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A New Tool for the Diagnosis and Management of Viral Hepatitis: Artificial Intelligence

Viral Hepatitin Teşhisi ve Yönetiminde Yeni Bir Araç: Yapay Zeka

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ABSTRACT

Artificial intelligence (AI) is rapidly transforming the field of hepatology, offering promising solutions for the diagnosis and treatment management of viral hepatitis. This review examines the various applications of AI in hepatology, including detection of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) using radiological (ultrasound, computed tomography, and magnetic resonance imaging) and pathological images, identification of individuals at high risk for viral hepatitis and its complications early identification of liver diseases through analysis of electronic health record data prediction of prognosis in HCC. Despite the remarkable potential of AI in hepatology, several challenges remain. Ethical concerns regarding data privacy, algorithmic biases, and regulatory compliance must be addressed. Collaborative efforts between healthcare professionals and data scientists are essential to navigate these challenges and unlock the full potential of AI in transforming hepatology.

Keywords: Artificial intelligence, cirrhosis, deep learning, HCC, chronic viral hepatitis, machine learning

ÖZ

Yapay zeka (AI), viral hepatitin tanısı, prognozun tahmini ve tedavi yönetimi için umut verici çözümler sunarak hepatoloji alanını hızla dönüştürmektedir. Bu derleme, radyolojik (ultrason, bilgisayarlı tomografi ve manyetik rezonans görüntüleme) ve patolojik görüntüleri kullanarak karaciğer fibrozu, siroz ve hepatoselüler karsinomun (HCC) saptanması, viral hepatit ve komplikasyonları için yüksek risk altındaki bireylerin belirlenmesi elektronik sağlık kaydı verilerinin analizi yoluyla karaciğer hastalıklarının erken teşhisi HCC'de prognozun tahmin edilmesi dahil olmak üzere hepatolojide yapay zekanın çeşitli uygulamalarını incelemektedir. AI'nın hepatolojideki dikkate değer potansiyeline rağmen, bazı zorluklar devam etmektedir. Veri gizliliği, algoritmik önyargılar ve mevzuat uyumluluğuna ilişkin etik kaygıların ele alınması gerekmektedir. Sağlık uzmanları ve veri bilimcileri arasındaki işbirlikçi çabalar, zorlukların üstesinden gelmek ve hepatolojiyi dönüştürmede yapay zekanın tüm potansiyelini ortaya çıkarmak için çok önemlidir.

Anahtar Kelimeler: Yapay zeka, siroz, derin öğrenme, HCC, kronik viral hepatit, makine öğrenmesi

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Introduction

Liver diseases cover a broad spectrum of illnesses, from common conditions such as viral hepatitis to more severe ones like cirrhosis and hepatocellular carcinoma (HCC) (1). Despite their clinical importance, the diagnosis and treatment of liver diseases have often been challenging because of the complex nature of liver functions and the complexity of diseases that can develop (2).

Artificial intelligence (AI), including machine learning (ML) and deep learning (DL) techniques, has emerged as a transformative force in different fields of healthcare, including hepatology (3,4). Recent advancements in AI have revealed novel perspectives in understanding, diagnosing, and managing liver diseases (4). This comprehensive review aims to provide an in-depth exploration of the various applications of AI in hepatology, elucidating its pivotal role in disease diagnosis, tailoring individualized treatments, optimizing decision-making, predicting patient outcomes, and facilitating continuous monitoring.

Let us start by delving into the foundational principles of AI, data sourcing, and preprocessing. By delving into these principles, we can gain a deeper insight into how these technologies can

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effectively tackle the complexities encountered in various aspects of hepatology. Subsequently, we will investigate the application of AI in addressing hepatology's challenges, delving into the specific AI technologies and data that can be harnessed for this purpose. In addition, we will explore the practical implementations of AI in hepatology and the potential outcomes that may arise. Finally, we will engage in a discussion concerning the ethical and regulatory dimensions, along with the challenges and future directions of this dynamic field.

With this review, I hope to make AI more understandable and to enable you to see the great opportunities it offers today in overcoming the difficulties in the diagnosis and management of viral hepatitis.

What is AI and How Does It Work?

AI Fundamentals

AI is a branch of computer science concerned with building machines that can perform intelligent tasks such as learning, recognizing patterns, problem solving, and decision making (5,6,7). Expert systems, also known as "hard-coded" AI systems, were dominant in AI in the pre-ML era. They relied on manually encoded rules and knowledge bases to solve problems, essentially replicating the expertise of human experts in a specific domain (8,9).

ML is a subfield of AI that focuses on developing algorithms that can learn from data without being explicitly programed. Instead of manually coding each step, ML algorithms can analyze large datasets and identify patterns, enabling them to make predictions and decisions on their own (9,10).

DL is a subfield of ML that uses artificial neural networks to learn from data. Neural networks are inspired by the structure and function of the human brain, and they can learn complex patterns and relationships that would be difficult or impossible to learn with traditional ML algorithms (10,11). ML requires human engineering and domain expertise to design feature extractors and structure data, whereas DL does not require structured data. DL has been highly successful in various applications, including image recognition, natural language processing, speech recognition, machine translation, and medical diagnosis (11,12,13,14).

AI is not magic. You may think of ML as a model that learns from historical data to forecast future data. Furthermore, AI is not a new technology. Its roots can be traced back to the 1950s (14,15).

Role of Data in Training AI Models for Healthcare

Data play a crucial role in training AI models for healthcare. It serves as the fuel that powers these models, enabling them to learn and improve over time. AI models learn by analyzing vast amounts of data. This includes medical records, imaging scans, lab results, genetic information, and patient surveys. These data points serve as examples for the model, allowing it to identify patterns and relationships between different variables. As the model analyzes more data, it refines its understanding and adjusts its internal parameters. This process of continuous learning ensures that the model becomes increasingly accurate and reliable. The type and quality of data used for training significantly impact the model's performance (16).

Data Sources and Data Pre-processing

AI algorithms rely on various data sources, including medical records, imaging data [e.g., computed tomography (CT) scans, magnetic resonance imagings (MRI)], genomic data, histopathological data, and clinical notes. Data preprocessing, which involves cleaning, normalization, and feature extraction, is a critical step to ensure the data's suitability for AI model training (3,9).

Types of Data

Structured data include medical records, laboratory results, and insurance claims, which are typically stored in databases and are easily accessible for training algorithms. Unstructured data include medical images, pathology reports, and clinical notes, which require additional processing and extraction techniques to be used by AI models. Real-time data includes data generated by wearable devices, sensors, and medical monitoring systems, which can be used to provide continuous feedback and improve the performance of AI models in real-time settings (9).

Data Quality

The quality of training data significantly affects an AI model's accuracy. Ensuring data accuracy, completeness, and absence of errors or biases is critical (16).

AI Applications Using Radiological Images for Viral Hepatitis

AI is rapidly transforming the field of radiology, and AI applications for radiological analysis in patients with viral hepatitis are no exception (17,18,19). AI algorithms can be trained on large datasets of medical images to identify patterns and features that may be indicative of viral hepatitis or its complications. This can help radiologists to detect and diagnose viral hepatitis and its complications more accurately and efficiently, even in cases where the findings are subtle or equivocal (19,20,21). Here are some specific examples of AI applications using radiological images in patients with viral hepatitis.

Identifying the Features of Liver Fibrosis and Cirrhosis on Ultrasound (US), CT, and MRI

Hepatic fibrosis is a crucial milestone in chronic liver disease, significantly impacting disease prognosis. However, the conventional method of detecting hepatic fibrosis involves a rather invasive procedure known as liver biopsy, which necessitates the removal of a small liver tissue sample for microscopic examination. Fortunately, AI algorithms present a promising avenue for identifying subtle indicators of liver fibrosis and cirrhosis through US, CT, and MRI images (22,23,24,25).

Several online systems have been developed to aid in staging hepatic fibrosis, offering accessible and efficient tools for clinicians. These computer-aided diagnosis systems generally work by incorporating specific patient data or test results into algorithms or scoring systems such as METAVIR and FIB-4 scores. The input parameters include laboratory values, patient demographics, and imaging findings. Algorithms then compute a score or index that correlates with the degree of fibrosis, aiding clinicians in staging liver fibrosis and guiding further diagnostic or treatment decisions (6,26).

These algorithms can discern nuanced changes in liver texture, volume, echogenicity, elasticity analysis, and vascularity. Popa et al. (27), in their systematic review encompassing 24 articles analyzing AI-assisted imaging techniques, concluded that these non-invasive AI-driven methods perform on par with human experts in accurately detecting and staging liver fibrosis.

In a prospective study conducted by Wang et al. (28), 1990 two-dimensional shear wave elastography (2D-SWE) images of 398 chronic hepatitis B patients who underwent liver biopsy from 12 hospitals were included. This study evaluated the performance of a developed DL Radiomics of elastography (DLRE) model using 2D-SWE images and a convolutional neural network (CNN) algorithm. Results indicated that the DLRE model outperformed other methods, including 2D-SWE and/or biochemical markers (APRI, FIB-4), in predicting liver fibrosis stages. Specifically, it exhibited significantly higher diagnostic accuracy than other techniques. It accurately predicted cirrhosis (F4) with 97% accuracy and advanced fibrosis (≥F3) with 98% accuracy. Moreover, unlike the varying cut-off values proposed when determining the degree of fibrosis using 2D-SWE, the DLRE model's performance remained consistent even when applied to different training cohorts (28).

This breakthrough offers a substantial advantage to clinicians, enabling them to diagnose and monitor the progression of liver disease in patients with viral hepatitis without resorting to invasive procedures.

Detection of HCC on US, CT, and MRI Images

Detecting HCC using imaging techniques like US, CT scans, and MRI presents several challenges. First, HCC lesions can vary in size and appearance, making it challenging to distinguish small tumors from surrounding healthy tissue or benign nodules. This difficulty increases when differentiating early-stage HCC from dysplastic or cirrhotic nodules (29,30). Second, especially when these liver lesions occur together with cirrhosis or steatosis, it becomes difficult for radiologists to distinguish malignant features among complex lesion types (31,32). Finally, the accuracy of HCC detection can be influenced by the skill and experience of the radiologist interpreting the images. Variability in interpretation can affect diagnostic reliability (33). AI algorithms can be used to detect HCC on CT and MRI images with high accuracy, even in the early stages. This is important because HCC is a major complication of chronic viral hepatitis, and early detection is essential for improving patient outcomes (34). AI models excel in identifying and characterizing liver lesions, including HCC, cysts, and metastatic tumors. They can accurately distinguish between benign and malignant lesions, thereby aiding in early cancer diagnosis (35).

