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Association of CSF glucose concentration with neurosyphilis diagnosis

Research Article

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Abstract: The most specific criterion for diagnosing neurosyphilis is a reactive CSF VDRL. Unfortunately, there are in Europe, including Poland small number of specialized laboratories for serological diagnosis of syphilis. Thus, CSF serology results are obtained with delay. Therefore, the decision on recommended therapy for neurosyphilis is taken on the basis of CSF basic tests. In this paper we attempt to determine the utility of CSF glucose concentration and its cut-off values in prediction of asymptomatic neurosyphilis. CSF and blood were collected from 55 HIV-uninfected patients with syphilis of unknown duration. Patients with neurosyphilis (14.5%) were characterized by higher CSF pleocytosis ($p<0.0001$), elevated CSF protein concentration ($p<0.05$) and lower CSF glucose concentration ($p<0.0001$). Multivariate regression analysis identified CSF pleocytosis and CSF glucose concentration as the two independent predictors of reactive CSF VDRL ($p<0.0001$). In the selected group of patients with CSF pleocytosis $\geq 5/\mu$L ($n=25$) CSF glucose concentration ≤ 2.72 mmol/L was associated with 100% sensitivity (95%CI: 63-100%) and 100% specificity (95%CI: 75.3-100%) for reactive CSF VDRL. CSF glucose concentration may be particularly useful as a predictive marker of neurosyphilis in HIV uninfected patients with syphilis of unknown duration with CSF plecytosis $\geq 5/\mu$L.

Keywords: *CSF glucose concentration • Neurosyphilis*

1. Introduction

Syphilis is caused by a spirochete *Treponema pallidum* subsp. *pallidum* that cannot be cultured *in vitro*. The diagnosis of syphilis is based on serological assays, grouped into non-treponemal tests (rapid plasma regain [RPR] and Veneral Disease Research Laboratory [VDRL] assays) and treponemal tests (*T. pallidum haemagglutination* assay [TPHA] and fluorescent treponemal antibody absorption test [FTA-ABS]) [1].

Invasion of the central nervous system (CNS) by *T. pallidum* appears early during the course of disease, and is defined by increased pleocytosis or elevated protein concentration and reactive CSF-VDRL in cerebrospinal fluid (CSF) [2]. It has been estimated that between 30 to 50% of patients with primary or secondary syphilis with no symptoms of CNS involvement may demonstrate such abnormalities on CSF examination [3]. Therefore, according to Center for Disease Control and Prevention (CDC) criteria of confirmed neurosyphilis has been defined as: (1) any syphilis stage and (2) a reactive CSF-VDRL [4].

The observational studies from preantibiotic era have shown that a majority of patients with CNS invasion (about 75%) appear to clear or restrain the growth of *T. pallidum* in CNS even without therapy. Those who fail to clear *T. pallidum* from CNS are at risk for symptomatic neuroinfection, including meningitis, hearing loss or uveitis [5]. The relevance of these data to the current era treatment is not fully known. However, it seems reasonable that syphilis patients with CSF abnormalities, especially with reactive CSF-VDRL, should be treated according to the protocols for neurosyphilis (intravenous (IV) aqueous crystalline penicillin G or intramuscular (IM) aqueous procaine penicillin G plus probenecid for 10 to 14 days) [6].

In the era before antibiotics, lumbar puncture in patients with syphilis was part of the clinical work-up. Today, widespread implementation of lumbar puncture is both impractical and unnecessary. Despite that, useful-

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ness of CSF examination in patients with asymptomatic syphilis is still debated [7]. A recent study suggested that serum RPR titer ≥ 1:32 regardless of syphilis stage, may be associated with increased risk of CNS involvement [8]. Therefore, this group of patients may benefit from performing the lumbar puncture.

Due to small number of reference laboratories the CSF serology results are obtained with considerable delay (up to 1 week). Therefore, the decision on recommended therapy for neurosyphilis is taken usually on the basis of CSF biochemical tests and CSF pleocytosis.

In early syphilis, a slight pleocytosis, which is lymphocyte predominant, may be the only sign of CNS involvement. A cutoff of greater than or equal to 5/μL has been the standard [9]. Normally the CSF glucose concentration is in the range 2.22-3.89 mmol/L, i.e. about two-thirds of that in the blood (60-70% of serum concentration). Low values of CSF glucose in the presence of pleocytosis usually indicate pyogenic, tuberculosis or fungal meningitis [10]. To our knowledge the significance of CSF glucose concentration in prediction of asymptomatic neurosyphilis has not been determined.

In this paper we attempt to identify CSF biochemical markers, with particular reference to CSF glucose concentration and their cut-off values which are associated with asymptomatic neurosyphilis in the group of HIV-uninfected patients with syphilis of unknown duration.

