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BRIEF REPORT

Risk factor analysis of invasive liver abscess caused by the K1 serotype *Klebsiella pneumoniae*

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Abstract The increasing prevalence of *Klebsiella pneumoniae* liver abscess in Asian countries is attributable to virulent strains of the K1 serotype. We investigated the risk factors for the K1 serotype *K. pneumoniae* liver abscess. A case-control study was performed using the database of a nationwide study of liver abscess in Korea. Multivariate logistic regression analysis was performed for 78 cases of the K1 serotype *K. pneumoniae* liver abscess and 81 controls with non-*Klebsiella*. Diabetes mellitus was the significant risk factor (OR 2.13; 95% CI 1.026~4.428; P=0.042) for the K1 serotype *K. pneumoniae* liver abscess. Biliary disorders had a strong negative association (OR 0.18; 95% CI 0.078~0.410; P<0.001). This study suggests that diabetes mellitus is a more significant risk factor for the K1 serotype *K. pneumoniae* liver abscess than for the non-*Klebsiella* liver abscess.

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An increasing prevalence of *Klebsiella pneumoniae* liver abscess has been reported in some Asian countries, especially in Taiwan and Korea [1, 2]. In these countries, *K. pneumoniae* has become the most common etiology in liver abscess in recent decades [1–3], and it is contradictory to the old dogma that pyogenic liver abscess is usually caused by mixed organisms including aerobes represented by *Escherichia coli* and anaerobes. It is noteworthy that this characteristic etiologic change in pyogenic liver abscess has been exclusively observed in a few Asian countries. Previous investigations into the K antigen serotype have revealed that K1 is the predominant serotype of *K. pneumoniae* strains causing liver abscess in both Taiwan and Korea, and it accounted for about 60% of *K. pneumoniae* strains causing liver abscess in these countries [2, 4]. Considering that the K1 serotype has been rare in the clinical isolates from the Western countries, this finding is very intriguing [5]. The reason why liver abscess caused by the K1 serotype *K. pneumoniae* strains has been emerging has not been elucidated. Although diabetes mellitus has been suggested as an important underlying disease in *K. pneumoniae* liver abscess, a considerable proportion of patients with this disease are nondiabetic, and the association between the K1 serotype *K. pneumoniae* liver abscess and diabetes mellitus has not yet been clearly determined. In this study, we investigated the risk factors for the K1 serotype *K. pneumoniae* liver abscess by case-control study

to further understand the reason for the increasing prevalence of this disease.

We performed an extension analysis using the database of the previous study by the Korean Study Group for Liver Abscess [2]. Only community-acquired, culture-proven liver abscesses were included. We defined a case as a patient with a liver abscess caused by *K. pneumoniae* the K1 serotype. A total of 78 cases, which were evaluable in terms of the potential risk factors, were included in the case group. A control was defined as a patient with a liver abscess caused by all other bacteria except *Klebsiella*. K antigen serotype was determined using both slide agglutination test with antisera (Denka Seiken, Tokyo, Japan) and *magA* PCR, as previously described [2]. We determined the presence of variable underlying diseases or conditions such as diabetes mellitus, heavy alcohol drinking, biliary tract diseases, malignancy, liver cirrhosis, end-stage renal disease, intra-abdominal infections, history of abdominopelvic surgery, history of steroid use, and history of previous antibiotic use. Diabetes mellitus was considered to be present if hemoglobin A1c ≥ 7% and a random blood glucose level ≥ 200 mg/dl, or a fasting blood glucose level ≥ 126 mg/dl in repeated tests during the hospital stay, or if the patient had had a previous diagnosis of diabetes mellitus. Variables with a P value of < 0.15 in univariate analysis were included in multivariate logistic regression analysis.

