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Acquired immunodeficiency syndrome and infection with hepatitis viruses in individuals abusing drugs by injection

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ABSTRACT

The abuse by injection of heroin or other drugs has long been associated with liver disease caused by hepatitis B virus (HBV) and other viruses. Increasingly severe hepatic and virological complications of parenteral drug abuse have been reported due to infection with new viruses or concomitant alcohol abuse. The hepatitis delta virus (HDV) can replicate and cause liver infection only in the presence of HBV; such infection in HBV carriers may cause rapidly progressive and clinically significant liver disease. Liver cirrhosis is frequently detected in parenteral drug abusers who have chronic infection with both HBV and HDV or who also abuse alcohol.

More than one quarter of those persons with acquired immunodeficiency syndrome (AIDS) in the United States of America are homosexual or heterosexual males who are parenteral drug abusers. Existing evidence implicates parenteral drug abusers in the spread of hepatitis viruses and the retrovirus associated with AIDS to the general population. To cope with these serious problems the authors suggest that more intensive international co-operation is needed, particularly with a view to promoting data collection, research and the exchange of knowledge and experience on measures that have been effective in dealing with parenteral drug abuse and its complications.

Introduction

Several significant changes have recently taken place in the hepatic and virological complications of parenteral drug abuse. Liver disease of particular severity occurs in individuals abusing drugs by injection who

have both chronic infection with hepatitis B virus (HBV) and superinfection with hepatitis delta virus (HDV) [1]. Recent evidence suggests that abuse of alcohol by parenteral drug abusers increases the risk of cirrhosis and accelerates its development [2]. In the United States of America, parenteral drug abusers comprise the second largest group afflicted with the acquired immunodeficiency syndrome (AIDS), which is causally related to a retrovirus [3, 4].

Despite many difficulties in estimating the extent of parenteral drug abuse, it is clear that the problem has been increasing in terms of both the number of abusers and the number of countries to which this dangerous method of drug abuse has spread [5–7]. Available evidence suggests that in recent years heroin abuse has rapidly increased in South-East and western Asia and in a number of European countries, including the Federal Republic of Germany, Italy and Switzerland [7]. In both North America and Europe, there has been concern over a further significant increase in heroin abuse by injection during the period 1983–1985. The propensity of parenteral drug abuse to spread rapidly in an epidemic manner in communities where it has not previously existed is a particular cause for concern. It is obvious that any increase in the prevalence of parenteral drug abuse results in an increased dissemination of viruses causing liver disorders and AIDS.

This article provides a brief review of the developments relating to infection with hepatitis viruses and AIDS in individuals abusing drugs by injection. Measures for the treatment of affected individuals are recommended, as well as educational programmes and research in this vitally important area.

Liver disease

Liver disease has long been noted as a complication of parenteral drug abuse [8]. About two thirds of all parenteral drug abusers display biochemical abnormalities of the liver function that may be etiologically related to several factors. These include chronic infection with HBV, superinfection of chronic HBV carriers with HDV, one or more non-A, non-B viruses,* adulterants of heroin or other injected substances, and alcohol abuse. Neither the abused opiates [9] nor methadone [8], used in the maintenance of chronic narcotic addicts, are hepatotoxic. Cocaine, which is often abused parenterally alone and sometimes in combination with heroin, has been shown to cause hepatotoxicity in animals [10], but its effect on hepatic functions in humans requires further research. Liver disease has been observed in khat *(Catha edulis)* users in countries of the Arabian

* There appear to be at least two separate non-A, non-B viruses, but they have not been identified and serological tests have not yet been developed.

peninsula and east Africa, but a causal relationship between khat use and liver disease has not been established. The use of khat has, however, created a number of other public health and social problems [11].

Viral hepatitis

Parenteral drug abusers are almost universally exposed to HBV, but only 5–12 per cent of the exposed individuals become chronic carriers of hepatitis B surface antigen (HBsAg) who are able to transmit the virus to others [12]. More than half of all patients infected with HBV do not have an acute episode of hepatitis and may remain completely asymptomatic. Because parenteral drug abusers have liver function abnormalities more often than chronic HBV infection, it has been postulated that non-A, non-B viruses play a major role in the occurrence of the liver disease in drug abusers [13]. Non-A, non-B virus infections have been reported by different authors to cause a disturbingly high rate of chronicity, ranging from 23 to 55 per cent in various studies. The liver pathology in non-alcoholic parenteral drug abusers infected with HBV or non-A, non-B viruses is usually chronic hepatitis, but cirrhosis is rare in this group.