2. Materials and methods

Fifty five patients (3 women, 52 men - 70% of them were men who have sex with men) with asymptomatic syphilis of unknown duration (diagnosed based on reactive serological nontreponemal and treponemal tests), who were admitted to the Department of Dermatology (Jagiellonian University Medical College) in years 2008 - 2009, were enrolled into the study. Exclusion criteria were as follows: a previous history of syphilis, concomitant HIV infection, taking antibiotics for other reasons in the last 12 months, diabetes mellitus (excluded on the basis of blood fasting glucose level). After written informed consent was obtained, patients underwent a clinical assessment (with neurological examination), followed by fasting blood sampling and lumbar puncture. In all patients, lumbar puncture proceeded without complications. Furthermore, in each case clear CSF was obtained, without evidence of blood contamination of the CSF. Routine laboratory blood tests and CSF examination (biochemical parameters and pleocytosis) were assessed immediately after sample collection. CSF VDRL, TPHA, FTA, FTA-ABS tests were performed at a single reference laboratory in Narutowicz City Hospital in Krakow. Neurosyphilis was defined as a reactive CSF VDRL.

Blood and CSF glucose levels were assessed using GLUC3 test (Roche, Switzerland) on Cobas Chemistry Analyzer (Roche, Switzerland) with low and high end of measuring range for CSF 0.11 mmol/L and 41.6 mmol/L, respectively.

Statistical analysis was performed with Statistica 7.1 PL package (StatSoft, Inc. 2005). Data are expressed as median and interquartile range (IQR) if not otherwise stated. Between-group comparisons were performed with the Mann-Whitney U test or chi-square test. The associations between the individual parameters were measured using Spearman's rank correlation coefficient. To identify independent factors, a step-wise multivariate linear regression analysis model was used, including only significant covariates (CSF pleocytosis, CSF protein and glucose concentration). The cutoff values for CSF biochemical tests, distinguishing patients with reactive CSF VDRL, were analyzed separately in the group of 24 patients with CSF pleocytosis ≥ 5 mononuclear cells/uL, using ROC analysis, P-value <0.05 was considered statistically significant.

3. Results

All patients were stratified into two groups: (1) those with reactive CSF-VDRL (n=8), and (2) non-reactive CSF-VDRL (n=47). The characteristics of CSF-VDRL reactive group and CSF-VDRL non-reactive group are shown in Table 1. The groups did not differ with respect to age, blood VDRL and FTA titer, fasting blood glucose concentration, white-blood or lymphocyte count. All patients with reactive CSF-VDRL had also reactive CSF FTA-ABS and CSF TPHA. Similarly, all from nonreactive CSF VDRL group had negative CSF FTA-ABS and CSF TPHA.

Patients with reactive CSF-VDRL were characterized by higher CSF pleocytosis ($p<0.0001$), elevated protein concentration in CSF ($p<0.05$) and lower glucose concentration in CSF ($p<0.0001$). CSF glucose concentration referred to blood glucose concentration and expressed as per cent of blood concentration was lower in the CSF-VDRL reactive group (<0.001). Multivariate regression analysis identified CSF pleocytosis ($R2=0.8$, $\beta=0.57$; $p<0.0001$) and CSF glucose concentration ($R2=0.8$, $\beta= -0.49$; $p<0.0001$) as the two independent predictors of reactive CSF VDRL.

Using ROC curve analysis we calculated diagnostic sensitivity and specificity of different values of CSF pleocytosis in determining the reactive CSF-VDRL

Table 1. Characteristics of patients.

Variable	CSF VDRL reactive group (n=8)	CSF VDRL non-reactive group (n=47)	p
Age, years (min-max)	28 (21-52)	27 (19-59)	NS
Blood VDRL, titer (min-max)	64 (16-128)	32 (2-128)	NS
Blood FTA, titer (min-max)	16000 (4000 - 32000)	8000 (450-32000)	NS
Reactive blood FTA-ABS, n (%)	8 (100)	47 (100)	
Reactive blood TPHA, n (%)	8 (100)	47 (100)	
Blood glucose concentration (mmol/L)	4,45 (0,79)	4,97 (0,6)	NS
Blood WBC x 10^3/ uL	5,44 (1,23)	5,99 (1,94)	NS
Blood lymphocytes x 10^3/ uL	1,64 (1,28)	1,73 (0,63)	NS
CSF FTA-ABS, n (%)	8 (100)	0 (0)	
CSF pleocytosis (cells/uL) (min-max)	36 (7-55)	2 (0-41)	<0.0001
CSF pleocytosis >5/uL n(%)	8 (100)	17 (36,2)	
CSF protein concentration (mg/dL)	55 (53)	38 (20)	0.02
CSF glucose concentration (mmol/L)	2,48 (0,22)	3,08 (0,27)	<0.0001
CSF glucose % of blood concentration	55,6 (5,6)	62,8 (4,07)	<0.001

Values are given as median (interquartile range)
NS-non significant, VDRL-Veneral Disease Research Laboratory, FTA-fluorescent treponemal antibody test, FTA-ABS-fluorescent treponemal antibody absorption test, TPHA- Treponema pallidum haemeagglutination test, WBC-white blood count, CSF-cerebrospinal fluid

(ROC curve area=0.95 [95%CI: 0.8-1.0]; p<0.01). Pleocytosis equal or higher that 5/μL was associated with 100% sensitivity (95%CI: 54-100%) and 68% specificity (95%CI: 52-81%) for reactive CSF-VDRL.

