

Hepatitis Delta: The Rediscovery

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KEYWORDS

- Hepatitis D (delta) • Hepatitis D (delta) virus • HDV epidemiology • HDV transmission
- HDV drug addicts • HDV rediscovery

KEY POINTS

- Control of hepatitis B Virus worldwide is diminishing the circulation of hepatitis D virus (HDV).
- The epidemic of HDV in southern Europe in the 1980s has been brought under control; however, HDV is returning to Europe through immigration from areas where this infection remains endemic.
- The prevalence of HDV remains high and has a major medical impact in the poorest countries of the world and in many areas of the developing world.
- Although forgotten in the Western world, hepatitis D has not disappeared but remains an important medical issue, in particular in drug addicts.

INTRODUCTION

The Virus and its Biology

The 1970s were a time of excitement in hepatology. The discovery of the hepatitis B virus (HBV) at the end of the 1960s provided the key to unravel the mysteries of viral hepatitis; by the middle of the 1970s, hepatitis A was discovered and diagnostics were developed for hepatitis A and B.

A few years later, by simple medical scrutiny, a novel hepatitis agent was unexpectedly discovered in association with HBV infection. In the mid-1970s, in Torino, Italy, clinical and immunologic discrepancies led to the recognition of a new antigen-antibody system named delta in carriers of the hepatitis B surface antigen (HBsAg). The new reactivity was initially thought to be an antigen of HBV but its true nature emerged at the end of the 1970s from studies in chimpanzees at the National Institute of Health in the United States.¹ From the different expression in the liver of animals naive to HBV and in animals carrying HBsAg, both inoculated with the same HBsAg-positive serum containing delta, it became clear that the delta antigen, rather than being a component of the HBV, was the hallmark of a new defective RNA virus

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requiring HBV for its own infection.² The new virus received the name of hepatitis D virus (HDV). In the 30 years that followed its discovery, the unique virology of HDV and its interplay with HBV have been elucidated.³ It is the smallest animal virus possessing a circular RNA genome made up of only 1700 bases; its circular structure is driven by intramolecular base pairing into a rodlike conformation; it contains a ribozyme (ie, an RNA segment that retains the genetic information but is also able to self-cleave the viral RNA⁴); the ribozyme is essential to HDV replication, which occurs by a rolling-circle mechanism similar to the viroids of plants.⁵

The limited genetic capacity of HDV is not sufficient to code for enzymatic functions of its own; thus the initial enigma was how HDV is replicated.

Transcriptional experiments using low-dose amanitin,³ a toxin that blocks the transcription of RNA polymerase, have shown that HDV RNA is replicated by the host cell polymerases, raising the question of how mammalian RNA polymerases that only accept DNA could replicate an RNA molecule. To explain this puzzle, it is postulated that the host RNA polymerases are deceived by the rodlike conformation of native HDV (resembling double-stranded DNA) to copy the viral RNA as if it were endogenous DNA.³ Thus HDV turns to its advantage the replicative machinery of the infected host and needs HBV only for the HBsAg coat necessary for virion assembly and for the binding to hepatocytes; the corollary is that there is no specific enzymatic function of the virus to target for therapy, such as the polymerases and proteases of HBV and hepatitis C virus (HCV), and its synthesis is not influenced by the level of HBV DNA in serum.

The Current Perception of the Epidemiology of HDV

Assays for the antibody to HDV (anti-HD) as the serologic signature of HDV infection were developed soon after the discovery of the virus and became available commercially in 1984, expediting epidemiologic surveys. At the end of the 1980s, data collected throughout the decade suggested that no less than 5% of HBsAg carriers worldwide were also infected with the HDV, corresponding with about 15,000,000 individuals, and that dual HBV-HDV infection was usually associated with a severe and rapidly progressive liver disease resistant to treatment.⁶

