Original Article

TUBERCULOUS MENINGITIS: DO MODERN DIAGNOSTIC TOOLS OFFER BETTER PROGNOSIS PREDICTION?

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Summary

***Background*:** The British Medical Research Council (BMRC) staging has been extensively used to evaluate the disease severity and establish the approximate prognosis of tuberculous meningitis.

***Aims*:** This study aimed at analyzing the predictive accuracy for mortality and neurological sequelae of a set of clinical features, laboratory tests and imaging.

***Methods*:** We compared the British Medical Research Council (BMRC) staging with a new scoring proposal to predict the prognosis of patients with Central Nervous System Tuberculosis. Data from Ecuador was collected. A score was built using a Spiegelhalter and Knill-Jones method and compared with BMRC staging with a ROC curve.

***Results*:** A total of 213/310 patients (68.7%) were in BMRC stage II or III. Fifty-seven patients died (18.3%) and 101 (32.5%) survived with sequelae. The associated predictors were consciousness impairment (p= 0.010), motor deficit (p = 0.003), cisternal effacement (p=0.006) and infarcts (p=0.015). The new score based on these predictors yielded a larger area under the curve of 0.76 (95% CI: 0.70-0.82), but not significantly different from the BMRC (0.72: 95% CI: 0.65-0.77).

***Conclusions*:** This modern score is easy to apply and could be a sound predictor of poor prognosis. However, the availability of modern tests did not improve the ability to predict a bad outcome. **[*Indian J Tuberc 2013; 60: 5 - 14*]**

Key words: Tuberculosis, Meningitis, Prognosis, Predictors.

INTRODUCTION

Despite effective antituberculous treatment, mortality and morbidity remain high in patients with Central Nervous System Tuberculosis (CNSTB).[1,2] Clinical, laboratory and image findings are not very sensitive or specific for diagnosis.[1] Early recognition and treatment of CNSTB may improve the outcome. The British Medical Research Council (BMRC) staging has been extensively used to evaluate the disease severity and establish the approximate prognosis of tuberculous meningitis (TBM).[3] Additionally, some clinical and neuro imaging predictors have also been evaluated.[2,4-11] However, uptill now, no clear indications are given to assess the prognosis of such a devastating disease.[12]

In 1989, we started a prospective CNSTB Data Registry, collecting clinical, laboratory, radiological, therapeutical and follow-up data of all patients with CNSTB admitted to the Department of Neurology as well as other wards of the Eugenio Espejo Hospital in Quito. All patients were examined and treated by a neurologist from the Department of Neurology.

With this study, we aimed at analyzing what the predictive accuracy for mortality and neurological sequelae was of a set of clinical features, laboratory tests and imaging of patients with a definite or probable diagnosis of CNSTB. We developed a user-friendly approach to deal with several positive and negative features to predict severe disability or mortality in patients suspected of having CNSTB and to compare its discriminatory power with the BMRC staging.

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METHODS

All patients admitted between 1989 and 2004 at the Eugenio Espejo Hospital, a major public care centre located in Quito – Ecuador, in whom an antituberculous treatment was started for a clinical diagnosis of CNSTB, were included. Patients were carefully followed-up until the end of antituberculous treatment. Their clinical files, which included a description of signs and symptoms at admission, laboratory results, imaging, and therapy, as well as the outcome in terms of neurological disability and mortality, were reviewed.

DATA

In all patients, we established the length of evolution of the disease before admission to the hospital, the severity of the disease upon admission based on BMRC staging (Box 1), the time span between admission to the hospital and start-up of treatment, contact with known cases of tuberculosis, the clinical and neurological features upon admission (including degree of coma) and during the first four weeks after admission. Complementary examinations included blood leukocyte count, serum sodium, Mantoux intradermal test (purified protein derivate; PPD), bacteriological analyses of sputum, gastric aspirate, urine collection, magnetic resonance imaging (MRI) and/or computer assisted tomography (CT-scan) of the brain and/or spinal cord. In the cerebrospinal fluid, we included a differential cell count, protein and glucose levels, acid-fast bacilli (AFB) staining, culture in Lowenstein-Jensen (LJ) medium, immunobiological study by enzyme-linked immunosorbent assay (ELISA) for detecting anti-Bacille Calmette-Guerin (BCG) antibodies, and the dosage of adenosine deaminase activity (ADA). Indian ink staining was performed in order to exclude cryptococosis. Three patients had a lymph node biopsy done, and three patients had a culture performed on material obtained from a draining peri-renal abscess. Surgery was done for two patients with intracranial abscesses, four with hydrocephalus and two with spinal tuberculosis.