B-mode US is the first recommended imaging test for focal liver lesions because of its cost-effectiveness and real-time diagnostic capability. However, it has limitations compared with other tomographic imaging modalities, such as equipment quality, physician expertise, and lack of perfusion information (36,37). In a multicenter study with external validation, a DCNN-US model developed using CNN achieved 92% accuracy in distinguishing malignant liver masses from benign ones. The diagnostic performance of this model was compared with that of 236 radiologists, demonstrating significantly higher accuracy than even experienced radiologists with 15 years of expertise (92% vs. 76.1%) (36).

In another study comparing the performance of different human experts with varying levels of experience in classifying four focal lesions (HCC, metastatic tumor, hemangioma, cyst), the AI system, developed using B-mode US and a CNN algorithm, outperformed human experts with an accuracy rate of 89.1%. In contrast, the median number of human experts stood at 67.3%. Furthermore, the likelihood of accurate diagnosis by the AI system increases with more training data, whereas in human experts, as the experience level decreases, the accuracy rate could be as low as 40% (35). Consequently, DL models can serve as a rapid and reliable "second opinion" tool for radiologists, particularly in cases where imaging features are ambiguous (35,36,38). In the future, AI's aid promises biopsy-equivalent data from radiological images, even through cost-effective, noninvasive US scans, revolutionizing diagnostic capabilities.

AI Applications Using Histopathological Images for Viral Hepatitis

Histopathological examination of liver biopsies remains the gold standard for the diagnosis and staging of liver fibrosis, inflammation, and other pathological changes associated with viral hepatitis. However, analyzing these images manually is time-consuming and subjective, leading to potential variability in interpretation and diagnosis (39).

The advancement of AI and whole-slide imaging scanners has made it possible to combine the two technologies to reduce medical burden, increase diagnosis accuracy, and even forecast prognosis and gene mutations (25).

AI-powered algorithms can analyze histopathological images with remarkable accuracy and efficiency, offering several advantages.

Early Detection of Pre-Cancerous Lesions

AI can be trained to identify subtle changes in hepatocytes and other liver cells that may indicate the presence of pre-cancerous lesions, such as dysplastic nodules, even before they are visible to the naked eye (40). This can enable early intervention and potentially prevent the development of HCC.

In a study comparing the performance of pathologists (having different levels of experience) with a DL model (trained using histopathological H&E images and CNN algorithm) in the prediction of malignant-benign differentiation and gene mutations affecting prognosis in focal liver lesions, the performance of the model was found to be equivalent to that of a 5-year pathologist. The model achieved 96% accuracy in distinguishing between malignant and benign lesions and 86.9% accuracy in classifying HCC into good, moderate, and poor prognosis categories (41). These findings highlight the potential of CNN in helping pathologists detect gene mutations in HCC. This can enhance diagnostic accuracy and contribute to precision medicine.

HCC-SurvNet, an AI-assisted pathology tool, uses digital histopathological images to predict disease recurrence risk after primary surgical resection for HCC. Risk scoring categorizes patients into low-and high-risk subgroups, showing substantial variations in survival outcomes. This position HCC-SurvNet as a promising instrument to advance the clinical management of HCC patients, outperforming the standard Tumor-Node-Metastasis classification system in predictive accuracy (42).

Streamlining Workflow and Reducing Pathologist Workload

AI can automate many repetitive tasks involved in the analysis of histopathological images, such as image pre-processing, feature extraction, and quantitative analysis. This can free up pathologists' time to focus on complex cases and decision-making, thus improving overall workflow efficiency (43).

AI Applications Using Electronic Health Record (EHR) Data in Viral Hepatitis

Identifying High-Risk Individuals

AI algorithms can be used to analyze EHR data to identify individuals at high risk of developing viral hepatitis, such as those with a history of intravenous drug use, blood transfusions, or sexual contact with people with viral hepatitis. This information can guide targeted screening and prevention efforts (44).

Because a significant portion of the population goes undiagnosed, HCV remains a major infectious disease-related public health issue, even with the availability of very effective therapies (19,45). AI models can be trained to identify individuals with risk factors like past blood transfusions, intravenous drug use, or unsafe sexual practices, highlighting those who should be prioritized for testing. For instance, an easy-to-implement risk score for targeted HCV testing developed by Martínez-Sanz et al. (46), consists of five items (gender, place of origin, use of intravenous drugs, self-perceived risk of acquired HCV infection, and past hepatitis or unexplained liver disease) that achieved high diagnostic accuracy, with a sensitivity of 98% and a negative likelihood ratio of 0.05 for participants with low scores, ruling out HCV infection with high probability. Scores like this can provide a cost-effective alternative to universal screening (46).

Early Identification of Treatable Liver Diseases

AI algorithms can analyze EHR data to identify subtle changes in laboratory tests, vital signs, and other clinical data that may indicate viral hepatitis infection, even before symptoms appear. This can help clinicians diagnose the disease earlier and initiate treatment promptly. By analyzing historical trends and comparing them with established diagnostic criteria, AI models can aid in early detection and diagnosis, leading to better patient outcomes (44,47).

For instance, the intelligent liver function test system is an experimental approach developed for automatically diagnosing and staging liver disease in primary care based on abnormal liver function test results from routine laboratory samples. This system has been demonstrated to be more successful than the standard of care in diagnosing liver disease, which has increased the accuracy of diagnosis to over 90% and enhanced detection rates by 43% (48). This system can facilitate the early identification of treatable liver diseases, creating an opportunity for early intervention and improving patient outcomes at a low cost.

More recently, a unique prediction CNN model was developed based on different abnormalities detected in ECG recordings of a total of 5212 patients who underwent liver transplantation at three Mayo Clinic transplant centers between 1988 and 2019. The DL-based model successfully differentiated patients with cirrhosis from control subjects with an accuracy of 90% (sensitivity: 84.9%; specificity: 83.2%) using only ECG images (49).

Predicting the Risk of Complications from Viral Hepatitis

AI algorithms can be used to analyze EHR data to predict the risk of developing complications from viral hepatitis, such as liver fibrosis, cirrhosis, and HCC (50). Recently, Wong et al. (51) developed a ML-based model tailored specifically to detect HCC in patients with chronic hepatitis infection. Known as the HCC ridge score (HCC-RS), this innovative model constructed using ML techniques demonstrates heightened accuracy compared with existing HCC risk assessment scores. Integrating HCC-RS into electronic health systems can enable real-time updates on HCC risk (51).

Despite the development of traditional regression models to predict HCC risk in the presence of cirrhosis (based on features like response to antiviral treatment, low platelet count, elevated aspartate aminotransferase: alanine aminotransferase ratio, male gender, advanced age, and core clinical findings), the fluctuation of HCC risk over time makes accurate prediction challenging for these models (52,53). Ioannou et al. (54) investigated this challenge by employing a DL approach. They analyzed data from 48,151 patients with HCV-related cirrhosis and tracked them for a minimum of 3 years post-cirrhosis diagnosis. They aimed to determine whether DL recurrent neural network (RNN) models, leveraging raw longitudinal EHRs, could offer enhanced performance in predicting HCC risk. The study found that RNN models exhibited notably better performance than traditional logistic regression models (ACC: 75% vs. 68%, $p<0.001$). This success suggests that DL models like RNNs hold significant potential in capturing temporal dynamics and long-term information, paving the way for improved predictions of HCC risk (54).

Challenges and Considerations

Ethical concerns constitute a primary area, especially regarding data privacy, confidentiality, and security. Ensuring that sensitive patient information remains protected and ethically used within AI frameworks is crucial. Additionally, addressing biases and disparities inherent in AI algorithms to prevent potential discriminatory outcomes is an ethical imperative (55,56).

Regulatory and legal aspects present another layer of complexity. Adhering to healthcare service regulations and obtaining necessary approvals, such as Food and Drug Administration clearance for medical devices integrated with AI, are essential. Ensuring compliance while advancing AI technologies is crucial for their ethical and lawful implementation (57).

The quality and integration of data are pivotal factors. Maintaining high standards of data quality, accuracy, and integrity is essential for the efficacy and reliability of AI-driven healthcare systems. Streamlining the integration of diverse datasets across healthcare platforms ensures comprehensive and cohesive AI-driven solutions (16).

Resistance to change within established healthcare systems poses a significant challenge. Implementing AI technologies often encounters reluctance due to shifts in traditional practices, necessitating thorough strategies for acceptance and adaptation within healthcare frameworks (58).

Addressing these multifaceted challenges is imperative to ensure the responsible and effective integration of AI into healthcare systems.

Conclusion

The advent of AI has ushered in a new era in hepatology, revolutionizing disease diagnosis, prognosis prediction, and management strategies. Despite the vast potential of AI in hepatology, significant challenges persist on ethical, regulatory, and technical fronts. Addressing concerns regarding data privacy, algorithmic biases, regulatory compliance, and inherent resistance to change is pivotal for the responsible and effective integration of AI into healthcare.

While AI integration holds promise for hepatology, it is crucial to highlight that these advancements are in ongoing development and require additional research and clinical trials for validation. Collaborative efforts between healthcare experts and data scientists, along with continuous innovation, are essential for realizing AI's full potential in enhancing patient outcomes and reshaping the field of hepatology.

Ethics

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Research Article

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Frequency of Hepatosteatosis and Relationship Between Laboratory Parameters and Hepatosteatosis in Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında Hepatosteatoz Sıklığı ve Laboratuvar Parametrelerin Hepatosteatoz ile İlişkisinin Değerlendirilmesi

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ABSTRACT

Objectives: Hepatosteatosis is very common worldwide and is defined as the accumulation of lipid droplets in hepatocytes. Hepatosteatosis is often associated with metabolic factors such as obesity, insulin resistance, and hypertriglyceridemia. The relationship between chronic hepatitis B (CHB) and hepatosteatosis remains unknown. We investigated the frequency of hepatosteatosis in patients with CHB and to evaluate the relationship between hepatosteatosis and laboratory parameters.

Materials and Methods: We retrospectively studied 262 patients with CHB. Patients were divided into two groups, hepatosteatosis and non-hepatosteatosis, according to liver ultrasonography findings. The groups were compared in terms of demographic characteristics and laboratory parameters.