Since then, the global scenario of HBV has distinctly changed. Vaccination, public health measures against acquired immunodeficiency syndrome (AIDS), and improvements in hygienic conditions have increasingly and efficiently controlled the spread of HBV in developed countries; by depriving the HDV of the biological substrate necessary to its propagation, the containment of HBV has led to the simultaneous decline of hepatitis D in all areas of the industrialized world where the infection was endemic in the 1980s. The reduction was so profound in southern Europe that it led at the end of the 1990s to the hypothesis that HDV infection was on the way to eradication and that hepatitis D would soon be cancelled from the list of communicable disease.⁷

Optimism has been premature. First, hepatitis D is reviving in Europe, where immigrants are reintroducing the disease. Second, the apparent absence of HDV in many developing areas was largely caused by lack of information; new attention and availability of diagnostics are showing that hepatitis D remains a major health problem throughout the world. Third, although the decline of HDV in industrialized countries is genuine, the extent of its decline is concealed by diminished testing because of the perception that hepatitis D is no longer a significant medical problem.

The current debate is whether HDV is returning or hepatitis D is simply a forgotten disease on the way to rediscovery.⁸ To understand the issue, this article discusses the epidemiologic changes in the developed world in the last 30 years, the problem and the degree of alertness in the developing countries, and the current standing in drug

addicts, the population that bears the highest medical brunt of the infection in the Western world.

THE EPIDEMIOLOGIC SCENARIO IN EUROPE

Consistent epidemiologic studies were carried out in the 1980s in Western countries, primarily in southern Europe where the prevalence of HBV was high.^{9,10} The epidemiology of HDV could not be assessed following the parameters of HBV infection; testing for HDV in acute HBsAg hepatitis as a measure of the incidence of HDV (ie, acute hepatitis D) was unreliable because, in the acute setting, expression of HDV markers is often weak and elusive and does not persist after the clearance of the HBsAg; likewise, prevalence studies for anti-HD in blood donors, who usually represent the reference population for serologic surveys of blood-borne infections, were unrewarding because HDV superinfection results in chronic hepatitis D and a sickness status that precludes blood donation.

Consistent data were obtained when the analysis was addressed by medical categories. In southern Europe, HDV was endemic and an important cause of chronic hepatitis leading to cirrhosis; in North America and northern Europe, the infection was largely confined to intravenous drug addicts, in whom it was a major cause of severe and fulminant HBsAg hepatitis.¹¹

Risk factors were the carriage of HBsAg, parenteral exposure to blood, sexual promiscuity, and living in unhygienic and overcrowded household conditions.^{9,10}

The Decline of HDV

At the end of the 1980s, the prevalence of HDV started to diminish in Europe. In Italy, anti-HD in HBsAg carriers with liver disease diminished from 24.6% in 1983 to 8% in 1997^{12,13}; the circulation of HDV had already consistently diminished at the time of the introduction of universal vaccination against HBV in 1991, because of behavioral changes and sexual restrictions fostered by the fear of AIDS and because of diminished natality and consequent reduction of family size.

Declines of HDV occurred in the 1990s throughout the Mediterranean and in Taiwan. In Turkey, the overall rates of anti-HD in chronic hepatitis and cirrhosis decreased from 29% to 12% and from 38% and 27%, respectively,¹⁴ and in Taiwan the incidence of HDV as a cause of superinfection diminished from 23.7% to 4.2% from 1983 to 1996.¹⁵

Infection with HDV also declined in areas of eastern Europe that enforced better public health measures and started HBV vaccination. A decrease from 47.6% to 15.4% in the prevalence of anti-HD in patients with HBsAg-positive cirrhosis was reported in Belarus from 1991 to 1997¹⁶; among institutionalized children with chronic hepatitis B in southeast Romania, the prevalence of HDV declined from 33% in the decade 1990 to 2000 to 21% in the decade 2000 to 2009¹⁷; in a recent population study in sub-Carpathian and southeast Romania, no HDV case was found in 2851 people examined.¹⁸