Diagnostic criteria

The diagnosis of definite CNSTB was based on AFB staining, mycobacterial culture and/or pathology on surgery or autopsy. In patients with probable CNSTB, the diagnosis was considered on clinical grounds based on the following criteria: 1) MRI or CT brain images compatible with cerebral abscess or tuberculoma; 2) CSF with inflammatory changes; 3) MRI spinal images compatible with tuberculomas, syringomyelitis, arachnoiditis, myelitis, spondylitis, or para-spinal abscesses; 4) positive ELISA or ADA in the CSF; 5) positive direct smears or culture isolates of *M. tuberculosis* from another tissue or body fluid. Other clinical arguments consisted of Mantoux test; chest x-ray; hydrocephalus, leptomeningitis, basal cistern effacement, or infarction on the MRI or CT;[13] or a previous history of tuberculosis or clinical response to antituberculous treatment.

Box 1: British Medical Research Council staging

Stage I: No definite neurological symptoms on admission or in the history before admission, with or without meningismus

Stage II: Signs of meningeal irritations with or without slight clouding of consciousness with focal neurological signs such as cranial nerve palsies or hemiparesis

Stage III: Severe clouding of consciousness or delirium, convulsions and serious neurological signs such as hemiplegia, paraplegia, involuntary movements.

Treatment

All patients received oral administration of isoniazid, rifampicin and pyrazinamide. Ethambutol was added in 126 patients, simultaneously with a quinolone in 18 cases. Streptomycin was added in 78 cases, simultaneously with a quinolone in five cases. In five additional cases, a quinolone alone was added to the regimen of three drugs. The anti-tuberculous drugs were started between one hour and seven days after admission. The first phase, which lasted two months, included all the drugs, and the second phase, which lasted four to 10 months or more, was restricted to isoniazid and rifampicin. Steroid therapy with prednisone was given to patients with severe impairment of consciousness, bilateral motor deficit, vasculitis, spinal tuberculosis and cerebral tuberculomas with intracranial hypertension and focal deficit. We determined that treatment was complete when all the CSF parameters were within normal limits and abnormal image findings were cleared.

Outcome

We established the outcome when treatment had ended, using the approach advocated by Smith for tuberculous meningitis which recognizes five categories:[8,14-16] 1) apparently normal patients; 2) patients with slight mental abnormality, or normal intelligence but with some degree of hemiparesis, minor behavioural problems, deafness or epilepsy, with the possibility of leading relatively normal autonomous lives without assistance; 3) patients with mild sequelae, that is mild mental abnormality and/or having a well-established physical impairment, being able to lead relatively normal lives with some assistance; 4) patients with severe sequelae, that is severe mental abnormality and/or having a severe physical impairment being totally dependent; 5) death.

Statistics and score

We used bivariate analysis for statistical comparison of age, sex, pre-admission duration of the symptoms of tuberculous meningitis, clinical manifestations upon admission and abnormal movements during the first month of treatment, blood and CSF examination, and MRI- and/or CT scan upon admission, early onset of anti-tuberculous treatment, and use of steroids related to the prognosis. For categorical predictors, contingency tables were drawn to estimate Pearson's chi-square coefficients with its related two-tailed asymptomatic p values. For continuous predictors, analysis of variance (ANOVA) was performed; the corresponding F coefficient with its related p value was computed for each predictor.

For the multivariate analysis, we selected predictors that had statistical significance on bivariate analysis. Steroid prescription was not included, since it could have been biased, due to use only in severe cases. The outcome variable at discharge was the above described five-category scale.

To develop the severity score for predicting mortality, we used the methodology advocated by Spiegelhalter and Knill-Jones.[17] Since this method requires a dichotomized outcome, we explored different models of splitting the scale of five ordinal categories into two categories. The adjusted logLRs (adjusted weights) were multiplied by 10, rounded and summed for every subject in order to obtain an individual score.