Results: A total of 262 patients with CHB were included. The mean age was 45.1±15.3 years, 136 (51.8%) of whom were male. Liver biopsy was performed in 86 (32.8%) of the patients, 20 (7.6%) had fibrosis, and 163 (62.2%) had steatosis. Among the patients with steatosis, grade 1 steatosis was observed in 30.9 (81/163), grade 2 in 26 (68/163), and grade 3 in 5.3 (14/163). Hypertension, hepatomegaly, and cirrhosis were correlated with the presence of steatosis. Patients with steatosis were older than those without. Fasting glucose levels, low-density lipoprotein levels, and triglyceride levels of patients with steatosis were higher than those of patients without steatosis. High-density lipoprotein levels were lower in the steatosis group. No correlation has been found

ÖZ

Amaç: Hepatosteatoz, karaciğer enzim yüksekliğinin dünyadaki en yaygın nedenidir ve hepatositlerde lipid damlacıklarının birikmesi olarak tanımlanmaktadır. Hepatosteatoz, sıklıkla santral obezite, insülin direnci ve hipertrigliseridemi gibi metabolik faktörlerle ilişkilidir. Kronik hepatit B (KHB) ile hepatosteatoz ilişkisi ise halen gizemini korumaktadır. Bu çalışmanın amacı, KHB hastalarında hepatosteatoz sıklığının araştırılması ve hepatosteatoz varlığı ve şiddeti ile biyokimyasal, virolojik ve metabolik parametreler arasındaki ilişkinin değerlendirilmesidir.

Gereç ve Yöntemler: KHB tanılı 262 hasta retrospektif olarak incelendi. Hastalar karaciğer ultrasonografi bulgularına göre hepatosteatozu olan ve hepatosteatozu olmayanlar olarak iki gruba ayrıldı. Gruplar demografik özellikler ve laboratuvar parametreleri açısından karşılaştırıldı.

Bulgular: KHB tanılı 262 hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 45,1±15,3 yıldı. Hastaların 136'sı erkekti (%51,8). 86 hastaya (%32,8) karaciğer biyopsisi yapılırken, 20 hastada (%7,6) fibrozis vardı. Hastaların 163'ünde (%62,2) steatoz vardı. Steatozu olan hastaların %30,9'unda (81/163) grade 1, %26'sında (68/163) grade 2 ve %5,3'ünde (14/163) grade 3 steatoz görüldü. Hipertansiyon, hepatomegali ve siroz steatoz varlığı ile korelasyon gösterdi. Steatozu olan hastalar steatozu olmayanlara göre daha yaşlıydı. Steatozu olan hastaların açlık kan şekeri, düşük dansiteli lipoprotein düzeyleri ve trigliserit düzeyleri steatozu olmayanlara göre daha yüksekti. Yüksek dansiteli lipoprotein düzeyleri steatoz

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with gender, body mass index, hepatitis delta virus co-infection, hepatitis B virus (HBV)-DNA levels, or hepatitis B e antigen status between steatosis.

Conclusion: We found that hepatosteatosis is present in a significant proportion of patients with CHB. Although the presence of hepatosteatosis was associated with some metabolic parameters, the relationship between it and HBV parameters was not statistically significant.

Keywords: Cirrhosis, hepatitis B, non-alcoholic fatty liver diseases

grubunda daha düşüktü. Cinsiyet, vücut kitle indeksi (VKİ), hepatit delta virüs ko-enfeksiyonu, hepatitis B virüs (HBV)-DNA düzeyleri ve hepatitis B e antijen durumu ile steatoz arasında bir ilişki saptanmadı.

Sonuç: Çalışmamızda KHB hastalarının önemli bir kısmında hepatosteatoz eşlik ettiğini bulduk. Hepatosteatoz varlığı, non-alkolik yağlı karaciğer hastalığı için iyi bilinen risk faktörleri olan VKİ ve açlık glukoz seviyeleri ile ilişkili saptanırken HBV parametreleri ile arasındaki ilişki istatistiksel olarak anlamlı saptanmamıştır.

Anahtar Kelimeler: Siroz, hepatit B, non-alkolik yağlı karaciğer hastalığı

Introduction

Hepatitis B virus (HBV) infection affects millions of people worldwide (1). After an acute infection, the progression to chronic hepatitis B (CHB) increases the risk for the progression of fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), contributing to increased morbidity and mortality (2). The number of patients with CHB ranges from 240 million to 350 million (3). The prevalence of CHB varies worldwide, with the highest prevalence in western sub-Saharan Africa (12%), followed by East Asia and Southeast Asia (5%-7%) (1,2,3,4,5). In our country, the prevalence of hepatitis B surface antigen (HBsAg) positivity varies between 4% and 10%, and it is considered to be a moderately endemic region in terms of HBV incidence (6).

Hepatosteatosis is the most common cause of elevated liver enzyme levels worldwide and is defined as the accumulation of lipid droplets in hepatocytes (7). It is frequently associated with metabolic factors, including central obesity, insulin resistance, and hypertriglyceridemia (8). The prevalence of hepatosteatosis is increasing due to the increasing prevalence of obesity and/or metabolic syndrome worldwide (9). Since liver fibrosis is a shared pathological process in patients with chronic viral hepatitis (CVH) and hepatosteatosis, recent studies have been conducted to evaluate the interaction between HBV, hepatitis C virus (HCV), and hepatosteatosis (10).

Hepatosteatosis is a common histopathological feature of chronic hepatitis C (CHC) infection and has been shown to be particularly associated with genotype 3 (11). Although controversial, the presence of hepatosteatosis in patients with CHC has been associated with advanced fibrosis (12,13). However, the relationship between HBV and hepatosteatosis has not been explained. The aim of this study was to investigate the frequency of ultrasonography (USG) defined hepatosteatosis in patients with CHB and the relationship between the presence and severity of hepatosteatosis and biochemical, virological, and metabolic parameters.

Materials and Methods

Patient Population

We retrospectively studied all patients with CHB who were admitted to the infectious diseases and clinical microbiology outpatient clinic between January 2022 and June 2022.

The inclusion criteria considered were the following: HBsAg positivity for a period over 6 months. Exclusion criteria were as follows: co-infection with other viruses such as HCV, HDV, and human immunodeficiency virus (HIV), co-existence of liver disease of any other cause, consumption of alcohol more than 30 g/day for males or 20 g/day for females, obese patients body mass index (BMI) >30, diagnosis of dyslipidemia, and treatment with tenofovir alafenamide fumarate.

Patients were divided into two groups, hepatosteatosis and non-hepatosteatosis, according to liver USG findings. The groups were evaluated in terms of variables such as age, gender, liver enzymes, Hepatitis B e antigen (HBeAg) status, HBV-DNA level, hepatitis B infection stage (chronic infection, chronic hepatitis), antiviral treatment status, BMI, glucose, triglyceride, and cholesterol levels.

Statistical Analysis

The distribution of the data was analyzed by the Kolmogorov-Smirnov test, and group comparisons were made by the Independent samples t-test for continuous variables with normal distribution and the Mann-Whitney U test for continuous variables without normal distribution. Relationships between categorical variables were analyzed using Pearson's chi-square or Fisher's exact tests.

Categorical variables are shown as n (%). Continuous variables with normal distribution are shown as mean ± standard deviation, while the median (interquartile range) (minimum-maximum) was used for continuous variables that did not show normal distribution. Statistical analyses were performed using SPSS v.22 Package program, and the significance level was set at 0.05. Before starting the study, the approval of the Scientific Research Ethics Committee of the Faculty of Medicine of Ağrı İbrahim Çeçen University was obtained (approval number: 229, date: 08.11.2022).

Results

A total of 262 patients with CHB were included in the study. The mean age was 45.1±15.3 years. There were 136 males (51.8%) and 126 females (48.2%). The majority of patients were HbeAg negative 238/262 (90.8%), whereas only 24/262 were HbeAg-positive (19.2%). A liver biopsy was performed in 86 patients (32.8%), whereas 20 patients (7.6%) had fibrosis. In addition, 163 (62.2%) patients had steatosis and 99 (37.8%) did not have steatosis. Among the patients with hepatosteatosis grade

1, steatosis was observed in 30.9% (81/163), grade 2 in 26% (68/163), and grade 3 in 5.3% (14/163).

Hypertension (HT), hepatomegaly, and cirrhosis were correlated with the presence of steatosis. Patients with steatosis were older than those without steatosis (48.36±14.92 versus 39.82±14.52 years, p<0.001). Fasting blood glucose (97.42±17.5 mg/dL versus 93.09±13.94 mg/dL, p=0.040), low-density lipoprotein (LDL) levels (105.57±25.82 mg/dL versus 98.65±24.33 mg/dL, p=0.032) and triglyceride levels (114.57±25.82 mg/dL versus 98.65±24.33 mg/dL, p=0.003) of patients with steatosis were higher than those without steatosis. HDL levels were lower in the steatosis Grup (47.24±13.26 mg/dL versus 43.22±10.42 mg/dL, p=0.007). No correlation was found between gender, BMI, HDV coinfection, HBV-DNA levels, and HBeAg status between steatosis (Table 1).

Liver biopsy was performed on 102 patients, but biopsy results were available for 86 of them. Hepatosteatosis was detected in 30 (34.8%) patients. When the patients who had liver biopsy were divided into two groups, those with and without steatosis, according to the biopsy results, it was found that older age, presence of cirrhosis, high LDL, triglycerides, and low HDL were associated with steatosis, but HT was not found to be statistically significant, whereas HBV-DNA levels were found to be higher in the group with steatosis, and this difference was statistically significant (Table 2).