The Return of HDV

Since the end of the last century, HDV has not declined further in western Europe; although the major epidemic of HDV of the 1970s to 1980s was brought under control, the residual health burden of hepatitis D has remained stable in the last 10 years. In 1386 HBsAg carriers studied in Italy in 2006 to 2007, the overall prevalence of anti-HD has remained 8.1% with no further downtrend; among the incident cases the prevalence was 14.3%, suggesting a new wave of HDV-infected people.¹⁹

In London, United Kingdom, anti-HD has been detected in about 8.5% of HBsAg carriers between 2000 and 2006.²⁰ In Hannover, Germany, the prevalence of the infection declined from 18.6% to 6.8% in the period from 1992 to 1997, but anti-HD increased in the past decade, with 8% to 14% of the HBsAg carriers being positive from 1999 onward.²¹ Both in the United Kingdom and in Germany, most HDV carriers are migrants from eastern Europe, Africa, the Middle East, and Turkey; in France, HDV infection is seen predominantly in people from northern Africa.²² Contemporary data indicate that migration from areas where HDV remains endemic is reconstituting a reservoir of HDV infections in Europe (**Table 1**).

Clinical Changes

With the decline of HDV, the clinical scenario of hepatitis D has also changed. Although most patients with hepatitis D observed in Italy in the 1980s had a florid chronic hepatitis and cirrhosis was seen in fewer than 20% of cases, by the end of the 1990s the proportion of cirrhosis residual to burnt-out inflammation had increased to 70%.²³ In Barcelona, Spain, patients recruited from 1983 to 1995 were younger, had acquired HDV mainly by coinfection, and were often intravenous drug addicts and coinfecting by HCV and HIV.²⁴ In contrast, patients recruited from 1996 to 2008 were older, with a higher proportion of immigrants, most presenting with chronic hepatitis D acquired by superinfection.

THE EPIDEMIOLOGIC SCENARIO OUTSIDE EUROPE

The Scenario in the 1980s to 1990s

The largest epidemiologic studies in the 1990s were promoted by major health institutions interested in extreme scenarios.

The US Centers for Disease Control and Prevention, the French Institute Pasteur, and the Kashmir Institute of Medical Science investigated outbreaks of fulminant hepatitis occurring in the Amazon basin,^{25,26} the Central African Republic,²⁷ and the Himalayan foothills.²⁸ These epidemics resulted from the rapid spreading of HDV against a background of diffuse HBV infection in populations with poor hygienic conditions and overcrowding; those affected were mainly children and adolescents who had acquired HBV in infancy, and mortality was high.

Many small studies were carried out to establish local prevalences of HDV. However, there was no systematic or comprehensive survey; most studies were based on few patients with disparate clinical features. In many countries there was no facility or resource for local testing for HDV. It nevertheless became clear that the prevalence of HDV was not a simple replica of the HBV scenario, because the ratio of HDV to HBV varied widely throughout the world.

Most puzzling was the discrepancy between the high prevalence of endemic HDV in Taiwan and Okinawa and the very low prevalence in nearby Japan and Korea despite a

Table 1
Prevalence of immigrants among individuals with HDV infection in Europe

| | % Immigrants, Origin | Reference |
|----------|--|------------------|
| Greece | 65, from the Balkans, central Asia, Africa | 17 |
| Hannover | 80, from Turkey, eastern Europe | 21 |
| London | 85, from eastern Europe, Asia, Africa | 20 |
| Spain | 28, from Africa, eastern Europe, South America | 24 |

similar high endemicity of HBV¹⁷; in Korea HDV was virtually absent in another recent study,²⁹ suggesting that HDV may differ in the capacity to superinfect different populations of HBsAg carriers, possibly in relation to a genetic resistance or susceptibility to HDV of the host or to viral genetics leading to different interplays between HBV and HDV.

