2], DINA ELSHENAWY[3] ENAS ANWER KHATTAB[4]

Departments of Tropical Medicine[1], Neurology[2] and Clinical Pathology[3], Faculty of Medicine, Ain Shams University, Cairo 11566 and Department of Internal Medicine[4], Faculty of Medicine, Al-Fayoum University, Egypt

Abstract

Diagnostic procedures to predict the prognosis of acute meningitis are of paramount importance in order to choose the appropriate level of further surveillance. The aim of this study was to evaluate the predictive power of IgG–index as CSF biomarker for disease prognosis in patients with acute meningitis. This is a prospective study done on forty patients; group I: Twenty patients with the clinical diagnosis and CSF analysis of acute bacterial meningitis and group II: Twenty patients with the clinical diagnosis and CSF analysis of aseptic meningitis. All the patients were subjected to routine clinical and laboratory evaluation and complete CSF analysis. Intrathecal IgG synthesis was measured using radial immunodiffusion (RID) technique. Glasgow outcome scale (GOS) was done at discharge .The duration of hospital stay was recorded. The IgG-index was the only independent predictor for unfavorable outcome (GOS < 5) in patients' groups' especially aseptic group. The best cut off value of IgG index for early prediction of unfavorable outcome (GOS < 5) in bacterial meningitis group was ≥6.75 with AUC of 0.922 and 95% CI of 0.769-1.07 and sensitivity of 75% and specificity of 93.7%. While, in aseptic meningitis group was ≥7.9 with AUC of 1 and 95% CI of 1.00-1.00 and sensitivity of 100% and specificity of 100%.

Key words: Acute bacterial meningitis, Aseptic meningitis, IgG index.

Correspondence: Dr. Nadia Abdelaaty Abdelkader. Email: dr.nadiaabdelaaty@gmail.com.

Introduction

Meningitis is an extremely severe and life threatening infection that necessitates immediate diagnosis and prompt therapy. Bacterial meningitis is endemic in Egypt and sporadic cases occurring all over the year (Abdel Ghani *et al*, 2002). The clinical course of bacterial and viral meningitis is sometimes difficult to predict rate was approximately 5% and long-term morbidity mainly consisted of persistent neurological sequelae was 15% (Pelkonen *et al*, 2009). Although the diagnosis of bacterial and viral meningitis mainly relies on the analysis of cerebrospinal fluid (CSF), only limited data on the prognostic value of CSF parameters existed (Deisenhammer *et al,* 2006) yet, initial risk

assessment of individual patients was of paramount importance in order to choose the appropriate level of further surveillance i.e. general ward versus critical care unit (Flores-Corder *et al*, 2003).

The outcome is frequently assessed by the Glasgow outcome scale (GOS), which ranges from 1 to 5. A score of 1 indicates death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability (disabled but independent) and score 5, good recovery (Weisfelt *et al*, 2006). Limited data on prognostic value of CSF parameters exist (Deisenhammer *et al*, 2006). An elevated IgG index [(IgG_{CSF} / IgG_{serum})/ ($albumin_{CSF}$/$albumin_{serum}$)] may be added to the list of markers for the early identification of patients at high risk for neurological morbidity in infectious CNS diseases. Cut off value was suggested to be 0.75 (Lackner *et al*, 2010).

The aim of this study was to evaluate the predictive power of IgG-index as CSF biomarker for disease prognosis in patients with acute meningitis.

Patients, Materials and Methods

Study design: This study was designed to be a prospective study, carried out in Tropical Medicine Department, Ain Shams University Hospitals and Embaba Fever Hospital, during the period from January 2012 to December 2012, the sample size was forty patients with acute meningitis.

Patients' selection: Forty patients with acute meningitis were presented to emergency unit of Embaba fever hospital. The patients were divided according to certain inclusion and exclusion criteria into two groups: GI: Twenty patients with acute bacterial meningitis (12 were females and 8 were males with mean age of 21.2± 6.8 years), and GII: Twenty patients with acute aseptic meningitis (9 were females and 11 were males with mean age of 22.5±16.4 years).

Inclusion criteria: GI: 1- Patients presented for the first time to Embaba fever hospital with clinical diagnosis of acute bacterial meningitis. 2- CSF analysis fulfilling the criteria of acute bacterial meningitis with positive gram stain and culture for bacteria. G2: 1- patients with the clinical diagnosis of aseptic meningitis

2- CSF analysis fulfilling the criteria of aseptic meningitis with negative gram stain and culture for bacteria.

Exclusion Criteria (for both groups): 1- Clinical picture suggestive of cerebro-vascular disease. 2- Brain tumors or other neurological insults. 3- Other fever causes. 4 - Other coma causes.

