SHORT REPORT

Is multiple sclerosis a sexually transmitted infection?

C H Hawkes

Although opinion currently favours a genetic/immune process for multiple sclerosis, the possibility of sexual transmission has not been considered in depth. In this review I evaluate the evidence in support of such a hypothesis.

MIGRATION STUDIES

It is generally accepted that migration from high to low risk areas decreases the probability of developing multiple sclerosis if the move takes place before 15 years of age, and the likelihood of multiple sclerosis increases in migrants from low to high risk areas—for example, Algerian migrants to France and children of Caribbean migrants living in England. These studies are supportive of an environmental factor and raise the possibility that the risk of multiple sclerosis is established in the teenage years, the time of sexual debut.

CLUSTERS AND EPIDEMICS

Faroe Islands

Kurtzke et al described four small epidemics totalling 42 cases and suggested that multiple sclerosis is acquired two years after exposure from 11 years of age onward, and that the first cases resulted from contact of Faroese residents with asymptomatic but infected British troops. Indeed the Faroese were occupied by 1500–8000 British troops in 1940–45 and residence of multiple sclerosis cases corresponded with that of soldiers; also social contact including marriage between Faroese and troops was common. Sexual transmission of an infectious agent from British troops is a possibility, and the subsequent decline in multiple sclerosis prevalence in the Faroes is evidence of a small epidemic. Kurtzke’s data have been heavily criticised on account of incomplete ascertainment and variable diagnostic accuracy over several decades. By analogy with other regions where there has been an influx of troops and an increase in multiple sclerosis cases—for example, Iceland, Orkneys, Shetlands, Sitka, Macomer and Japan—the Kurtzke theory is appealing unless the same counterarguments are equally correct. For the multiple sclerosis–sexually transmitted infection theory to be valid one has to assume sexual contact with Faroese, some of whom would have been girls under 16 years of age.

Orkney and Shetland Islands

In repeated surveys, the prevalence of probable multiple sclerosis since World War II increased in the Orkneys and Shetland Islands, though more dramatically in the former where troop numbers were greater. In 1954 the prevalence rate of multiple sclerosis for the Orkneys was 82/10^5 and in 1974 it reached a record level of 309/10^5. The initial overall increase in new cases occurred 18 months after the arrival of British troops in 1940 (15 000 in Orkneys and 5000 in Shetlands), almost equalling the local population. Inevitably, it has been suggested that the increase reflected improved case ascertainment. For this to be true it was calculated that at least half the 15 or more Orkney and Shetland cases ascertained in the period 1930–39 would need to have been overlooked. Despite repeated searching, the prevalence fell to around 40×10^5 after 1970. Changes in age specific prevalence, mean duration of illness, and mean age of the multiple sclerosis population were consistent with a decline in the incidence of multiple sclerosis or a dwindling prevalence of canine distemper. The reduced incidence might be related to departure of troops in peacetime years. Similarly, the lower rate in the Shetlands could be explained by smaller numbers of soldiers. Others conclude that the high rate merely represents the effect of increased disease duration owing to better standards of care, improved ascertainment, and so on. These points do not account for the differences in multiple sclerosis frequency between Orkney and Shetland, nor do they explain the declining incidence.

Iceland

There was an apparent increase in the incidence of multiple sclerosis between 1945 and 1954. During World War II the island was occupied by some 50 000 Allied troops, when the local population was 125 000. The uplift starting in 1945–1954 continued until around 1990. There was close social contact and marriage between the troops and Icelanders (Benedikz J, personal communication). Poser and coworkers consider that the increase was related to changes in ascertainment, particularly of more benign cases, in the postwar era. Cohorts after 1940 show a non-significant trend to excess female cases, with male cases equalising in about 1960. Another complicating issue not applicable to the Faroes was the appointment of Iceland’s first neurologist in 1942, leading to a suggestion that the increase followed improved ascertainment from an expanding number of interested neurologists. Even if the gender shifts are representative, some argue that the increase in female cases in the 1970s onwards resulted from greater

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recognition of benign cases facilitated by the introduction of evoked potential studies and magnetic resonance imaging.

