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BRIEF REPORT

Interferon Lambda 4 Genotype Is Associated With Jaundice and Elevated Aminotransferase Levels During Acute Hepatitis C Virus Infection: Findings From the InC3 Collaborative

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Symptomatic acute HCV infection and interferon lambda 4 (IFNL4) genotypes are important predictors of spontaneous viral clearance. Using data from a multicohort database (Injecting Cohorts [InC3] Collaborative), we establish an independent association between host IFNL4 genotype and symptoms of acute hepatitis C virus infection. This association potentially explains the higher spontaneous clearance observed in some patients with symptomatic disease.

Keywords. acute infection; alanine aminotransferase; hepatitis C virus; IFNL4; jaundice.

Acute hepatitis C virus (HCV) infection has a variable course, with approximately 25% of infected persons spontaneously resolving infection, and the remainder developing chronic liver disease [1]. Acute HCV illness can occur between 2 and 12 weeks after infection, and it may include jaundice, nausea, anorexia, abdominal pain, fever, and general malaise [2]. Signs of hepatic necroinflammation, as indicated by elevated aminotransferases occurring within 4 to 12 weeks after infection, can be up to 10 times the upper limit of normal. However, the majority (64%) of incident HCV cases are asymptomatic, and few clinicians are likely to diagnose even 1 case of acute HCV a year [3].

Acute HCV illness, especially jaundice, has been associated with increased likelihood of spontaneous clearance of infection in most studies [3–6], but not all [7]. In the Australian Trial in Acute Hepatitis C (ATAHC) cohort, Grebely et al [8] demonstrated that acute HCV infection illness with jaundice was highly predictive of spontaneous clearance (adjusted hazards ratio [AHR] = 2.86). The single-nucleotide polymorphism linked to interferon lambda 4 (IFNL4), including rs12979860, is a strong predictor of HCV infection outcome, including both treatment-induced and spontaneous clearance [1].

With respect to spontaneous viral clearance, IFNL4 genotype may be the single most important predictor of outcome, as demonstrated in numerous patient populations, including those with a history of injection drug use [1]. In a large study with merged data from 9 prospective cohorts, our group has shown that homozygosity for rs12979860 CC, compared with CT and TT, more than doubled the likelihood of clearance. This observation was particularly striking among women in whom 50% of those who were CC positive cleared acute HCV infection [1]. Grebely et al [9] have also shown that rs8099917 TT homozygosity (vs GT/GG) was independently predictive of spontaneous clearance (AHR = 3.78).

These independent observations of symptomatic disease and host genetics with favorable virologic outcomes have not been correlated to determine whether clinical manifestations of acute HCV may be associated with the patient's specific genetic background. In this study, we evaluate the potential association between IFNL4 genotype and manifestations of acute HCV illness in a large multicohort study of participants with well documented acute HCV infection.

METHODS

The International Collaboration on Incident HIV and HCV in Injecting Cohorts (InC3) Collaborative, which merges clinical, behavioral, and biological data from 9 prospective cohorts evaluating human immunodeficiency virus (HIV) and HCV infection risk and outcomes among people at high risk of HCV, was analyzed. Details regarding InC3, including collaborating sites and recruitment method, are presented elsewhere [10]. For this study, data from 5 of the collaborating sites were used, including Sydney cohorts Australian Trial in Acute Hepatitis C (ATAHC cohort), Hepatitis C Incidence and Transmission Study - Community (HITS-c), Hepatitis C Incidence and Transmission Study - Prisons (HITS-p), Montreal St. Luc Cohort (HEPCO), and Boston Acute HCV Study: Transmission, Immunity, and Outcomes Network (BAHSTION) Study, which collected data on presence of a seroconversion illness. The inclusion criteria were incident HCV infection defined as follows: (1) documented HCV positive test (either anti-HCV or HCV ribonucleic acid) following HCV negative test within

Received 30 November 2015; accepted 21 January 2016.

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DOI: 10.1093/ofid/ofw024

2 years; or (2) symptomatic infection with seroconversion illness, which included any symptoms associated with acute hepatitis, including jaundice, nausea, abdominal pain, fatigues, low-grade fever, anorexia, or general malaise with serological evidence of HCV infection (and excluding other viral hepatitis infections).