All included patients (or their corresponding relatives if the patients are unconscious) signed a written informed consent form. Approvals of all the concerned authorities were obtained.

All patients were subjected to the following: 1- Clinical study: full medical history and thorough clinical examination were done for all patients with special emphasis on symptoms and signs of acute bacterial and viral meningitis. Glasgow outcome scale (GOS) which ranges from 1 to 5 was used to assess neurological outcome at discharge. A score 1 indicates death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability (disabled but independent) and 5, good recovery (Weisfelt *et al*, 2006)

Hospital stay duration was recorded.

2- Routine Laboratory investigations: The tests were done for all patients: a- CBC, ESR and CRP, b- Liver function tests (enzymes and serum albumin), c- Kidney function tests (Urea, creatinine), d- Random blood glucose.

3- CSF analysis: First spinal tap, under complete aseptic conditions, including: a- Physical examination: color, aspect and pressure, b- Chemical examination protein and glucose, c- Cell count: total and differential leukocytic count, d- Gram's stain and culture, e- CSF/serum glucose ratio, f- CSF/serum albumin quotient (Qalb), and f- Calculation of IgG-index: intrathecal IgG synthesis will be measured using radial immunodiffusion (RID) technique. IgG-index represents CSF/serum IgG ratio to CSF/serum albumin quotient (Qalb) (Deisenhammer *et al,* 2006).

Statistical analysis: Data were revised, coded, tabulated and introduced to a PC using, statistical package for social science (SPSS 15.0.1 in windows, SPSS Inc, Chicago, IL, 2001). Analysis was done according to the data type of each parameter. 1- Descri- ptive statistics: -Mean, standard deviation (±SD) and range for parametric numerical data:-Frequency and percentage: for non-numerical data. 2. Analytical statistics: Student t test -Mann Whitney test (U test) -Chi-Square test. -Fisher s exact test ROC curve (receiver operating characteristic). Level of significance: $p>0.05$: non-significant (NS), $p<0.05$: significant (S) and $p<0.01$: highly significant (HS).

Results

The main symptoms in both groups were fever, headache, vomiting, hallucinations, blurring of vision, convulsion, and disturbed level of consciousness. Signs of meningeal irritation as neck rigidity, positive kerning's sign and brudhzinski sign are more prevalent in bacterial meningitis than in aseptic group ($P <0.05$).

Table 1: Chemical and cytological characters of CSF in patients groups.

	Normal values	Meningitis				P-value	Sig.
		Bacterial		Aseptic			
		Mean	±SD	Mean	±SD		
CSF protein (mg /dl)	15 –50	234.1	79.9	56.7	21.5	0.0001	HS
CSF Glucose (mg /dl)	40 –85	29.2	16.0	95.6	77.9	0..001	HS
CSF /Serum glucose ratio	> 0.4	0.2	0.1	0.7	0.3	0.0001	HS
CSF Albumin (mg/dl)	< 50	10.5	2.2	10.5	2.2	> 0.05	NS
CSF/Serum Albumin	< 9	0.0049	0.0048	0.005	0.006	> 0.05	NS
CSF IgG (mg/l)	< 42	30.3	17.5	29.0	2.3	> 0.05	NS
CSF Cell (cells/mm^3)	0 -5	1281.0	1959.0	80.7	87.2	0.01	S
CSF neutrophils	0	83.0	8.3	21.7	10.5	0.0001	HS
CSF Lymphocytes	60- 70%	17.0	8.3	76.0	10.8	0.0001	HS

Table (1) showed a highly significant difference in WBCs, polymorph%, lymphocytes%, CSF protein, CSF glucose & CSF/serum glucose ratio between groups ($P<0.001$), without significant difference as to CSF albumin, CSF/ serum albumin & CSF IgG between groups ($P > 0.05$).

Table 2: Some laboratory findings of patients groups

	Normal values	Bacterial		Aseptic		P -value	Sig.
		Mean	±SD	Mean	±SD		
ESR (mm/hr)	< 15- 20	33.20	16.57	31.28	21.39	> 0.05	NS
TLC	4.300-10,800	11.99	3.95	9.35	4.07	0.04	S
CRP (mg/ l)	0 to < 6	15.90	4.32	5.82	4.42	0.0001	HS
Serum IgG(mg/dl)	605- 1563	1239.49	713.61	1456.7	602.45	> 0.05	NS
IgG index	< 0.7	5.71	2.79	6.31	3.90	> 0.05	NS

Table (2) showed a significant difference regarding TLC (P< 0.05) with higher mean in bacterial group than aseptic one. Significantly higher CRP mean was in bacterial meningitis patients as compared to viral meningitis one without significant difference in sera IgG & IgG index between both (P > 0.05).

Table 3: Medical status on discharge and hospital stay duration of patients.