Table 1. Comparative analysis of clinical and biochemical parameters in chronic hbv patients with and without hepatosteatosis

	With steatosis (n=99)	**Without steatosis (n=163)**	**p-value**
Age (year)	39.82±14.52	48.36±14.92	<0.001*
BMI (kg/m²)	24.67±2.67	24.85±2.99	0.624*
Gender, n (%) Female Male	 54 (54.5) 45 (45.5)	 72 (44.2) 91 (55.8)	0.103#
BMI >25, n (%)	36 (36.4)	58 (35.6)	0.898#
DM, n (%)	1 (1.0)	2 (1.2)	>0.999$
HT, n (%)	4 (4.0)	18 (11.0)	0.048$
Cirrhosis, n (%)	0 (0.0)	19 (11.7)	<0.001$
HDV, n (%)	3 (3.0)	7 (4.3)	0.747$
HBe, n (%) AntiHBe positive HBeAg positive	 88 (88.9) 11 (11.1)	 150 (92.0) 13 (8.0)	0.394#
Liver inflammation, n (%) Infection Hepatitis	 37 (37.4) 62 (62.6)	 61 (37.4) 102 (62.6)	0.994#
Age of the disease	6 (7) [1-23]	8 (5) [0-33]	0.151&
Fasting glucose (mg/dL)	93.09±13.94	97.42±17.75	0.040*
ALT (U/L)	23.99±14.00	25.54±13.44	0.373*
AST (U/L)	22.72±7.49	23.83±9.57	0.325*
Cholesterol (mg/dL)	163.69±41.88	168.05±38.24	0.389*
TG (mg/dL)	97 (59) [38-683]	114 (65) [29-417]	0.003&
HDL (mg/dL)	47.24±13.26	43.22±10.42	0.007*
LDL (mg/dL)	98.65±24.33	105.57±25.82	0.032*
AFP (ng/mL)	2 (1) [1-11]	2 (2) [1-13]	0.109&
HBV-DNA (IU/mL)	569 (944) [60-8590]	612 (1464) [90-9890]	0.635&
Hepatomegaly, n (%)	6 (6.1)	55 (33.7)	<0.001#
Treatment, n (%) TDF ETV	40 (40.4) 23 (57.5) 17 (42.5)	73 (44.8) 40 (54.8) 33 (45.2)	0.488# 0.782#
Liver biopsy, n (%)	39 (39.4)	63 (38.7)	0.905#
HAI (n=30 vs. 56)	7 (3) [3-13]	8 (3) [2-12]	0.599&
Fibrosis (n=30 vs. 56)	2 (1) [1-6]	2 (1) [0-5]	0.694&

*: Independent samples t-test, #: Pearson chi-square test, $: Fisher's exact, &: Mann-Whitney U test, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, HDV: Hepatitis delta virus, HBeAg: Hepatitis B envelope antigen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AFP: Alfa fetoprotein, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, TDF: Tenofovir disoproxil fumarate, ETV: Enticavir, HAI: Histological activity index

Discussion

Hepatosteatosis and CVH are both common chronic liver diseases worldwide (14,15,16). It is commonly associated with metabolic risk factors such as obesity, dyslipidemia, and insulin resistance (17). The estimated global prevalence of hepatosteatosis is 25% (18). The prevalence of hepatosteatosis in Turkey has been studied in several small-sized, single-center studies and was found to vary between 10% and 48% (19,20,21,22). The highest hepatosteatosis rate of 60.1% was reported from the Cappadocia cohort, an ultrasound-based study of 2792 apparently healthy individuals (60.1%) (23). Current studies show that Turkey is among the countries with a high prevalence of hepatosteatosis in the world (19,20,21,22,23).

HBV and HCV infection leads to a spectrum of liver diseases, including chronic hepatitis, cirrhosis, and HCC (24). Studies evaluating steatosis in patients with CHC have shown a direct relationship between HCV and steatosis (10). However, this is a feature-specific to genotype 3. In patients infected with genotype 3, fatty liver disease is directly proportional to viral load, and steatosis starts in the periportal area, not in the centrilobular area, unlike patients with hepatosteatosis (12,13). Fatty liver disease in patients infected with other HCV genotypes is associated with obesity, Diabetes Mellitus, and insulin resistance, as in other patients with hepatosteatosis.

It has been reported that hepatosteatosis is associated with 14-70% of patients with CHB (25,26,27). This rate is approximately 20% in biopsy-proven hepatosteatosis (26). In our study, the hepatosteatosis rate was found to be 63% in patients with CHB. Although this rate is similar to other studies evaluating hepatosteatosis in patients with CHB, it is higher than that in the normal population. The high prevalence of hepatosteatosis suggested that it may be related to CHB, but no statistical association was found. This might be because the diagnosis of hepatosteatosis is made by USG, not biopsy, because when the patients were compared with and without steatosis according to biopsy results, HBV-DNA levels were found to be higher in the group with steatosis, and this difference was statistically significant.

Table 2: Detailed characteristics of chronic hepatitis B virus patients with and without hepatosteatosis undergoing liver biopsy

	Without steatosis (n=39)	**With steatosis (n=63)**	**p-value**
Age (year)	43.15±13.23	50.30±13.93	0.012*
BMI (kg/m²)	24.46±2.78	25.24±3.47	0.240*
Gender n (%) Female Male	 19 (48.7) 20 (51.3)	 28 (44.4) 35 (55.6)	0.674
BMI >25, n (%)	15 (38.5)	25 (39.7)	0.902#
DM, n (%)	1 (2.6)	0 (0.0)	0.382$
HT, n (%)	3 (7.7)	11 (17.5)	0.164$
Cirrhosis, n (%)	0 (0.0)	11 (17.5)	0.006$
HDV, n (%)	1 (2.6)	5 (7.9)	0.403$
HBeAg, n (%) AntiHBe positive HBeAg positive	 33 (84.6) 6 (15.4)	 55 (87.3) 8 (12.7)	0.702#
Age of the disease	7 (7) [1-23]	8 (4) [1-23]	0.159&
Fasting glucose (mg/dL)	94.03±9.48	100.57±20.01	0.029*
ALT (U/L)	23.10±10.75	26.81±12.69	0.132*
AST (U/L)	23.62±8.56	25.59±11.51	0.358*
Cholesterol (mg/dL)	170.28±38.54	166.35±33.99	0.591*
TG (mg/dL)	96 (62) [40-240]	114 (57) [54-260]	0.007&
HDL (mg/dL)	48.74±15.56	41.65±9.26	0.013*
LDL (mg/dL)	103.87±26.28	105.02±24.48	0.824*
AFP (ng/mL)	2 (1) [1-11]	2 (1) [1-13]	0.716&
HBV-DNA	1278 (1958) [124-8590]	2096 (3262) [138-9890]	0,039&
Hepatomegaly, n (%)	1 (2.6)	21 (33.3)	<0.001$
Treatment, n (%) TDF ETV	33 (84.6) 19 (57.6) 14 (42.4)	60 (95.2) 34 (56.7) 26 (43.3)	0.082# 0.932#

*: Independent samples t-test, #: Pearson chi-square test, $: Fisher's exact, &: Mann-Whitney U test, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, HDV: Hepatitis delta virus, HBeAg: Hepatitis B envelope antigen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TG: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, AFP: Alfa fetoprotein, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, TDF: Tenofovir disoproxil fumarate, ETV: Enticavir

There has been an increase in the number of cases in which CHB and hepatosteatosis are observed together. In the study evaluating 132 CHB patients who underwent liver biopsy, it was shown that the presence of steatosis was not associated with age, gender, HBeAg status, HBV-DNA level, presence of fibrosis, serum cholesterol level, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. In univariate analysis, BMI, serum triglyceride, and fasting glucose levels were significantly correlated with hepatosteatosis. Multivariate analysis showed a correlation only between serum triglyceride level and hepatosteatosis (25). In another study, steatosis was independently found to be associated with fasting glucose level and BMI ≥25, no correlation between HBV-DNA levels and HBeAg status (28). In our study, similar to these studies, HT, hepatomegaly, and cirrhosis were correlated with the presence of steatosis. However, no correlation was found with HBV-DNA levels or HBeAg status (26).

In a meta-analysis and a study examining the risk factors for hepatosteatosis in HBV-infected patients, it was shown that hepatosteatosis may have a protective effect on CHB by reducing HBV viral markers (28). The lower incidence of cirrhosis and HCC in HBV-infected patients with hepatosteatosis is associated with higher HBsAg clearance (29). In another study evaluating the effect of HBV on steatosis in people co-infected with HCV, only BMI, not viral factors, was associated with the development of non-alcoholic fatty liver disease (NAFLD) in CHB patients. In the co-infected study population, only BMI and fasting plasma glucose levels were associated with NAFLD. In subgroup analysis, even in patients with genotype 3, CHC and CHB together showed less steatosis than patients with genotype 3 CHC alone (30). This suggests that there is an underlying mechanism in CHB infection that is protective against the development of NAFLD. In our study, we did not show a correlation of steatosis with HBV parameters when the patients were compared with and without steatosis according to liver USG findings results. However, HBV-DNA levels were found to be higher in the group with steatosis, and this difference was statistically significant when the patients who had biopsy were divided into two groups as with and without steatosis. This situation suggests that further studies are needed to evaluate the relationship between HBV and fatty liver disease defined by biopsy in many patients.

Study Limitation

The most important limitation of our study is that the diagnosis of steatosis was made by USG, not biopsy. Liver biopsy is probably the most reliable method for detecting fatty liver (33). However, liver biopsy is not a routine method for diagnosing hepatosteatosis in clinical practice because it is an invasive and costly procedure that may cause morbidity and mortality (17). Diagnosis of hepatosteatosis by USG is a subjective evaluation based on the radiologist's knowledge and visual perception (especially, grade 1 hepatosteatosis). Therefore, we believe that if hepatosteatosis rates were determined by biopsy in our study, a slightly lower rate might be obtained.

Conclusion

In conclusion, we found that hepatosteatosis is present in a significant proportion of patients with CHB. The presence of steatosis is associated with metabolic parameters such as elevated CVH, triglyceride levels, and fasting glucose levels. This study did not show a correlation of steatosis with HBV parameters, but additional well-designed studies are required to prospectively assess the role of steatosis in these patients.

Ethics

Ethics Committee Approval: The approval of the Scientific Research Ethics Committee of the Faculty of Medicine of Ağrı İbrahim Çeçen University was obtained (approval number: 229, date: 08.11.2022).

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: Y.Ç., M.Ö., Concept: Y.Ç., S.A.B., Design: Y.Ç., M.A.S., Data Collection or Processing: Y.Ç., M.A.S., M.Ö., Analysis or Interpretation: Y.Ç., M.A.S., Literature Search: Y.Ç., M.Ö., S.A.B., Writing: Y.Ç., S.A.B.

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Research Article

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Evaluation of Demographic Data, Clinical and Laboratory Findings, and Treatments Administered to Children Followed Up with a Diagnosis of Chronic Hepatitis B Infection

Kronik Hepatit B Enfeksiyonu Tanısıyla izlenen Çocukların Demografik, Klinik ve Laboratuvar Bulguları ile Birlikte Aldıkları Tedavilerin Değerlendirmesi

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ABSTRACT

Objectives: This study examined the demographic and clinical features of children who were followed up with a diagnosis of chronic hepatitis B virus (HBV) infection.

Materials and Methods: The study included 374 children who were followed up with a diagnosis of chronic HBV infection in our clinic between 2005 and 2023.

Results: The study included 249 (66.6%) males and 125 (33.4%) females. The frequency of chronic HBV infection seen in the siblings of females with chronic HBV infection was determined to be significantly higher than that in male patients (p=0.017). Chronic active hepatitis was present in 147 (39.3%) patients. The route of infection was perinatal in all cases. Of the study cases, 79% were born in or before 2003 and 20% were born after 2003. The treatments administered to the cases were tenofovir disoproxil fumarate in 61 cases, lamivudine in 54, interferon 2α in 53, and entecavir in 10. The frequency of active chronic HBV infection was significantly higher in children born in or after 2006 (p=0.036). Similarly, the incidence of inflammation was significantly higher in those born in 2006 and later (p=0.049). The rate of anti-hepatitis

ÖZ

Amaç: Bu çalışmada kronik hepatit B virüs (HBV) enfeksiyonu nedeniyle izlenen çocukların demografik ve klinik özelliklerinin incelenmesi amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya 2005-2023 yılları arasında kliniğimizde kronik HBV enfeksiyonu tanısı ile izlenen 374 çocuk alındı.

