

HIV and Pneumocystis Pneumonia (PCP): An Upto date

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Abstract

Pneumocystis pneumonia (PCP) is one of an important opportunistic infections in patients with human immunodeficiency virus (HIV) infection or taking immunosuppressive agents. The diagnosis, therapy and prophylaxis have been well-established. The counts of CD4 positive T cells (CD4) is a risk factor of PCP in HIV-infected patients, and the prevalence of PCP in the patients having CD4<200/ μ l is almost a half of them in Japan. However, among HIV-infected patients, risk factor other than CD4 have not been established, although in patients with rheumatic diseases some factors have been reported. Recently, our team reported the association between the genotypes in gene coding mannose-binding lectin (MBL) and the prevalence of PCP in HIV-infected patients. It may confer the strategy of PCP prophylaxis in the immunocompromised patients.

Keywords: HIV; AIDS; *Pneumocystis pneumonia*; Mannose-binding lectin (MBL)

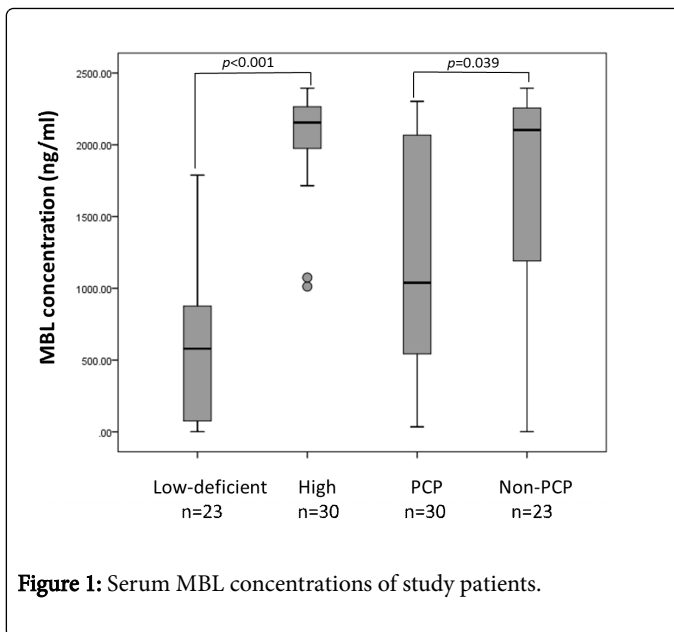
Introduction

The *Pneumocystis pneumonia* (PCP) is an opportunistic infections caused by *Pneumocystis jirovecii* well-known as a major manifestations of acquired immunodeficiency syndrome (AIDS) defining diseases. The number of CD4 positive T lymphocytes (CD4) <200/ μ l has been established as a risk factor of PCP. However, among the patients developed AIDS due to advanced human immunodeficiency virus (HIV) infection, the prevalence of PCP is varied in between countries; around 10% to 50% [1,2]. The frequency of PCP in African countries tend to be low than that of Western countries [3], and it may be affected by the limited medical resources for diagnosis in the developing or low-income countries. However, a study from Netherland reported the low prevalence of PCP in HIV-infected African race compared to that of European race, living in same country. The authors suggested that some genetic host factors rather than the environmental factor may confer the development of PCP [4]. Furthermore, one report from Japan reveals relatively high prevalence of PCP compared to those of Western countries among patients used TNF inhibitor for their rheumatoid arthritis [5]. Taken together those evidences, we can hypothesize that some variety of immunity based on the patients' genetic background may confer the frequency of PCP. Furthermore, the development of immunosuppressive therapy and increase of the immunocompromised patients require that appropriate evaluation of the risk factor of PCP to establish the prophylaxis and therapy.

For the diagnosis, detection of *Pneumocystis* organisms in the specimens from respiratory tract is crucial; for example, Giemsa staining or PCR detection from broncho-alveolar lavage fluid. The elevation of serum (1-->3) beta-D-glucan is a useful diagnostic biomarker with a high sensitivity [6]. In the therapeutic and prophylaxis options, trimethoprim-sulfamethoxazole is established for the efficacy against PCP, and intravenous pentamidine is selected as an alternative therapeutic options (inhalation is recommended only for

prophylaxis). Atovaquone has been developed as a choice for PCP therapy and prophylaxis in patient who cannot tolerate trimethoprim-sulfamethoxazole [7].

Risk factors of PCP have been also discussed in the field of rheumatic diseases; older age, baseline pulmonary diseases, higher prednisolone dose, lower counts of lymphocytes [8,9]. However, among HIV-infected patients, the host's risk factors other than CD4 have not been well-established. Recently, our team reported the association of Mannose-binding lectin (MBL) genotypes and the prevalence of PCP in HIV-infected patients in Japan [10]. MBL is one of well-studied pattern recognition receptors (PRR) [11,12], plays a pivotal role in innate immunity by directly opsonizing pathogens or by activating complement system via the mannose-associated serine protease (MASP), called lectin pathway [13,14]. Most mammals have two genes (MBL1 and MBL2) that encode functional MBL; however, MBL1 is a pseudogene in humans. Genetic mutations in promoter and exon1 of MBL2 influence functional MBL levels in human serum [13,14]. Polymorphisms in exon1 of MBL2 one each in codons 52, 54, and 57; these single nucleotide polymorphisms (SNPs) rs5030737, rs1800450, and rs1800451 are referred to as variants D, B and C respectively; the wild type is designated A. Additionally, three SNP sites in the promoter to the 5'-untranslated region (5'-UTR) at nt-550, nt-221, and nt+4 (rs11003125, rs7096206, and rs7095891, referred to as H/L, Y/X, and P/Q, respectively) also affect MBL production. From these six alleles, seven typical haplotypes have been determined as follows: HYPB and LYQA result in high serum MBL levels; LYPA results in intermediate levels; LXPA results in low levels; LYPB, HYPD, and LYQC result in MBL deficiency [15]. With these seven haplotypes, we can categorize the patients' MBL productivity into two classes: 1) high production and 2) low-deficient [16]. We confirmed that genetic variety of MBL coding gene confer the serum levels of MBL, and low-deficient genotypes were associated with the higher prevalence of PCP in baseline CD4 counts <200/ μ l (Figure 1) [10].



Low to deficient and high-producing genotype groups were compared with regard to median MBL levels; the PCP and non-PCP groups were also compared with regard to median MBL levels. All serum samples were collected at least 3 months after the onset of PCP to avoid acute phase reactions, and measured by MBL-oligomer ELISA kits (BioPorto, Gentofte, Denmark). The Mann-Whitney U test was used to assess between-group differences, and p values <0.05 was determined and considered significant.

Of course our results are insufficient to explain the all risks or molecular mechanisms of the PCP, some host factors, microorganism factors, and environmental factors other than MBL genotypes may confer the susceptibility against PCP. Ambient air pollution have been suggested to be as a risk factor of PCP [17]. However, we elucidated at least one component of the anti-PCP mechanisms of MBL in advanced HIV-infection. MBL genotypes and serum levels can be a useful and novel predictive factor for PCP, in addition with CD4 cell levels. Further study is needed in large sample size and among other ethnic groups to confirm this clinical issue.

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