We assessed the associations between IFNL4 genotype (rs12979860 CC vs non-CC [CT or TT]) and 3 outcomes: (1) an aggregate variable of any seroconversion illness as described above (yes/no); (2) jaundice (yes/no); and (3) elevated alanine aminotransferase (ALT) defined as ≥400 IU/mL (yes/no) using Pearson χ^2 test. We calculated the 95% confidence intervals (CIs) for the prevalence of symptoms using binominal distribution. Our selection of an ALT cutoff of 400 IU was chosen a priori, and it was based on the usual cutoff of 10 times the upper limit of normal level [11]. To assess independent associations, we used multivariate logistic regression, adjusting for age (in years) and sex to estimate adjusted odds ratios (AORs). We used the site as a cluster in our analysis to account for within-group correlation in Stata, version 12 (StataCorp, College Station, TX).

The InC3 Collaborative uses data that had been anonymized after primary data collection at each site and designated as exempt by appropriate institutional review boards.

RESULTS

Of 961 incident HCV cases, 294 (31%) had data on both presence and absence of symptoms and IFNL4 genotype. In addition, 71% were male; median age was 30 years (interquartile range [IQR], 25–38); 87% were white; and 89.6% reported some lifetime history of drug injection. A total of 158 patients (54%) reported any symptoms associated with acute hepatitis; jaundice was documented in 43 (15%); and elevated ALT in was documented in 100 (34%). Overall, 53% (155 of 294) had IFNL4 CC genotype.

The prevalence of acute HCV symptoms in subgroups of IFNL4 genotypes (CC or non-CC) is presented in Figure 1. Among 155 participants with IFNL4 CC genotype, 19% had jaundice compared with 10% with IFNL4 non-CC genotype ($\chi^2 = 4.38$, $P = .036$). Likewise, 43% of participants with IFNL4 CC genotype had elevated ALT compared with 24% with IFNL4 non-CC genotype ($\chi^2 = 10.72$, $P = .001$). Seroconversion illness was prevalent in 59% in those with IFNL4 CC genotype, slightly higher than among those with IFNL4 non-CC genotype (48%, $\chi^2 = 3.255$, $P = .071$).

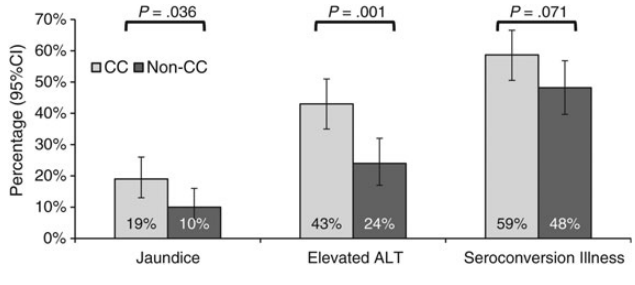

Figure 1. The prevalence of acute hepatitis C virus symptoms by interferon lambda 4 genotypes (CC vs non-CC). Abbreviations: ALT, alanine aminotransferase; CI, confidence interval.

In the age- and sex-adjusted model, the odds of having seroconversion illness was significantly higher among those with IFNL4 CC genotype (AOR, 1.5; 95% CI, 1.1–2.2; $P = .018$) compared with those with IFNL4 non-CC genotype; participants with IFNL4 CC genotype also had higher odds for elevated ALT (AOR, 2.4; 95% CI, 1.8–3.2; $P = .001$) and jaundice (AOR, 2.1; 95% CI, 1.4–3.1; $P = .001$) compared with those with IFNL4 non-CC genotype.

DISCUSSION

Among patients with well documented seroconversion illness, this study demonstrated that IFNL4 CC genotype is independently associated with symptoms and signs of acute HCV illness, including jaundice and marked elevation of ALT. The large sample size in this analysis allowed for the assessment and identification of an independent association between INFL4 genotype and symptoms. Our findings potentially explain the higher spontaneous clearance rate observed in some patients with acute HCV symptoms.

