

Hepatitis E in Pakistan

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التهاب الكبد بالفيروس E في باكستان افتخار أحمد مالك ووحيد الزمان طارق

خلاصة تظهر حالات فردية من التهاب الكبد بالفيروس E في باكستان على مدار العام . غير أنه أبلغ عن حدوث فاشيات وأوبئة صغيرة من هذا المرض في مدن بيشاور وماردان وأبوت آباد وروالبندي - إسلام آباد ، وسرغودة ومولتان وحيدر آباد وكويته وكراتشي . ولقد وقع وباء كبير لالتهاب الكبد بالفيروس E في معسكر للجيش في لاهور في أوائل عام ١٩٩٥ حيث عولجت ستمئة حالة بالأقسام الداخلية . ولقد تبين من جميع التقصيات الوبائية التي أجريت أن سبب الفاشيات كان على الدوام تلوث إمدادات المياه بالمجاري . وتتناول هذه المقالة وبائيات التهاب الكبد E في باكستان ، وتشخيصه ، وملامحه السريرية ، ومعالجته ، والوقاية منه ومكافحته .

ABSTRACT In Pakistan, sporadic cases of hepatitis E occur throughout the year. However, small outbreaks and epidemics of hepatitis E have been reported from the cities of Peshawar, Mardan, Abbottabad, Rawalpindi-Islamabad, Sargodha, Multan, Hyderabad, Quetta and Karachi. A large epidemic of hepatitis E occurred in one of the army garrisons at Lahore in early 1995, when more than 600 cases were treated as inpatients. Wherever epidemiological investigations have been carried out, the cause of the outbreak has always been found to be contamination of water supplies with sewage. This paper considers the epidemiology, diagnosis, clinical features, treatment, prevention and control of hepatitis E in Pakistan.

L'hépatite E au Pakistan

RESUME Au Pakistan, des cas sporadiques d'hépatite E se produisent toute l'année. Toutefois, de petites flambées épidémiques et épidémies ont été signalées dans les villes de Peshawar, Mardan, Abbottabad, Rawalpindi-Islamabad, Sargodha, Multan, Hyderabad, Quetta et Karachi. Une importante épidémie d'hépatite E s'est produite dans l'une des casernes à Lahore au début de l'année 1995, avec plus de 600 cas hospitalisés pour traitement. Chaque fois que des enquêtes épidémiologiques ont été réalisées, la cause de la flambée épidémique s'est toujours avérée être la contamination des approvisionnements en eau par les effluents d'égouts. Le présent article étudie l'épidémiologie, le diagnostic, les caractéristiques cliniques, le traitement, la prévention de l'hépatite E et la lutte contre cette affection au Pakistan.

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Introduction

It is now realized that acute viral hepatitis (AVH) is caused by many hepatotropic viruses. Previously, there were only two broad categories of AVH recognized: infectious hepatitis and serum hepatitis. The so-called "infectious hepatitis" referred to cases thought to be caused by hepatitis A virus. In fact at present most cases of infectious hepatitis are due to hepatitis E virus (HEV), which till recently was known as enterically transmitted non-A, non-B hepatitis.

The causative agent of hepatitis E was characterized in 1988, when it was given its present name [1]. The first massive outbreak of HEV in the subcontinent of Indo-Pakistan can be traced back to 1955, when drinking water was contaminated by the overflow of an open sewer in Delhi. The number of clinical cases of the disease was 29 300, who mainly developed a benign course of viral hepatitis of a self-limiting nature [2]. During that outbreak, 10% of the females affected in their last trimester of pregnancy died of severe disease (hepatic failure) [3]. Contrary to conventional belief, it was later discovered that a virus other than hepatitis A virus (HAV) was the cause of such epidemics, as the stored sera collected from these outbreaks did not react to the newly developed anti-Hep A IgM (immunoglobulin M) in 1970s. This clearly excluded the involvement of the hepatitis A virus [4] in these outbreaks.

It took many years to identify and characterize the causative viral agent. In 1983, virus-like particles (27–32 nanometres) were demonstrated by immune electron microscopy (IEM) in the stools of three of the nine cases of what turned out to be HEV infection in Tashkent, Uzbekistan (then in the USSR) [5]. The virus was passed orally to a volunteer, and the virus was subsequently

isolated from his stool; thus the faeco-oral transmission was proved [5].