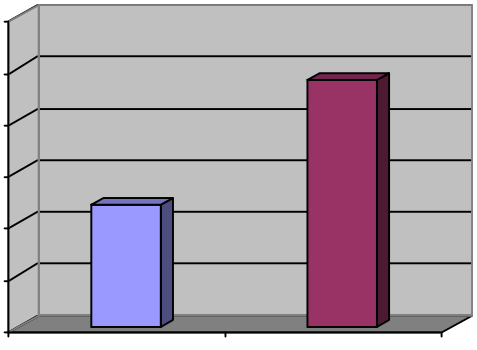
		Bacterial		Aseptic		P-value	Sig.
		N	%	N	%		
Fever on discharge	Present	1	5	0	0	> 0.05	NS
	Absent	19	95	20	100		
Consciousness on discharge	Alert	18	90	17	85	> 0.05	NS
	Semiconscious.	1	5	1	5		
	Coma	1	5	2	10		
Meningeal signs on discharge	Present	0	0	0	0	……	…
	Absent	20	100	20	100		
Duration (days)	Mean± SD	12.3	1.5	12.3	1.3	> 0.05	NS

Table (3) showed no significant difference regarding fever, consciousness & meningeal signs at discharge between groups (P>0.05), but without significant difference regarding duration of hospitalization between the groups (P > 0.05).

Table 4: GOS and complication of patients groups.

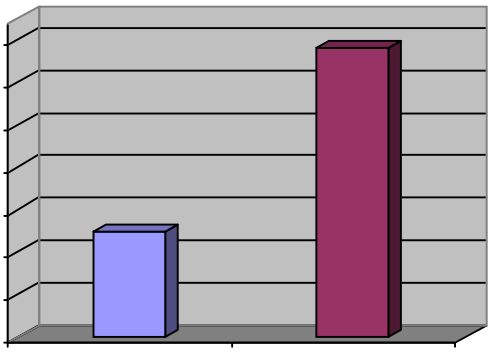
		Bacterial		Aseptic		P-value	Sig.
		N	%	N	%		
G.O.S	Dead	2	10	2	10	> 0.05	NS
	Vegetative state	0	0	1	5		
	Severe disability	1	5	0	0		
	Moderate	1	5	0	0		
	Good recovery	16	80	17	85		
GOS	5	16	80	17	85	> 0.05	NS
	<5	4	20	3	15		
Complications	Death	2	10	2	10	> 0.05	NS
	Hemiparesis	2	10	1	5		
	No-neurological	16	80	17	85		

Table (4) showed no significant difference in GOS and complications between patient's groups (P > 0.05).



IgG index (4.74±1.57) (9.59±3.43)

Fig. 1: IgG index in relation to GOS in bacterial meningitis group



IgG index (5.01±1.55) (13.65±5.53)

Fig. 2: IgG index in relation to GOS in aseptic meningitis group

Table 5: Diagnostic validity test of IgG index for prediction of GOS< 5 in bacterial and aseptic meningitis groups.

IgG index	AUC	95% CI	Sensitivity	Specificity	P-value	Sig.
G1: GOS<5 if greater than or equal to 6.745	0.922	0.769-1.07	75%	93.7%	0.011	S
G2: GOS<5 if greater than or equal to 7.9	1	1.00-1.00	100%	100%	0.007	HS

From the ROC curve, cut off value of IgG index for early prediction of unfavorable outcome (GOS < 5) in bacterial meningitis group was ≥ 6.75 with AUC of 0.922 and 95% CI of 0.769-1.07 and sensitivity of 75% and specificity of 93.7%. The ROC curve, cut off value of IgG index for early prediction of unfavorable outcome (GOS<5) in aseptic meningitis group was ≥7.9 with AUC of 1 and 95% CI of 1.00-1.00 and sensitivity of 100% and specificity of 100%.

Discussion

In the present study, there was no significant difference in age and gender in both patients groups (p >0.05). Singhi and Bansal (2006) and Abro *et al.* (2009) reported similar results.

The study present showed a highly statistical significant difference in TLC, polymorphs and CRP between both patients groups (P <0.001) with higher values in bacterial group than aseptic group. While, there is no significant difference in ESR. The present data agreed with Dubos *et al.* (2008) and Abro *et al.* (2009)

In contrast, Singhi and Bansal (2006) reported no significant difference in CRP and TLC between patients with acute bacterial and aseptic meningitis.

There was a highly significant difference in CSF WBCs and CSF polymorphs between both patients groups (p < 0.001) with higher values in bacterial meningitis than aseptic meningitis. The present results agreed with Dubos *et al.* (2008) and Abro *et al.* (2009) who reported that, the patient with bacterial meningitis had a significantly

higher CSF WBCs and polymorphs than those with aseptic meningitis.

