Clinical evaluation of the anti-tubercular-glycolipid antibody and IFN-γ release assay for the diagnosis of latent tuberculosis infection(LTBI) in TB-endemic countries

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論文内容要旨

Abstract

Background: Antibodies against tubercular-glycolipid (TBGL-Ab) have been proposed as a useful serodiagnostic tool for active tuberculosis (TB) in Japan. Humoral immunity is believed to be less affected in HIV/AIDS infection. But diminished T-helper1 immunity can cause pseudo-negative response by Quantiferon TB-gold test (QFT) by low CD4+ counts for the detection of latent tuberculosis infection (LTBI). **Aim**: We evaluated both IgG and IgA responses against TBGL-antigen in pulmonary TB patients and healthy controls. The TBGL-IgG and -IgA assays were then compared with the QFT assay for the assessment of their LTBI detection ability in healthcare workers (HCW) and non-TB, asymptomatic HIV-carriers (HIV_AC) in two TB-endemic countries. **Method**: A case-control study-I was conducted to measure the TBGL-IgG and -IgA titers in the sera of both adults [24 pulmonary-TB (PTB), 28 healthy (HA)] and children [19 TB cases (CTB) and 24 controls (HC)] in Thailand. In case-control study-II, QFT, TBGL-IgG and -IgA assays were performed in 31 HCWs and 56 HIV_ACs without active TB and the responses were evaluated in the Philippines. TB-related markers including leptin and KL-6 or osteopontin (OPN) levels were also measured. **Results**: In the study-I, both the TBGL-IgG and -IgA titers were significantly higher only in adult PTB cases than controls ($p<0.001$ for both) but not in pediatric cases. The TBGL-IgG was found as highly sensitive (91.6%) in PTB patients. But frequent positive proportions of TBGL-IgG (46%) and –IgA (38%) observed in HAs were the causes of low specificities of TBGL-IgG (53.5%) and –IgA (64%), respectively. The specificity of TBGL-IgG+IgA (75%) was the highest. The antibody titers were positively correlated in the TBGL-IgG+IgA double-positive HAs (HA+;7/28), ($p<0.01$) but not in HA-, ($p>0.05$). Serum IgG or IgA levels were not correlated with TBGL-IgG or –IgA levels. The KL-6 titers were elevated only in PTB patients and were significantly higher than HAs. The levels of KL-6 and leptin were normal and were not different between HA+ and HA-, indicating the absence of active-TB in HA groups. In the study-II, 15/31 HCWs had positive QFT reactions. The TBGL-IgG-positive percentages were 73% in QFT-positive and 31% in

QFT-negative HCWs and were significantly different between (P=0.02; κ: 0.42; 95% CI: 0.10~0.73; indicates moderate association between two tests). That of TBGL-IgA was only 6% in QFT-negative HCWs. None of the QFT-negative HCWs had a double-antibody positive (TBGL-IgG+IgA) response. There was a significant positive correlation between the IFN-γ concentrations measured in non-stimulated QFT plasma and TBGL-IgA titers in all HCWs (p=0.049) and their QFT-positive group (p=0.006). That of the TBGL-IgG had also a similar tendency in the later group (p=0.06). The rate of QFT-positivity in HIV_AC was significantly lower than that in HCWs (p=0.03) and was associated with high CD4+ counts (P=0.012). The positive proportions of TBGL-IgG and -IgA responses in HIV_ACs were 57% and 28%, respectively. Interestingly, TBGL-IgA positive responses were inversely correlated with CD4+ counts (P=0.018) and were significantly higher in the HIV_AC with CD4+ count <350/μl (HIV_LCD group) than those with CD4+ count ≥350/μl (HIV_HCD group). Furthermore, a higher proportion of double-antibody positive responders were observed in the HIV_LCD (29%) than HIV_HCD group (15%). None of the titers of TBGL-IgG and -IgA had significant association with the concentrations of IFN-γ, serum IgG and IgA in any group of HIV_AC. **Conclusions**: TBGL-Ab detection in children may not have any significance for the detection of TB infection. The inadequacy of TBGL-Ab assay for the diagnosis of active TB in adults was due to frequent TBGL-Ab-positive proportions in HA subjects that might be related to LTBI. The correlation between TBGL-IgG and QFT assays responses only in HCWs suggests that TBGL-IgG could be helpful for LTBI detection in healthy adults. However, higher specificity of *TBGL-IgA* assay, the positive correlation between the TBGL-IgA titers and IFN-γ concentrations in QFT-positive HCWs and observed double antibody-positive responses only in QFT-positive HCWs also might be very importance in LTBI detection in adults. We do not have any gold standard to identify LTBI in HIV infected individuals. However, our findings suggest that TBGL-IgG and/or -IgA or at least double antibody-positive cases in HIV_AC especially in HIV_LCD could be specific may indicate LTBI. HIV carriers especially who are with low CD4+ counts have higher risk of active TB. Therefore, TBGL-Ab could have great value to overcome the limitation of QFT assay in LTBI detection in advanced HIV infection and HIV patients could be benefitted by early anti-TB therapy if they can be recognized as LTBI in their early stage.