The infection was found in Israel, Brazil, Colombia, Afghanistan, China, Saudi Arabia, India, the Soviet Union but not in Malaysia or in Indonesia. In Brazil and Saudi Arabia, pockets of hyperendemic HDV were close to areas where the infection was negligible or nonexistent⁹; likewise north of Mount Kenya, 30% of the HBsAg carriers had anti-HD as opposed to none of 123 patients with HBsAg liver disease south of Mount Kenya,³⁰ and in China anti-HD varied from 20% to 40% in Chongqing and Wuhan to 0% in Heinan and Hubei.⁹

Throughout the 1990s new entries extended the geographic horizon of HDV, whereas other candidates were discounted. Significant rates of the infection were reported from Moldova, West Greenland, Tunisia, and several other countries, but no marker of the infection was detected in a study in Nigeria and in rural areas of the high Andean Plateau; rates of anti-HD were low in sub-Saharan African immigrants and in northwest Mexico.¹⁶

At the end of the century, the HDV was a worldwide infection inducing severe clinical courses, whose real medical impact remained unknown in much of the developing world; most studies were designed to establish whether HDV infection was present or not in a given area rather than to provide relevant medical information.

The Current Scenario

Outbreaks of hepatitis D

The risk of HDV has not changed in the poorest communities of the world where HBV remains unchecked. In the 2010s, outbreaks of severe hepatitis D similar to the epidemics of the 1980 to 1990s in the Amazon basin, were reported in Samara (Russia), in Greenland, and in Mongolia; as in the Amazon, these epidemics occurred through superinfection against a background of high HBV endemicity and affected mainly the young.

In a cluster of fulminant HBsAg hepatitis that occurred in Samara at the end of the 1990s, HDV infection was found in 39% of 94 cases.³¹ An outbreak of hepatitis D occurred in the mid-2010s in a village of 133 inhabitants in the west coast of Greenland,³² where 48% of the inhabitants were less than 20 years of age and 27% were carriers of the HBsAg; within 1 year, 68% had become anti-HD positive, all with increased liver enzymes. In an outbreak in Mongolia in 2004 to 2005,^{33,34} HDV superinfection was the cause of acute hepatitis in 30 young HBsAg carriers.

Endemicity in Africa and Asia

Awareness of hepatitis D as a major health problem has increased in countries of Africa and Asia where facilities are now available for more extensive testing to establish the burden of hepatitis D at national levels.

In Africa (**Fig. 1**), a rate of anti-HD of 66.7% was reported in 2009 in both urban and rural populations with HBsAg in Gabon.³⁵ In Cameroon,³⁶ the antibody was found in 17.6% of 233 HBsAg carriers collected at 2 medical centers; in Nigeria,³⁷ HDV was found in 12.5% of 96 patients with HBsAg liver disease; and, in Mauritania,³⁸ the prevalence of the infection was 19.1% among 162 HBsAg-positive patients.

In Asia (**Fig. 2**), HDV remains a major medical problem in the southeastern and eastern parts of Turkey where, among patients with chronic hepatitis B, anti-HD was found in 27.5% and in 45.5%, respectively.^{39,40} The endemicity of HDV is

