Infection phase is a predictor of pruritus in patients with hepatitis B virus infection

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Abstract. Pruritus is a common pathogenesis in liver diseases, including chronic hepatitis B (CHB). The phases of hepatitis B virus (HBV) infection are defined in the American Association for the Study of Liver Diseases guidelines. However, it still remains unclear whether the phase independently affects pruritus. The aim of this study was to clarify the effect of HBV infection phase on pruritus in patients with HBV. Of the 1,631 patients that attended the joint research facilities and were interviewed regarding their pruritus between January and June 2016, 196 patients with HBV infection were selected for the present analysis. One-to-one propensity score-matching using 13 variables was performed between participants in the hepatitis B e antigen (HBe-Ag)-positive/negative immune-active phase group and the inactive CHB phase group. Data from 47 patients per group were included in the final analysis. The prevalence of pruritus in the inactive CHB phase was significantly lower than in the HBe-Ag-positive/negative immune-active phase (23 vs. 47%; P=0.031). Being in the inactive CHB phase was determined to be an independent risk factor for pruritus (odds ratio, 0.35; 95% confidence interval, 0.143-0.842; P=0.019). The progression to inactive CHB phase may contribute to the amelioration of pruritus in patients with HBV infection.

Introduction

Pruritus is one of the common symptoms of chronic liver disease (1) and it impairs patients’ quality of life (2-4). Therefore, the assessment of pruritus is important in the clinical management of chronic liver disease. Hepatitis B is a liver disease caused by hepatitis B virus (HBV) infection. The World Health Organization estimates that ~257 million people have chronic hepatitis B (CHB) infections worldwide (5). The clinical course and outcome of HBV infections vary according to immune balance between the viral replication and host immune responses (6). Although interferon-α (IFN-α) or nucleoside analogues are available against chronic infection of HBV, a complete elimination or cure is still difficult with current treatment strategies (7), suggesting that CHB infection-associated comorbidities will remain issues in patients.

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Abbreviations: HBV, hepatitis B virus; CHB, chronic hepatitis B; HBe-Ag, hepatitis B e antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APR, aspartate aminotransferase-to-platelet ratio index; VAS, visual analogue scale; IFN, interferon

Key words: hepatitis B, pruritus, itching, dermatology, propensity score
Pruritus is observed in the patients with HBV infection and previous studies reported on the prevalence of pruritus in these patients (8,9). Bonacini (8) reported that 8.0% of patients with HBV infection had pruritus. Another previous study showed the prevalence differed according to the phase of HBV infection: It is significantly lower in the inactive CHB phase than in the hepatitis B e antigen (HBe-Ag)-positive/negative immune-active phase (22 vs. 41%), indicating that immune response and disease phase are associated with pruritus (9). However, it remains unclear whether the phase of HBV infection independently affects the prevalence of pruritus.

A study of the patients with chronic hepatitis C showed that liver fibrosis is an independent factor associated with pruritus (10). Furthermore, a study of primary biliary cholangitis, serum alkaline phosphatase was identified as an independent predictor of pruritus (11). These studies suggest that the pathogenesis of pruritus is different among chronic liver diseases and may be multifactorial. Therefore, an appropriate procedure is required to test statistical independence of factors that are potentially associated with pruritus in clinic. The current study aimed to investigate the effects of HBV infection phase on the prevalence of pruritus in patients with HBV infection using propensity score-matching.