Because of their very high exposure to HBV and, presumably, to non-A, non-B viruses, parenteral drug abusers infected with these viruses comprise a major reservoir from which the viruses are spread to other people, including other parenteral drug abusers who share needles and syringes with them and other individuals from the general population who have sexual or other close contact with them. A recent survey in New York City showed that 78 per cent of a group of 50 male parenteral drug abusers had stable sexual relationships with women who did not inject drugs [14]. The capacity of parenteral drug abusers to transmit viruses to the general population was confirmed by a study carried out in Ireland in which it was found that the major source of HBV infection in individuals who were not in a known high-risk group for that disease was sexual or other close contact with parenteral drug abusers [15].

HDV was first described in 1977 in the serum and liver cell nuclei of Italian HBsAg carriers [1]. This virus requires the presence of HBV in order to replicate and to produce HDV infection. Infection with HDV may occur either simultaneously with HBV infection or as a superinfection in chronic HBsAg carriers. In both types of HDV infection its duration and outcome are dependent on the course of the HBV infection.

Infection with both HDV and HBV causes chronic liver disease that is more severe and progressive than that caused by HBV infection alone. A study of children in Italy with HBsAg-positive chronic liver disease showed that 28 of 34 children who were also infected with HDV had either chronic active hepatitis or cirrhosis [16]. Cirrhosis was found in 4 of 34

children infected with both HBV and HDV and in only 5 of 236 children infected with HBV alone. Fulminant hepatitis occurs at an increased rate not only in co-infection with HBV and HDV but also in HDV superinfection of patients with chronic HBV infection [1].

Infection with HDV is distributed world-wide and is endemic in southern Italy and parts of South America, Africa and the Middle East. Its spread to non-endemic areas has been facilitated by parenteral drug abusers. The great majority of patients with HDV infection in non-endemic areas have been either parenteral drug abusers or polytransfused hemophiliacs [17]. Retrospective analysis of sera from HBsAg-positive parenteral drug abusers from Malmö, Sweden, collected between 1970 and 1981, revealed that HDV first became detectable in that population in 1973 and its prevalence increased to 72 per cent by the end of the study period [18]. Non-addicts from the same city rarely had HDV infection.

Concomitant abuse of alcohol with parenteral drug abuse is an additional cause of severe liver disease [2, 12]. Cirrhosis has been observed primarily in parenteral drug abusers who also abuse alcohol. In the United States, cirrhosis is usually seen in the fifth and sixth decades of life, whereas in parenteral drug abusers who also abuse alcohol it has frequently been diagnosed in the "24–34-year" age group. An examination of biopsies taken from patients under the age of 35 who abused alcohol only, parenteral drugs only or both, showed that cirrhosis was significantly more frequent among patients who abused both alcohol and drugs (by injection).

Acquired immunodeficiency syndrome

The number of new cases of AIDS and the number of countries in which it has appeared have continued to rise since its initial description in 1981. AIDS is manifested by opportunistic infections and malignancies of the type usually associated with cellular immunodeficiency [19]. *Pneumocystis carinii* pneumonia and Kaposi's sarcoma are common clinical features and are a result of a profound depletion of the helper/inducer subset of T lymphocytes. By definition, patients with AIDS have no other conditions associated with immunodeficiency and have received no immunosuppressive therapy. The underlying cause of AIDS is infection with a new agent, the lymphadenopathy-associated virus (LAV) [3], also known as human T-cell lymphotropic virus subgroup III (HTLV-III) [4], which, in the following text, will be referred to as LAV/HTLV-III. Evidence that LAV/HTLV-III is the cause of AIDS includes the following: the isolation of LAV/HTLV-III from AIDS patients and members of all high-risk groups; the high prevalence of antibody to LAV/HTLV-III in AIDS patients and persons at high risk; the affinity of this virus for the helper/inducer subset of T lymphocytes, and the cytopathic effect of

LAV/HTLV-III on these lymphocytes. For further details on the clinical, epidemiological and virological features of AIDS, the reader is referred to a recent review article [20].

AIDS in parenteral drug abusers is associated with opportunistic infections in more than 96 per cent of the cases [21]. Only 4 per cent of parenteral drug abusers with AIDS have Kaposi's sarcoma, with or without opportunistic infections [21]. Patients with Kaposi's sarcoma without opportunistic infections have a longer survival rate. The prognosis of parenteral drug abusers with AIDS is therefore poorer than that of the overall group of AIDS patients.

