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Case Series

The Role of Host in the Spectrum of Outcomes in Family Clusters of Hepatitis Infection: From Asymptomatic to Hepatocellular Carcinoma

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Chronic hepatitis B · Family clusters · Host factors

Abstract
Hepatitis B virus infections are prevalent worldwide, but the outcomes of infection vary greatly from host to host. In many endemic regions, vertical transmission from mother to child is most common. In this transmission setting, virus genotype and shared patient genetics make for an interesting comparison of outcome of chronic hepatitis B infection. This case series demonstrates four family clusters which display disparate outcomes among family members with hepatitis B virus infections, further stressing the role of host and non-genetic factors in the natural history of the disease. Many host factors have been theorized, from epigenetic mechanisms to the role of chronic stress, but more research is needed to better understand those at higher risk of feared complications such as hepatocellular carcinoma and cirrhosis.

Introduction

Hepatitis B virus (HBV) infections are still prevalent and responsible for 50% of hepatocellular carcinoma (HCC) worldwide [1–3]. In endemic regions of the world, the majority of people with chronic HBV (CHB) infection are infected at birth (perinatally) or horizontally

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during early childhood [4]. They can classically remain asymptomatic for many years, often not receiving a diagnosis until adulthood during routine screening or, after developing symptoms.

It has become an interesting topic of discussion within the fields of virology and hepatology as to why some patients with CHB infection for many years have low viral load and low immune activation, remaining asymptomatic, while others develop serious complications including cirrhosis and HCC. One approach to studying various clinical manifestations from the same virus infection has been through examining family members who obtained HBV infection through vertical transmission. In endemic areas, maternal transmission of HBV is common, resulting in most, if not all, offspring being infected. Outcomes among the infected offspring of a family may vary greatly. Differences may depend on what occurs in the individual host, and what risk factors the host is exposed to. The goal of this case series is to present family clusters of HBV transmission in which clinical manifestations and outcomes varied greatly among infected offspring, in the second and third generation, while having similar genetic makeup of host and virus.

Case Report

We observed 4 family clusters that display disparate courses of CHB infection among family members. Most infections were through vertical transmission. All patients also had no significant past medical history, such as metabolic disease or alcohol use, that might otherwise contribute to liver disease. If patients were started on antiviral therapy, they had good control of HBV DNA. Furthermore, patients visited our clinic from many different locations within the country and extended family history was primarily reported by the propositus in each presented family tree. Therefore, details surrounding extended family members past medical history were not possible to obtain.

In Family 1, a 41-year-old man developed chronic hepatitis B and was started on antiviral therapy. His mother died of HBV-associated HCC at age 59. The mother's younger sister also died of HCC at age 55. The patient has five siblings. Of them, his older sister died of HCC at 36, 6 years before, while his 38-year-old brother and 36-year-old sister both, HBsAg (+), are not on antiviral therapy. His youngest sister, also HBsAg (+), died of a myocardial infarction at age 31 (Fig. 1).

In Family 2, a woman, currently aged 83, has remained a CHB carrier since her first visit at our institution at age 68. Among her three sons, all perinatally infected, one died of HCC at the age of 44, while two others (ages 42 and 46) have CHB on treatment (Fig. 2).

In Family 3, we observe a woman who died of HBV-HCC at 78, who has seven (four males, three females) children. Of those, five (two sons, three daughters) are HBV infected and two have unknown HBV infection status. Of the four sons, two at ages 63 and 48 have CHB and cirrhosis receiving antiviral therapy. Of the three daughters, the oldest daughter, aged 59, has CHB on antiviral treatment. The second daughter, aged 56, suffered from advanced cirrhosis but died of gastric cancer. The youngest daughter aged 56 presented with severe edema attributed to HBV-associated glomerulonephropathy. These three daughters presented with 3 different clinical manifestations, while their mother died of HCC (Fig. 3).

In Family 4, a 77-year-old woman with CHB is on antiviral treatment. All her 3 sons were HBV infected at birth. Of these sons, the oldest, aged 51 with CHB, is on antiviral therapy. The younger sons, the identical twins, have remained HBV carriers until at age 50; one twin developed HCC (1.2 cm in diameter), while the other twin has remained a carrier.