Materials and methods

Patients. The current study performed a retrospective subgroup analysis of the cohort included in a previous multi-center, cross-sectional study (9). Continuous outpatients with various chronic liver diseases who attended the joint research facilities at Saga University Hospital, Yokohama City University Hospital, Kochi Medical School Hospital, JA Hiroshima General Hospital, Kurume University Hospital, Osaka City Juso Hospital, Kawasaki Hospital or Nara City Hospital between January and June 2016 were included in the present study. Participants with overt skin disease, including eczema and atopic dermatitis, were excluded from the survey and a total of 1,631 patients were included. Out of these patients, 235 were infected with HBV, of whom 39 patients were excluded due to missing data (n=33) or co-infection with hepatitis C virus (n=6). A total of 196 patients were enrolled in the current study and divided into two groups according to their HBV disease phase, as defined in the American Association for the Study of Liver Diseases guidelines (6). Patients in HBe-Ag-positive/negative immune-active phase were classified as belonging to the active HBV infection (n=149) group, and those in inactive CHB phase were classified as belonging to the inactive HBV carrier (n=47) group. No patients were in the immune-tolerant phase. The location of any itch, the duration of itching and its circadian variation and seasonality. The severity of pruritus was evaluated using the visual analogue scale (VAS) (16), which quantified the degree of pruritus from 0 (no pruritus) to 10 (maximum pruritus), according to the patients’ subjective perception. Differences in the VAS scored between day and night were evaluated.

Statistical analysis. Two statistical experts (SK and AK) analyzed the data. Patient characteristics were compared according to the HBV infection phase and the presence of itching. The \( \chi^2 \) and Fisher’s exact test were used to perform intergroup comparisons of categorical variables. The Mann-Whitney U or Wilcoxon signed-rank tests were used for intergroup comparisons of continuous variables. To identify independent predictors of pruritus, a univariate analysis was performed using a logistic regression model in patients after propensity score-matching using the ‘Matching’ package in R (version 3.3.2; https://www.r-project.org/index.html). All statistical analyses were performed using R. \( P<0.05 \) was considered to indicate a statistically significant difference.

Results

Characteristics of the study group. Patient characteristics are summarized in Table 1. Before propensity score-matching, the prevalence of pruritus was significantly lower in inactive HBV carriers than in patients with active HBV infection (23 vs. 41%; \( P=0.045 \)). Prior to matching, liver cirrhosis was significantly less prevalent in inactive HBV carriers than in patients with active HBV infection (8.5 vs. 25%; \( P=0.022 \)). The prevalence of pruritus in inactive HBV carriers was also significantly lower than in patients with active HBV infection, after propensity score-matching (23 vs. 47%; \( P=0.031 \)).

Features of pruritus. A total of 33 patients with pruritus (active HBV infection, 22; inactive HBV carrier, 11) were identified in the propensity-matched cohort and their itch locations are summarized in Table II. Patients with pruritus selected all applicable locations out of 15 listed areas. For all patients, the most common location was the back (73%) and the least common locations included the head (9.1%), hands (9.1%), groin (9.1%), foot (9.1%) and fingers (3.0%); no patients reported toe pruritus. The most common itch location in both groups was the back, but the proportion with back pruritus was...
significantly higher in patients with active HBV infection than in inactive HBV carriers (86 vs. 46%; P=0.038). No significant differences were observed for any other locations.

The duration for which pruritus lasted is shown in Fig. 2. Itching lasted ≥6 months in 30, 27 and 36% of all patients, patients with active HBV infection and in inactive HBV carriers, respectively. No patients in the inactive HBV carrier group reported itching of a duration ≥1 and <6 months, and there was no significant difference in the duration of pruritus between the two groups (P=0.153).

Fig. 3 shows the severity of itching according to VAS score and the difference in severity between day and night in the 33 patients with pruritus. There were no differences in VAS score between day and night across all the patients (P=0.680), in patients with active HBV infection (P=0.550) or in inactive HBV carriers (P=0.878). Seasonal exacerbation was identified at interview in 49% (16/33) of patients; 88% (14/16) reported exacerbation during the winter and 13% (2/16) reported exacerbation during the summer (data not shown).

Independent factors associated with pruritus. In the propensity-matching cohort, patient characteristics according to the presence of pruritus are presented in Table III. The proportion of inactive HBV carriers in patients without pruritus was higher than that in patients with pruritus (59 vs. 33%; P=0.031). AST and APRI in patients without pruritus were significantly higher than in patients with pruritus (23 vs. 25 U/l; P=0.031; and 0.286 vs. 0.337; P=0.030). Being an inactive HBV carrier was identified as the only independent factor associated with pruritus (odds ratio, 0.35; 95% confidence interval, 0.143-0.842; P=0.019; Table IV).