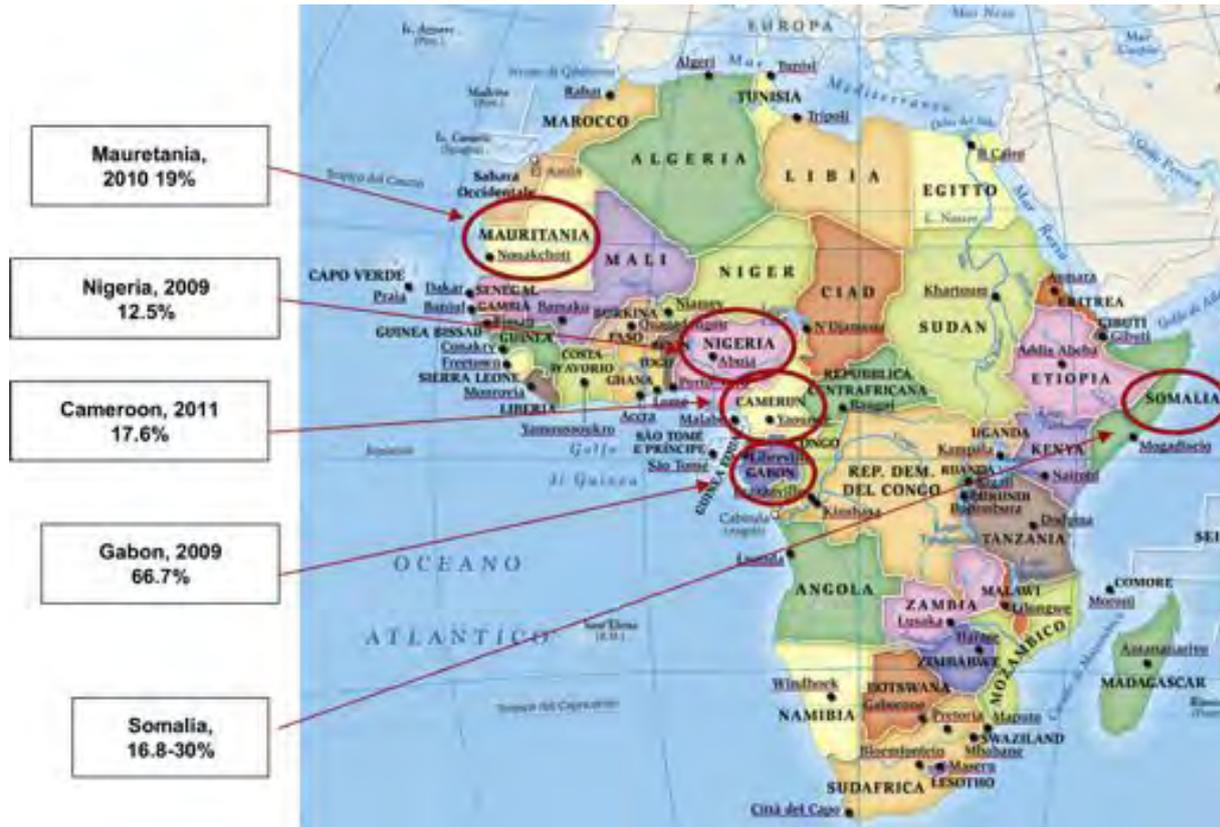


Fig. 1. HDV among HBsAg carriers with liver disease: Africa; high prevalence areas.

