

# ***Prevalence of Multiple Sclerosis and Human Thymus lymphocyte Virus-I infection in Khorasan Territory***

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## **Abstract**

**Introduction:** HTLV1 infection is an endemic disease of Khorasan state in Iran. Distribution of Multiple Sclerosis (MS) is different around the world.

**Methods and Materials:** Data of MS patients were taken of MS registries for interferon prescription in Razavi, Northern and Southern Khorasan provinces. MS was diagnosed by neurologists based on McDonald criteria. Records from clinics and hospital based researches constituted data of distribution of patients infected with HTLV1 with or without spastic paraparesis in Razavi and Southern Khorasan provinces. Serologic tests of blood and/or CSF for HTLV1 and neuroexam by neurologists formed the methodology of HTLV1 investigation. Statistical centers of health deputy of medical universities in the Khorasan provinces provided the population data.

**Results:** Total Prevalence of MS in Razavi, Northern and Southern Provinces of Khorasan is 12.9, 8.7 and 5.3 cases per 100000 population respectively. Prevalence of MS in female population of Razavi, Northern and Southern provinces of Khorasan is 19.9, 11.2 and 8.3 cases per 100000 women respectively. Prevalence of MS in male population of Razavi, Northern and Southern Provinces of Khorasan is 5.9, 6.2 and 2.5 cases per 100000 men respectively. Total prevalence of HTLV1 infection in Razavi and Southern provinces of Khorasan is 2.4 and 0.5 cases per 100000 population respectively. Prevalence of HTLV1 infection in female population of Razavi and Southern provinces of Khorasan is 2.9 and 0.3 cases per 100000 women respectively. Prevalence of HTLV1 infection in male population of Razavi and Southern provinces of Khorasan is 1.9 and 0.6 cases per 100000 men respectively. Spastic paraparesis was found in 46 % and 50% of cases infected with HTLV1 in Razavi and Southern provinces of Khorasan respectively.

**Conclusion:** Frequency rate of MS is less than half in Southern province compared to Razavi province of Khorasan. HTLV1 infection is 10 times more frequent in female population of Razavi compared to Southern province. There is considerable difference in geographical distribution of MS and HTLV1 cases in Khorasan territory.

**Key Words:** Multiple Sclerosis, HTLV1, Prevalence, Khorasan

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## Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) and its distribution is different around the world.<sup>(1)</sup> Several studies have shown that multiple sclerosis is associated with an elevated risk for death, especially in youth. Also, Human T-cell lymphotropic virus type 1 (HTLV-I) is a member of a group of mammalian retroviruses with specific biological properties and tropisms for T lymphocytes. HTLV-1 is the causative agent of adult T-cell leukemia/lymphoma<sup>(18)</sup> and tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM).<sup>(5)</sup> It has also been associated with pediatric infectious dermatitis,<sup>(10)</sup> uveitis,<sup>(13)</sup> some cases of arthropathy and polymyositis.<sup>(7)</sup> HTLV-I infection has specific endemic areas around the world which makes it a unique infection.<sup>(24)</sup> It seems that HTLV-1 is endemic in populations which are recognized as having low risk of multiple sclerosis.<sup>(23)</sup> Both of these diseases are common in Khorasan territory. We studied the prevalence and sex trends of these two groups of patients (MS and HTLV-I infected patients) and compared them in three Khorasan provinces.

## Methods and Materials

This descriptive and population based study was performed in 2008. Comprehensive data of population in the Razavi, Northern and Southern Khorasan provinces were provided by

Iranian people and home statistical organization. Statistical centers of Health deputy of medical universities in the Khorasan provinces participated in providing population based data.