Hepatitis E virus

The causative agent of hepatitis E is an RNA virus and is 27–34 nanometres in diameter. The virus is faeco-orally transmitted and initially affects the intestines, later causing viraemia, with the virus attacking the target organ (liver). The causative virus is excreted through the gut in the faecal material.

The virus is extremely sensitive to freezing and thawing. If it is held at a temperature of 4–8 °C for more than five days, it undergoes a spontaneous degradation process. It can, however, be preserved in liquid nitrogen for five months or more. So far, HEV has been passed between nonhuman primates like cynomolgus monkeys and *Sanguinus mystax* tamarins by many workers.

Epidemiology

Hepatitis E virus passes into the sewage, and wherever there are chances of contamination of potable water with sewage containing HEV, outbreaks of HEV infection are likely to occur. The incubation period of the disease is on an average 40 days, and the highest attack rate is seen in young adults (15–39 years of age), equally affecting both sexes. The disease is usually mild in nature and is self-limiting, without any long-term sequelae. However, if it affects females during the third trimester of pregnancy, it can lead to high maternal mortality and frequent fetal loss [6].

Epidemiologically, there may be frequent explosive epidemics of HEV infection, but sporadic cases of hepatitis E may

also occur throughout the year, especially in endemic areas. Sporadic cases may be seen in developed countries in visitors from endemic countries and in people who may have recently returned from the developing world.

It is not known whether immunity against HEV is short-lived or there are more than one serological types (without cross-protection against the other HEV serovars).

Hepatitis E infection in Pakistan

In Pakistan, epidemics of acute viral hepatitis (AVH) were reported as early as the 1950s and 1960s. In 1972, an outbreak of AVH was observed in an army battalion on field exercises. In three weeks, about 250 cases of acute viral hepatitis were reported, and all of the infected persons had had a common source of drinking water (untreated river water) [7]. Many similar outbreaks of hepatitis E had been wrongly labelled to be caused by HAV (so called infectious hepatitis). However, it subsequently became clear that all the outbreaks were caused by HEV and not by HAV [6, 7]. In Pakistan, HEV remains highly endemic, mainly affecting the adult population [8]. A number of mini-epidemics have recently been reported in Pakistan and all of these appear to have been due to faecal contamination of the water supply.

Sporadic cases

HEV infection is endemic in Pakistan and may result in many sporadic cases of acute viral hepatitis. HEV endemicity in urban areas is mainly due to the inadequate supply of clean running water. The rural population uses water mostly from wells, streams, canals, rivers and even stagnant ponds. Such sources of water are often contaminated by

human waste carrying HEV. Furthermore, in urban areas, where the supply of running tap water is intermittent, low pressure in the water pipes between supply times sucks in, through joints or leaks in the pipes, soil that may have been contaminated by faecal matter [9].

A vast majority of adult patients hospitalized with acute viral hepatitis in Pakistan are infected with HEV: a number of studies on adults and children during the early 1990s (Table 1) show HEV to be responsible for at least 70% of the cases.

Epidemics of hepatitis E in Pakistan

1. An outbreak of AVH was reported from a military unit at Mardan, in north Pakistan. It continued from August to October 1987. About 10% of the exposed personnel developed jaundice. The maximum number of cases (21) occurred in a company whose main water supply was near a polluted area (where a leaking pipe of water supply passing through a drain). None of the patients showed any residual symptoms or raised transaminase levels on follow-up examination. The serum markers of HAV and HBV were done in all cases, and no case was found to be due to recent infection with these viruses. This AVH epidemic stopped when the pipeline was repaired and the contamination of the water was prevented [11].
2. A number of outbreaks of AVH were reported from Karachi in 1985 and 1986, with several peaks. HEV infection was diagnosed in five cases who returned from Karachi to California and fell ill with jaundice.
3. In the central region of Punjab in Pakistan, a college campus that suffered outbreaks of AVH due to HEV at Sargodha was reported by Ticehurst et al. in

Table 1 Hepatitis E in Pakistan. Findings from six studies

Type	Study result (%)					
	1	2	3	4	5	6
Anti-HAV IgM	1					
HBsAg+	12					
Anti-HBc+	21					
HBsAg +Anti-HBc	6					
Hepatitis A		1	2	1	3	63
Hepatitis B		26	23	26	14	7
Hepatitis D			1	3		
Hepatitis E		70	72	70	76	30
All negative	*60	3	3	2	4	
	100	100	100	100	100	100

