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ORIGINAL RESEARCH

Hepatitis B Virus (*Hepadnaviridae: Orthohepadnavirus: Hepatitis B virus*) among Hospitalized Mentally Disabled Patients is not transmitted by their nurses or family members

Hoorieh Sarbandi[1], Seyed Masoud Hosseini[1], Kimia Vakili[2], Mobina Fathi[2], Niloofar Deravi[2], Maryam Vaezjalali[3]

[1]Department of Microbiology, Faculty of Biological Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
[2]Student Research committee, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
[3]Department of Microbiology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Background. Prevalence of hepatitis B virus (HBV) infection has been reported to be higher in the institutionalized mentally disabled patients than that of the general population previously reported in Iran. This study aims to investigate HBV infection among nurses and families of the hospitalized mentally disabled patients.
Material and methods. This study was conducted on 110 nurses and family members of the mentally disabled patients who were hospitalized in five residential care centers of Tehran. The presence of hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) was examined using the enzyme-linked immunosorbent assay (ELISA). Afterwards, HBV DNA was extracted, and then propagated via a nested polymerase chain reaction (PCR) and specific primers. Finally, a phylogenetic tree was constructed using the neighbor-joining method to compare virus genomes in the nurses' serum with other isolated HBVs worldwide.
Results. Out of 102 studied nurses, three (3%) were positive for HBsAg (100% female). Also, no patient was positive for the HBV genome, while eight (7.3%) nurses were positive for HBcAb including two (25%) males and six (75%) females. Genome sequencing of one DNA positive sample showed that the isolated virus from this patient contained sub genotype D1 and subtype ayw2. The results of none of the family members were positive for HBsAg, HBcAb, or HBV DNA.
Conclusion. This study showed a higher prevalence of HBsAg among nurses (3%) compared to the Iranian general population (1.7–2.1%). The virus isolated from the nurses belonged to subgenotype D1 and subtype ayw2 in accordance with previous Iranian reports. Also, there was no drug-resistant or vaccine-escape mutations in the obtained viral genome. Moreover, low immune pressure on the virus in the asymptomatic chronic HBV patients might be responsible for low nucleotide divergence among the derived HBV genome.

Keywords: *Hepatitis B virus; Mentally disabled patients; Nurses; Family members; Phylogenetic analysis.*

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For correspondence: Maryam Vaezjalali, PhD, Velenjak St., Department of Microbiology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: maryam.vaezjalali@sbmu.ac.ir

Information about the authors:

Hoorieh Sarbandi: http://orcid.org/0000-0003-3243-9803
Seyed Masoud Hosseini: http://orcid.org/0000-0002-0007-5833
Kimia Vakili: http://orcid.org/0000-0001-7296-3218
Mobina Fathi: http://orcid.org/0000-0002-4811-3982
Niloofar Deravi: http://orcid.org/0000-0002-6965-6927
Maryam Vaezjalali: http://orcid.org/0000-0003-3370-7566

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Отсутствие случаев передачи вируса гепатита В (*Hepadnaviridae: Orthohepadnavirus: Hepatitis B virus*) госпитализированным пациентам с психическими расстройствами от медицинского персонала или членов семьи

Сарбанди Х.[1], Хоссейни С.М.[1], Вакили К.[2], Фатхи М.[2], Дерави Н.[2], Вайезджалали М.[3]

[1]Кафедра микробиологии, факультет биологических наук, Медицинский Университет Шахида Бехешти, Тегеран, Иран;
[2]Студенческий исследовательский комитет, факультет медицинских наук, Медицинский Университет имени Шахида Бехешти, Тегеран, Иран;
[3]Кафедра микробиологии, факультет медицинских наук, Медицинский Университет имени Шахида Бехешти, Тегеран, Иран

Введение. Ранее было установлено, что в Иране распространенность инфекции, вызываемой вирусом гепатита В (ВГВ), выше среди пациентов с психическими расстройствами, находящимися в специализиро-

ванных учреждениях, чем в общей популяции. Целью данного исследования было изучение ВГВ-инфекции среди медсестер и членов семей госпитализированных пациентов с психическими расстройствами.