The Iranian provincial MS registry is a complete record of all MS patients which contains sufficient data to show prevalence and sex trends. These MS registries are organized for correct distribution of free interferon among Iranian MS patients. The MS associations of Razavi, Northern and Southern Khorasan provinces provided epidemiologic data of MS patients in these Khorasan provinces. In the Iranian provincial MS registries, MS is diagnosed by a committees of neurologists based on the McDonald criteria\*. Clinical findings, MRI, evoked potential studies and CSF examination are recruited for MS confirmation. Data of HTLV-I infection in Khorasan territory are available from provincial blood bank records. Serologic tests for some viruses such as HTLV-I are done routinely in all blood banks in Iran. In Khorasan Razavi area, blood donors seropositive to HTLV-I infection are referred to HTLV-I research unit of Ghaem tertiary care center, Mashhad. Thereafter serologic tests of blood and/or CSF for HTLV-I infection is performed by PCR on these seropositive patients. Neurological exam is carried out by neurologists to find any signs of HTLV-I associated myelopathy. In southern Khorasan province, blood donors seropositive to HTLV-I infection are referred to Valie-

Asr tertiary care center for a laboratory and clinical evaluation similar to the above description. Although Serologic tests for s HTLV-I infection is routinely performed in all blood banks of norther Khorasan province, however the above organization for confirmation of HTLV-I infection with or without myeopathy is not routinely stablished in northern Khorasan area. Therefore people of this province were excluded of the population based research of HTLV-I infection.

## Results

7041071 people including 3533410 men and 3507661 women residing Khorasan territory were evaluated for MS and HTLV1 infection.

Population data and prevalence of MS and HTLV1 infection in Khorasan area are presented in Table 1. Spastic paraparesis was found in 46 % and 50% of cases infected with HTLV1 in Razavi and Southern provinces of Khorasan respectively.

	General Information			MS Patients			Prevalence		
Khorasan Province	Population	Male	Female	Total	Male	Female	Total	In Males	In Females
Razavi	5593079	2809403	2783676	721	166	555	12.89093181	5.908728652	19.93766516
Northern	811572	401865	409707	71	25	46	8.748453618	6.220994613	11.22753578
Southern	636420	322142	314278	34	8	26	5.34238396	2.483376896	8.272930336
	General Information			HTLV-I Patients			Prevalence		
Khorasan Province	Population	Male	Female	Total	Male	Female	Total	In Males	In Females
Razavi	5593079	2809403	2783676	137	54	83	2.449455836	1.922116549	2.981668844
Northern	811572	401865	409707		-	-	-	-	-
Southern	636420	322142	314278	3	2	1	0.47138682	0.620844224	0.318189628

## Discussion

More than one million people worldwide and at least 350,000 individuals in the United States alone are affected by MS, which is second only to trauma as a cause of acquired disability in young adults in most Caucasian populations.<sup>(1)</sup> About 250 prevalence surveys have been carried out, serving as the basis for the delineation of geographical risk for MS (Bradley-2008). The disease prevalence of MS varies between 60 and 200 per 100,000 people in North America and

Northern Europe and generally follows a north-to-south gradient in the northern hemisphere and the opposite in the southern hemisphere, with very low rates or a virtual absence of the disease near the equator.<sup>(2)</sup> The worldwide distribution of multiple sclerosis (MS) can be described within three zones of frequency: high, medium, and low (25, Bradley-2008). High-frequency areas of the world, with current prevalence of 60 per 100,000 or more, include all of Europe (including Russia), southern Canada,