Bulgular: Olguların %66,6'sı (n=249) erkek, %33,4'ü (n=125) kız idi. Kronik HBV enfeksiyonu olan kızların kardeşlerinde kronik HBV enfeksiyonu görülme sıklığı erkek hastalardan istatistiksel olarak anlamlı düzeyde daha yüksekti (p=0,017). Çalışmaya alınan olguların %39,3'ünde (n=147) kronik aktif hepatit vardı. Olguların tümünde bulaş perinatal yolla olmuştu. Olguların %79'u 2003 yılı ve öncesinde doğan çocuklardan oluşmaktaydı. Buna karşın, olguların %20'si ise 2003 yılından sonra doğan çocuklardan oluşmaktaydı. Olguların 61'i tenofovir disoproksil fumarat, 54'ü lamuvidin, 53'ü interferon 2α ve 10'nu entekavir tedavisi almıştı. 2006 yılı ve sonrası doğumlularda aktif kronik HBV enfeksiyonu sıklığı daha önce doğanlara göre istatistiksel olarak daha yüksekti (p=0,036). Benzer şekilde, 2006 yılı ve sonrası doğumlularda enflamasyon

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A virus immunoglobulin G positivity was statistically significantly higher in children born between 2003 and 2006 than in other age groups (p=0.003).

Conclusion: Family members of these children should be screened for HBV infection. Because of studies in Türkiye in recent years, there has been a significant decrease in the frequency of HBV infection in children.

Keywords: Children, hepatitis B virus, infection, vaccination

görülme sıklığı anlamlı olarak daha yüksekti (p=0,049). 2003-2006 yılları arasında doğanlarda ise anti-hepatit A virüs immunoglobulin G pozitiflik oranı diğer yaş gruplarına göre istatistiksel olarak daha yüksekti (p=0,003).

Sonuç: Bu çocukların aile bireylerinin HBV enfeksiyonu yönünden taraması yapılmalıdır. Son yıllarda ülkemizde yapılan çalışmaların sonucu olarak çocuklarda HBV enfeksiyonunu görülme sıklığında belirgin azalma olmuştur.

Anahtar Kelimeler: Çocuklar, hepatit B virüsü, enfeksiyon, aşılama

Introduction

Viral hepatitis is widely observed throughout the world and is a significant health problem of great concern in Turkey. Viral hepatitis is as old as human history and was first clinically described by Hippocrates. With the discovery in 1963 of the hepatitis B virus (HBV) antigen by Blumberg in Australia, a new period opened in the history of viral hepatitis (1). However, HBV infection continues to be a significant global public health problem. According to current estimations of the frequency of HBV infection by the World Health Organization, there is chronic infection in 296 million people. This causes approximately 1.5 million deaths per year because of acute or chronic diseases and viral infection complications (2).

The hepatitis B superficial antigen (HBsAg) seropositivity rate in Türkiye is 4% (3). Each year throughout the world, a new diagnosis of HBV infection is reported in 2 million children under the age of 5 years. The infection has been reported to pass most frequently from mother to child through the vertical route and via the horizontal route in the early period of life (4). To protect against hepatitis B infection, it is aimed for at least 90% of infants to receive the first dose of HBV vaccine within the first 24 hours postnatally and for three or more doses to be administered (5).

The aim of this study was to evaluate the demographic data, clinical and laboratory findings, and treatments administered to children who were followed up with a diagnosis of chronic HBV infection.

Materials and Methods

This study was planned as a retrospective cohort study. The study included pediatric cases with chronic HBV infection with HBsAg antigen positivity for >6 months, who were followed up in the Pediatric Gastroenterology, Hepatology, and Nutrition Polyclinic of Fırat University Medical Faculty Hospital between 2005 and 2023. The demographic, clinical, and laboratory data obtained from examinations of the cases' files were recorded on previously created study forms together with the treatments administered, and were then compared with the literature. This study was approved by the Ethics Committee of Fırat University Faculty of Medicine (approval number: 11/03, date:10/08/2023).

Cases with negative hepatitis B e antigen (HBeAg), HBV-DNA <2000 IU/mL, and normal transaminase levels were defined as the "inactive carrier" group. Those with HBeAg positivity, high HBV-DNA levels, and normal or close to normal transaminase levels were accepted as the "immunotolerance" group. Cases with HBeAg positive, high HBV-DNA and transaminase levels, and inflammation determined by biopsy were defined as the "immunoreactive" group (6).

Statistical Analysis

Data obtained in the study were statistically analyzed using SPSS vn. 22.0 software. The distribution of continuous variables was examined using the Shapiro-Wilk test. Descriptive statistics were stated as mean ± standard deviation and median (minimum-maximum) values for continuous variables and as number (n) and percentage (%) for categorical variables. In the analysis of categorical variables, the chi-square test and/or Fisher's exact test were used. The post-hoc Bonferroni test was applied for paired comparisons. In the comparisons of continuous variables between two independent groups, the Mann-Whitney U test was used. A value of $p<0.05$ was set as statistically significant.

Results

The study included 374 patients diagnosed with chronic HBV infection, comprising 249 (66.%) males and 125 (33.4%) females with a mean age of 10.97±3.87 years. In boys, the average serum alanine aminotransferase (ALT) level was 45.0 U/L and aspartate aminotransferase (AST) level was 41 U/L. In girls, the average serum ALT and AST levels were 42 U/L and 41 U/L, respectively. AST level was 41 U/L. In boys, the average serum HBsAg level was 480 and HBeAg level was 234. In girls, the average serum HBsAg level was 387 and HBeAg level was 259. When evaluated according to gender, no statistically significant difference was determined with respect to mean age, serum ALT and AST levels, and HbsAg and HbeAg positivity (Table 1). There was no statistically significant difference between the two genders with respect to chronic HBV infection, the presence of inflammation, and anti-hepatitis A virus immunoglobulin G [anti-hepatitis A virus (HAV), immunoglobulin G (IgG)] positivity. Of the 374 patients, 70 siblings had a history of chronic HBV infection. Siblings of 32 (25.6%) girls and 38 (15.3%) boys had a history of chronic HBV infection. The frequency of chronic HBV infection seen in the siblings of females with chronic HBV infection was determined to be significantly higher than that in male patients. There was no significant difference between the two genders with respect to HBV-DNA positivity (Table 2).

Chronic active HBV infection was present in 147 (39.3%) of 374 patients. In all patients, the infection was of maternal origin. Treatment with tenofovir disoproxil fumarate was started in 61 cases, lamivudine in 54, interferon alpha (IFN-α) in 53, and entecavir in 10. The treatments administered to patients diagnosed with chronic active HBV infection are shown in Figure 1.

Table 1. Comparisons of demographic and laboratory data of cases according to gender			
	Male, n=249 (66.6%)	**Female, n=125 (33.4%)**	**p-value**
	Median (range)	**Median (range)**	
Age (years)	12.0 (1.0-18.0)	11.0 (1.5-17.0)	0.944
ALT (U/L)	45.0 (10.0-3559.0)	42.0 (7.0-1698.0)	0.710
AST (U/L)	41.0 (11.0-3560.0)	41.0 (2.0-1934.0)	0.754
HbsAg (+)	480.0 (17.0-14600.0)	387.0 (13.0-5416.0)	0.692
HbeAg (+)	234.0 (0.0-18100.0)	259.0 (0.0-3977.0)	0.684
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HbsAg: Hepatitis B surface antigen, HbeAg: Hepatitis B e antigen			

Table 2. Comparisons of some clinical characteristics of cases according to gender			
	Male, n=249 (66.6%)	**Female, n=125 (33.4%)**	**p-value**
Pathology	**n (%)**	**n (%)**	
Normal (biopsy not performed)	150 (60.2)	77 (61.6)	0.823
Active hepatitis B (biopsy performed)	99 (39.8)	48 (38.4)	
Inflammation			
Biopsy not performed	152 (61.0)	77 (61.6)	0.917
Biopsy performed (inflammation)	97 (39.0)	48 (38.4)	
Sibling history of chronic HBV			
Absent	211 (84.7)	93 (74.4)	0.017
Present	38 (15.3)	32 (25.6)	
Anti-HAV IgG (+)			
Absent	181 (72.7)	81 (64.8)	0.121
Present	68 (27.3)	44 (35.2)	
HBV-DNA			
Negative	76 (30.5)	39 (31.2)	0.906
Positive	173 (69.5)	86 (68.8)	
HAV: Hepatitis A virus, HBV: Hepatitis B virus, IgG: Immunoglobulin G			

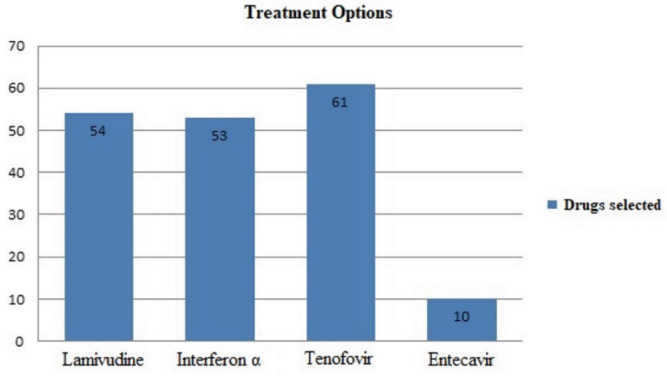

Figure 1. Treatments received by the patients followed up with a diagnosis of chronic active HBV infection
HBV: Hepatitis B virus

The frequency of active chronic HBV infection was statistically significantly higher in children born in or after 2006 than in other age groups. The frequency of inflammation was also significantly higher in those born in or after 2006. The rate of anti-hepatitis A virus (HAV) IgG positivity was determined to be significantly higher in children born between 2003 and 2006 than in other age groups (Table 3).

Discussion

Chronic HBV infection continues to be an important health problem worldwide. Previous studies have reported that chronic HBV infection occurs more often in male children than in females (7,8). The male/female ratio of the patients included in this study was 2:1.

The mean age of children with chronic HBV infection has been reported to be 8, 9, and 15 years according to various sources of reference (7,8,9). The data of the current study were consistent with the literature in this respect.