This score was plotted against the outcome in a Receiver Operator Characteristics (ROC) curve. The Area Under the Curve (AUC) with 95% confidence intervals was computed. Analysis was performed using SPSS V. 13 (SPSS Inc, Chicago, IL, USA).

RESULTS

Patient characteristics

From our prospective CNSTB Data Registry, we report 312 patients who developed definitive or probable CNSTB. Two of them were excluded for having missing values. Female to male ratio was 0.57, the mean age was 34.5 years (95% CI: 32.7-36.4). Two patients had HIV infection. One hundred and forty patients (45.1%) had a definite diagnosis, 40 with AFB staining, 28 with culture, 11 with autopsy and 61 with combined results.

Table 1: BMRC Stage at admission and functional prognosis at discharge in 310 patients with Central Nervous System Tuberculosis

		Functional prognosis at discharge					
		total recovery n=152	mild sequelae n=47	moderate sequelae n=26	severe sequelae n=28	Death N=57	Total n=310
BMRC I	Count	66	13	10	5	3	97
	Percentage	43.4	27.7	38.5	17.9	5.3	31.3
BMRC II	Count	53	23	12	9	22	119
	Percentage	34.9	48.9	46.2	32.1	38.6	38.4
BMRC III	Count	33	11	4	14	32	94
	Percentage	21.7	23.4	15.4	50.0	56.1	30.3
Total	Count	152	47	26	28	57	310
	Percentage	49.0	15.2	8.4	9.0	18.4	100

BMRC Stage = British Medical Research Council Stage
BMRC staging: Pearson´s R^2=0.12 B=0.69 p value<0.001

Table 2: Results of Bivariate Analysis of data for neurological signs at admission, steroid treatment and functional status at discharge.

		Functional status at discharge					
		total recovery n=152	mild deficit n=47	moderate deficit n=26	severe deficit n=28	Death N=57	p value
Impaired consciousness N=310	Count	106	29	16	21	55	<0.0001
	%	69.7	61.7	61.5	75.0	96.5	
headache N=306	Count	127	31	17	24	41	0.011
	%	84.7	66.0	65.4	88.9	73.2	
irritability N=308	Count	125	32	18	26	43	0.027
	%	82.2	68.1	69.2	96.3	76.8	
papilloedema N=310	Count	19	12	3	8	22	<0.0001
	%	12.5	25.5	11.5	28.6	38.6	
motor deficit N=310	Count	52	38	18	21	41	<0.0001
	%	34.2	80.9	69.2	75.0	71.9	
involuntary movements N=310	Count	19	13	7	7	11	0.081
	%	12.5	27.7	26.9	25.0	19.3	
Cranial nerves palsy N=310	Count	27	14	4	9	25	0.002
	%	17.8	29.8	15.4	32.1	43.9	
meningeal signs N=310	Count	118	32	16	20	55	0.001
	%	77.6	68.1	61.5	71.4	96.5	
seizures N=309	Count	24	1	2	3	12	n.d.
	%	15.8	2.1	7.7	11.1	21.1	
Unconjugated gaze N=309	Count	9	5	0	2	13	n.d.
	%	5.9	10.6	0.0	7.1	23.2	
Steroid use N=	Count	20	16	10	17	17	<0.0001
	%	13.2	34.0	38.5	60.7	29.8	

n.d.: non definable, cells with too few patients.

One hundred two patients (32.9%) showed a time span from onset of symptoms to initial presentation of less than three weeks. For 92 patients (29.6%), it was three to four weeks and for 116 patients (37.4%), it was more than four weeks. Two hundred nine patients (67.5%) received early anti-tuberculous treatment the first three days after admission, and 80 patients (25.8%) were prescribed steroids. Two hundred thirteen patients (68.7%) were in BMRC stages II and III; 57 patients (18.4%) died; 101 (32.5%) survived with sequelae and a complete clinical recovery was observed in 152 (49.0%) (Table 1).

General and neurological symptoms are summarized in Table 2. Laboratory examinations and image studies are summarized in Table 3.