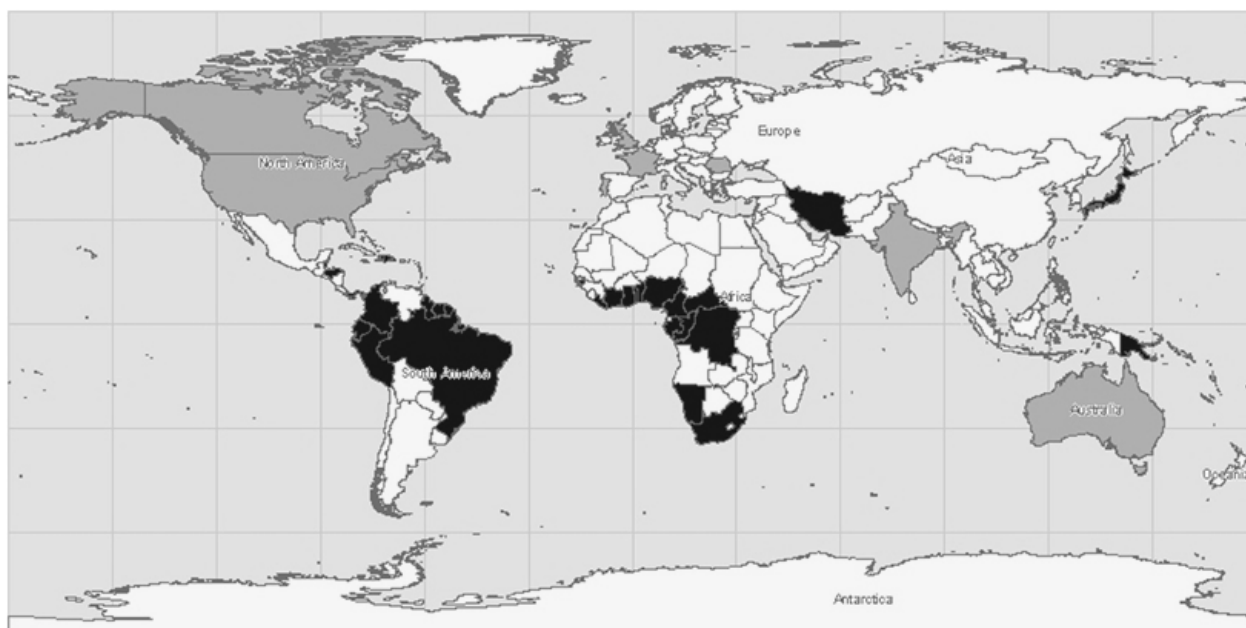
the northern United States, New Zealand, and the southeastern portion of Australia. In many of these areas the prevalence is more than 100 per 100,000, with the highest reported rate of 300 per 100,000 occurring in the Orkney Islands. In the United States, the prevalence when measured during the 1990s was approximately 350,000. Several studies suggest that the prevalence is increasing beyond what might occur due to enhanced recognition and better appreciated diagnostic techniques. Medium frequency areas comprise most of Australia, the southern United States, the Mediterranean basin (other than Italy), the Asian parts of the former Soviet Union, parts of South America, and the white population of South Africa. Low-risk areas include most of South America, Mexico, most of Asia, and all of Africa. One possible conclusion is that MS is a location-related illness, with a latitude gradient. However, notable exceptions then need to be explained. Japan, which has the same latitude as areas of high prevalence in Europe, is a low-risk area (Bradley-2008). Second-generation Japanese in the United States retain their parents' low risk of MS (Bradley-2008), So, It seems plausible that race is a determinant of MS risk, with populations of white extraction, especially from Northern Europe, being the most susceptible. People of Asian, African, or Amerindian origin have the lowest risk, whereas other groups are variably intermediate (Bradley-2008). According to our research in

Khorasan territory, we can classify Khorasan Razavi province as an area of medium prevalence ( $P=12$  in  $10^5$ ). Like other researches it shows a reduction in prevalence by going to the south (Equator) in Southern Khorasan Province (Prevalence: 5 in  $10^5$ ). Despite our expectance to have an increase in prevalence of MS Patients in Northern Khorasan province, we found a lower prevalence of MS (Prevalence: 8 in  $10^5$ ) in this area in comparison to Khorasan Razavi province (Khorasan Razavi Province has lower latitude).

