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Polyneuropathy in patient with human T-cell lymphotropic virus 1-associated myelopathy/tropical spastic paraparesis (HAM-TSP) and HTLV-1 carriers

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ABSTRACT

It is long known that HTLV-1 can affect both central and peripheral nervous system leading to progressive demyelination motor neuron axons. HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM-TSP) isthemajor HTLV-I-associated diseases. HTLV-1-infected carriers are also at risk of HTLV-1-associated diseases. Therefore, in this study we aimed to systematically review the literatures in which the prevalence of polyneuropathy had been investigated in patient with HAM-TSP as well as in HTLV-1 carriers. A systematic literature search was conducted in PubMed, Scopus and Google scholar using following search strategy(((polyneuropathy OR neuropathy OR neurologic disease OR myelopathy OR neuronal injury)) AND (human T-cell lymphotropic virus 1- associated myelopathy/tropical spastic paraparesis OR HTLV-1-associated myelopathy/tropical spastic paraparesis OR HAM-TSP OR HTLV-1 carriers) AND (frequency OR prevalence OR incidence) to study the prevalence of polyneuropathy in patient with HAM-TSP as well as in HTLV-1 carriers on December 2015.Then, after collecting relevant documents, the data were extracted and analyzed. Of total 801collected documents in PubMed, Scopus, and Google scholar, only 11 eligible articles with overall 1443 studied populations were selected and analyzed. The results showed that the incidence of neurological diseases, especially peripheral neuropathy and myopathy is rather high in patients with HAM/TSP and asymptomatic carriers. The results of articles included in this literature review showed that HTLV-1 resulted in the incidence or exacerbation of various forms of neuropathy.

Keywords: Human T-lymphotropic virus 1, HTLV-1-associated myelopathy-tropical spastic paraparesis, Myelopathy, Polyneuropathy.

INTRODUCTION

Human T-cell lymphotropic virus 1 (HTLV-1), which was the first discovered human retrovirus, belongs to the Retroviridae family that predominantly affects T-lymphocytes. Seven HTLV-1 genotypes (HTLV-1a, to HTLV-1g) are recognized so far. The prevalence of each genotype varies in different geographical region, but it is estimated that the most widespread genotype is type A(1). HTLV-1 is involved in spreading epidemics that affected 15 to 20 million people worldwide (2).Since in most cases, the HTLV-1 associated infections are asymptomatic, the transmission is silent. Also, because there is no vaccine for these types of infections; therefore, the transmission is very fast particularly in many areas including Asia, Africa, South and Central America and the Caribbean region (3). It is estimated that 20 million people are infected with HTLV-1 worldwide (4). The results of studies demonstrated that HTLV-1-infected carriers are also at risk of HTLV-1-associated diseases; moreover, it is shown that HTLV-1-

infected carriers without adult T-cell leukemia/lymphoma (ATL) may also be susceptible to some immune deficiency associated infectious diseases including strongyloidiasis, tuberculosis, and leprosy (5, 6).

Studies show that HTLV-1 may be involved in the incidence, progression, or exacerbation of several diseases such as arthritis, infective dermatitis, urinary tract disorders and increased vulnerability to other infectious diseases. Findings have also shown that HTLV-I is linked with polymyositis(7), synovitis(8), thyroiditis (9) and bronchio-alveolar pneumonitis (10). Other reported HTLV-1-associated infections include Norwegian scabies, disseminated molluscumcontagiosum, and extrapulmonary histoplasmosis(2, 6). In addition, ATL and HTLV-1 associated myelopathy (HAM), also known as tropical spastic paraparesis (TSP), are two major HTLV-I-associated diseases, which are prevalent in almost all endemic areas, but with different prevalence and incidence rates (3, 11). Findings suggested that the cumulative incidence rate of ALT in HTLV-1-infected carriers is 1 to 5% in endemic areas(2). The demographic characteristics of patients with HAM/TSP and HTLV-1 infected asymptomatic populations show the preponderance of women infected with HTLV-1 (12).

The results of studies have shown that HTLV-1 can affect both central and peripheral nervous system leading to a progressive demyelination of upper motor neuron axons. Although HAM-TSP is the most important neurological manifestation caused by HTLV-1, but other complications such as polyneuropathy, polyradiculopathy, myopathy and peripheral facial palsy may also be observed (13).Polyneuropathy also known as symmetrical polyneuropathy is a neurological abnormality in which peripheral nerves are affected that can result in peripheral neuropathy. Since most of these HTLV-1-associated diseases are not curable; therefore, early detection of these disease as well as study the prevalence of such disease in different populations will be of great importance(3).In this study, we aimed to systematically review the literatures in which the prevalence of polyneuropathy had been investigated in patient with HAM-TSP as well as in HTLV-1 carriers.