In the present study, the patients of G1 had a higher CSF protein than those of group 2 and these results were statistically highly significant ($p < 0.001$). Dubos *et al.* (2008) found that patients with bacterial meningitis had a significant higher CSF protein than those with aseptic meningitis. The elevated CSF protein in bacterial meningitis may be attributed to the disruption and marked increased permeability of the blood brain barrier (Swartz, 2004), caused by the bacteria and by the response of the immune system to the entrance of bacteria into the CNS (Sáez-Liorens and McCracken, 2003).

In the current study, the patients of G1 had a lower CSF glucose than in G2, which were statistically highly significant ($p < 0.001$). Dubos *et al.* (2008) reported the same results. In contrast, Singhi and Bansal (2006) and Abro *et al.* (2009) did not find significant difference in CSF glucose between patient with acute bacterial and viral meningitis. The hypoglycorrhachia characteristic of pyogenic meningitis might be due to interference with normal carrier-facilitated diffusion of glucose and to increased utilization of glucose by host cells (Swartz, 2004).

There was no significant difference regarding CSF albumin, CSF/ serum albumin and CSF IgG between both groups ($P > 0.05$). These results agreed with Lackner *et al.* (2010).

The present study showed no significant difference in GOS & complications between patients groups ($P > 0.05$). Also, there was no significant difference in length of hospitalization between G1 & G2 ($p > 0.05$). Abro *et al.* (2009) stated that there was a significant difference in length of hospitalization between patients with bacterial meningitis and those with aseptic meningitis. There was no significant difference in serum IgG & IgG index between both groups ($P > 0.05$).

In the present study, the IgG-index was the only independent predictor for unfavorable outcome (GOS <5) in patients' groups especially aseptic group. There is no significant association between unfavorable outcome and all other studied parameters. The best cut off value of IgG index for early prediction of unfavorable outcome (GOS < 5) in bacterial meningitis group was ≥6.75 with AUC of 0.922 and 95% CI of 0.769-1.07 and sensitivity of 75% and specificity of 93.7%. Also, the best cut off value of IgG index for early prediction of unfavorable outcome (GOS<5) in aseptic meningitis group was ≥7.9 with AUC of 1 & 95% CI of 1.00-1.00 and sensitivity of 100% and specificity of 100%.

Although several studies have demonstrated the value of different serum and CSF biochemical parameters (serum procalcitonin (PCT), CSF lactate, CSF ferritin, CSF IL8…etc.) in clinical and laboratory prediction of morbidity (Huy *et al,* 2010; Pinto-Junior *et al,* 2011; Viallon *et al,* 2011). Few data are available concerning value of IgG index in prediction of neurological morbidity or differential diagnosis of acute meningitis.

The average time to obtain results for immunoglobulin indices with modern analyzers is well below half an hour. Therefore this rapid test is easily applicable in the emergency setting and the current data suggest that patients with an IgG-index of 0.75 and above at initial presentation should be in mind (Lackner *et al,* 2010). They stated that the IgG-index was the only independent predictor for unfavorable outcome (GOS <5) in patients with infectious CNS diseases. The sensitivity and specificity of an IgG-index of 0.75 and higher for predicting unfavorable outcome was 40.9% and 80.8% in bacterial meningitis and 40% & 94.8% in viral meningoencephalitis, respectively. No significant associations between CSF parameters and outcome were seen in follow-up CSF samples. The association of an elevated IgG-index with unfavorable outcome may be explained by secondary neuronal damage due to early intrathecal immunoglobulin reaction. This means that specific microorganism-driven immunoglobulin production is more likely to cause inflammatory brain damage resulting in the neurological morbidity. In bacterial meningitis, Giasuddin *et al*. (1998) showed similar results. Although only a smaller number of patients were included in the mentioned study, patients with neurological morbidity due to bacterial meningitis showed a significantly higher IgG-index in the initial CSF than patients who fully recovered.

Molyneux *et al*. (2011) stated that bacterial meningitis causes morbidity and mortality in developing countries, and that children beyond the neonatal age-group with purulent meningitis caused by *S pneumoniae*, *H influenzae* type b, or *N meningitidis* who are stable by day 5 of ceftriaxone treatment 5 & 10 days of parenteral ceftriaxone.

Conclusion

The elevated IgG-Index is a good indicator for the early identification of patients at high risk for neurological morbidity in acute aseptic and bacterial meningitis. Patients of aseptic meningitis with IgG-Index ≥7.9 and patients of bacterial meningitis with IgG-Index ≥6.75 both need special attention (Critical Care Unit).

Accordingly, IgG index should be considered in evaluation of the patients with acute meningitis as it is rapid, simple and easily applicable in emergency setting.

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