MS has a predilection for women (Bradley-2008, 25). In a summary of 30 incidence and prevalence studies, a cumulative ratio of female to male subjects was 1.77 to 1.00. (Bradley-2008). In our research female to male ratios are about 3.8, 1.8 and 3.2 for northern, Razavi and southern Khorasan provinces respectively. On the other hand, as you may know, HTLV-I was the first retrovirus linked to human disease. It has been convincingly associated with adult T-cell leukemia/lymphoma (ATL), HTLV1 Associated Myelopathy /Tropical Spastic Paraparesis (HAM/TSP), uveitis, and infective dermatitis\*\*. HTLV-I has also been linked to cases of polymyositis, synovitis, thyroiditis and bronchio-alveolar pneumonitis. Definitive epidemiologic proof of HTLV-I association is lacking. The two major HTLV-I-associated diseases, ATL and HAM/TSP, are present in all endemic areas, although prevalence

and incidence rates show significant geographic heterogeneity.<sup>(3, 4, 17, 19, 21, 22)</sup> The geographic distribution of the virus has been defined with Japan, Africa, Caribbean islands and South America emerging as the areas of highest prevalence.<sup>(24)</sup> In Asia, high prevalence in southwestern Japan and low prevalence in Korea, China and eastern Russia, and seemingly isolated pockets of infection in Iran is present.<sup>(24)</sup> The

reasons for HTLV-I infection clustering, such as the high ubiquity in southwestern Japan and North eastern Iran is still unknown. About 15–20 millions people live with HTLV infection worldwide\*. The overall prevalence of severe HTLV-1-associated disease (HTLV-I infection plus hematologic or neurologic findings) is 2 to 8% among these infectious patients.<sup>(3, 4, 17, 19, 21, 22)</sup>



**Figure 1-1: Worldwide Distribution of Endemic Areas for HTLV-I**

Countries which are endemic for HTLV-I that defined as prevalence between 1 and 5% in some populations (black areas) and also, countries with reports of low prevalence (less than 1% in some groups), due mainly to immigration from endemic areas, which are shown in gray. It should be noted that HTLV-I endemic areas do not correspond exactly to the country boundaries shown in the map, for example, Brazil, Japan and Iran, where

HTLV-I is limited to residents of certain areas of each country (24.) High HTLV-I seroprevalence rates in the general population or specific groups of individuals, as pregnant women and/or blood donor candidates, was reported in southwestern Japan\*, several countries in the Caribbean basin including Jamaica and Trinidad (up to 6%)\*and in several sub-Saharan Africa countries, for example Benin, Cameroon and Guinea-Bissau (up to 5%)\*and **localized areas of Iran and**

**Malesia (less than 5%)\***. Our data show that the prevalence of HTLV-I in Khorasan territory is about 2.44 and 0.47 in 100,000 for Khorasan Razavi and southern Khorasan. Khorasan Razavi province could be considered as a high prevalence (1-5%) according to prior classification and southern Khorasan province is a low risk area for HTLV-I infection. In most HTLV-I endemic areas, HTLV-I seroprevalence rates are strongly age and sex dependent, increasing with age and are higher in females\*. Higher prevalence in females may be due to a more efficient male-to-female transmission during sexual intercourse; also, hormonal effects may play a role in female susceptibility\*). The dynamics of HTLV-I infection may differ among countries, and variations in sexual behavior (more frequent use of condoms) or breastfeeding practices (duration, use of wet nurses) could contribute to the heterogeneity in prevalence rates.<sup>(24)</sup> In our research, we found Female to male ratio for HTLV-I infectivity of 1.55 for Khorasan Razavi province and 0.51 for souther Khorasan province. In populations in which these viruses are endemic, HTLV-1 is transmitted between sexual partners and from mother to child during breast-feeding (Harrison's internal medicine, 2008).