Multivariate analysis

The multivariate analysis model retained as features related with poor prognosis, following the five point scale by Smith, impairment of consciousness ($p<0.001$), motor deficit ($p<0.001$), papilloedema ($p=0.043$), AFB smear or positive culture ($p=0.002$), cisternal effacement ($p<0.001$) and cerebral infarcts ($p=0.029$). An early start (within the first three days after admission) of anti-

Table 3: Results of Bivariate Analysis of data in CSF examination and neuro-imaging

		Functional prognosis at discharge					p value
		total recovery n=152	mild deficit n=47	moderate deficit n=26	severe deficit n=28	Death N=57	
Findings in CSF							
Cells in CSF	Mean	300.0	183.7	95.3	194.0	177.1	0.306
	95% CI	186.0-413.9	49.9-317.5	49.7-141.0	26.6-362.3	97.9-256.3	
Glucose in CSF	Mean	35.6	35.4	32.7	33.1	32.3	0.909
	95% CI	31.2-40.0	29.0-41.9	25.4-40.1	25.3-40.8	25.4-39.3	
Proteins in CSF	Mean	172.6	168.6	395.9	262.1	282.8	0.048
	95% CI	130.5-214.6	124.7-212.5	68.7-723.1	112.2-411.3	154.3-411.3	
ELISA	Mean	0.7	0.6	0.6	0.7	0.8	0.847
	95% CI	0.4-0.9	0.4-0.8	0.3-0.9	0.5-0.9	0.7-1.0	
Adenosine Deaminase Activity	Mean	4.9	4.2	3.3	5.8	7.6	0.087
	95% CI	3.7-6.2	2.2-6.2	0.3-6.2	2.4-9.2	5.6-9.7	
Neuroimaging in CT or MRI							
Hydrocephalus 142/310	Count	54	20	8	18	42	<0.001
	%	35.5	42.6	30.8	64.3	73.7	
cisternal effacement 80/310	Count	25	10	5	12	28	<0.001
	%	16.4	21.3	19.2	42.9	49.1	
Leptomeningitis 100/310	Count	37	12	9	13	29	0.002
	%	24.3	25.5	34.6	46.4	50.9	
Infarcts 72/310	Count	21	13	3	11	24/57	<0.001
	%	13.8	27.7	11.5	39.3	42.1	
Granuloma 62/310	Count	35	10	4	4	9	0.651
	%	23.0	21.3	15.4	14.3	15.8	
Calcifications 9/309	Count	4	2	2	0/28	1	n.d.
	%	2.6	4.3	7.7	0.00	1.8	

CSF = Cerebrospinal Fluid; CT = Computed Tomography; MRI = Magnetic Resonance Image

tuberculous treatment was a predictor of good prognosis ($p < 0.001$). The model showed a Pearson R^2 of 0.35. (Table 4)

Scoring system

Table 5 shows the logistic regression model with a dichotomous outcome for severe sequelae or mortality *versus* minor or absent sequelae identified impairment of consciousness, motor deficit, cisternal effacement, and brain infarcts as significant predictors. All were considered for the construction of the scoring system for which we suggested the name of Score Quito (Table 6).

Individual scores were plotted in a ROC curve and compared with the BMRC staging. The area under the curve of Score Quito was nearly the same [AUC: 0.76 (95% CI: 0.70 – 0.82)] as the area under the curve of the BMRC staging [AUC:0.72 (95% CI: 0.65 – 0.78)]. (Figure) Separate analysis for confirmed and probable TB cases did not change the conclusions. (AUC for confirmed TB cases: Score Quito 0.75, BMRC 0.71; AUC for probable TB cases: Score Quito 0.77, BMRC 0.73).

Table 4: Significant predictors following multivariate analysis, with the Smith 5 point scale as outcome parameter.

	Unstandardized Coefficients		Standardized Coefficients		95% Confidence Interval for B	
	B	Std. Error	Beta	Sig.	Lower Bound	Upper Bound
(Constant)	0.287	0.189		0.130	-0.085	0.659
Impairment of consciousness	0.402	0.091	0.224	0.000	0.223	0.581
Motor deficit	0.481	0.077	0.307	0.000	0.331	0.631
Papiledema upon admission	0.406	0.2	0.102	0.043	0.012	0.799
Bacteriological confirmation in CSF	0.468	0.152	0.149	0.002	0.168	0.767
Cisternal effacement	0.679	0.184	0.189	0.000	0.316	1.042
Cerebral infarcts	0.416	0.190	0.113	0.029	0.042	0.790
Early treatment	-0.637	0.165	-0.189	0.000	-0.962	-0.312

Pearson´s R^2 coefficient =0.35

Table 5: Logistic regression model with dichotomous outcome: mortality or severe sequelae vs. minor or no sequelae.