The mother's two older sisters also died of HCC at 58 and in her 70's, respectively. Her older (6 years older) brother died of unknown cause (Fig. 4). The CARE Checklist has been

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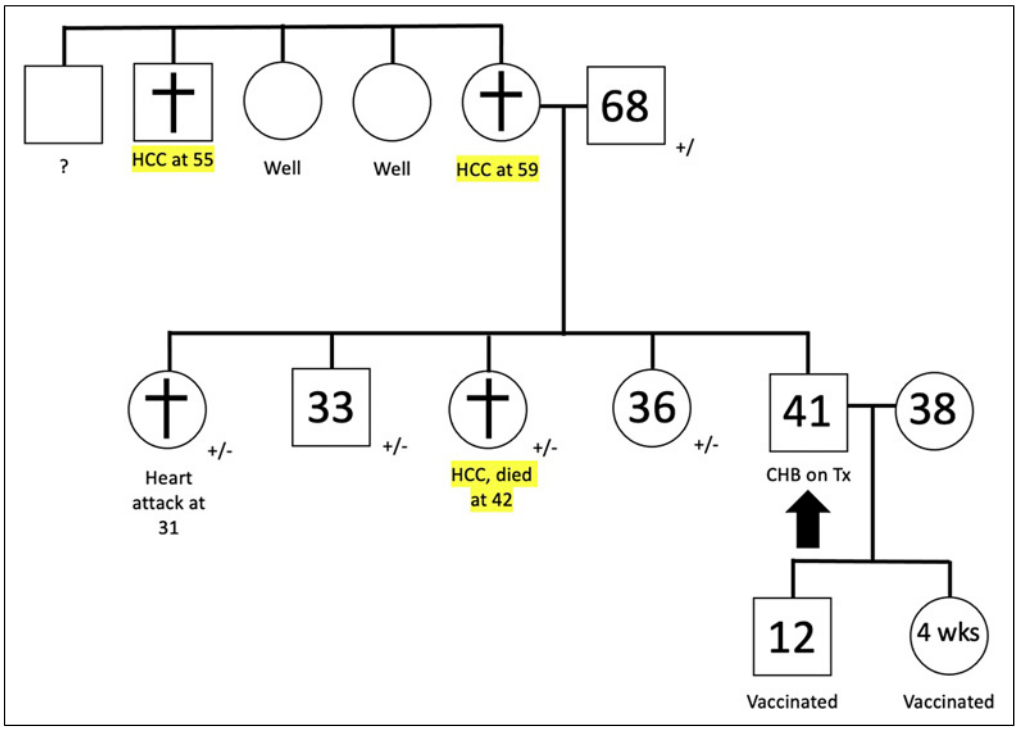

Fig. 1. Family 1 pedigree. † = deceased; numbers correspond to age at time of presentation; +/− indicates HBsAg and HBsAb status, respectively. Larger arrow indicates the propositus.

completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529153).

Discussion

This case series exhibits that patients with HBV infection obtained through vertical and early horizontal transmission can have very different clinical manifestations; some have serious complications such as HCC and liver cirrhosis, while others remain asymptomatic carriers. Within families, the genetic makeup of the virus is likely to be the same or very similar. There is, of course, similarity in genetic makeup of the hosts as well, as they are all related. The questions as to the difference in outcomes then shift to what other factors contribute to the host response to HBV infection.

Previous studies on family clusters of HBV infection have displayed how similarities in genetic makeup can lead to comparable outcomes. For example, an identical twin study by Lin et al. found that monozygotic twins are more likely to be infected with HBV than age-matched controls [5]. Another case of identical twins highlighted the near simultaneous presentation and diagnosis of HCC attributed to HBV infection [6]. These twins expired shortly after diagnosis, within a short time period of each other [6]. Further, studies have found certain gene polymorphisms associated with either clearance of HBV or development of CHB infection [7]. Many of these are genes that code for proteins involved in the immune system response, such as those for the human leukocyte antigen [7]. Two specific examples among several include the human leukocyte antigen class I allele *A*0301* that has been associated with clearance of virus and *B*08* that has been associated with persistence of virus [8].