Screening of family members was performed for the current study cases followed up because of chronic HBV infection. Cases with HBV infection determined in a family member were followed up, and family members with no immunity against HBV infection were administered three doses of HBV vaccine in accordance with the immune schedule.

Of all the cases in this study, 41.4% were born between 1998 and 2003, 13.6% between 2003 and 2006, and 7.5% were born after 2006. In the national vaccination program, the first dose of HBV vaccine was administered at birth in 2003. Accordingly, there was a significant decrease in chronic HBV infection after 2003. This can be attributed to the inclusion of the HBV vaccine in the national

Table 3. Characteristics of cases with HBV infection according to date of birth

	Born before 1998 n=140 (37.4%)	Born 1998-2003 n=155 (41.4%)	Born 2003-2006 n=51 (13.6%)	Born in or after 2006 n=28 (7.5%)	p-value
Pathology					
Normal	79 (56.4)	99 (63.9)	37 (72.5)	12 (42.9)	0.036
Active hepatitis	61 (43.6)		14 (27.5)	16 (57.1)	
Inflammation (biopsy)					
Absent	81 (57.9)	99 (63.9)	37 (72.5)	12 (42.9)	0.049
Present	59 (42.1)	56 (36.1)	14 (27.5)	16 (57.1)	
Anti-HAV IgG					
Negative	111 (79.3)	107 (69.0)	27 (52.9)	17 (60.7)	0.003
Positive	29 (25.9)	48 (31.0)	24 (47.1)	11 (39.3)	
Sibling history of chronic HBV					
Absent	116 (82.9)	124 (80.0)	40 (78.4)	24 (85.7)	0.794
Present	24 (17.1)	31 (20.0)	11 (21.6)	4 (14.3)	

HBV: Hepatitis B virus, HAV: Hepatitis A virus, IgG: Immunoglobulin G

vaccination program from 2003 (10). The decrease in the number of cases in this study after 2003 demonstrates that HBV infection was prevented to a large extent due to effective vaccination. Families stated that all children born after 2003 were vaccinated against HBV during the newborn period. On the other hand, they said that only 15 of the families had their children administered Hepatitis B immunoglobulin (HBIg) during the newborn period. It was determined that HBIg was administered to these 15 children in State or University hospitals. Similarly, all babies born to HBsAg-positive mothers were also vaccinated against HBV in private health institutions. However, it was observed that these babies were referred to other health institutions (State or University Hospitals) for HBIg application. Despite the administration of the hepatitis B virus vaccine and HBIg, perinatal transmission can be observed at a rate of at least 10% (11). The most important reasons for this may include transplacental and intrauterine infection or insufficiency of vaccination and immune prophylaxis (12). According to health statistics in Türkiye, with a decrease over time, the frequency of acute HBV infection seen in children below the age of 5 years fell to 0.09 per 100,000 in 2022 (13). In 2021 in Türkiye, the coverage of three doses of HBV vaccine reached 95% (14). The data of the current study and other studies show that the application of HBV vaccine in Türkiye is effective for the eradication of HBV infection.

HBV infection is most often spread from HBsAg-positive mothers during childbirth (7,9,15). All the cases in the current study were found to have contracted HBV infection perinatally, which was consistent with the literature.

In 70% of the current study cases, there was a sibling history of chronic HBV infection. The frequency of chronic HBV infection seen in the siblings of females with chronic HBV infection was determined to be significantly higher than that in male patients. Female children with chronic HBV infection may marry and become pregnant later in life. Therefore, infected female children must be closely followed up, and it is extremely important to determine the stage of chronic HBV infection, especially during pregnancy. The initiation of treatment in pregnant patients with chronic active HBV infection and immediate HBV and HBIg vaccination of the infant can prevent the spread of the infection (16).

Chronic active HBV infection was present in 147 (39.3%) patients in the current study. Of these patients, 26 developed chronic HBV infection during follow-up in a previously immunotolerant stage. Of the total cases, 227 (60.7%) were chronic inactive HBV carriers. Although 47 cases were at the immunotolerant stage on first presentation, they were observed to develop as chronic inactive HBV carriers during follow-up. According to these data, the inactive carrier form is the most common form of chronic HBV infection (8,9).

The group with the lowest number of cases in the current study was children born in or after 2006. The frequency of chronic active HBV infection in this group was significantly higher than that in the other age groups (p=0.036). Despite the administration of HBV vaccine and HBIg as prophylaxis in the neonatal period, perinatal infection can be seen at a rate of 10% (11). Infants who have received the HBV vaccine and HBIg are diagnosed with chronic HBV infection in a later period because of deficiencies experienced during follow-up. Following the administration of the HBV vaccine and HBIg to infants born to mothers with chronic HBV infection, the infants should be screened again when they are 9-15 months old (17).

Hepatitis A virus infection in individuals with chronic HBV infection may cause superinfection. High morbidity and mortality can be encountered in these cases (18). All the cases in the current study were examined with respect to immunity against HAV infection. For those with a low anti-HAV IgG level, two doses of hepatitis A vaccine were recommended. The rate of anti-HAV IgG positivity was determined to be significantly higher in children born between 2003 and 2006 compared with the other age groups (p=0.003). The HAV vaccine was added to the national vaccination program in Türkiye on November 15, 2012. The free-of-charge HAV vaccination of children with chronic HBV infection since that date has contributed to immunity against HAV infection in that age group.

It is recommended that liver biopsy be performed before starting treatment for chronic HBV infection (19). Liver biopsy is required according to the Social Security Healthcare Practices

Communique (20). In the current study, liver biopsy was performed in 99 (39.8%) of 249 male patients and 48 (38.4%) of 125 female patients. According to the pathology results, there was no statistically significant difference between the genders (p=0.823).

For treating chronic HBV infection in children, oral antivirals (lamivudine, adefovir dipivoxil, tenofovir disoproxil fumarate and entecavir), IFN-α, and pegylated IFN-α-2A are used starting from the age of 2 years (21). Drug treatment was initiated for 125 of the 147 patients with chronic HBV infection in the current study. Treatment with tenofovir disoproxil fumarate was started in 61 cases, lamivudine in 54, IFN-α in 53, and entecavir in 10. Side effects such as fever, headache, and abdominal pain were observed in patients using IFN-α similar to those reported in the literature (21). Before IFN-α treatment was administered, acetaminophen was administered to the children as an antipyretic. The treatment of the children who were started on IFN-α was continued with lamivudine. Lamivudine is used safely in children and adults. The most common side effects are pancreatitis, peripheral neuropathy, neutropenia, and fatigue (21). Drug resistance may develop during lamivudine treatment; resistance was observed in five cases in the present study. In children who developed resistance, lamivudine was discontinued and tenofovir disoproxil fumarate was started. No side effects were observed due to tenofovir disoproxil fumarate treatment. For 21 patients who did not attend regular follow-up appointments, treatment could not be started. It was seen that the patients who were followed up in the Adult Gastroenterology Clinic after turning 18 years old had been started on entecavir treatment. No entecavir-related side effects were observed in any patient. The development of resistance to entecavir is very rare (21). The drugs used in this study were consistent with those reported in the literature (22,23).

A significant decrease in chronic HBV infection was determined in children born after 2003. This decrease suggests that it could be due to the routine HBV vaccination of every newborn infant and the administration of HBIg to infants born to HBsAg-positive mothers. It also suggests that increased awareness of HBV infection over the years has been helpful in preventing this infection.

Study Limitations

The main limitation of this study was that the majority of patients lived outside Elazığ's city and could not regularly attend follow-up appointments.

Conclusion

Recent studies in Türkiye for protection against HBV infection have been extremely effective. With regular follow-up of children with chronic HBV infection, morbidity and mortality can be reduced. Family members of these children must be screened for HBV infection, and with the vaccination of family members with no immunity to HBV infection, the spread can be prevented.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Fırat University Faculty of Medicine (approval number: 11/03, date:10/08/2023).

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: U.D., Y.D., Concept: U.D., Y.D., M.H., Design: U.D., Y.D., M.H., Data Collection or Processing: U.D., Y.D., A.M.K., Ş.A., F.K., M.H., Analysis or Interpretation: U.D., A.M.K., Ş.A., F.K., M.H., Literature Search: U.D., Y.D., M.H., Writing: U.D., Y.D., M.H.,

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Hepatitis B Virus Reactivation with Ibrutinib Treatment in a Patient with Chronic Lymphocytic Leukemia: A Case Report and Literature Review

Kronik Lenfositik Lösemili Bir Hastada İbrutinib Tedavisi ile Hepatit B Virüsü Reaktivasyonu: Olgu Sunumu ve Literatür Değerlendirmesi

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is a common hematological neoplasm in adults with an abnormal increase in monoclonal B lymphocytes. Ibrutinib is a small molecule class oral cancer drug that inhibits Bruton's tyrosine kinase (BTK) enzyme. They are widely used for treating CLL. Ibrutinib suppresses peripheral lymphocytes, causing both lymphopenia and neutropenia. It has little effect on serum immunoglobulin levels and reportedly does not cause reactivation of tuberculosis or opportunistic infections. Hepatitis B prophylaxis during treatment remains controversial. However, there have been cases of acute liver failure and severe hepatitis B reactivation associated with its widespread use. In this case report, we report a patient with no previous history of immunosuppressive therapy who developed hepatitis B reactivation in the early period after ibrutinib treatment for CLL.

Keywords: Chronic lymphocytic leukemia, ibrutinib, hepatitis B, reactivation

ÖZ

Kronik lenfositik lösemi (KLL), monoklonal B lenfositlerde anormal artışla seyreden ve yetişkinlerde sık görülen hematolojik bir malignitedir. İbrutinib, Bruton tirozin kinaz enzimini inhibe eden küçük molekül sınıfı bir oral kanser ilacıdır. Günümüzde KLL tedavisinde yaygın olarak kullanılmaktadır. İbrutinib, periferik lenfositleri baskılayarak hem lenfopeniye hem de nötropeniye neden olur. Serum immünoglobulin düzeyleri üzerinde çok az etkisi vardır ve tüberküloz veya fırsatçı enfeksiyonların yeniden aktivasyonuna neden olmadığı bildirilmektedir. Tedavi sırasında Hepatit B profilaksisi tartışmalıdır. Ancak, yaygın kullanımı ile birlikte akut karaciğer yetmezliği ve ciddi hepatit B reaktivasyonu olguları bildirilmiştir. Bu olgu sunumunda, daha önce immünosüpresif tedavi öyküsü olmayan ve KLL için ibrutinib tedavisi sonrası erken dönemde hepatit B reaktivasyonu gelişen bir olgu bildirilmektedir.