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審　査　結　果　の　要　旨

博士論文題名　Clinical evaluation of the anti-tubercular-glycolipid antibody and IFN-γ release assay for the diagnosis of latent tuberculosis infection (LTBI) in TB-endemic countries.

（結核高蔓延国における抗 TBGL 抗体とインターフェロンガンマリリースアッセイの臨床評価）

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結核蔓延国において抗 TBGL-IgG/-IgA 抗体の評価を行うために 2 つのケース・コントロール研究を行った。研究 1 ではタイの活動性肺結核患者を対象に血清診断のために TBGL-IgG/-IgA の評価を行った。血清は成人(肺結核患者：PTB、非結核：HA)、小児(肺結核患者：CTB、非結核：HC)の 4 群より採取した。研究 2 では Quantiferon-TB gold (QFT)法の結核潜伏感染(LTBI)検出力を評価するために、フィリピンにおいて医療従事者(HCW) と結核に感染していない HIV 感染者を対象に抗体価の測定を行った。研究 1 では TBGL-IgG/-IgA の抗体価は PTB においてのみ高かった($p<0.01$)。TBGL-IgG は PTB において高い感受性をもつ (91.6%)ことが示された。しかし HA においては抗体陽性率は高かったものの(TBGL-IgG (46%) –IgA (36%))特異性は TBGL-IgG(53.5%)、IgA(64%)であった。TBGL-IgG/IgA の特異性は最も高かった(75%)。TBGL-IgG/IgA の抗体価は両方共に陽性の HA では正の相関を示した(HA+;7/28), ($p<0.01$)。しかし両方とも陰性の場合(HA-)には相関は見られなかった ($p>0.05$)。血清中の IgG /IgA の値は TBGL-IgG/–IgA との相関がみられなかった。HA+および HA-において KL-6 およびレプチンの値は正常で差は見られず、このことは HA には活動性の結核は含まれないことを示している。研究 2 では 31 名中 15 名の HCW が QFT 陽性であった。TBGL-IgG 陽性の割合は QFT 陽性/陰性の HCW で異なった ($P=0.02$; κ: 0.42; 95% CI: 0.10~0.73; 2 つの検査の間には中程度の関係があることを示している)。TBGL-IgA については 6%が QFT も陽性であり、QFT 陰性では TBGL-IgG/IgA 共に陽性の例はなかった HCW 群全例において非刺激の QFT 血漿中の IFN-γ と TBGL-IgA との間に相関がみられた($p=0.049$、QFT 陽性群では $p=0.006$)。HIV_AC における QFT 陽性率は HCW と比較して低く($p=0.03$)、CD4+細胞数と正の相関がみられた($p=0.012$)。さらに、TBGL-IgG/IgA ともに陽性の例がみられた。HIV 陽性例では TBGL-IgG/IgA どちらも IFN-γ、血清中の全 IgG、IgA との関連は見られなかった。以上より TBGL 抗体の検出は小児においてはその意義は低い可能性、TBGL 抗体価の上昇は健康な成人においては LTBI と関連する可能性があり、HCW における TBGL-IgG と QTF への反応もこれを支持することが示された。さらに、TBGL-IgA 陽性と TBGL-IgG/IgA とも陽性の例は、HIV_AC とくに結核発症リスクの高い HIV_LCD 同様に健常者の LTBI 検出に重要である。それゆえに、TBGL 抗体は LTBI の検出において HIV 感染に先立って QFT 法の欠点を補うものである。HIV 感染者において早期に LTBI が発見されれば抗結核療法を早期に開始できる。簡便な LTBI 検出方法は資源の限られた国でこれらのことに特に貢献するものである。

よって，本論文は博士（医学）の学位論文として合格と認める。