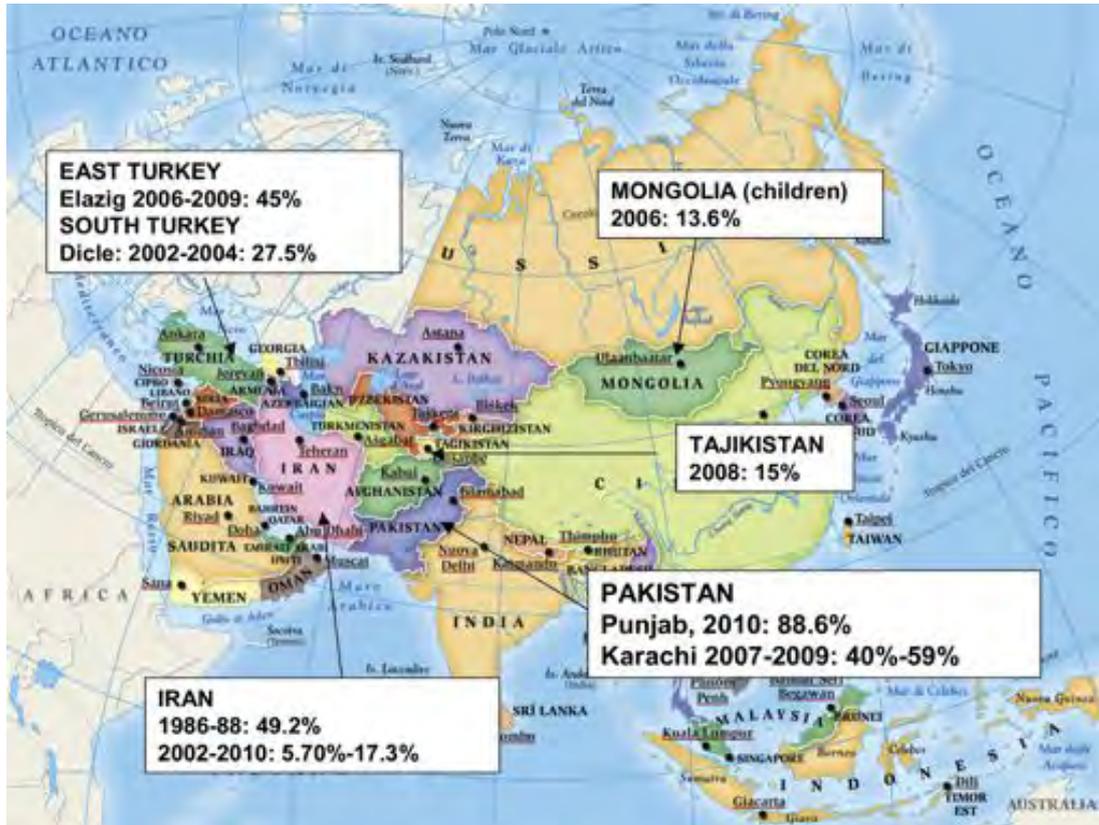


Fig. 2. HDV among HBsAg carriers with liver disease: Asia; high prevalence areas.

consistent in Tajikistan,⁴¹ where 15% of patients with HBsAg-positive cirrhosis and hepatocarcinoma were coinfecting with HDV.

Past and recent evidence indicates that HDV is highly endemic in and around the Middle East.^{42,43} In this area, the analysis according to clinical categories has shown that, among asymptomatic HBsAg carriers, the pooled HDV prevalence was 24.6% in Sudan,⁴⁴ 18.33% in Pakistan,⁴⁵ 10.7% in Egypt,^{46,47} 7.2% in Saudi Arabia,⁴⁸ 4.94% in Iran,^{49–53} and 1.56% in Yemen.⁵⁴ Single studies from Lebanon,⁵⁵ Djibouti,⁵⁶ and Jordan⁵⁷ reported a prevalence from 1% to 2%; higher rates, of 16.8% and 28.6% respectively, were reported from Somalia^{58,59} and Afghanistan.⁶⁰ Overall, in the previous countries the prevalence of anti-HD among asymptomatic HBsAg carriers was 14.74%.

Among patients with chronic HBsAg hepatitis, the pooled prevalence of HDV was 47.36% in Somalia, 37.38% in Pakistan, 24.37% in Egypt, 14.4% in Iran, and 8.15% in Saudi Arabia, with a weighted mean HDV prevalence of 27.8% in these countries.⁴² Among cirrhotics and patients with hepatocellular carcinoma, it was 53.77% in Pakistan, 33.20% in Somalia, 30.47% in Iran, and 29.6% in Egypt, with a weighted mean HDV prevalence of 36.57% in these countries.⁴²

HDV IN DRUG ADDICTS AND IN THE UNITED STATES

The Past

Since the discovery of HDV, injection drug users sharing needles were recognized as the major victims of the infection, with rates of anti-HD among HBsAg-positive patients varying in the 1980s from 17% in Italy to more than 90% in Taiwan and Thailand.⁹ The burden of HDV was also high in HBsAg addicts in the United States; 42% of those treated from 1972 to 1975 at Veterans Administration facilities had anti-HD⁶¹; the antibody was found in 54% during an hepatitis B outbreak in the mid-1980s in Massachusetts,⁶² and in 67% of the HBV-positive addicts recruited in New York City in 1988.⁶³ The virus was acquired predominantly by coinfection, spreading from acute case to acute case through the recruitment of new addicts; the rapid interhuman passage increased the virulence of HDV and several outbreaks of fulminant hepatitis D were reported in the United States, United Kingdom, Sweden, Ireland, and Italy.¹⁷

The Current Impact

Attention to HDV in drug addicts decreased in Europe from the end of the 1980s because of the reduction of HBV in these communities but also because interest was diverted to the newly discovered hepatitis C.