Discussion

The prevalence of pruritus was significantly lower in inactive HBV carriers than in patients with active HBV infection. Furthermore, it was found that the phase of HBV infection was significantly associated with the presence of pruritus in the propensity score-matched cohort. Previous studies have characterized the predictors of pruritus in various liver diseases, including HBV infection (17,18); however, the effects of HBV infection per se and the phase of HBV infection on pruritus have not been assessed. A previous report suggested that active HBV infection is an independent positive risk factor for pruritus in patients with various chronic liver diseases (9). To the best of our knowledge, there have been no studies that established a predictor of pruritus in patients with HBV infections. The current study demonstrated that in patients with
HBV, matched by propensity score, being an inactive HBV carrier was an independent negative risk factor for pruritus.

A previous study indicated the clinical features of pruritus in various chronic liver diseases. The following observations have been reported: i) The most frequent itch location is the back; ii) the duration of pruritus is ≥6 months in 38% of patients; and iii) the severity of pruritus is significantly higher during the day than during the night, and seasonal exacerbation occurs in the winter (9). In the present study, the back was identified as the most frequent itch location in both groups, while the frequency itself was significantly higher in patients with active HBV infection than in inactive HBV carriers. No HBV infection phase-associated differences in the duration of itching or the severity of pruritus were observed.

Table I. Patient characteristics according to HBV infection phase before and after propensity score-matching.

|                          | Before matching | After matching | P-value |
|--------------------------|-----------------|---------------|---------|
|                          | Active HBV infection (n=149) | Inactive HBV carrier (n=47) | P-value |
|                          | Active HBV infection (n=47) | Inactive HBV carrier (n=47) | P-value |
| Sex, female              | 66 (44)         | 16 (34)       | 0.283   |
| Age (years)             | 83 (26-97)      | 61 (35-85)    | 0.792   |
| BMI                     | 22.4 (15.0-34.7)| 22.5 (18.6-31.4) | 0.624   |
| Pruritus                | 61 (41)         | 11 (23)       | 0.045   |
| Cirrhosis               | 37 (25)         | 4 (8.5)       | 0.022   |
| Diabetes                | 27 (18)         | 5 (11)        | 0.325   |
| Hypertension            | 36 (24)         | 7 (15)        | 0.256   |
| Hyperuricemia           | 7 (4.7)         | 3 (6.4)       | 0.705   |
| PLT (x10^9/µl)          | 18.7 (5.4-94.9) | 21.1 (12.5-34.0) | 0.063   |
| AST (U/l)               | 24 (13-182)     | 24 (13-58)    | 0.870   |
| ALT (U/l)               | 20 (5-275)      | 24 (5-97)     | 0.737   |
| T–BIL (mg/dl)           | 0.8 (0-4.9)     | 0.8 (0.5-1.5) | 0.589   |
| FIB‑4 index             | 1.800 (0.331-12.573) | 1.508 (0.400-5.057) | 0.107   |
| APRI                    | 0.363 (0.096-3.233) | 0.336 (0.146-0.969) | 0.100   |

Data are presented as n (%). "Data are presented as median (range). Matching was performed by one-to-one nearest-neighbor matching without replacement based on a propensity score techniques. HBV, hepatitis B virus; BMI, body mass index; PLT, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T‑BIL, total bilirubin; FIB‑4, fibrosis‑4; APRI, AST to platelet ratio index.

Table II. Location of the itch in propensity-matched patients with pruritus, according to HBV infection phase.