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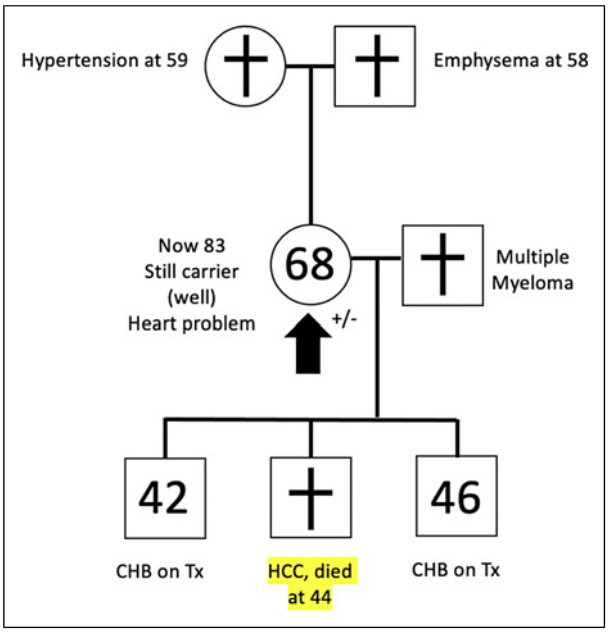

Fig. 2. Family 2 pedigree. † = deceased; numbers correspond to age at time of presentation; +/− indicates HBsAg and HBsAb status, respectively. Larger arrow indicates the propositus.

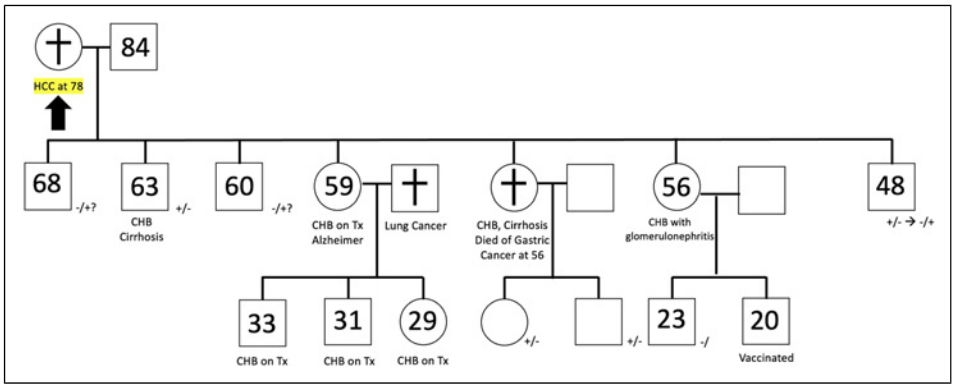

Fig. 3. Family 3 pedigree. † = deceased; numbers correspond to age at time of presentation; +/− indicates HBsAg and HBsAb status, respectively. Larger arrow indicates the propositus.

Our case series contrasts the above literature by presenting 4 family clusters in which patients had disparate courses: some with long-standing indolent CHB infections, some requiring treatment, while others developed HCC or cirrhosis, without having other known risk factors that would otherwise affect their natural history such as exposure to toxins like alcohol, medications, etc. We have observed similar patterns in other family clusters not included in this case series, over time. Thus, this is a repeated theme in our cohort of patients. Our findings complement a previous case series of five family clusters of HCC that also found that there is a varied response to HBV infection within families [9].

Our observation of such variety in these families, with the presumed assumption that other risk factors such as alcohol use and other external stress on the liver were not present or were to a similar degree, supports that there must be other factors more intrinsic to the host's response to the virus. The most striking contrast was our observation in identical twins infected at birth in Family 4. Throughout young adulthood, these twins have remained CHB carriers not requiring antiviral treatment. However, at age 50, during the routine semiannual