Study

1. Army Medical College, Rawalpindi, Pakistan, 1989. Sample: 857 adult males.
2. Army Medical College, Rawalpindi, Pakistan, 1991. Sample: 1180 adults both sexes.
3. Armed Forces Institute of Pathology, Rawalpindi, Pakistan, 1991-93. Sample: 2091 adults, both sexes.
4. Army Medical College, Rawalpindi, Pakistan, 1992. Sample: 432 adult males.
5. Army Medical College, Rawalpindi, Pakistan, 1992. Sample: 240 adult females.
6. Military Hospital, Rawalpindi, Pakistan, 1994. Sample: 235 children.

* probably hepatitis E

1987 [11] with 133 clinical cases of AVH (an attack rate of approximately 20%). All these cases required hospitalization and had a prolonged period of convalescence. The affected students used a common water source. The AVH epidemic ended as a result of an improvement in the water supply. On testing the sera of these patients, HAV and HBV infections were excluded serologically [11]. In this outbreak of AVH, virological evidence was sought for HEV infection. Paired sera from two patients were tested by immune electron microscopy (IEM), and these cases of AVH were confirmed to be due to HEV infection. Ten out of 85 patients showed the

presence of HEV particles. These were serologically identified by IEM using reference serum obtained from HEV-infected chimpanzees. The faecal concentration of HEV appeared to be lower than that observed with many other enteric viruses [11].

4. Islamabad, the capital of Pakistan, has an ample supply of potable water and a good drainage system. In the past there had been no recorded outbreaks of HEV in this city. However, between December 1993 and March 1994, a massive outbreak of AVH due to HEV affected the city and created a lot of concern in the general population [13]. The main reason was the change in the demograph-

ic features of Islamabad created by the establishment of shanty towns along Lai Nullah, the stream that is the main water source of the city. These town's inhabitations had no civic amenities, and the excreta from the shanty towns polluted the tributaries of Lai Nullah. The common water supply of G/9, G/10 and H/11 sectors of Islamabad was badly affected by faecal pollution from these shanty towns. At the same time, because of modifications to the water treatment system for these sectors, the quality of the water reaching them was substandard. An increasing load of organic waste and defects in the water treatment plant functioning were the most probable causes of improper chlorination of the water supply. Consequently, during the outbreak, 3827 cases of AVH (associated with HEV) were recorded in these sectors. The nearby residential areas with independent water supplies were largely spared. The overall incidence of AVH in the affected areas was 10% of the total population (varying from 1% to 16% in various subsectors). The disease affected people in their second (31.4%), third (31.8%) and fourth (16.6%) decades of life. The AVH epidemic subsided quickly after the rectification of the suspected water purification plant [14].

5. HEV is gradually becoming a threat to Pakistan army personnel because of the pressure of increasing population on the existing sewerage system and the rusting of pipelines of old water supply systems. In December 1994 the Lahore garrison was badly affected by an outbreak of AVH, with 283 cases being admitted to the army hospital at one time. On investigation, the pipes of the water supply, rusted with holes, were found to be practically submerged in the open drains. As a short-term measure, the troops were

provided with boiled water until the total replacement of the existing water supply system could be undertaken along with the modification of the drainage system in the cantonment. Food and water discipline was enforced, and the epidemic was finally controlled. However, after three months hundreds of fresh cases of AVH were reported. The probable reason for this increase was a relaxation in water and food discipline, which occurred due to the influx of fresh troops from other stations, who were not accustomed to the strict water and food discipline enforced previously in the Lahore cantonment. The problem was gradually brought under control, and the outcome of efforts to supply pure water to troops was soon obvious.

All the above epidemics of HEV infection were caused by consumption of water that was polluted with faeces. These epidemics could have been avoided if proper measures had been followed. Investigations of possible sources of spread have always led to the same conclusion: that someone's faeces find their way to someone's mouth. The seed (virus) is present, the soil is fertile and the environment is conducive to epidemics of hepatitis E in much of the developing world. There is no vaccine available for HEV infection. There is no specific immunoglobulin that can act prophylactically. This means that the existing civic amenities need improvement and the chlorination and supply of water must be consistent and uninterrupted. Medical inspections of kitchens and water sources must be carried out regularly, and inspection reports should be acted upon without hesitation.