Hordaland, Norway
In a space-time cluster analysis, 381 patients from a stable population developed multiple sclerosis between 1953 and 1987. Those within the same birth cohort lived significantly closer to each other than would be expected by chance during age 13–20 years, peaking at 18 years. It was proposed that a common infectious agent such as Epstein–Barr virus (EBV) transmitted by close physical adolescent contact was responsible. While EBV is spread orally and could be viewed as a sexually transmitted infection, virological data do not support a link (see below). However, other sexually transmitted diseases could be relevant.

INFECTIONS
Retroviruses became of major interest with the discovery that HTLV-1 caused tropical spastic paraplegia. These strongly neurotropic viruses produce demyelinating disease in animals and delayed systemic disease in humans—for example, AIDS after HIV. In 1989 a retrovirus (MSRV) was isolated from leptomeningeal cells of patients with multiple sclerosis. A related virus (HERV-W) has been reported but it is unknown whether either represents an epiphenomenon because a similar viral sequence may be found endogenously. If it were exogenous then sexual transmission would be plausible. This is of considerable interest in view of the longstanding hypothesis that herpes virus may be involved in the pathogenesis of multiple sclerosis, perhaps by triggering retrovirus reactivation. It has been shown many times that EBV infection is universal in multiple sclerosis, compared with a 90% prevalence in controls, but EBV cannot be demonstrated at the earliest stages of multiple sclerosis nor can the EBV genome be detected consistently at the time of worsening clinical symptoms.

TROPICAL SPASTIC PARAPLEgia
Tropical spastic paraplegia is most often related to infection with the retrovirus HTLV-1 and has considerable similarity to primary progressive multiple sclerosis. It is spread chiefly by sexual contact and most efficiently from male to female, but even this takes one to four years for a 50% probability of seroconversion, and 95% of those infected with HTLV-1 are asymptomatic. Of 719 Japanese patients with antibodies to HTLV-1, 28% of children were positive when both parents were HTLV-1 positive and 20% when the mother alone was infected. There were no cases of transmission from father to child. They estimated the probability of HTLV-1 transmission from husband to wife at 61% and from wife to husband at 0.4% over a 10 year period. These family viral transmission figures resemble “familial” multiple sclerosis. Although tropical spastic paraplegia is primarily transmitted sexually, concordant conjugal pairs are rare. The above similarities between multiple sclerosis and tropical spastic paraplegia imply that multiple sclerosis is weakly contagious and related to novel viral infection.

GENERAL CHARACTERISTICS OF SEXUALLY TRANSMITTED INFECTIONS AND POSSIBLE RELATION TO MULTIPLE SCLEROSIS
In general, more sexually transmitted infection is found in populations with lower standards of medical care and fewer sexual health clinics. Female cases predominate in the early phase of evolution in Western cultures; for example, the age and sex distribution of gonorrhoea in the USA shows more affected women under the age of 24 years, followed by an excess of male cases thereafter. Sexually transmitted infections develop at an earlier age in women, as they have sex with men earlier. In general this pattern of gender shift is also found in multiple sclerosis. Male to female transmission of sexually transmitted infections is more efficient than female to male, as shown for HIV (20 times more efficient). HTLV-1, hepatitis B, herpes simplex, gonorrhoea, and chlamydia. The incidence of sexually transmitted disease increases during wartime; and a high prevalence is found in permissive societies.

Worldwide prevalence
If there is genetic resistance to multiple sclerosis in black people there should be continued immunity in those who migrate to high risk areas, but this is probably untrue. The prevalence of multiple sclerosis in North American blacks is intermediate and children of Caribbeans who migrate to the United Kingdom show an increased risk of multiple sclerosis. It is suggested that black people living in developing countries have general immunity to infection through repeated childhood exposure, which increases their resistance to multiple sclerosis in a non-specific manner. If so this theory would strengthen the possibility that multiple sclerosis is an infection (venereal or otherwise). It could offer another explanation for the rarity of multiple sclerosis in black Africans and the infrequency of multiple sclerosis and AIDS in the same patient. The scarcity of multiple sclerosis in black Africans does not necessarily mean that infection is unimportant; taking a reciprocal situation, there is only one published case of tropical spastic paraplegia in a white (female) person.