Anahtar Kelimeler: Kronik lenfositik lösemi, ibrutinib, hepatit B, reaktivasyon

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Introduction

Chronic lymphocytic leukemia (CLL) is the most commonly observed hematological neoplasia in adults and is characterized by an abnormal increase in the mature appearance of small monoclonal B lymphocytes in peripheral blood, bone marrow, or lymphoid tissue. Ibrutinib is a cancer medication in the small molecule class that is used orally and displays an effect by inhibiting Bruton's tyrosine kinase (BTK). An essential component

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of the B-cell receptor signal path, BTK enzyme is essential for B-cell proliferation and survival of leukemic cells (1). In the United States, it was approved for refractory mantle cell lymphoma in 2013 and for the treatment of refractive CLL in 2014. Side effects are common but usually mild to moderate. Elevated liver enzyme levels may be observed at 20-30% rates; however, this is generally self-limiting. Ibrutinib suppresses peripheral lymphocytes, causing both lymphopenia and neutropenia, has minimal effect on serum immunoglobulin levels, and is not associated with reactivation of tuberculosis or opportunistic infections (2). However, acute liver injury cases are reported, like acute liver failure and severe hepatitis B virus (HBV) reactivation, have been reported with the popularization of their use. In this case report, we present a patient with a CLL diagnosis who began ibrutinib treatment with no previous immunosuppressive treatment and developed HBV reactivation in the early period.

Case Report

A 70-year-old male patient was diagnosed with modified RAI system staging stage 4 high risk, Binet stage C CLL from the hematology clinic in July 2019. There were accompanying progressive bone marrow failure symptoms, widespread lymphadenopathy, and massive splenomegaly. Follow-up and treatment could not be provided because the patient did not come for clinical check-ups until May 2020. The patient's incomplete examinations were completed on this date, and 420 mg/day ibrutinib treatment was initiated. Fluorescence *in situ* Hybridization deletion 17 p negative. Ibrutinib was chosen as the treatment because of its ability to use oral medication during the pandemic and the accompanying chronic obstructive pulmonary disease. In the comparative evaluation of thoracic and abdominal computed tomography performed in July 2019 (diagnosis) and June 2020, a regression in lymph node size of 50% was detected and was considered a partial response.

In the past medical records of the patient, hepatitis B surface antigen (HBsAg) was negative and anti-HBs was positive. The anti-HBc IgG test was not available. The patient's Infectious Diseases Polyclinic evaluation was only possible at the end of June. The control serology is shown in Table 1. HBsAg positive, anti-HBs negative, hepatitis B e antigen positive (previously negative), and HBV-DNA 8.28 105 international unit (IU)/mL (Roche Light Cycler® 480, Roche Molecular Systems, Inc., Branchburg, NJ). Were detected in control tests. Liver function tests were normal during this period. The patient began antiviral treatment with tenofovir alafenamid fumarate. The patient did not attend follow-up examinations on the recommended dates. Medication compliance was poor according to the anamnesis and prescription dates. Serologic follow-up revealed dynamic changes. HBV-DNA negativity under treatment was observed at the end of the second year. The patient was last evaluated in September 2023. Antiviral drug use continued and HBV-DNA was found to be negative.

Discussion

Patients infected with hepatitis B may have reactivation observed during immunosuppressive treatment or when these treatments are stopped and the immune system returns to normal. The risk of HBV reactivation in patients receiving immunosuppressive therapy is related to the HBV serological status, viral load, underlying disease, type, dose, and duration of the immunosuppressive agent used. The most common HBV reactivations are reported in patients receiving chemotherapy because of hematological malignancies and in patients undergoing hematopoietic stem cell transplantation (3). In terms of reactivation, situations increasing risk are male sex,

Table 1. Hepatitis serology follow-up

Tarih	HBsAg (ng/mL)	Anti-HBs (IU/L)	HBeAg (S/CO)	Anti-HBe (S/CO)	Anti-HBc IgM (S/CO)	Anti-HBc IgG (S/CO)	HBV-DNA (IU/mL)	ALT/AST (U/L)
02.01.2019	0.716 (negative)	**17.08 (positive)**	0.134 (negative)	1.63 (positive)				
02.07.2019	0.546 (negative)	**26.48 (positive)**						
08.06.2020	**7.21 (positive)**	**222.6 (positive)**	**129.0 (positive)**		**0.064 (positive)**	**0.735 (positive)**		10/25
30.06.2020	**4.91 (positive)**	**292.7 (positive)**	**58.60 (positive)**	**1.86 (positive)**	**0.065 (positive)**	**0.177 (positive)**	**$8.28x10^5$**	12/20
06.08.2020	**13.09 (positive)**	**215 (positive)**					**$5.69x10^2$**	16/25
13.06.2022	**15.05 (positive)**	4.66 (negative)	**49.19 (positive)**	1.64 (negative)	0.072 (negative)	1.32 (negative)	<1.00 (negative)	
11.09.2022	**9.22 (positive)**	**24.70 (positive)**						54/45
17.04.2023	**6.78 (positive)**	7.06 (negative)						17/25
13.09.2023	**4.39 (positive)**	<2.00 (negative)	**14.94 (positive)**	1.57 (negative)	0.053 (negative)	1.84 (negative)	<1.00 (negative)	18/23

Values in bold to indicate reactivation date and positive values, HBsAg: Hepatitis B surface antigen, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus, IU: International unit, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Table 2. Reactivation cases related to ibrutinib reported in the literature

References	Diagnosis	Patients (age, sex)	History of İ.T.*	Reactivation time
de Jésus Ngoma et al. (11)	CLL	80, M	+	20 week
Hammond et al. (12)	CLL CLL	57, M 75, M	+ +	42 week 22 week
Malek et al. (13)	NHL	68, M	+	24 week
Herishanu et al. (14)	CLL	79, M	+	48 week
Akkurd et al. (15)	MCL	54, M	+	36 week
İskender et al. (16)	CLL	58, M	+	48 week
Lam et al. (17)	CLL	61, F	+	16 week
Choi et al. (18)	CLL	81, F		12 week

*İ.T.: Immunosuppressive treatment, CLL: Chronic lymphocytic leukemia, NHL: Non-Hodgkin's lymphoma, MCL: Mantle cell lymphoma

advanced age, hepatitis B e antigen (HBeAg), HbsAg positivity, and HBV-DNA elevation. In many guidelines, immunosuppressive treatments are classified in terms of the risk of reactivation and the need for prophylaxis (4,5,6). With the introduction of many new agents, the issue of HBV reactivation needs to be updated. There should be a clear recommendation regarding ibrutinib. However, there are increasing numbers of publications reporting the risk of HBV reactivation and recommending serologic tests for HBV before treatment.

The guidelines state the risk of HBV reactivation with the use of tyrosine kinase inhibitors and ibrutinib differently. It is reported as moderate, no, or uncertain (7,8,9). Ibrutinib has been shown to irreversibly inhibit T helper 2 cell activation after T cell receptor stimulation and to cause compensatory activation of T helper cells and cytotoxic T lymphocytes (10). This dynamic change in the immune response after ibrutinib treatment may be a clue for HBV reactivation in this setting. However, these mechanisms remain unclear. Case reports of reactivation with ibrutinib are increasing (11,12,13,14,15,16,17,18) (Table 2). When the cases were evaluated, most patients were over 50 years of age and mostly male. Except for two patients with non-Hodgkin's lymphoma and mantle cell lymphoma, all patients were diagnosed with CLL and had a history of immunosuppressive treatment before ibrutinib. Our patient was similar to these patients in terms of CLL diagnosis and age. The fact that our patient was HBsAg negative, anti-HBc IgG and anti-HBsAg positive, HBeAg negative, and anti-HBe positive has been shown to be included in the natural immune profile. Patients who receive immunosuppressive treatment with HBsAg positivity have a higher risk of reactivation. As a result, our patient actually had a lower risk of reactivation. In published cases, the mean time between the use of ibrutinib and the determination of reactivation was 34 weeks (20-48 weeks). In this patient, the interval between ibrutinib initiation and HBsAg positivity was 34 days. We believe that the advanced stage of the patient's primary disease and the late initiation of treatment are the reasons for the short duration of this period.

Dynamic changes in hepatitis serology in the patient are also noticeable. HBsAg became positive, anti-HBs became negative, and anti-HBc IgG became negative in the follow-up. Anti-HBc is a sensitive and widely used marker for detecting HBV exposure. Hepatitis B core antigen is not normally found in serum. It occurs in liver cells or HBV particles in serum. It triggers the humoral and cellular immune response and leads to anti-HBc. Anti-HBc negativity may result from immunosuppression, core promoter gene mutations, infection by vertical transmission, and analytical test errors (19,20). This rare serological condition was evaluated by Avettand-Fenoel et al. (21) in 39 patients, and it was reported that HBsAg detection without HBc antibodies may occur in highly immunocompromised patients. We believe that HBV serology and HBV-DNA requirement should be carefully evaluated in immunosuppressed patients. Hepatitis B reactivation is usually recognized by an increase in serum alanine aminotransferase or aspartate aminotransferase levels with or without symptoms. It is characterized by an earlier increase in HBV-DNA frequency. With awareness of serologic variations in our patient, HBV-DNA was requested and it was identified as 8.28x10.5 IU/mL. Check-up serology observed HbsAg positivity and HBeAg positivity. We think that beginning antiviral treatment before liver function tests prevented active hepatitis. The moderate increase observed at follow-up may be related to additional factors and drug compliance problems.

Conclusion

In conclusion, although there are cases reported in the literature, we believe that this case is the most clear example that indicates the ibrutinib-reactivation relationship. Our patient did not receive immunosuppressive therapy before, and reactivation developed after short-term use. Therefore, we believe it is appropriate to assess the hepatitis serology of patients before ibrutinib treatment and to begin prophylactic treatment in the patient group with contact with the HBV.

Ethics

Informed Consent: Informed consent form was obtained.

