

## MINI REVIEW

## HTLV-I infection in human disease

Retroviral infection has been shown to cause neurological disease and leukaemia in man and there has recently been some interest, principally in Japan, on whether retrovirus infection might have ocular manifestations in its own right. The human T Lymphotropic virus (HTLV-I) is a member of the family Retroviridae, which has, as its name suggests, an affinity for T cells. Retroviruses are a single group of diploid RNA viruses, which encode synthesis of double-stranded DNA from a single strand of viral RNA (the usual flow of genetic information being in the opposite direction<sup>1</sup>). The DNA, or provirus, subsequently becomes integrated into the host cell genome and serves as a template for viral replication.

There are four major classes of human retroviruses, but only two are linked causally with human disease: the oncoviruses, to which HTLV-I and the closely related HTLV-II belong, and the lentiviruses, which includes the human immunodeficiency viruses HIV-I and II. Although HTLV-I and HIV belong to different subgroups, they have a number of molecular, biological, and clinical features in common. These include a similar genomic arrangement and a tropism for CD4+ T lymphocytes, though the HTLV-I receptor has yet to be described. Both viruses are transmitted by the same routes, and infection can lead to neurological disorders, immunodeficiency, and cancer. HIV, however, unlike HTLV-I is not oncogenic in its own right and probably exerts its influence by derangement of immune surveillance. Although it was established that viruses now known as retroviruses were associated with animal tumours as long ago as 1908, when Rous described a sarcoma of chickens,<sup>2</sup> the first human retrovirus was not isolated until 1978. Robert Gallo and his coworkers isolated the virus from a cutaneous T cell lymphoma in a black American patient.<sup>3</sup> This adult T cell leukaemia (ATL) is common among the people of the south-west islands of Japan.<sup>4</sup> A second area of endemicity was found in 1982 in the Caribbean following the discovery of ATL in London patients all of whom were of Caribbean origin. HTLV-I is also endemic in parts of Africa.<sup>5</sup> Further sporadic cases of ATL have been described in Caucasians in England and Italy and most recently from Brazil.<sup>6</sup> Evidence from serological and molecular biological studies for the association of HTLV-I and ATL is convincing.<sup>7</sup> In 1985 an association with tropical spastic paraparesis (TSP) was described in Martinique,<sup>8</sup> and in Japan HTLV-I was shown to be associated with a second disease, known as HTLV-I associated myelopathy (HAM).<sup>9</sup> TSP and HAM are now recognised as being the same disease and occur in the Caribbean, Africa, and South America as well as Japan and the Indian Ocean Islands and among migrants in the UK, USA, France, and Canada.

What then is the natural history of HTLV-I? How is it transmitted, and, once acquired, what are the risks for developing disease? Seroprevalence studies have shown that up to 20% of the inhabitants of south-west Japan and up to 10% of those of the Caribbean have antibodies to HTLV-I<sup>10,11</sup> the seroprevalence showing a linear increase with age. The virus has been shown to be transmitted by three major routes; from mother to child,<sup>12</sup> through sexual intercourse,<sup>13</sup> and by blood and blood products.<sup>14</sup> The risk of perinatal infection is about 25%, transmission being mainly via breast milk and saliva with very little being transmitted in utero. The rate of

sexual transmission is about 6% per annum from male to female but only 1% from female to male, though this may increase in the presence of ulcerative genital disease. HTLV-I is highly cell associated and therefore, unlike HIV, can be transmitted only by whole blood or blood products but not by cell-free products such as plasma. It has been estimated that there is approximately a 60% chance of acquiring infection from a contaminated blood transfusion. It is interesting to note that both HTLV-I and HTLV-II are being found with increasing prevalence among intravenous drug abusers in Europe and the USA.<sup>15</sup> The overall life time risk of ATL is 1-5% in persons affected before the age of 20.<sup>16</sup> Both sexes are equally affected, which is probably a consequence of infection in childhood.