Differences in morality and culture offer an alternative explanation for the unequal distribution of multiple sclerosis. Permissive societies have high rates of multiple sclerosis and sexually transmitted disease, and the worldwide variance of multiple sclerosis normally attributed to genetic makeup could be explained on the basis of infrequent social contact. Multiple sclerosis is rare in native populations physically or culturally isolated from white populations. Examples include Australian aboriginals, New Zealand Maoris, South African blacks, North American Hutterites, Inuits, Yakutes, Norwegian Sami, native Americans, Guamanians, South Kashmir dwellers, and Hungarian and Bulgarian gypsies. If there were a genetic predisposition to multiple sclerosis, a high prevalence of the disease would be expected in at least some of these areas, especially where consanguinity is high. Others argue that their immunity reflects a lack of Europol genes. Against this proposal is the loss of “genetic” resistance in Caribbeans who migrate to Britain, and the medium prevalence rate of multiple sclerosis in American blacks. Before the abolition of apartheid, white South Africans suffering from multiple sclerosis had no opportunity to transfer it to blacks. Racial variation in multiple sclerosis may just reflect racial separation. If social contact with whites increases, as it might with the abolition of apartheid, then more multiple sclerosis in African blacks would be expected. Indeed suspected multiple sclerosis in eight patients has now been reported from the Soweto district. In Martinique, where multiple sclerosis was almost unknown in French Afro-Caribbeans before 1970, 62 cases of multiple sclerosis have since been found. Of these, 17 had lived in continental France for at least a year before the onset of multiple sclerosis.

Three broad categories of sexual behaviour have been proposed: type A is characterised by few lifetime partners for both men and women and is seen in active members of religious groups, for example strict Moslems or Mormons. In type B, most women have one lifetime partner but men have several, with a minority of women having multiple partners. In type C, both men and women have several lifetime partners, as in permissive societies. Here the male to female ratio will be determined by the ease of transmission of sexually transmitted disease, which is usually male to female, resulting in a preponderance of female sufferers. Clearly the incidence of sexually transmitted disease will be low in type A societies and high in type B for the same reason, as they have sex with their partners. In broad terms these patterns concur with the high multiple sclerosis rate of countries with type C patterns (for example, Britain, Scandinavia, USA), and with
the medium rate in Italy, where type B behaviour is expected. In the Moslem areas of Kashmir and Thugbah, a door to door study showed a virtual absence of multiple sclerosis. In both Jordan and Kuwait the disease is twice as common in Palestinian Moslem communities as in native Arab Moslem communities. A genetic component was proposed for the higher rate in Palestinian Kuwaitis, but type B conduct in male Palestinians might explain this better.

**Childhood multiple sclerosis**

The largest surveys of children under 16 years age reveal a female to male ratio of 2.2–3 to 1. Apart from genetic mechanisms, childhood multiple sclerosis might represent delayed expression of a maternally transmitted agent or child abuse. Most abuse victims are female in a ratio of 3 to 1, similar to the childhood multiple sclerosis rate. It is estimated that 1% of female North American children experience sexual abuse yearly. The predominance of girls in childhood multiple sclerosis would support the concept of sexual transmission. Whether abused children subsequently develop multiple sclerosis has not yet been examined.