Authorship Contributions

Surgical and Medical Practices: A.A.Y., C.K., B.Ü., Y.Ç., Concept: A.A.Y., C.K., Design: A.A.Y., C.K., Data Collection or Processing: A.A.Y., C.K., B.Ü., Analysis or Interpretation: A.A.Y., C.K., B.Ü., Literature Search: A.A.Y., C.K., Writing: A.A.Y., C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Hepatitis B Surface Antigen Seroconversion Developed with Tenofovir Disoproxil Fumarate: HIV/HBV Case Report and Literature Review

Tenofovir Disoproksil Fumarat ile Gelişen Hepatit B Yüzey Antikoru Serokonversiyonu: HIV/HBV Olgu Sunumu ve Literatürün İrdelenmesi

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ABSTRACT

Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) coinfections are important health problems worldwide and in our country. While acute HBV infections are relatively rare in patients with HIV infection, the chronicity rate is more prevalent in HIV-HBV co-infections. A 49-year-old male patient who was admitted with acute HBV symptoms is presented in this case. During the investigation of the cause of hepatitis, HIV infection was also detected, and emtricitabine + tenofovir disoproxil fumarate + dolutegravir treatment was initiated. While the patient developed a virological and immunological response to HIV infection, hepatitis B surface antigen seroconversion also occurred. This case report aimed to draw attention to HIV-acute HBV coinfection and analyze HBV reactivation and immune reconstruction syndrome in HIV-positive individuals. It is obvious that there is a need for research on the prevalence, risk factors, and prognosis of co-infection in our country.

Keywords: HIV, acute HBV, prognosis, coinfection, HBsAg seroconversion

ÖZ

Hepatit B virüsü (HBV) ve insan immün yetmezlik virüsü (HIV) koenfeksiyonları dünyada ve ülkemizde önemli sağlık sorunudur. HIV enfeksiyonlu olgularda akut HBV enfeksiyonları nadir görülmesine karşın, HBV enfeksiyonunun kronikleşme oranı HIV-HBV koenfeksiyonlarında daha sıktır. Bu olguda 49 yaşında, akut HBV kliniği ile başvuran erkek hasta sunulmuştur. Hepatit etiyoloji araştırılırken HIV enfeksiyonu da saptanmış ve emtrisitabin + tenofovir disproksil + dolutegravir başlanmıştır. Hastada HIV enfeksiyonunda virolojik ve immünolojik yanıt alınırken, hepatit B yüzey antikoru serokonversiyonu da gelişmiştir. Bu olgu sunumu ile HIV-akut HBV koenfeksiyonuna dikkat çekmek istenirken, HIV-HBV reaktivasyon ve HBV ilişkili immün rekonstitüsyon inflamatuar sendromu ilişkisi de irdelenmiştir. Ülkemizde koenfeksiyonun sıklık, risk faktörleri ve prognozunu ortaya koyan araştırmalara ihtiyaç bulunmaktadır.

Anahtar Kelimeler: HIV, akut HBV, prognoz, koenfeksiyon, HBsAg serokonversiyonu

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Introduction

The prevalence of hepatitis B surface antigen (HBsAg) is 4.57%, and the most commonly affected group is between the ages of 25 and 34 (6.36%) in our country (1). In addition, there are 39437 individuals living with human immunodeficiency virus (HIV), most frequently in the 25-29 age group (18%) (2). HIV/hepatitis B virus (HBV) coinfection is found at a rate of 5.8-7% (3,4). The exact number of HIV/acute HBV cases is not precisely known. Acute HBV is rarely seen in individuals living with HIV. For example, only 18 individuals among 3,098 HIV (+) individuals developed acute HBV during 18 years of follow-up in Spain (5).

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Since hepatitis B was not included in the routine vaccination program in our population before 1998, acute HBV is observed more frequently in older individuals (1). Besides, the fact that HIV and HBV infections are often seen in the same age groups and the transmission routes of the two infections being similar, indicates that HIV/acute HBV co-infection will increase over time, especially in older individuals. As in the present case, HIV infection may be manifested by acute HBV in middle-aged or elderly individuals.

Currently, national and international guidelines recommend; screening patients diagnosed with HIV for chronic, acute, or occult HBV infection, including HBV-effective agents in the antiretroviral therapy (ART) plan in chronic or occult HBV, as well as vaccination of susceptible individuals (6,7).

In this article, a case of HIV infection diagnosed while investigating the etiology of acute hepatitis is reported. The HIV course and prognosis of acute HBV, HBV reactivation that can be seen in HIV (+) patients, HBV-related IRIS and HIV-HBV relationships are discussed.

Case Report

A 49-year-old male patient with complaints of widespread body pain and weakness persisting for a month was redirected to our outpatient clinic because of elevated transaminase level detection. The patient was admitted to our clinic with a prediagnosis of acute hepatitis. There was also no evidence of secondary hepatotropic viral or bacterial infection, and the patient had no symptoms of primary HIV infection. The patient's medical history revealed previous diabetes mellitus, hypertension, chronic obstructive pulmonary disease, hyperlipidemia, and coronary artery disease, whereas there was no drug, substance, or alcohol abuse other than medications for chronic diseases. It was noted that the patient, who is heterosexual, underwent a coronary bypass operation two years prior in which he received blood transfusion during and had suspicious sexual contact within the last 6 months of admission. On physical examination, the patient's general condition was good, consciousness was clear, oriented, and cooperative, and no icterus or organomegaly was detected. The results of the tests performed on admission were as follows: alanine aminotransferase, 531 U/L, aspartate aminotransferase: 220 U/L, total bilirubin: 1.1 mg/dL, delta bilirubin: 0.35 mg/dL, gamma-glutamyl transferase: 657 U/L, laktat dehidrogenaz: 182 U/L, alkaline phosphatase: 170 U/L. There was no abnormality in the lung or abdominal radiological examinations performed for control. Serologic tests showed HBsAg, hepatitis B core antibody (anti-HBc) IgM, hepatitis B e antigen (HBeAg), anti-HBe, and anti-HIV positivity. Anti-hepatitis A virus (HAV) IgM and anti-hepatitis C virus were negative, anti-HAV IgG was positive, and the other results were; HBV-DNA: $1.2x10^7$ IU/mL, HIV-RNA: 2350000 copies/mL, CD4+ T lymphocytes: 338 hc/uL, CD8+ T lymphocytes: 734 hc/uL.

After a thorough review of the patient's medical records, it was observed that HBsAg and anti-HIV tests were negative in the preoperative examinations, but the tests were not repeated for any reason in the following period. No anti-HBc IgG analysis was performed.

The patient was hospitalized for a period of 12 days with a diagnosis of acute HBV and HIV infection. Because liver function tests regressed and symptoms improved, the patient was discharged with a diagnosis of HIV infection, and treatment with emtricitabine + tenofovir disoproxil fumarate (TDF) + dolutegravir was initiated.

The patient was monitored at regular intervals, and the initial 3-month follow-up revealed that transaminases reached normal limits and the CD4+ T lymphocyte count was 700 hc/uL. HIV-RNA levels that had long been low positive dropped to undetectable levels after approximately 12 months. After 20 months, the patient was HBsAg negative and the anti-HBs titer was >1000 mIU/mL.

Discussion

Although the rate varies from region to region, chronicization develops in 7.7-11% of HIV (+) patients after acute HBV (5,8). In addition, HBV-DNA levels tend to be higher in people living with HIV, and the risk of progression to end-stage liver disease, cirrhosis, and hepatocellular cancer is higher. In addition, reactivation is more frequent in HIV (+) in conjunction with CD4+ T lymphocyte count (9).

Our patient was started on ART, including TDF, in accordance with guideline recommendations because of the negative effect of HIV on HBV (6,7). In contrast to the high expectation of chronicization in the literature, HBV infection resolved with cure in our patient (5,8). Depending on the genotype of the study group or the length of follow-up, the frequency of HBsAg clearance can range from 3.7-18% (10,11). Audsley et al. (12) conducted a follow-up of 92 HIV-HBV patients treated with ART including TDF for 5 years and found HBsAg clearance in 11 patients (12%) after a mean treatment duration of 48 months (range 3-88 months), and in only 4 of these patients, anti-HBs became concurrently positive. Yang et al. (10) have shown that HBsAg seroclearance correlates with ART duration; while the clearance rate was 1.8% between 2 and 4 years, increasing to 29.4% up to 10 years. Our patient achieved HBsAg seroconversion in a considerably shorter time (20 months).

A study conducted in China revealed that older age, high CD4+ T lymphocyte level, and initial HBeAg positivity ease HBsAg clearance in HIV/HBV coinfections using ART containing TDF (13). The development of HBsAg seroconversion in this study supports the facilitation of these factors.

Although the prognosis for HBV in this study was favorable, the late suppression of HIV-RNA was remarkable. However, CD4+ T lymphocytes increased rapidly. The effect of HBV over the course of HIV treatment has not yet been fully clarified. While some studies have shown that HBV decreases CD4+ T lymphocyte levels and increases the risk of progression to AIDS (14,15), there are also studies that have reached the contrary results (16). More data are required for certainty on this aspect.

Hepatic exacerbation observed in HBsAg-positive individuals living with HIV after ART initiation is called HBV-related IRIS. There is an immunopathogenesis implicated in HBV-specific CD8+ T lymphocytes and non-HBV-specific mononuclear cells that is believed to be associated with reconstruction, but this has yet to be fully clarified. There is no widely recognized definition for the diagnosis of HBV-related IRIS; therefore, the diagnosis is made

by first excluding other causes and demonstrating HBV-related hepatic exacerbation on liver biopsy. HBV-related IRIS can generally be managed by maintaining current ART without worsening the patient's general condition (17). Because acute hepatitis symptoms started before ART, IRIS was not considered in this study.

In addition to IRIS, in HIV (+) patients, occult HBV reactivation occurring after cessation of ART, which is proven to be effective against HBV, may also lead to transaminase elevation. A similar situation may also occur in HIV (+) patients on ART without HBV efficacy. HBV reactivation is identical in terms of clinical and laboratory findings to the process experienced in HIV (-) individuals who are started on immunosuppressive therapy for various reasons. In these patients, switching to an ART effective against HBV is considered sufficient to obtain desired outcomes; however, HBsAg seroconversion may develop again (18). No anti-HBc IgG result was observed in our patient's medical history. However, our case was not considered reactivation because there was no ART experience.

Conclusion

It is rare that our case has resulted in a good prognosis in a short time despite being HIV (+). In addition, this patient is a robust reminder that HIV infection should be investigated together with acute HBV in age groups in which the risk of acute HBV persists. It should also be noted that HBV reactivation and HBV-related IRIS can develop in patients with HIV. This case also highlighted the fact that there are not enough data on HIV/HBV at the national level. Our country requires studies to determine the incidence, risk factors, and prognosis of HIV-acute HBV coinfection and to evaluate IRIS or reactivation processes.

Ethics

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: Z.K., E.D., C.B., A.Y., Concept: Z.K., E.D., C.B., A.Y., Design: Z.K., E.D., C.B., A.Y., Data Collection or Processing: Z.K., E.D., C.B., A.Y., Analysis or Interpretation: Z.K., E.D., C.B., A.Y., Literature Search: Z.K., E.D., C.B., A.Y., Writing: Z.K., E.D., C.B., A.Y.

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