Материал и методы. В исследовании участвовали 110 медсестер и членов семей пациентов с психическими расстройствами, госпитализированных в пяти интернатах в Тегеране. Частоту выявления поверхностного антигена ВГВ (HBsAg) и антител к капсидному белку вируса В (анти-HBc) определяли методом иммуноферментного анализа (ИФА). ДНК ВГВ выявляли методом полимеразной цепной реакции (ПЦР) с вложенными праймерами. Для сравнительного анализа вирусных геномов, выделенных из образцов сыворотки крови медицинского персонала, с последовательностями ВГВ, выделенными в мире, было построено филогенетическое дерево методом присоединения соседей.

Результаты. Из 102 обследованных медсестер три (3%) были позитивными по HBsAg (100% женщины). Ни один из этих образцов не был положителен по ДНК ВГВ, при этом восемь (7,3%) медработников были положительны по анти-HBc, из них двое (25%) были мужчины и шесть (75%) – женщины. Секвенирование единственного положительного по ДНК ВГВ образца показало, что данный геноизолят относится к субгенотипу D1, серотипу ayw2. Никто из членов семей пациентов не был положительным по HBsAg, анти-HBc или ДНК ВГВ.

Заключение. Результаты исследования продемонстрировали более высокую частоту выявления HBsAg среди медсестер (3%) по сравнению с общей популяцией в Иране (1,7–2,1%). Выделенный от медсестер геноизолят ВГВ принадлежал субгенотипу D1, серотипу ayw2, что соответствует предыдущим исследованиям в Иране. В вирусном геноме не были выявлены мутации, связанные с лекарственной устойчивостью или ускользанием от иммунного ответа. Низкий уровень иммунного давления на вирус при бессимптомной хронической ВГВ-инфекции может служить объяснением консервативности нуклеотидной последовательности выявленного генома ВГВ.

Ключевые слова: *вирус гепатита В; пациенты с психическими расстройствами; медсестры; члены семьи; филогенетический анализ.*

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Для корреспонденции. Марьям Вайезджалали, Ph.D., кафедра микробиологии, факультет медицинских наук, Медицинский Университет имени Шахида Бехешти, Велендж ак, Тегеран, Иран. E-mail: maryam.vaezjalali@sbmu.ac.ir

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Introduction

Hepatitis B virus (HBV) infection is a public health issue worldwide. It is estimated that nearly two billion people globally have serological evidence of past or present HBV infection [1]. The natural course of HBV infection can be determined by the interactions between the host and the virus [2].

The patients hospitalized in care centers for the mentally disabled are at a higher risk of hepatitis B (HBV) infection compared to the general population [3]. In 1994, a study from Spain [4] reported the prevalence of HBV as 23.3% in a care center for the mentally disabled patients. Moreover, another study conducted in Spain in 2000 [5], with the aim of determining the prevalence of HBV in the patients who were hospitalized for a long period in mentally disabled care centers, showed that 81.3% of patients were positive for hepatitis B surface antigen (HBsAg).

In another study conducted in 2003 in Iran [6], the prevalence of HBsAg was estimated as 4% among the mentally disabled patients from five care centers. In agreement with the results of studies performed earlier in other countries, it was confirmed that the prevalence of HBsAg in the institutionalized mentally disabled patients was higher than the general population of Iran.

The world can be divided into three regions in terms of the HBV prevalence as follows: regions with high endemicity, moderate endemicity, and low endemicity [7]. Perinatal infection is the main route of transmission in high-prevalence areas, whereas horizontal transmission, especially in early childhood, is considered as the main route in regions with a moderate prevalence [8]. The presence of HBV DNA in the saliva, sweat, and urine of the HBV-infected patients is certain and dermal or non-dermal transmission is highly probable in the patient's family [7].

In Iran, a vaccination program is applied for the patient's family members; however, there is no specific program for screening the patients with HBV, even for their family members. Accordingly, most patients are diagnosed by chance or after blood transfusion. This unawareness leads to failure in observing the necessary precautions for preventing the transmission of HBV and the high prevalence of positive HBV among their family members [9].

So far in Iran, few studies have been conducted on the family members of the patients with HBV, all of which applied serological methods. Moreover, diseases that are communicable through blood and bodily fluids, are

considered as a risk to people attending these centers [10]. In all previous studies, the highest rate of positive HBsAg was observed among the surgical department staff or those with a needle stick history [11]. Other studies included people who never received HBV vaccination, but had positive HbsAb [10]. In a study performed on nosocomial HBV infection, it has been shown that almost half of the people who are at a high risk of HBV in the health system, are not immune to it [10]. Therefore, attendees of care centers for the mentally handicapped patients are always at the risk of HBV, and to decrease this risk factor, HBV vaccination is essential [11, 12].

