Cerebrospinal fluid 14-3-3-γ protein level in eight HIV-negative cryptococcal meningitis adults


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The clinical data and cerebrospinal fluid (CSF) 14-3-3-γ protein detection of eight adult HIV-negative cryptococcal meningitis (CM) cases were examined. The eight cases included six males and two females aged 35–70 years (mean = 49.8 years). The duration between the onset of CM symptoms and the first CSF study ranged from 1 to 60 days. Initial neuroimaging study was abnormal in 87.5% (7/8) of the cases. All the eight had positive initial and subsequent follow-up CSF 14-3-3-γ protein detection. The densitometric values of CSF 14-3-3-γ protein were not correlated with either the CSF white blood cell counts or the therapeutic results. The therapeutic results showed that three cases died and five survived. Significant neurologic deficits were shown in 60% (3/5) of the survivors. This study revealed that HIV-negative CM patients have elevated CSF 14-3-3-γ protein levels, and that this level is not changed with a short-term treatment.

Introduction

The therapeutic result of cryptococcal meningitis (CM) is usually far from satisfactory [1,2]. Previously, the 14-3-3 protein, a real-time marker of neural cell destruction, was adopted for the diagnosis of prion diseases but has also been detected in the cerebrospinal fluid (CSF) of different neurologic disorders, including bacterial meningitis [3–6]. Amongst the seven 14-3-3 protein isoforms, the gamma subtype (14-3-3-γ) is relatively brain-specific [7]. Based on this assumption, we prospectively examined the level of CSF 14-3-3-γ protein detection in eight HIV-negative CM patients and made a clinical correlation.

Case reports

The baseline clinical and laboratory data of the eight enrolled CM cases are listed in Table 1. The eight cases were six men and two women, aged 35–70 years (mean = 49.8 years). The clinical diagnosis of CM was based on the criteria of our previous report [2]. Neuroimaging studies, including brain computed tomography and/or magnetic resonance imaging were applied to all the eight cases. The initial neuroimaging abnormalities are shown in Table 1 and follow-up neuroimaging findings revealed sub-dural effusion in Case 3, left basal ganglion infarction in Case 4, hydrocephalus and cerebellar inflammation in Case 6, and hydrocephalus in Case 8.

The opening pressures in initial lumbar puncture study of the eight cases ranged from 196 to 472 mm H2O, and their CSF parameters were as follows: white blood cell (WBC) count, 0.165 ± 0.168 × 109/l (median = 0.12; range = 0.012–0.55); total proteins, 1.00 ± 0.31 g/l (median = 0.90; range = 0.72–1.69), and glucose level, 2.02 ± 1.50 mmol/L (median = 1.54; range = 0.38–5.8). Following the procedural details of other reports [5–7], we analyzed the CSF 14-3-3-γ protein detection using polyclonal rabbit antibodies SC-731 for 14-3-3-γ (Santa Cruz Biotechnology, Santa Cruz, CA, USA).

The total amount of 14-3-3-γ protein as quantified from each CSF sample was expressed in arbitrary units. Densitometric values of each sample were obtained with a computer-assisted laser scanner, after correction for the background, and the content was assessed by densitometry using ImageQuant 3.3 (molecular Dynamic, Sunnydale, CA, USA). CSF WBC count and 14-3-3-γ data of the eight CM cases are listed in Fig. 1. There was no statistical significance between the CSF WBC count and 14-3-3-γ densitometric value (P = 0.349, Spearman’s rho rank correction study).

In addition to the anti-fungal treatment (amphotericin B and fluconazole), Cases 1, 3, and 4 received an insertion of ventriculoperitoneal (VP) shunt, whilst Case 7 underwent both burr hole craniotomy and VP shunt insertion. The therapeutic result showed that
Case 1 died on the 18th hospital day, whilst Cases 2 and 8 expired on the 62nd and 96th hospital day, respectively. With at least six months of follow-up, Cases 3 and 7 had fully recovered; Case 4 had consciousness disturbance and paraparesis; Case 5, dysphasia and quadriparesis, and Case 6, ataxic gait.

Discussion

The CM cases included in this study had a 37.5% mortality rate and a high incidence of significant neurologic deficit amongst the survivors (60%, 3/5). All the eight cases had positive detection of 14-3-3-\(c\) protein in the initial CSF study and this finding may indicate that all of the patients had evident neural cell destruction at the time of initial CSF study. The densitometric values of the initial CSF 14-3-3-\(c\) protein of these eight cases were different but did not correlate with the final therapeutic results.

Follow-up CSF 14-3-3-\(c\) protein values were also not correlated with the concomitant CSF inflammatory cell values. This discrepancy can be partially explained because, aside from the sole inflammatory reaction, there are many other adverse processes that damage neural cells in CM [1,2,8,9]. These adverse factors can occur at any stage of the disease process of CM if the therapeutic...
course is not completed. The appearance of new abnormalities in follow-up neuroimaging studies may also explain this discrepancy.

In this study, Cases 3–5 had a longer CSF follow-up study (>2 months) and a positive 14-3-3-γ protein detection persisted. Although CM has a longer disease course than bacterial meningitis, which is different with that of purulent meningitis in which an early clearance of CSF 14-3-3 protein, usually within 2 weeks, is noted amongst survivors [6].

In conclusion, although CM is a chronic CNS infection, all the CM patients have positive 14-3-3 protein detection in the first CSF study. Because of the complex clinical course of CM, there is a mismatch between the detection of CSF 14-3-3-γ protein and either the CSF inflammatory reaction or the therapeutic result. This study also revealed that HIV-negative CM patients have elevated CSF 14-3-3-γ protein levels, and that this level is not changed with a short-term treatment. However, because of the limited case number of this study, further large-scale and longer follow-up studies are needed for validation.

References