A total of 78 liver abscess cases caused by K1 serotype *K. pneumoniae* were included in the case group and 81 cases of the non-*Klebsiella* liver abscess were enrolled in the control group. The most common etiology in the control group was *E. coli* (40.7%) and the next was *Enterococcus* (16.0%). The others were viridans group streptococci (13.6%), β-hemolytic streptococci (12.3%), alpha-hemolytic streptococci (8.6%), *Citrobacter* (8.6%), *Enterobacter* (7.4%), and anaerobes (6.2%). There was no significant difference in age and gender between the two groups. In terms of expected port of entry, the biliary route was more common in controls (12.8% vs 50.6%), whereas cryptogenic infection was more common in the case group (84.6% vs 42.0%). The proportion of accompanying bacteremia did not show any difference; however, septic shock was more frequently observed in cases than in controls (14.1% vs 8.6%, P< 0.001). None of the patients in case group died. An antibiogram of the K1 serotype *K. pneumoniae* strains showed that all the isolates were susceptible to most antimicrobial agents except ampicillin and piperacillin. Among the variables investigated, diabetes mellitus was the most significant possible risk factor in the case group (47.4%). Biliary tract diseases were less frequently observed in cases than in controls (12.8% vs 50.6%, P<0.001). A previous history of abdominopelvic surgery was also rare in case patients compared with the controls (1.3% vs 12.3%, P=0.006). Neither of the groups showed any difference in the habit of heavy alcohol drinking. The variables showing the causal relationship were re-analyzed by multivariate logistic regression analysis (Table 1). Diabetes mellitus was the only significant risk factor (OR, 2.13; 95% CI, 1.026~4.428; P=0.042) for the K1 serotype *K. pneumoniae* liver abscess. That is, diabetes mellitus was more strongly associated with the occurrence of the K1 serotype *K. pneumoniae* liver abscess than with the non-*Klebsiella* liver abscess. In contrast, biliary tract diseases had a strong negative association with the K1 serotype *K. pneumoniae* liver abscess (OR, 0.18; 95% CI, 0.078~0.410; P<0.001). Previous history of abdominopelvic surgery also tended to be negatively associated with the K1 serotype *K. pneumoniae* liver abscess (OR, 0.14; 95% CI, 0.153~1.816; P= 0.077), even though it did not reach statistical significance.

Our study shows that diabetes mellitus is a more significant risk factor for the K1 serotype *K. pneumoniae* liver abscess than for the non-*Klebsiella* liver abscess. Multivariate analysis revealed that the K1 serotype *K. pneumoniae* liver abscess has a 2.1-fold higher association with diabetes mellitus than the non-*Klebsiella* liver abscess. To our knowledge, this is the first report of a case-control study with multivariate analysis for *K. pneumoniae* liver abscess focusing on the K1 serotype, although diabetes mellitus has been addressed in earlier reports on *K. pneumoniae* liver abscess. In fact, diabetes has long been recognized as a disease predisposing to bacterial infection, including pyogenic liver abscess [6]. Furthermore, *Klebsiella* has been considered as a common pathogen causing infections in diabetic patients [7]. A recent case-control study performed in Denmark showed that persons with diabetes have a 3.6-fold increased risk of experiencing pyogenic liver abscess compared with the control population

Table 1 Risk factor analysis for the K1 serotype *K. pneumoniae* liver abscess by multivariate logistic regression analysis

Variables	Odds ratio	95% CI	P
Diabetes mellitus	2.13	1.026~4.428	0.042
Biliary tract diseases	0.18	0.078~0.410	<0.001
Previous history of abdominopelvic surgery	0.14	0.153~1.816	0.077
Malignancy	0.53	0.016~1.239	0.310

[8]. Diabetes was present in 11.2% of the patients with pyogenic liver abscess in Denmark [8]. In our study, the patients with a non-*Klebsiella* liver abscess had a higher prevalence of diabetes (27.2%) than those in the Danish study; however, we demonstrated that the K1 serotype *K. pneumoniae* liver abscess has a 2.1-fold higher association with diabetes than the non-*Klebsiella* liver abscess. Recent findings that poor glycemic control plays a role in impairing neutrophil phagocytosis of K1/K2 type *K. pneumoniae*, whereas it does not significantly affect the phagocytosis of non-K1/K2 *K. pneumoniae* [9], partially explain a high association between diabetes and the K1 serotype *K. pneumoniae* liver abscess.