The purpose of this study was to investigate the prevalence of hepatitis B virus infection in nurses and family members of the mentally handicapped patients, and also to determine the possible transmission way of HBV infection among the mentally disabled patients.

Material and methods

Study population

This cross-sectional study included nurses of children hospitalized in care centers for the mentally handicapped patients, as well as the children's family members. Blood samples of 110 nurses and family members of the hospitalized children were collected from these five mentally handicapped care centers in different districts of Tehran. Written informed consent was acquired from each person who was willing to participate in the study. The current study was approved by the Ethics Committee of Shahid Beheshti University of medical sciences.

Nurses were selected from five districts of Tehran who had contacts with HBV-positive children and were included based on a previous study by our research team [13].

Sample collection

A 5-mL blood sample was obtained from the participants. The serum of blood samples was isolated and then stored at -20 °C. The required arrangements for sampling were made through frequent phone calls and meetings with the center managers. The questionnaire obtained from the participants included information such as sex, age, marital status, number of children, occupation, duration of service at the centers, history of surgery, history of blood transfusion, history of liver disease, HBV infection, and history of HBV vaccination.

Serological and molecular laboratory tests

Serological and molecular tests were performed on the serum samples. Presence of HBsAg (bioELISA HBsAg 3.0, Barcelona, Spain) and HBcAb (bioELISA HBcAb, Barcelona, Spain) were monitored using ELISA assay. After extracting viral nucleic acid (high pure viral nucleic acid kit, Roche, Germany), those samples with positive results from ELISA tests (HBsAg or HBcAb) were submitted to detect HBV DNA using homemade nested PCR technique [14] with specific primers. Also, positive PCR samples were sequenced using an Applied Biosystems Inc. sequencer by 2nd round PCR specified primers. The sequences acquired in the FASTA format as chromatogram curves were analyzed by BioEdit 7.0.0. Then, the sequences were compared with the reference viral genomes, which had been derived from GenBank. The predicted protein sequence of HBsAg from the samples was determined by translating these sequences using BioEdit software. The genomic sequence of 78 HBVs was selected from various GenBank genotypes, and the phylogenetic tree of HBV was also prepared using Mega 6.0 and neighbor-joining method.

Statistical Analysis

SPSS version 19 was used for data entry and performing statistical analysis. Descriptive data are presented as mean deviation or percentage. Chi-square test or Fisher's exact test was used to comparing nominal data. In addition, Mann–Whitney U test was used to compare numerical data in terms of data distribution, and t-test was applied for independent variables. A P value of < 0.05 was regarded as statistically significant.

Results

The HBsAg test was performed for all 102 nurses who agreed to participate in this study including 89 (87%) women and 13 (13%) men. 73.6% of the individuals were married and 26.4% – unmarried. Also, 0.9% of them had no contact with the patients, 41.8% had less than five contacts, 11.8% had between five and ten contacts, 16,4% had between ten and 15 contacts, and 29.1% had more than 15 contacts. Addiction (0.9%), blood transfusion (8.8%), surgery (56.7%), hepatitis (11%), and vaccination (64.5%) were the risk factors in this research.

75% and 25% of nurses were under and over 50 years old, respectively. Three (3%) nurses were positive for this antigen, and all of them were female (100%). No positive cases of HBsAg were reported among the family members. There was no significant relationship between positive HBsAg and nurses' service time at the centers ($P< 0.05$). Also, there was no significant relationship between the prevalence of HBsAg with the risk factors and the number of patients in contact with a nurse ($P< 0.05$). The highest prevalence of HBsAg infection among nurses was reported to be in center No. 2 in northern Tehran. Out of 25 nurses working at this center, three (12 of the total) tested positive for this antigen. There was no significant relationship between the presence of HBsAg and the location of the center ($P < 0.05$). HBcAb test was performed for all 102 nurses, eight (8%) of whom tested positive for this antibody (25% male and 75% female); and, on the other hand, 94 (92%) nurses tested negative.