MATERIALS AND METHODS

Search methods

A systematic literature search was conducted to evaluate the frequency of polyneuropathy in patient with HAM-TSP as well as in HTLV-1 carriers. For this purpose, PubMed, Scopus, and Google scholar were searched separately for "*HAM-TSP*", "*polyneuropathy*" and "*HTLV-1 patients* and *carriers*" in the title, abstract and keywords of articles. To conduct the literature search, following search method (((*polyneuropathy* OR *neuropathy* OR *neurologic disease* OR *myelopathy* OR *neuronal injury*)) AND (*human T-cell lymphotropic virus 1- associated myelopathy/tropical spastic paraparesis* OR *HTLV-1-associated myelopathy/tropical spastic paraparesis* OR *HAM-TSP* OR *HTLV-1 carriers*)) AND (*frequency* OR *prevalence* OR *incidence*) was used in PubMed and Google scholar with customized search in which the results were limited to those literatures with English language. A similar method was used to find relevant articles in the Scopus. For this purpose, TITLE-ABS-KEY *(human t-cell lymphotropic virus 1- associated myelopathy/tropical spastic paraparesi)* OR TITLE-ABS-KEY *(ham-tsp)* AND TITLE-ABS-KEY *(htlv-1 carriers)* was searched and then the *neuropathy* was searched within the results. Subsequently, the results were limited to only articles published in English language. In addition to the electronic database search, and in order to minimize the possibility of data loss, manual search of the reference lists was also conducted to include other potentially eligible documents.

Study selection and inclusion/exclusion criteria

No time limitation was defined for the collection of the qualified articles during study selection. Hence, all documents relevant to the main purpose of this study in which the frequency of neuropathy had been studied in patient with HAM-TSP and HTLV-1 carriers were included in this review. Moreover, articles with almost all types of study design including clinical trials, Cross-Sectionals, prospective cohorts, comparative, evaluation and multicenter studies were included to this survey to collect all published data on the subject. However, to avoid any misconceptions we limited the search to only those publications with English language. Articles with subject or language irrelevancy were excluded in the first step of article selection. Moreover, letters, conference abstracts or presentations, review articles and meta-analysis were excluded from additional data processing. Likewise, we excluded duplicated documents as well as articles with inaccessible full text from further evaluation. Therefore, according to aforementioned, inclusion criteria in this literature review were all articles in which the prevalence of various forms of neuropathy had been studied in patient with HAM-TSP and HTLV-1 carriers.

Data extraction

All necessary information including the name of first author, publication date, the country or region of the studied population, sample size, and total number of patients enrolled in each study was extracted. Other informative data including demographic data of studied population, target population, type of study design, methods of interventions, and the key findings of each study were extracted and analyzed based on the main purpose of this study. All

procedures including literature search, study selection, data processing and analysis were performed according to the recommended protocol in PRISMA checklist 2009 (14). The relevant articles among the collected literature were identified and data were independently extracted by two investigators. To avoid potential errors and therefore possible misinterpretation during data analysis, any probable disagreements between the authors were resolved in each step prior to additional data processing.

Measured variables

Different methods such as clinical and neuro-radiological examinations, quantitative spasticity assessment, Western blot and serological analysis, immunological assays, neurological and physiatrist examination, and detection of antibodies against viral antigens have been used for clinical evaluation of the patients. The variables of interest included frequency of physical activity, use of walking aids, low back pain, peripheral neuropathy and the number of falls. Other variables that were extracted and compared included neurological signs, incidence rate of leg hyperreflexia or leg weakness, bowel and bladder dysfunction, lumbar pain, paresthesias/dysesthesias, disability status scale, and muscular power indexes.

RESULTS

Literature search results

Of total798 articles collected from data base search, 602 potentially relevant articles were found in PubMed, 188 were found in Scopus and 8 other in Google scholar. At final reviewing process, 3 other potentially relevant documents were also found through reference list screening of the included documents. Of the collected documents, 583 studies excluded after title and abstract screening in the first step due to subject irrelevancy. After limiting the records to those studies conducted on human, 112 additional documents were also excluded. Moreover, 39 documents were excluded due to language irrelevancy. Additional 28 articles were further excluded from collected document pool due to full text unavailability. Moreover, 13review articles were excluded from additional assessment. Finally, full text of 25 articles in which the prevalence of various forms of neurologic disease had been studied in patient with HAM-TSP and HTLV-1 carriers were collected and used for data analysis. After reviewing the full text of the remained documents, only 11eligible articles that fully met the inclusion/exclusion criteria were included and used for data extraction and analysis. The step by step literature selection process is illustrated in Figure 1.

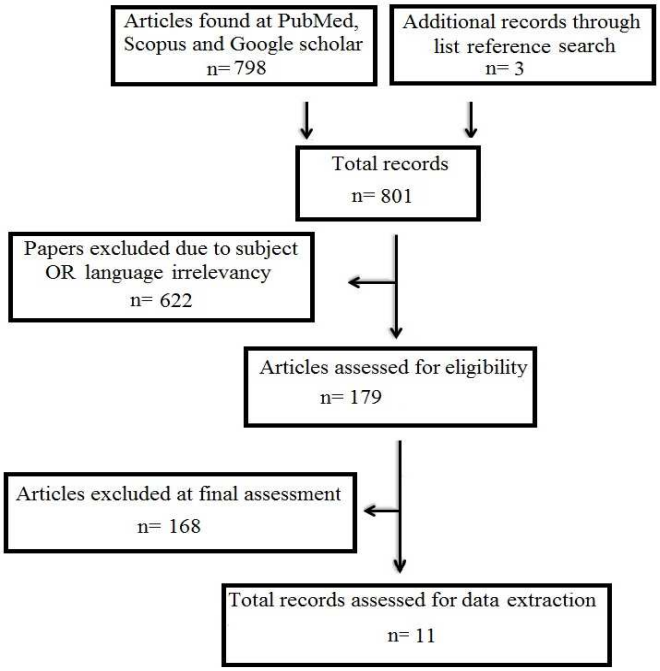

Figure 1.Flowchart of the literature search and strategy for the selection of relevant document