This study also revealed that the K1 serotype *K. pneumoniae* liver abscess has a strong negative association with biliary tract diseases compared with the non-*Klebsiella* liver abscess. It implies that ascending infection through the biliary tract is not a main port of entry for the K1 serotype *K. pneumoniae* liver abscess. Cryptogenic cases were more common; however, the possibility that minor infection or bacterial invasion into the portal drained area without significant localized symptoms was followed by bacterial entry through the portal vein into the liver and initiation of the liver abscess cannot be excluded.

Although diabetes mellitus only shows a higher association with the K1 serotype *K. pneumoniae* liver abscess than with the non-*Klebsiella* abscess, it does not seem to be absolutely necessary for the development of this disease. Many previous reports have stated that a considerable proportion of the patients with *K. pneumoniae* liver abscess are not diabetic [10]. Our study has also shown that 52.6% of the patients with the K1 serotype *K. pneumoniae* liver abscess were non-diabetic. We need to identify other significant risk factors, including genetic susceptibility and the ethnicity factor, intestinal colonization, environmental exposure, and living conditions. Differences in the global epidemiology of the *K. pneumoniae* liver abscess has suggested that the ethnicity factor is very important in this disease. Although some recent reports from Western countries have addressed the increasing incidence of the *K. pneumoniae* liver abscess, the patients studied were mostly of Asian origin. Multinational collaborative studies should be followed to elucidate this issue.

In conclusion, diabetes mellitus is a more significant risk factor for the K1 serotype *K. pneumoniae* liver abscess than for the non-*Klebsiella* liver abscess. A strong negative association is observed between biliary tract disorder and the K1 serotype *K. pneumoniae* liver abscess. It is suggested that there should be a high index of suspicion for the possibility of the K1 serotype *K. pneumoniae* liver abscess when diabetic patients without biliary tract disorders have clinical manifestations of liver abscess, although it cannot be excluded in non-diabetic patients.

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Conflicts of interest None.

References

1. Wang JH, Liu YC, Lee SS, Yen MY, Chen YS, Wann SR et al (1998) Primary liver abscess due to *Klebsiella pneumoniae* in Taiwan. Clin Infect Dis 26:1434–1438
2. Chung DR, Lee SS, Lee HR, Kim HB, Choi HJ, Eom JS et al (2007) Emerging invasive liver abscess caused by K1 serotype *Klebsiella pneumoniae* in Korea. J Infect 54:578–583
3. Ko WC, Paterson DL, Sagnimeni AJ, Hansen DS, von Gottberg A, Mohapatra S et al (2002) Community-acquired *Klebsiella pneumoniae* bacteremia: global differences in clinical patterns. Emerg Infect Dis 8:160–166
4. Fung CP, Chang FY, Lee SC, Hu BS, Kuo BI, Liu CY et al (2002) A global emerging disease of *Klebsiella pneumoniae* liver abscess: is serotype K1 an important factor for complicated endophthalmitis? Gut 50:420–424
5. Cryz SJ Jr, Mortimer PM, Mansfield V, Germanier R (1986) Seroepidemiology of *Klebsiella* bacteremic isolates and implications for vaccine development. J Clin Microbiol 23:687–690
6. Holt JM, Spry CJ (1966) Solitary pyogenic liver abscess in patients with diabetes mellitus. Lancet 2:198–200
7. Ayvazian LF (1948) Friedlander bacillus meningitis successfully treated with streptomycin: consideration of Friedlander bacillus infections in diabetes. Am J Med 5:470–477
8. Thomsen RW, Jepsen P, Sorensen HT (2007) Diabetes mellitus and pyogenic liver abscess: risk and prognosis. Clin Infect Dis 44:1194–1201
9. Lin JC, Siu LK, Fung CP, Tsou HH, Wang JJ, Chen CT et al (2006) Impaired phagocytosis of capsular serotypes K1 or K2 *Klebsiella pneumoniae* in type 2 diabetes mellitus patients with poor glycemic control. J Clin Endocrinol Metab 91:3084–3087
10. Fang CT, Lai SY, Yi WC, Hsueh PR, Liu KL, Chang SC (2007) *Klebsiella pneumoniae* genotype K1: an emerging pathogen that causes septic ocular or central nervous system complications from pyogenic liver abscess. Clin Infect Dis 45:284–293