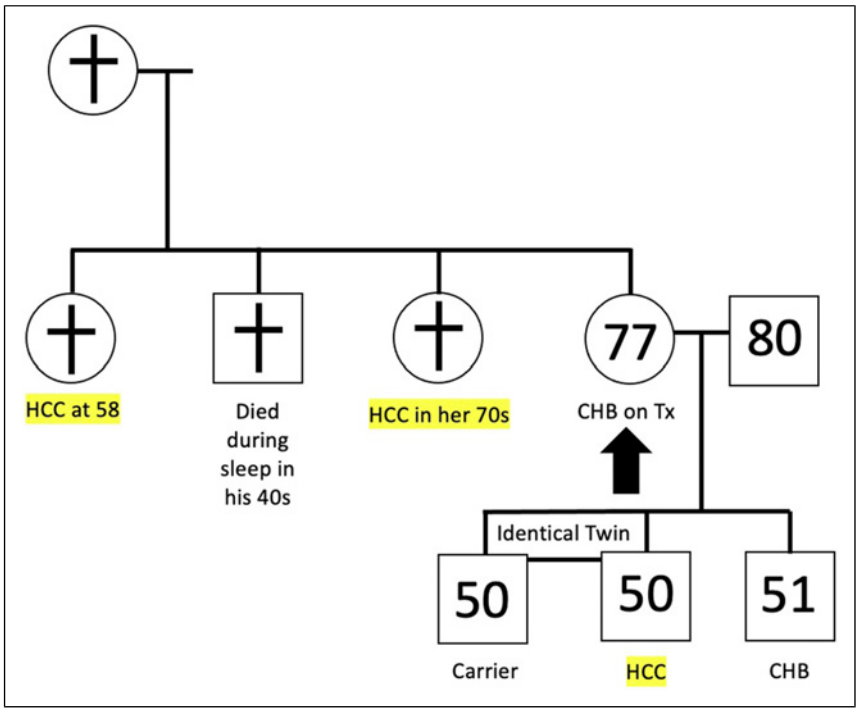

Fig. 4. Family 4 pedigree. † = deceased; numbers correspond to age at time of presentation; +/− indicates HBsAg and HBsAb status, respectively. Larger arrow indicates the propositus.

imaging survey, one twin was found to have developed HCC (1.3 cm) while the other has remained an asymptomatic HBV carrier. One possible relevant life history is that the twin with HCC has led a competitive professional life and was highly successful while the other without HCC tended to avoid competition and lived with a comfortable and non-competitive job. Neither had features of liver cirrhosis.

This case series is limited in that it is a small sample of patients with limited history based on what was available through patient reporting. Previous literature has suggested that chronic stress can strongly influence the immune system's response to virus [10–13]. One case study even displayed tumor regression after significant life stressors were relieved [14]. Other factors might include gender disparities, with studies showing worse outcomes among males [15]. The role of epigenetic mechanisms on liver tumorigenesis has also been investigated, acknowledging the importance of host interaction with the environment [16]. Another study has proposed that younger siblings may clear HBV quicker and thus have less of an HCC risk, as a result of vertical transmission during a time when their mother had a lower viral load [17]. Although this may be a reasonable theory for some families, our case series presented disparate outcomes among similarly aged offspring.

One may wonder what factors play a role in some patients developing cancer while others remaining asymptomatic HBV carriers without treatment. Consequently, it is important to identify potential risk factors in the future that predict who may develop HCC.

Conclusion

CHB infections are common in endemic areas where vertical transmission is prevalent. The vertical transmission results in families that span multiple generations of

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HBV infection, and allows for displaying outcomes of infection among people who have similar genetic makeup and likely near-identical virus. Our case series displays families with multiple HBV-infected members who have manifested contrasting long-term outcomes. This observation leads one to shift one's focus to other risk factors that are unique to the host. Our observation supports the theory that genetics alone cannot predict the natural history of HBV-related disease. Future studies need to identify specific risk factors which are most impactful in the development of serious complications such as HCC.

Statement of Ethics

This study was submitted to the Thomas Jefferson University Institutional Review Board (IRB) and deemed EXEMPT from IRB review on 05/12/2022 pursuant to Title 45 Code of Federal Regulations Part 46.101(b) governing exempted protocol declarations by the Office of Human Research under the Thomas Jefferson University IRB. Written informed consent was not obtained given that there are only four patients that served as propositus in each family tree and provided medical history and information for the remainder of the patients. This was approved by our institution's Office of Human Research under the IRB.

Conflict of Interest Statement

Hie-Won Hann serves the National Advisory Board of The Gilead Sciences and receives grant funding from Gilead and Assembly Biosciences. Dina Halegoua-DeMarzio: consultant for Intercept, Glympse Bio, Pfizer, and 89Bio and receives research grant support from Intercept, BMS, Genfit, Novo Nordisk, Viking, Galmed, Pfizer, and Galactin.

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Author Contributions

All authors contributed substantially to this manuscript. Conceptualization: Nicholas Noverati and Hie-Won Hann; writing – original draft preparation: Nicholas Noverati and Anh Nguyen; writing – review and editing: Divya Chalikonha, Dina Halegoua-DeMarzio, and Hie-Won Hann; supervision: Hie-Won Hann.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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