In this study, only four out of 20 mentally disabled people at care centers had families; three consented to participate in the study. All of the family members were under 50 years old and had a negative HBsAg test. There was no significant relationship between positive HBsAg and the duration of the patient's contact with his/her family ($P< 0.05$). Also, there was no positive case of HBcAb among the family members.

Nested PCR assay was performed using specific internal and external primers for viral surface protein. In examining 3 HBsAg-positive and 8 HBcAb-positive

samples using specific primers of HBV surface genome, only one HBcAb-positive sample was identified, which showed a specific band in the analysis of the PCR product via electrophoresis. This sample was diagnosed as occult hepatitis B infection (OBI) based on the HBsAg negative, HBcAb positive, and detectable HBV DNA.

With bidirectional sequencing of the derived HBV genome and its phylogenetic analysis, genotype D, sub-genotypes D1 and ayw_2 subtype were revealed (**Fig. 1**). BioEdit analysis of the derived sequence indicated no nucleotide or amino acid changes in comparison with a reference sequence, thus no nucleotide mutations were reported.

Discussion

Several reports have revealed the higher prevalence of HBV infection in mentally disabled patients compared to the general population (4-6). It has been also shown that the risk of positive HBsAg in the mentally disabled people at care centers is much higher than in the patients living at home [15]. A meta-analysis performed by Salehi-Vaziri in 2016 reported that the prevalence of HBV infection in the general Iranian population was 2.2 % [16], while another study showed 7.0% HBV infection in hospitalized mentally disabled patients [13]. In a study on mentally disabled patients at care centers in Brazil, it was indicated that 12.9% showed HBV infection, while 9.2% had occult HBV infection (OBI) [17]. This study confirms the higher prevalence of infection among mentally disabled patients compared to the general population. It is notable that in these studied centers, each nurse was responsible for more than one patient. In our study, there was no significant relationship between the prevalence of HBsAg and the number of patients in contact with a nurse. Therefore, if the contacts between the patient and nurse are not sanitized and there is a risk of contact with the patient's blood and body fluids, HBV transmission is possible among the attendees. This issue was addressed in a study conducted on HBV and human immunodeficiency virus (HIV) in the United States in 2012, which has analysed HBV and HIV transmissions among the mentally disabled people and staff of care centers. Absence of HBV vaccination, risk-reduction education, access to birth control methods and regular screening for blood-borne infections were the key factors for spreading the infection [18].

There was also a study on people with intellectual disability in Iran in 2019. It concluded that the frequency of HBV infection in disabled patients was higher than in the general Iranian population (blood donors) [19]. In this study, derived HBV strain showed an indigenous genotype D1 which was matched with other reported Mediterranean and Iranian strains. The high frequency of immune escape strains, despite vaccination and detection of identical mutations in different genes, might represent that the persons with intellectual disability have shared drug-resistant and vaccine-escape HBV strains [13]. As the prevalence of HBV infection was reported high in mentally disabled patients, we assumed that the prevalence of HBV infection would also be high in the parents and caregivers of these patients as well. Therefore in this study, 102 blood samples were collected from the nurses at five care centers in Tehran, Iran. Overall, 3% were HBsAg positive, which indicated the higher prevalence of HBV among nurses compared to the general population, while another study reported a prevalence of 1.7–2.1% [17]. The greater risk of HBV infection had been earlier reported among nurses [12, 20]. In another study on hospital nurses in Fars province, Iran, a higher risk was reported for acquiring HBV infection compared to the general population (5% were HBsAg positive, while 12% were HBcAb positive) [21]. Therefore, they had reported an intense program for education, vaccination, and post-vaccination assessment that is compulsory for health care workers.

Based on the serological analysis, 6% of nurses tested positive for HBcAb. Positive HBcAb indicates exposure to virus among these nurses; however, as HBV DNA was negative, they recovered after the infection. A study performed in 2000 showed that 35% of the general population of Iran had a positive record of HBcAb. This figure has declined in recently conducted studies. On the other hand, in a study by Merat et al. [22] on people in the age range of 18–65 years old in three major cities of Iran, the prevalence rate of HBcAb was estimated as 16.4%. Lower HBcAb levels can be explained by the execution of the HBV vaccination program in Iran since 1994. Accordingly, exposure of nurses to HBV showed a reduction in comparison with the general population.