	B	Sig.	Exp(B)	95,0% C.I.for EXP(B)	
				Lower	Upper
Impaired consciousness	0.792	**0.010**	2.208	1.210	4.031
Motor Deficit	0.926	**0.003**	2.525	1.381	4.620
Papilloedema	0.535	0.100	1.707	0.903	3.227
AFB staining	-0.768	0.814	0.464	.001	276.388
Culture	0.741	0.288	2.098	0.535	8.224
Brain image Hydrocephalus	0.342	0.223	1.408	0.812	2.439
Brain image cysternal effacement	0.771	**0.006**	2.161	1.250	3.736
Brain image Leptomeningitis	-0.118	0.747	0.888	0.433	1.823
Brain image infarcts	0.655	**0.015**	1.926	1.138	3.259

Bolded values are statistically significant predictors.

Table 6: Score Quito

	Present	Absent
Impaired consciousness	2	-9
Motor deficit	4	-6
Cysternal effacement	8	-3
Cerebral infarcts	6	-2
Sum of score	20	-20

Present and absent findings can be summed up to a maximum of 20 points, and a minimum of -20. This score predicts the outcome in two classes: death or serious sequelae on one side, healing or minor sequelae on the other.

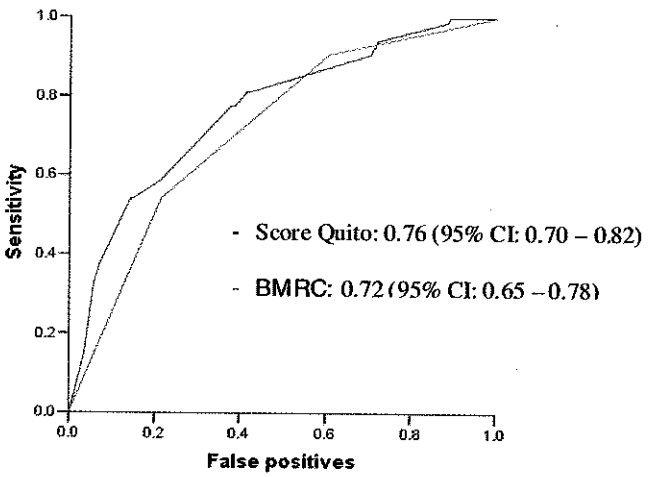

Figure: ROC curve of Score Quito compared with BMRC staging.

DISCUSSION

General

This study is one of the largest validating prognostic scores in CNSTB. Most patients presented with a BMRC Staging of the disease of II or III, which is similar to previous reports about CNSTB.[18-24] The percentage of patients in Stage III was lower than that from a study reported previously by us.[16] This can be explained by an improved capacity to establish early diagnosis and treatment in patients arriving at the emergency room of our hospital. Some patients who started treatment in Stage III had a good recovery; this could be due to early and correct management of hydro electrolytic disturbances and secondary infections.

Limitations

This study presents a retrospective analysis on an existing prospectively gathered dataset. Conception of this analysis from the beginning would have influenced the definition of certain parameters and strengthened the conclusions.

One might argue that diagnostic criteria were not strict in this cohort. The diagnosis of tuberculous meningitis is a presumptive part of the time, without definite microbiological proof. Direct stain, culture and polymerase chain reaction, if anyhow available in low to middle income countries, lack sensitivity.[1] Moreover, the inevitable fatal outcome without treatment sets the treatment threshold at a very low level.[25] As shown also through our results, prompt

treatment, not awaiting further confirmation, is a factor of good prognosis.

Scoring systems have to be validated in other cohorts. The rarity of CNSTB makes this a difficult to realize research, necessitating a multicentre setup, if one does not want to wait for 15 years, the time of case sampling for this study.

Prognosis

Previous studies have established the outcome of CNSTB as "good" or "poor", the latter usually including both mortality and morbidity.[2,10] In our study, clinical variables that predict complete recovery, survival with disability and fatal outcome have been identified separately.