However, recent surveys prompted by the concern of HDV in immigrants^{20–24} have acknowledged that in European countries there are still consistent communities of drug addicts in which HDV remains endemic. In surveys in the United Kingdom, Germany, and Spain^{20–24} more than 70% of the HDV-infected patients born in these countries were injection drug users. In the Czech Republic, HDV could be found only in drug addicts,¹⁷ and in Switzerland,⁶⁴ a country with a low general prevalence of HDV infection (5.9%), a 2011 study reported that 62% of the HDV cases were contaminated by intravenous drug use; throughout Europe a consistent proportion of drug addicts with HDV also had HCV infection.

A consistent rate of HDV was also determined in patients coinfecting with HIV/HBV; in 1319 cases recruited throughout Europe by the Euro-Syndrome d'immunodépression acquise (SIDA) study,⁶⁵ the prevalence of anti-HD was 14%, and a similar figure was recently reported in HIV/HBV subjects in Romania.⁶⁶

The situation is similar and more emblematic in the United States. Although no further attention was apparently paid to HDV since the late 1980s, recent studies are urging reconsideration. In 2005, Bialek and colleagues⁶⁷ reported a 34.5% prevalence of HDV infection among 58 cases of acute HBsAg hepatitis reported in 2000; all the patients coinfecting with HDV were drug addicts. In 2010, Kucirka and colleagues⁶⁸ compared the prevalence of anti-HD between 48 drug addicts in Baltimore with chronic HBsAg infection collected in 1988 to 1989 and 38 such patients collected in 2005 to 2006; the prevalence of anti-HD increased from 25% in the early cohort to 50% in the recent cohort.

In a retrospective review of 1296 chronic HBV carriers at California Pacific Medical Center,¹⁷ 82 patients were positive for HDV (6.3%), and 34% were also infected with HCV. Sixty-three percent of the patients were born in North America, and most of the others came from south and east Asia and the Middle East; 23% of the patients reported a history of drug use.

Although these studies include a limited number of patients and were conducted too far away to draw nationwide conclusions, they nevertheless provide a warning that HDV is found from Baltimore to California not only in significant proportions of drug addicts but also in a more composite epidemiology including, as in Europe, immigrant populations.

SUMMARY

Hepatitis D is both returning and rediscovered. It is returning to western Europe through immigration. Immigrants account for the largest proportion of contemporary hepatitis D in the United Kingdom, Germany, and France; in Italy, Spain, and Greece they are reconstituting a reservoir of the infection, overtaking the decreasing and aging domestic patients with HDV. Their clinical presentation recapitulates the typical features of a florid hepatitis D seen in European patients in the 1970s to 1980s when HDV was endemic in southern Europe. Although the return of HDV is unlikely to have an impact in domestic European populations vaccinated against HBV, knowledge of the problem will be useful to enforce more vigilance and public health measures among newcomers.

Hepatitis D is being rediscovered in the developing world and in the United States. In the developing world, increased diagnostic facilities are raising awareness that HDV remains endemic in many countries; efforts are underway to map the infection at local levels and improve the medical alert to hepatitis D.

In the United States it is generally thought that HDV has gone and hepatitis D is no longer a problem; this perception seems to derive from lack of testing rather than from updated serologic surveys. Awareness of hepatitis D in the country has recently been revived, pointing to drug addicts as the major, but possibly not the only, residual reservoir of HDV in the country. Although long forgotten, HDV has not gone and should be considered in all patients with HBsAg liver disease, in particular in those with a history of drug addiction.⁶⁹

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