**Conjugal multiple sclerosis**

If multiple sclerosis is acquired by sexually transmitted infection mainly during adolescence, then an excess of disease concordant pairs would not be expected. If multiple sclerosis is acquired chiefly in adult life then such pairs should be detectable. In the United Kingdom conjugal study no excess was seen; however, the method of data acquisition was not systematic. In a Canadian study, only 23 of 13 550 spouses were concordant for multiple sclerosis and this was not significant when adjusted for lifetime risk. Conversely, five of 659 cases of conjugal multiple sclerosis have been identified in a Sardinian survey (0.98%), times higher than chance. Many factors can spuriously raise or depress the expected rate, and this is debated elsewhere. The issue of conjugal transmission is unresolved but for adults it is probably not a major factor.

**Transmission through parents, breast milk, drugs, or blood transfusion**

In one large population based study of parent–child multiple sclerosis transmission, there was significant deficit (1 in 75) of affected father–son pairs (comparable to HTLV-1 infection) but only a trend was found in two other studies. If the multiple sclerosis agent were infectious it could be spread in utero or during parturition. Transmission through breast milk is not supported by three small surveys. Multiple sclerosis is not transmitted by blood transfusion according to the only substantial survey; however, many received blood after disease onset, and from 1980 onward Scottish multiple sclerosis patients were not permitted to donate blood (Swinger R, personal communication). Drug abuse was the only significant risk factor (odds ratio 4.4) in a case–control study of 108 multiple sclerosis patients, but the authors did not record whether the drugs were taken intravenously (Brosseau L, personal communication).

**Longitudinal studies**

The Danish multiple sclerosis registry has accumulated over 12 000 verified cases since 1949. From 1950 to 1968 the corrected multiple sclerosis incidence rate for both sexes fell

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### Table 1 Summary of arguments for and against possibility of multiple sclerosis as a sexually transmitted infection

<table>
<thead>
<tr>
<th>Evidence potentially linking MS to STI</th>
<th>For an association</th>
<th>Against an association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migration studies</td>
<td>MS risk lowered by migration before age 15 years. Prevalence increased in Caribbeans who migrate to the UK. Neither phenomenon is explicable by genetic factors.</td>
<td>Small numbers. Ascertainment bias. Healthier people emigrate.</td>
</tr>
<tr>
<td>Clusters and epidemics</td>
<td>MS follows entry of young males in some MS naive populations, especially in wartime: eg, Faroese, Okinney and Shetland, Iceland, Macomer, Sika. Rate now declining.</td>
<td>Ascertainment bias, small numbers, more neurologists.</td>
</tr>
<tr>
<td>Tropical spastic paraplegia</td>
<td>Known retroviral STI with many similarities to primary progressive MS.</td>
<td>No retrovirus definitely found in MS so far.</td>
</tr>
<tr>
<td>Spread by IV drug abuse, breast feeding, or blood transfusion</td>
<td>High rate in drug abusers (one study). The single large blood transfusion study is flawed. Drug abuse study did not specify if agents used intravenously. No link with blood transfusion or breast feeding.</td>
<td></td>
</tr>
<tr>
<td>Family studies</td>
<td>MS transmits frequently from mother but rarely from father to son (one study). Pattern is similar to HTLV-1. Adoption studies do not address possibility of STI. Genetic factors explain pattern. Two other studies do not support alleged rarity of father–son concordance. Adoption studies show no increased risk.</td>
<td></td>
</tr>
<tr>
<td>Twin studies</td>
<td>French study has least bias and shows little or no genetic influence. Canadian and UK studies have ascertainment problems. UK and Canadian studies support major genetic component. French study has ascertainment bias.</td>
<td></td>
</tr>
<tr>
<td>Age of onset and gender pattern</td>
<td>MS mimics that of some STI—that is, earlier onset and higher initial rate in females. Male rate increases later. Correct, but could be explained also by genetic factors.</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>Raised MS incidence after six or more years use owing to increased and unprotected sexual activity. Might be immunosuppressive effect of OCT.</td>
<td></td>
</tr>
<tr>
<td>Low MS rate in societies</td>
<td>MS and STI rare in strict Moslem but MS rate increased in some liberalised Moslem populations. Could be explained by genetic resistance/susceptibility or ascertainment bias.</td>
<td></td>
</tr>
<tr>
<td>with strict sexual moral code</td>
<td>Follows sexual revolution of 1960s—eg, increased female MS rate in Denmark with less use of barrier methods for contraception and higher rate of STI. Contraceptive pill use might increase susceptibility to MS through immune mechanism. Higher rate of affected female cases because of improved detection. The largest (Canadian) study shows no increased risk. Adoption and other family studies infer that infection is not relevant.</td>
<td></td>
</tr>
<tr>
<td>Longitudinal gender shifts in prevalence</td>
<td>Low conjugal rate in two studies; raised in one. Transmission might be mainly male-female as in HTLV-1. Low conjugal rate in HTLV-1. Risk of transmission may be highest in teenagers. Once established MS may be less infectious. Explained more convincingly by susceptibility and resistance alleles.</td>
<td></td>
</tr>
<tr>
<td>Conjugal MS</td>
<td>Follows sexual transmission, with strict STI populations.</td>
<td></td>
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<tr>
<td>World wide distribution</td>
<td>Corresponds to countries with permissive attitude to sex. Low MS rate in Central Africa may be due to separation from white population, early exposure to infections, and genetic resistance. Low rate in many isolated communities with high consanguinity may also be result of isolation from white populations.</td>
<td></td>
</tr>
<tr>
<td>Childhood MS</td>
<td>Might result from delayed maternally transmitted infection or from sexual abuse which, like childhood MS, is commoner (3:1) in girls. Effect of genetic loading.</td>
<td></td>
</tr>
</tbody>
</table>