|          | All (n=33) | Active HBV infection (n=22) | Inactive HBV carrier (n=11) | P-value |
|----------|------------|----------------------------|-----------------------------|---------|
| Head     | 3 (9)      | 2 (9.1)                    | 1 (9.1)                     | 1.000   |
| Face     | 6 (18)     | 4 (18)                     | 2 (18)                      | 1.000   |
| Neck     | 7 (21)     | 5 (23)                     | 2 (18)                      | 1.000   |
| Upper arm| 5 (15)     | 4 (18)                     | 1 (9.1)                     | 0.864   |
| Lower arm| 5 (15)     | 1 (4.5)                    | 4 (36)                      | 0.059   |
| Hands    | 3 (9.1)    | 1 (4.5)                    | 2 (18)                      | 0.521   |
| Fingers  | 1 (3.0)    | 0 (0)                      | 1 (9.1)                     | 0.720   |
| Abdomen  | 8 (24)     | 5 (23)                     | 3 (27)                      | 1.000   |
| Back     | 24 (73)    | 19 (86)                    | 5 (46)                      | 0.038   |
| Lower back| 7 (21)     | 5 (23)                     | 2 (18)                      | 1.000   |
| Groin    | 3 (9.1)    | 2 (9.1)                    | 1 (9.1)                     | 1.000   |
| Thigh    | 7 (21)     | 5 (23)                     | 2 (18)                      | 1.000   |
| Calf     | 11 (33)    | 8 (36)                     | 3 (27)                      | 0.896   |
| Foot     | 3 (9.1)    | 2 (9.1)                    | 1 (9.1)                     | 1.000   |
| Toes     | 0 (0)      | 0 (0)                      | 0 (0)                       | -       |

Data are presented as n (%). HBV, hepatitis B virus.
The mechanism of pruritus in HBV infection remains unclear. The association between HBV infection and skin lesions has been studied in a previous systematic review, in which ~2% of patients with HBV were found to have skin lesions and essential mixed cryoglobulinemic vasculitis was the most frequent type (19). It is well known that acute HBV infection causes Gianotti Crosti syndrome (GCS), which causes papular acrodermatitis, but skin lesions in GCS are not generally accompanied by itching (20,21). Therefore, the mechanism and pathogenesis of skin lesions in GCS may be different from those causing pruritus in the cases reported here. However, the presence of skin lesions in acute HBV infections suggested that HBV affected the skin independent of chronic liver damage or cirrhosis.

Immune complexes targeting hepatitis B surface antigen are considered to cause immune reactions that result in the skin lesions in GCS (22). Additionally, a study described cutaneous changes with itching following IFN administration to treat HBV infection or hepatitis B vaccination (23). Lupus, lupus-like lesions and bullous pemphigoid are generally accompanied by itching and have been observed during or after IFN treatment (23-25); while lichen planus, lichen-planus-like lesions and granuloma annulare have been described following hepatitis B immunization (26,27). These pieces of evidence suggest that extraordinary immune signaling is involved in the development of the skin lesions and itching present in HBV infection, and the immune response to HBV is likely to be key to pruritus. Liver dysfunction in HBV infection is caused by the host immune response,
because HBV is a non-cytotoxic virus that does not cause liver damage (28,29). Therefore, the adverse effects of HBV infection depend on the extent of the immune response, which might also influence the development of skin lesions and pruritus. Indeed, the results of the current study suggested that HBV infection phase significantly affected the prevalence of pruritus.

In conclusion, the current study identified that the HBV infection phase was a predictor of pruritus in patients with HBV infection. The prevalence of pruritus was significantly lower in patients with inactive CHB phase than in those with HBe-Ag-positive/negative immune-active phase, implying that an inactive CHB phase suppressed pruritus. Thus, the progression to an inactive CHB phase may contribute to the amelioration of pruritus in patients with HBV infection.

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Availability of data and materials
The datasets of the present study are available from the corresponding author on reasonable request.

Authors' contributions
YE conceived and designed the study. SO, HT, HI, KY, MO, HH, TK, HF, MK, YS, ST, HK, TT, TS, AN and YE collected and interpreted clinical data. SO curated data. SK and AK statistically analyzed data. SO wrote the first draft of the manuscript and HT and YE contributed to the writing of the manuscript. HI, KY, MO, HH, TK, HF, MK, YS, ST, HK, TT, TS and AN reviewed and revised the manuscript. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate
The original study was conducted in accordance with the Helsinki Declaration of 1964, as revised in 2013. The original study protocol was approved by the Clinical Research Ethics Review Committee of each facility. Opt-out informed consent was obtained from all participants at time of hospitalization.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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