The viruses are also transmitted via blood by needle sharing among intravenous drug users,<sup>(16)</sup> and the transmission of HTLV-1 by blood transfusion has been documented in several studies.<sup>(15,20)</sup> One report indicated that 65% of patients who received whole blood or cellular blood components from HTLV-1-seropositive donors seroconverted.<sup>(8)</sup> It has also been reported that patients with histories of blood transfusion rapidly develop HTLV-1-associated diseases, such as myelopathy and uveitis, after seroconversion. Posttransfusion cases of TSP/HAM appear to be more severe and to evolve faster than non-posttransfusion cases.<sup>(11)</sup> Therefore, public health authorities in many countries have implemented routine screening for antibodies to HTLV-1 in blood banks.

It has been reported that HTLV-1 is endemic in populations which are recognized as having low risk of multiple sclerosis.<sup>(23)</sup> However our research revealed that in Khorasan Razavi province we have a middle prevalence of MS with a high prevalence of HTLV-I. Therefore, any endemic area for HTLV-I essentially doesn't have a low risk for MS. More epidemiologic researches must be done in other territories of Iran about these diseases.

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# میزان بروز مولتیپل اسکلروزیس و عفونت با ویروس لنفوسیت تیموس انسانی در قلمرو خراسان

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## چکیده

**سابقه و هدف:** عفونت با ویروس لنفوسیت تیموس انسانی ۱ بیماری بومی در استان خراسان است. توزیع فراوانی بیماری مولتیپل اسکلروزیس در دنیا متفاوت است.

**روش بررسی:** اطلاعات بیماران ام اس از مراکز ثبت ام اس مربوط به تجویز اینترفرون در استان های خراسان بدست آمد. تشخیص ام اس توسط متخصصین مغز و اعصاب و بر پایه معیار مكدونالد انجام شد. مستندات بالینی و بیمارستانی تحقیقات در مورد عفونت با ویروس لنفوسیتی انسانی ۱ در بیماران با و بدون پاراپارزی اسپاستیک. در استان های خراسان رضوی و جنوبی منشاء این تحقیق بوده و آزمایشات سرولوژیک خون و مایع مغزی نخاعی و معاینه عصبی توسط متخصص و اطلاعات آماری جمعیتی مراکز آمار معاونت بهداشتی دانشگاه های علوم پزشکی سه استان فوق بکار رفتند.

**یافته ها:** بروز کلی ام اس در استان های خراسان رضوی و شمالی و جنوبی بترتیب  $12/9$  و  $8/7$  و  $5/3$  به ازای  $100000$  نفر جمعیت بود. بروز ام اس در جمعیت زنان سه استان فوق بترتیب  $19/9$  و  $11/2$  و  $8/3$  بیمار و در جمعیت مردان سه استان فوق نیز بترتیب  $5/9$  و  $6/2$  و  $2/5$  بیمار بوده است. بروز کلی عفونت با ویروس لنفوسیتی تیموس انسانی ۱ در استان های خراسان رضوی و جنوبی بترتیب  $2/4$  و  $0/5$  بیمار به ازای  $100000$  نفر جمعیت بود. بوز عفونت فوق در جمعیت زنان دو استان فوق بترتیب  $2/9$  و  $0/3$  بیمار و در جمعیت مردان دو استان فوق نیز بترتیب  $1/9$  و  $0/6$  بیمار بود. پاراپارزی اسپاستیک در  $46\%$  و  $50\%$  موارد عفونت با این ویروس در خراسان رضوی و جنوبی یافت شد.

**نتیجه گیری:** فراوانی نسبی بیماری ام اس در استان خراسان جنوبی کمتر از نصف خراسان رضوی است. عفونت با ویروس لنفوسیتی تیموس انسانی ۱ در جمعیت زنان استان خراسان رضوی ۱۰ برابر زنان خراسان جنوبی است. تفاوت قابل توجهی در توزیع فراوانی این دو بیماری در قلمرو خراسان وجود دارد.

**واژه گان کلیدی:** مولتیپل اسکلروزیس - ویروس لنفوسیت تیموس انسانی ۱ - بروز - خراسان