IV, intravenous; MS, multiple sclerosis; OCT, oral contraceptive; STI, sexually transmitted infection.
significantly from 5/10° to 3.5/10°. This could have been a fall from a high wartime rate, similar to that seen elsewhere. Thereafter the female rate increased significantly to around 6/10°. This started in the early 1970s, and may be associated with the introduction of oral contraceptives and a consequent reduction in the use of barrier methods in the previous “sexual revolution.” Similar trends have been documented elsewhere: the More and Romsdal areas of Norway; the Bergen area, Norway; Minnesota, USA; Japan; and North African migrants to France. Ascertainment bias would be unlikely to account for gender shifts, but some maintain this trend reflects improved detection of mildly affected female cases.

Animal models suggest that oestrogens protect against multiple sclerosis. If so, oral contraceptives should cause a reduction in the prevalence or severity of multiple sclerosis. Consequently, oral contraceptives assist the transmission of sexually transmitted infections because barrier methods of contraception are used less and sexual activity increases within and outside marriage. If multiple sclerosis is a sexually transmitted infection, then a higher rate of multiple sclerosis in those using oral contraceptives would be expected. In the large prospective US nurses health study, it was concluded oral contraceptives did not protect against multiple sclerosis; in fact closer scrutiny of their study reveals that the risk of multiple sclerosis after six or more years of oral contraceptive use doubles.

CONCLUSIONS
I propose that multiple sclerosis is a sexually transmitted infection acquired principally during adolescence and mainly from infected and not necessarily symptomatic males (table 1). I do not suggest that sexual transmission is the only cause, but that inherited factors create a susceptibility to a sexually transmitted neurotropic agent. The occurrence of high risk zones may be a compound effect of white racial predominance, cultural values (particularly attitudes to sexual morality), and patterns of cross-racial sexual contact. Low risk areas such as central Africa may exist because of competition from other infection or early exposure to multiple infections, thereby producing immunity. The increased incidence in apparently multiple sclerosis-naive, isolated areas worldwide following exposure to military personnel implies a transmissible agent. The similarity of multiple sclerosis to HTLV-I infecting its familial transmission, and the profile of gender shift and prevalence in most longitudinal incidence studies suggests the “multiple sclerosis agent” may be spread by sexual contact. This theory provides a testable hypothesis which could be addressed by a case–control study of multiple sclerosis patients and their partners, by examination of concordant and discordant twin pairs, and by study of multiple sclerosis in social groups adhering to a strict moral code, such as Mormons or nuns.

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