Two other studies assessing IFNL4 and spontaneous viral clearance have suggested that acute HCV illness with jaundice is associated with IFNL4 genotype. Tillmann et al [12] assessed the association between IFNL4 and spontaneous clearance in the German women's anti-D immunoglobulin cohort. Among 136 women with clinical data on seroconversion illness in that cohort, 64% of CC positive women resolved infection, compared with 19% of women who were IFNL4 heterozygous (CT/TT). Half of the women who presented with jaundice (15 of 30) cleared infection compared with 27% (14 of 52) without jaundice. Jaundice was more common among the CC compared with non-CC positive women (33% vs 16%), and CC positive women were more likely to have other symptoms as well. It is interesting to note that among those who were not CC, jaundice was associated with a significantly higher chance of viral clearance (43% vs 13%); a difference not observed in CC positive women. These findings are especially interesting to compare, because this cohort of young pregnant women present a very different health profile than the populations assessed in this report.

We found that the jaundice was an infrequently reported, consistent with other studies showing that this symptom is not commonly observed in acute HCV infection [13]. Nevertheless, the difference in the proportion of subjects with these symptoms and with IFNL4 CC genotype was almost double that of asymptomatic persons, and the observed associations in the same direction as other symptoms were statistically significant. In the Australian ATAHC cohort (one of the InC3 collaborating

sites), in which the IFNL4 rs8099917 was assessed, 32% of participants with jaundice were TT homozygotes compared with 5% of participants without jaundice [9]. Among the 3 variables that we assessed, seroconversion illness had the weakest association with IFNL4 genotype. Because there are no uniform criteria to define and report seroconversion illness, there is always a potential for misclassification. However, given the systematic approach each cohort used to assess symptoms, we do not think misclassification of such would be differential by IFLN4 genotype. Our findings are strengthened by the observed strong association between IFNL4 CC genotype and the objective measure of elevated ALT. These results are compatible with hypothesis that patients with IFNL4 genotype CC mount a vigorous and effective immune response to HCV, contributing to a high probability of spontaneous resolution [3, 6, 7], whereas symptoms and signs of jaundice and elevated ALT may simply be clinical markers of this favorable host background. Further research on clinical markers of spontaneous clearance will help to improve clinical management of acute HCV infection.

Our findings have some limitations. Only a modest proportion (294 of 961) of the total incident cases in InC3 had data on clinical presentation and could be included in this study. However, missing information was not differential; the proportion of IFNL4 CC genotype in the sample was not different between groups in whom data on symptoms was collected (50.4%) or not collected (52.7%). Two of the 5 cohorts (ATAHC and BAHSTION) that systematically assessed symptoms of acute HCV infection had targeted recruitment for patients with symptoms, thus enriching the evaluable population. Other groups in InC3 did not assess or document symptoms of HCV seroconversion illness, limiting the potential to analyze other factors that may have contributed to these associations. Nevertheless, this group represents one of the largest available, with data on both symptoms and IFNL4 status. The study sample was largely white men, which may limit the generalizability of our findings beyond that population. However, we think our data are reflective of the current HCV epidemic situation in North America [14, 15], Australia [16], and elsewhere [17].

CONCLUSIONS

In conclusion, our findings suggest that the association between symptoms of acute HCV and viral clearance reported in many studies is linked to host IFNL4 genotype. Future intermediate outcome analyses examining innate and adaptive immune responses to HCV in acute infection are needed to understand the underlying mechanism of this association and its effect on clearance.

Acknowledgments

Disclaimers. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of National Institute on Drug Abuse or the National Institutes of Health (NIH).

Financial support. This work was funded by the National Institute on Drug Abuse (grants R01DA031056, R01DA033541, and R01DA1599901), the NIH (grants U19AI088791, U19AI066345, and R01DA016017), the National Institute of Allergy and Infectious Diseases (grant U19AI082630), the National Health and Medical Research Council of Australia (grants 222887, 630483, 331312, and 545891), the Victorian Operational Infrastructure Support Programme, and the Canadian Institutes of Health Research (grants MOP103138 and MOP106468).

Potential conflicts of interest. B. H. M. is currently employed with Seres Therapeutics and is also affiliated with Tufts Medical School. J. G. is a consultant/advisor and has received grants from Merck and Gilead. G. J. D. is a consultant/advisor and has received research grants from Roche, Merck, Janssen, Gilead, and Bristol Myers Squibb. M. H. has received research grants from Gilead and Abbvie. A. Y. K. has received research grants from Gilead. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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