Approximately 80 per cent of individuals die within the first two years following the manifestation of AIDS, and there have been few long-term survivors [19].

Risk groups for AIDS

The table below shows the number of AIDS patients in the major risk groups reported in the United States as at 12 August 1985. Homosexual or bisexual men were the major group affected (64 per cent). Heterosexual parenteral drug abusers were the next largest group, comprising 17 per cent of all cases. An additional 9 per cent of the cases consisted of homosexual or bisexual men who were parenteral drug abusers. A smaller percentage (10 per cent) included heterosexual partners, paediatric cases, individuals with hemophilia or coagulation disorders and individuals who

Number of cases of acquired immunodeficiency syndrome in the major risk groups reported in the United States as at 12 August 1985

Category	*Number of cases*	*Percentage*
Homosexual or bisexual men[a]	7 919	64
Parenteral drug abusers (heterosexual)	2 097	17
Parenteral drug abusers (homosexual or bisexual)	1 061	9
Transfusion with blood or blood products	185	1
Heterosexual contact[b]	122	1
Hemophilia or coagulation disorders	76	1
Paediatric cases[c]	149	1
None of the above[d]	799	6
Total	12 408	100

Source: Center for Disease Control, Atlanta, Georgia, United States.

[a] Having no history of parenteral drug abuse.

[b] With persons affected by acquired immunodeficiency syndrome or in major risk groups for acquired immunodeficiency syndrome.

[c] Including 104 cases involving children with one of their parents having acquired immunodeficiency syndrome or in a major risk group for acquired immunodeficiency syndrome.

[d] Including 336 cases involving individuals born in countries in which acquired immunodeficiency syndrome had not been associated with known risk factors.

received transfusions of blood or blood products. The male–female ratio in adults with AIDS in the United States is approximately 15 to 1. Among heterosexual parenteral drug abusers, the male–female ratio is approximately 4 to 1.

Parenteral drug abusers frequently have sexual partners who do not inject drugs, and those parenteral drug abusers who are contaminated by HTLV-III may transmit the virus to their partners, who, in turn, may spread it to the general population [14]. AIDS has already been reported in female sexual partners of male parenteral drug abusers with AIDS and in children whose mother or father has abused drugs by injection. The data on cases of AIDS in a population of Zaire [22] and among patients in Belgium from countries in central Africa [23] suggest that heterosexual contact is responsible for the spread of AIDS in the population of those countries. The incidence rates of AIDS in countries in central Africa are approximately the same for males as for females [22, 23]. In Zaire, many cases involving heterosexual transmission of AIDS (from males to females or from females to males) have been reported [22]. These observations suggest that there is a great risk for the spread of AIDS through heterosexual contact.

Data on the prevalence of antibody to LAV or HTLV-III (anti-LAV) in parenteral drug abusers are available from New York City [24], Zurich [25] and London [26]. Using an assay to test the presumed core protein of the virus, 50 of 86 (58 per cent) parenteral drug abusers from New York had a positive anti-LAV. Among patients who had participated in long-term methadone maintenance programmes and who had entered those programmes prior to the onset of increasing prevalence of anti-LAV in the drug-abusing population, the prevalence of anti-LAV was found to be below 10 per cent [24] and positive reactions were found only in patients with continued parenteral drug abuse during methadone maintenance. At both San Francisco and Chicago, approximately 10 per cent of those active parenteral drug abusers examined were positive for anti-LAV [27]. At Zurich, 37 of 103 (36 per cent) parenteral drug abusers were positive [25]. In London, anti-LAV was detected in only 4 of 269 (1.5 per cent) parenteral drug abusers [26]. An overwhelming majority of parenteral drug abusers with AIDS were reported in the New York metropolitan area and the part of New Jersey that is adjacent to it [21]; although the reason for this is unclear, it may be related to a greater overlapping of the homosexual and parenteral drug abuser populations in that area.

Suggested measures

The adoption of measures that may decrease the use of hypodermic needles among parenteral drug abusers is necessary in order to limit the spread of AIDS, and such measures should be instituted as soon as

possible. To date, methadone maintenance remains the most effective treatment approach for hard-core opiate addicts [28]. Research findings indicate that methadone maintenance is acceptable to a large number of parenteral opiate addicts and is associated with a high retention rate (greater than 70 per cent per year) in voluntary treatment programmes [28].