In our previous study, we discovered HBV infection in 8% of the mentally disabled patients [23]. The present study, which was conducted on nurses caring for the same patients, showed an infection rate of 3%, which indicates a strict control of the HBV prevalence among the staff.

In the present study, HBV DNA isolated from the blood sample of one nurse showed negative HBsAg and positive HbcAb, which indicated OBI and also suggested that nurses are at a high risk of both chronic HBV and OBI infections. It can be concluded that nurses are at a higher risk of HBV and should be frequently examined by HBsAb test. If nurses do not have adequate immunity, they should be vaccinated against this virus. Monitoring this high-risk group and conducting regular tests can be effective in controlling the prevalence of HBV. However, increasing awareness of HBV infection among the population has been reported to recently improve the community health. For instance, in a study in South Asia in 2013, a total of 156 nurses were examined, 15 of whom tested HBsAg negative and HBcAb positive, while two tested HBsAg positive (0.01%) [24]. Moreover, in a study in Libya, the prevalence rates of HBsAg, HbcAb, and HBV DNA were 1.8%, 8.5%, and 0.9%, respectively. Lower chronic infection among compared to the general population can be explained by nurses awareness on HBV transmission, knowledge of infection control measures and access to a free vaccination program [25]. Occult HBV infection provides an opportunity of progression to carcinoma and cirrhosis for the patient and has not been reported previously among nurses caring for mentally disabled patients. A higher prevalence of HBV infection among the healthcare workers who are in contact with mentally disabled patients has been addressed in this research. Therefore,

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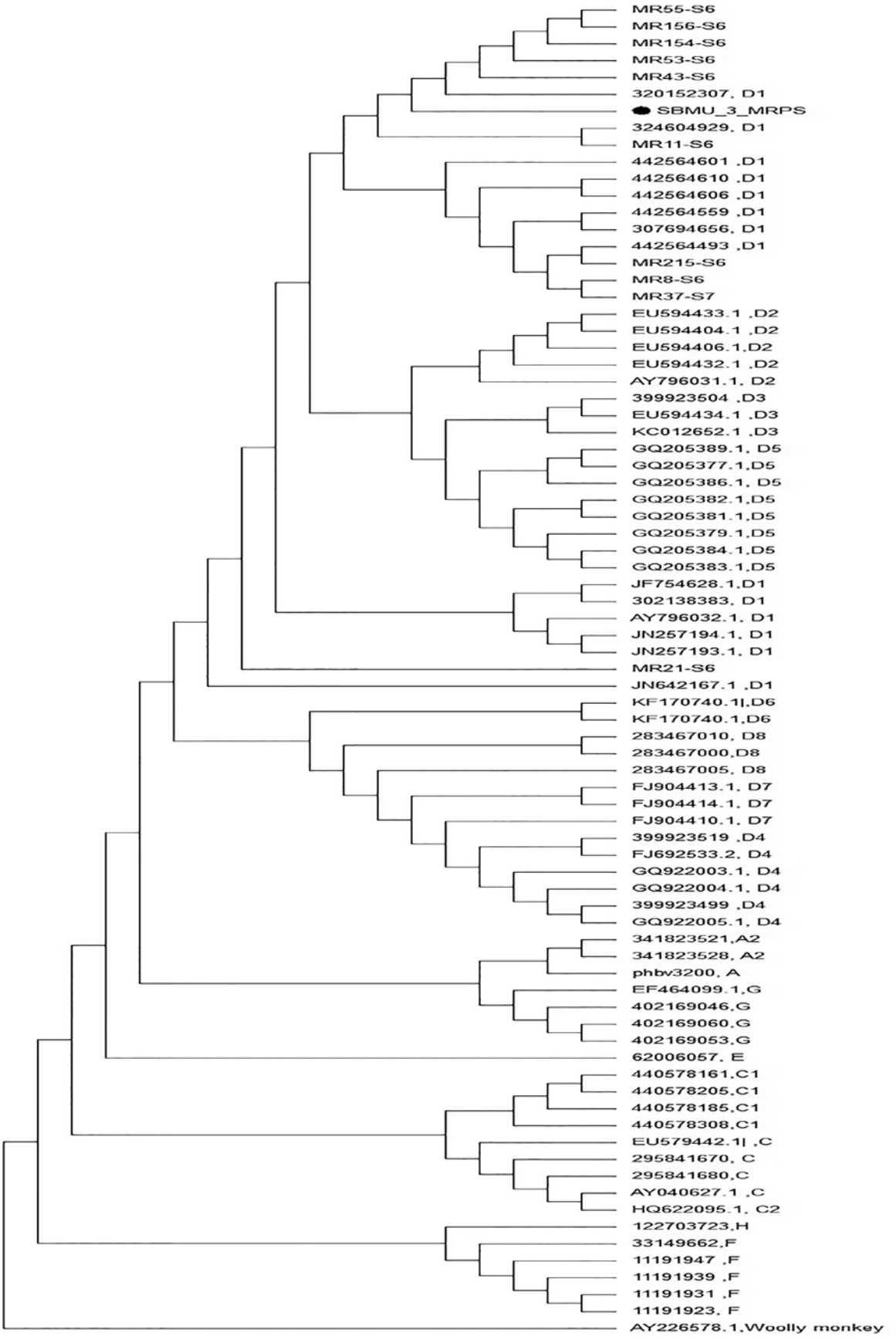