Tropical spastic paraparesis was first associated with HTLV-I in 1985 in Martinique, when 68% of patients with that condition were found to have antibodies to HTLV-I in their peripheral blood.<sup>17</sup> This association has since been confirmed and expanded, and there appears to be no doubt that HTLV-I infection is the cause of this disease. The prevalence of TSP is about 12-28/100 000 of total population in endemic areas, which is partly due to the length of survival of patients with TSP. Women are three times more likely to develop the disease than men, which reflects the greater seroprevalence in adult women, infection being acquired either in childhood or in adult life.

The clinical picture of TSP is of a chronic progressive paraparesis without remissions starting in adulthood which predominantly affects the pyramidal tracts with sphincter involvement. Back and radicular pain are common, and the upper limbs are relatively spared. The disease has some similarity with certain forms of multiple sclerosis (MS), which has led to considerable interest in the role of retrovirus infection in the pathogenesis of MS. However, TSP in its recognised form is clinically, pathologically, and virologically different. Antibodies to HTLV-I are found in the serum and cerebrospinal fluid. The virus has been identified in neurological tissue, and the pathology is of an adhesive arachnoiditis and vasculitis.<sup>18</sup> Magnetic resonance imaging scans can show similar white matter lesions in the cerebrum, pons, and cerebellum to those of MS, but, in contrast to MS, involvement of the visual system is usually subclinical. A French study<sup>19</sup> of 167 patients with chronic idiopathic myelopathies identified 10 cases with HTLV-I infection. In this study eight of these patients were from endemic areas, but two had never lived outside France. Although there was subclinical optic nerve involvement in four out of the nine patients tested, no patient appears to have been symptomatic. A link between TSP and West Indian amblyopia<sup>20</sup> has been suggested, but it remains to be established whether dietary factors are more likely to be contributory.

Although HTLV-I is associated with ATL and TSP, most patients with HTLV-I infections remain asymptomatic throughout their life. Whether a patient develops ATL or TSP may depend on genetic susceptibility,<sup>21,22</sup> and it is rare for both conditions to exist in the same patient. HTLV-I infection has also been associated with polymyositis in Jamaica<sup>23</sup> and Sjögren's syndrome<sup>24</sup> as well as a variety of visual disorders in south-west Japan which, apart from opportunistic retinopathies in patients with ATL, include

idiopathic cotton-wool spots, pigmentary retinopathy, and granulomatous uveitis.<sup>25</sup> Five of 34 consecutive patients with TSP had a granulomatous anterior uveitis,<sup>26</sup> and in another series four of 38 patients with TSP had an idiopathic pigmentary retinopathy.<sup>27</sup>

A paper in last month's issue of the *BJO* from the same authors explores this further and suggests that HTLV-I is associated with idiopathic granulomatous anterior uveitis in a considerable number of their patients with this condition (41% or 18 of 44 patients; two of these had recurrent episodes). Although these patients were HTLV-I positive, they had no other signs of neurological or haematological disease. Potential analogies could be drawn both to multiple sclerosis, in which some patients have a very similar type of uveitis, and to the high incidence of ocular pathology in patients with HIV infection, though this is of a rather different nature. It remains to be established in these patients whether uveitis is predictive of the development of neurological or haematological disease. Also undetermined is whether HTLV-I represents a truly causative agent of uveitis in these patients and, if so, whether it is a disease of significance only in areas of high endemic infection, or whether HTLV-I or other retrovirus infections are an important factor in ocular disease elsewhere.

The prevalence of HTLV-I seropositivity in Britain is unknown, but a local study in Lambeth showed that there was an incidence of 0.37% in patients screened routinely for antenatal assessment. Half of these were of West Indian origin, a quarter West African, and the remainder unknown. This low incidence in the indigenous UK population may suggest that HTLV-I infection is itself unlikely to be an important association of granulomatous anterior uveitis here.

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