A few factors have shown a significant association with prognosis. The BMRC staging which was developed to establish the degree of severity of the patients with CNSTB at the start of anti-tuberculous treatment has been used in some studies to establish its association with the outcome.[3] The weakness of BMRC is that it is a descriptive scale with overlapping features which do not include images nor CSF analysis and was not built with a multivariate procedure.[3,16,26-30]

Mortality and morbidity (sequelae) rates of CNSTB remain high, ranging from 5.1% to 63% and 8.3% to 50% respectively.[7,10] In our series, as in other, 34 % of the patients who started anti-tuberculous treatment in Stage III died.[10] In 13.8% of the patients admitted in Stage III of the BMRC, the deficit was severe at the end of treatment. This could be related with the cerebral infarcts, hydrocephalus, tuberculomas or spinal tuberculous lesions.[31-34]

Multivariate analysis

Non-significant predictors

Seizures were present in 13.7% of the cases, which is similar to other findings, not being a predictor of poor prognosis.[2,21] The damage of cranial nerves, meningeal signs, loss of weight, hyponatremia and high initial CSF protein levels were not predictors of morbidity-mortality in our patients in contrast with other studies.[2,7,20,22,28] Our results confirm other series where the MRI or CT scan findings of hydrocephalus and leptomeningitis were not significant in the multivariate analysis.[2,6,10,19,21,33,34] The tuberculomas or tuberculous abscesses were also not associated with morbidity-mortality.[2,6,20]

The use of steroids in our patients was associated with poor prognosis in contrast to a recently published paper.[35] This may be because in our study we used steroids in patients with severe tuberculosis who would have a poor prognosis anyway; furthermore, this study was not designed with the purpose of testing the effect of steroids in predicting prognosis.

As in other series, impairment of consciousness was significantly associated with mortality disability.[4,6,7,11,16,26-30,36] This association suggests that severe intra-cranial damage with or without intra-cranial hypertension, found in a high percentage of these patients, may be progressive or irreversible.

The irreversibility of neurological deficit in patients with CNSTB may be related with ischemia, edema or distortion of the adjacent structures.[24] The fact that papilloedema is associated with poor prognosis but not hydrocephalus, could be explained by other factors including venous thrombosis.[31] Positive CSF Ziehl Neelsen (ZN) stain or culture for *M. tuberculosis* represents a high concentration of mycobacteria in the CSF. In our patients, as in other series, it was associated with morbidity-mortality.[17]

Imaging by cranial MRI or CT-scan is a useful tool for diagnosis and follow-up of tuberculous meningitis cases.[2,6,20,33,34] Cisternal effacement has been shown to be associated with poor prognosis.[20] Infarction is a common complication of CNSTB.[16] Two patients who started treatment in Stage I and who had brain infarcts in the first MRI died.

Our study confirms that early anti-tuberculous treatment, before the third day after admission, exerts a protective impact on the morbidity-mortality of patients with CNSTB.[16,26]

Scoring systems

Initially, we hypothesized that correctly analyzing predictors and adding imaging findings would generate a much better score than the rather rough indicators of the BMRC prognostic score. Although the AUC of the Score Quito is somehow larger, the confidence intervals clearly overlap. In any case, the Score Quito shows superiority in its simplicity (only four independent predictors) and in its soundness: confirming and excluding powers are taken into account. It is also important to consider that BMRC staging, when it was built 50 years ago, was not aimed at predicting prognosis, but to classify patients who were submitted to a new therapy (streptomycin) in degrees of severity.[3]

Future research

As suggested in the limitations, this prediction score should be validated in a multi centre study, with a large sample size and a diagnosis as definite as possible. This brings us to the most wanted research result of all, a better diagnostic tool for tuberculous meningitis, CNSTB and tuberculosis in general.

CONCLUSION

An important challenge in CNSTB is the prediction of disability and death on the basis of different indicators exhibited by the patients at the start of treatment. The Score Quito is easy to apply and is a good predictor of poor outcome. The score tested in this study is a valuable indicator of prognosis, but does not outperform the BMRC prognostic score. On the other hand, the predictors resulting from our multivariate analysis discriminate well for a broad prognostic range.

Past decades of scientific breakthroughs, including new techniques of laboratory and imaging diagnostic aid, have contributed very little to a better prediction of prognosis in patients with CNSTB.

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