Phylogenetic tree of derived HBsAg genome, along with 68 reference samples (GenBank). Woolly Monkey HBV (226578) was used as out-group.

HBV infection screening (including classic and occult) among this group is suggested.

On the other hand, blood samples were collected from three families of patients with HBV. Few studies have been conducted in the past on the HBV-infected patients' families, confirming virus transmission among family members by considering the homology of isolated viruses [8]. However, in our study, information was limited due to the lack of cooperation of many families. In serological tests, no positive samples were found in terms of HBsAg or HBcAb among family members, which implies that neither classic nor occult infection was observed in this population. The limited number of individuals participating in the research and separate living places of the patients and their families due to hospitalization from early years of life can be considered as the interferer (influential) factors.

The phylogenetic studies imply that subgenotype D1 has been introduced as the dominant strain reported in Iran, Turkey, and Pakistan [26]. This subgenotype has been described as the dominant strain of genotype D in the Middle East. Therefore, HBV is slightly heterogeneous in this region, and the virus has not spread for a long time in this population. Moreover, it seems that genotype D has the highest degree of inter-genotype and subgenotype variations, compared to genotypes A, G and F [27]. However, the HBV genome isolated in this study has no change compared to the reference virus genome; and this finding is in accordance with other Iranian studies [28]. One of the reasons for viral change may be the time of virus entrance to the body. If the virus enters the patient's body during childhood, it can oppose the immune system, and the virus undergoes changes. Since the virus did not change in our study, it might have recently entered the nurse's body, which may lead to limited contact with the immune system pressure and limited mutations as well.

In the present study, subtype ayw2 was observed, which is one of the prevalent subtypes reported in genotype D. Observation of different subtypes can indicate great viral changes [29]. Studies performed in many countries have confirmed the presence of genotype D1 with subtype ayw2 [30]. Furthermore, there are many reports from the Middle East, indicating subtypes ayw2 and awy3 [28, 31, 32]. Also in Iran, this subtype has been reported in subgenotype D1 [28, 29, 33].

As many hypotheses were mentioned in this study, the main cause of the high prevalence of HBV infection in mentally disabled patients is still unclear. Unfortunately, due to many obstacles such as non-cooperation of family members and nurses and inaccessibility to family records of many patients (because they were orphans), there is inadequate data to strongly support any of our hypotheses. Despite all of these obstacles, there has been little evidence in our results that can support the connection between nurses and patients' HBV infection. Nevertheless, further studies, especially on family members and hospitalization quality, are suggested to clarify the source of infection in these children, and consequently to find a way to alleviate this infection among them.

Conclusion

In the present study, the HBV infection rate among the nurses caring for mentally disabled patients was 3%, which is higher than the general Iranian population (1.2–1.7%). On the other hand, 8% of them tested positive for HbcAb. However, there were no positive cases in terms of HBsAg, HBcAb, or HBV DNA in the family members of the mentally disabled patients, which were lower than among the general population. The interferer factors include a limited number of participants (as most hospitalized patients were orphan) and separate living environments of the patients and their family members. The isolated virus from nurse contained genotype D1 and subtype ayw2, which is the most common strain in Middle Eastern countries like Iran. Moreover, no drug-resistant or vaccine-escape mutations were observed among HBV-isolated strain.

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