Based on these results we further analyzed patients with CSF pleocytosis ≥ 5/μL (n=25). In the selected group CSF glucose concentration equal or lower than 2.72 mmol/L was associated with 100% sensitivity (95%CI: 63-100%) and 100% specificity (95%CI: 75.3-100%) for reactive CSF VDRL. Furthermore, CSF glucose concentration equal or lower than 59% of blood glucose concentration was associated with 100% sensitivity (95%CI: 63-100%) and 92% specificity (95%CI: 64-99,8%) for reactive CSF VDRL (ROC curve area=0.94 [95%CI: 0.83-1.0]; p<0.01).

4. Discussion

In the current study we aimed to examine the relationship between neurosyphilis and CSF glucose concentration in HIV uninfected patients with syphilis of unknown duration. Our goal was to determine whether this measure can predict neurosyphils. We found that CSF pleocytosis ≥5 /uL, CSF glucose concentration ≤ 2.72 mmol/L and CSF glucose concentration ≤ 59% of blood glucose concentration are associated with reactive CSF VDRL in studied group of patients.

The diagnosis of neurosyphilis is not difficult when patients have typical symptoms and signs of the disease. However, the diagnosis of asymptomatic neurosyphilis is based solely on CSF abnormalities, including CSF-VDRL reactivity. The specificity of reactive CSF-VDRL is of 100%, but sensitivity is between 30-70% [11]. Thus, some specialist recommend performing the more sensitive (100%), but less specific (94%), FTA-ABS test in CSF to confirm the diagnosis and emphasize that a nonreactive result excludes neurosyphilis [12,13]. However, the "gold standard" for diagnosis of neurosyphilis remains the rabbit infectivity test (RIT), in which CSF is inoculated into the laboratory rabbits and *T. pallidum* infection is confirmed by subsequent evaluation of the animal.

Currently, most studies on syphilis are focused on patients with concomitant HIV infection. Such patients are usually strictly controlled, involving regular follow-up visits. But more than 40% of patients with latent syphilis who are HIV negative fail to attend for any post-treatment serological tests [14]. Therefore, there is a need for the most effective treatment (targeted for neurosyphilis) to be initiated in a patient who underwent lumbar puncture as soon as possible. Unfortunately, in many European countries, including Poland, there is a limited access to laboratories performing serological tests in blood and CSF, with a delay of final diagnosis up to 1 week since lumbar puncture. In our center, we have developed a model in which the decision to start crystalline penicillin treatment is based on the result of CSF pleocytosis ≥ 5/μL. However, it was connected with the fact that as many as 30% of patients

were treated with crystalline penicillin unnecessarily, what prolongs hospitalization and increases costs of treatment. In this study we suggest that combination of two laboratory measurements of CSF, namely pleocytosis and glucose concentration, which are available immediately after lumbar puncture, could help to distinguish patients with high probability of *T. pallidum* CNS infection. In the current study, by using the cut-off value criteria for pleocytosis ≥ 5/μL and CSF glucose concentration ≤ 2.72 mmol/L, we could identify asymptomatic patients with reactive CSF-VDRL (that means, with certain neurosyphilis) with 100% sensitivity and specificity.

Our study has some limitations. First, the sample size is small, which is reflected in the wide confidence intervals. Secondly, we did not have any "gold" standard for neurosyphilis diagnosis. Fortunately, all patients from reactive CSF VDRL had reactive CSF FTA-ABS and CSF TPHA as well, and all from nonreactive CSF VDRL had non reactive CSF FTA-ABS and CSF TPHA, what enabled to exclude neurosyphils on the basis of nonreactive CSF VDRL in the analyzed group. Furthermore, we need to emphasize that the analyzed group is strictly selected (HIV uninfected patients with syphilis of unknown duration without any symptoms of syphilis and neurosyphilis), so that the results probably cannot be extrapolated to the whole group of patients with syphilis, especially to those with concomitant HIV-infection.

Our results have some important implications for clinical practice. Importantly, they suggest that CSF pleocytosis and glucose concentration can be used to select the group of patients in whom neurosyphilis is very likely. Further studies in a broader population are required to see the real practical value of our observation.

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