It is obvious that HEV has been an important cause of acute viral hepatitis in Pakistan, particularly in adults from lower socioeconomic groups. The problem is more

serious for those living in military camps, hostels, residential institutions and in segregated areas who consume untreated water from a common source. Fortunately, awareness of the problem has increased, and efforts are being made to prevent water contamination.

Diagnosis

As seen in the case of other types of acute viral hepatitis, the biochemical changes in patients with HEV infection are not typical of the disease. It is not possible to make a specific diagnosis of the type of acute viral hepatitis on the basis of biochemistry. The definitive diagnosis can be made only when tests for virological markers are done on sera from the patients.

Within two days of the onset of jaundice, it was found that the serum bilirubin and alkaline phosphatase levels were elevated to three times that of normal, and serum alanine transferase (ALT) was elevated to 35 times that of normal [12]. It is worthwhile to do the tests for hepatitis B surface antigen (HBsAg), antibody against hepatitis B core IgM (Anti-HBc IgM) and hepatitis A IgM antibody to exclude diagnosis of both hepatitis B and hepatitis A. Specific assays for HEV infection have been recently introduced. Testing for anti-HEV IgM has been mentioned by various workers in their studies [15,16] yet the diagnostic value of such a test is still controversial, as the currently available commercial kits for anti-HEV IgM testing have not shown consistent results. On the other hand, a test for anti-HEV IgG antibodies is reliable and has been used for diagnostic purposes. Two serum samples have to be taken, one during the acute phase and one after two weeks from onset of the disease. The prior absence of the antibody and its appearance after two weeks may re-

veal the specific diagnosis. Anti-HEV IgG persists for some years in the sera of patients, and its presence in a single specimen should be interpreted with care, at least in endemic areas [17]. The use of immune electron microscopy has been suggested for the diagnosis of HEV [18]. Faecal specimens of acutely ill patients were treated with the convalescent sera of hepatitis E patients, and the clumps of the virus particles were observed under the electron microscope. Subsequently, it was observed that in many specimens not enough virus particles were found (especially during the later stages of the disease). This lack of sensitivity and the need for the procurement and maintenance of such costly apparatus have discouraged the routine use of this methodology as a diagnostic technique [19]. Other diagnostic tools based on the polymerase chain reaction (PCR) for the detection of HEV-RNA (with a reverse transcription step) have been introduced recently and may become popular in future for the detection of HEV from the stools of acute hepatitis E patients [20,21].

Clinical features

The incubation period is three to nine weeks (21–63 days) and on average 40 days. The attack rate of HEV is higher in young adults than in children and those older than 40 years. There is a brief prodromal phase of anorexia, nausea, vomiting and abdominal pain, followed by jaundice. The disease is benign and self-limiting in nature.

In a series of 562 cases of hepatitis E studied in China, the clinical findings were recorded. The onset of disease was abrupt in most of the patients. About half of the patients had fever, malaise, nausea, abdominal pain, dark coloured urine and jaundice, whereas hepatomegaly was observed in 8%

of the cases. Headache (42.9%), diarrhoea (29.7%), splenomegaly (29.4%), itching (30.7%), arthralgia (13.7%) and rash (3.2%) were also recorded. As has been repeatedly mentioned, excessive mortality in pregnancy is the most significant feature of this disease.

Treatment

Treatment is purely supportive; there is no special antiviral drug available for HEV. Patients may be managed at home. However, in case of more serious cases with persistent vomiting, hospitalization may be necessary, and it is indicated mostly when there is marked disturbance in prothrombin time (at least 2 seconds more than the nor-

mal control) and the patient shows severe lethargy. There is usually no need for strict restriction on food or physical activity.

Prevention and control

Prevention and control purely depend upon the improvement of the sanitary conditions of society—proper disposal of waste, avoidance of contamination of food and the provision of pure water. Health education of the general public on personal hygiene is very important.

There is, so far, no protective vaccine available against the HEV infection. Studies on human serum immunoglobulin for passive prophylaxis have, so far, proved of no worth [22].

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