Methadone maintenance programmes should be established on a scale large enough to accommodate hard-core opiate addicts who desire such treatment. In order to reduce the risk of infection from the use of nonsterile needles, such programmes can be complemented by alternative measures for those addicts who do not accept, or for any other reason are not involved in, such programmes. One such approach has been adopted in the Netherlands: the issuance of a sterile syringe and needle to a registered parenteral drug abuser on receipt of a used syringe and needle. This measure may help to reduce the spread of viral infection through needle sharing by parenteral drug abusers, but, in this connection, the symbolic role which needle sharing plays in the drug abuse subculture should be taken into account [29]. Almost invariably, a drug abuser's first injection is administered by a friend using the friend's needle. Among small groups of abusers who help each other procure illegal drugs, needle sharing is a form of social bond. Needle sharing is particularly rampant in so-called "shooting galleries" – settings in which abusers inject their drugs [29]. It is not clear at this time whether the fear of AIDS among parenteral drug abusers will result in a decreasing trend in needle sharing and a possible increasing trend in using other methods such as sniffing and smoking drugs rather than injecting them; there is at present preliminary evidence supporting the former trend [30].

Educational programmes to advise individuals at risk of parenteral drug abuse are also urgently needed. Recently, fact sheets on AIDS with particular reference to parenteral drug abuse have been published [31]. Personnel in drug clinics must be prepared to provide accurate and up-to-date information concerning hepatitis viruses and AIDS. There is preliminary evidence suggesting that intensive educational efforts might reduce needle sharing among parenteral drug abusers [31], but such efforts should not be regarded as a substitute for the therapeutic measures mentioned above. Health care professionals should acquire the necessary knowledge concerning addiction and generate appropriate attitudes towards drug abusers and their treatment [32].

Research

Additional research is needed to gain a better understanding of the transmission of viruses by parenteral drug abusers. The following topics are among those that deserve priority in such research:

(a) The long-term outcome of patients who are sero-positive for anti-LAV;

(b) The interrelationships of hepatitis viruses and LAV/HTLV-III in parenteral drug abusers, and the possible modulating effects of alcohol abuse;

(c) The effects of treatment of drug addicts on the prevalence of HBV, HDV and LAV/HTLV-III;

(d) The effects of injected nonsterile material on the immunological systems of parenteral drug abusers.

All the foregoing factors should be investigated with a view to determining whether they play a role in altering the immunological host response and, if so, to what extent they may be involved. As indicated in recent recommendations on AIDS made by the World Health Organization [33], surveillance studies of groups at risk for AIDS, including parenteral drug abusers, should be carried out in all countries, including those where AIDS has not yet appeared. Research aimed at developing a safe and effective vaccine for LAV/HTLV-III should also be given high priority. A safe and effective vaccine already exists against HBV infection; by preventing HBV infection, this vaccine can also effectively prevent HDV infection. There is little information on experience derived from administering hepatitis B vaccine to parenteral drug abusers. Once the HBV vaccine produced using techniques of molecular biology becomes more widely available, however, its cost should decrease; this, in turn, may facilitate its being administered to a broader segment of the population – one that will include drug abusers.

Concluding remarks

In many parts of the world, parenteral drug abuse is a very widespread problem with severe health consequences, such as viral hepatitis and AIDS, which threaten the health and survival of the drug abusers themselves and lead to the spread of viral infections within the general population. The World Health Organization is striving to promote co-operation and increase efforts at both the national and international level in order to control the problem. There is clearly a need for intensified international co-operation in research with a view to gaining more knowledge and understanding of the interrelationships of parenteral drug abuse, liver disease, drug hepatotoxicity and the spread of AIDS and other forms of viral infection. There is also a need for promoting international co-operation in collecting and disseminating relevant information on drug abuse problems, including viral hepatitis and AIDS, and on methods that have proved to be effective in coping with such problems, as well as in helping to identify areas where further research is needed.

Conscious that AIDS and other manifestations of LAV/HTLV-III infection are becoming a major public health concern in many areas of the world, the Executive Board of the World Health Organization adopted resolution EB77/SR/16 at its January 1986 session, in which it urged Member States:

> "(1) to maintain vigilance and carry out as necessary public health strategies for the prevention and control of AIDS; (2) to share information, in all openness, with the Organization and other Member States on AIDS incidence, the seroprevalence of LAV/HTLV-III, laboratory methods, clinical experience, and approaches to prevention and control of LAV/HTLV-III infection; (3) to call upon the Organization as necessary for support in the prevention and control of AIDS and other LAV/HTLV-III infections."

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