General characteristics of the included articles

The present analysis included 11 articles with total of 1443studied populations. The sample size of included articles ranged from 9in a cross-sectional study to414 in a prospective cohort study. Of the total 1443studied populations, 760 were patients with HAM-TSP and 683 were HTLV-1 carriers. Both male and female patients had been enrolled in the selected literatures, and of them, 508 were male and 926 were female; moreover, in a cross-sectional analysis

the sex of 9 patients had not been reported. The age of the included patients also varied from 7 to 82 among the included studies. The most old and recent articles that were included in this survey had been published in 1995 and 2015, respectively. Among the included documents that were used for data processing, 3 were prospective cohort, 4 were comparative and 4 were cross-sectional study. The general data of included documents are demonstrated in Table 1 in the chronological order of their published time. As shown in Table 1, 10 of 11 studies with overall 1320 studied populations have been conducted in South America, indicating that HTLV-1 is more prevalent in these areas.

Table 1.General information of the included literatures

No	First author	Year	Country	Study design *	Sex ratio Male/Female	Patients number	
						HAM/TSP	**Carrier**
1	Tanajura D (15)	2015	Brazil	PCS	162/252	163	251
2	Facchinetti LD (16)	2013	Brazil	CSS	-	9	-
3	Grassi MF (17)	2011	Brazil	CS	83/198	92	189
4	Kendall EA (18)	2009	Peru	CSS	22/36	-	58
5	Silva MT (19)	2007	Brazil	CS	113/208	197	124
6	Olindo S (20)	2006	France	PCS	27/96	123	-
7	Zunt JR (21)	2006	Peru	CSS	6/18	24	-
8	Franzoi AC (22)	2005	Brazil	CS	23/49	72	-
9	Leite AC (23)	2004	Brazil	CSS	11/10	-	21
10	Silva MT (24)	2003	Brazil	CS	41/36	37	40
11	Araújo AQ (25)	1995	Brazil	PCS	20/23	43	-
					Male: 508 Female: 926	N= 760	N= 683

*PCS: Prospective cohort study, CSS: Cross-sectional study, CS: Comparative study,

Study findings

The results of this study showed that HTLV-1 viral load was associated with the incidence and progression of neurological abnormalities such as leg and bowel dysfunction, abnormal mental status, difficulty in walking and running, incidence of leg hyperreflexia and leg weakness. The results of included documents also showed that prevalence of falls and injuries, as signs of neurologic motor dysfunction, was rather high in patients infected with HTLV-1 compared with the healthy peoples. Lumbar pain, paresthesias/dysesthesias, motor disability, low back pain, lower extremity hyperreflexia and urinary incontinence are other neurological abnormalities reported in the selected literatures. Findings also demonstrated that the incidence rate of neurological diseases such as peripheral neuropathy and myopathy may be rather high in both patients with HAM/TSP and asymptomatic carriers. The main findings of each document included in this survey are demonstrated in Table 2.

Table 2.Main findings of included literatures

No	First author	Methods of evaluation ®	Main findings
1	Tanajura D	VAD, WB, NE, IA	HTLV-1–infected patients had high rates of developing neurologic symptoms.
2	Facchinetti LD	HPL, FCA, NF	Falls occur in approximately two-thirds of ambulatory HAM/TSP patients.
3	Grassi MF	SE, HPL	HTLV-1 proviral loads are higher in groups of infected patients with neurological symptoms.
4	Kendall EA	NE	Patients infected with HTLV-1 are at risk for developing HAM/TSP-like neurologic abnormalities.
5	Silva MT	SE, WB, NE, IA	HTLV-1 may be responsible for neurogenic bladder dysfunction in symptomatic and asymptomatic HTLV-1 carriers.
6	Olindo S	DSS, NE	HAM/TSP is a rapidly disabling disease.
7	Zunt JR	NE, QSA, WB, IA	HTLV-1 viral load may play a role in expression of symptomatic neurologic disease.
8	Franzoi AC	NE, MPI, PE	HAM/TSP may cause bladder dysfunction, and locomotion disability.
9	Leite AC	SNB, EPT	HTLV-I infected individuals can have a peripheral neuropathy in the absence of TSP/HAM.
10	Silva MT	NPE, WB, IA	HTLV-1 infection was associated with psychomotor slowing, decreased verbal fluency, and visual memory deficit
11	Araújo AQ	DSS, NE	The neurological disability in HAM/TSP occurs mainly during the first year of the disease and becomes relatively stable.

® VAD: Viral antibodies detection, WB: Western blot, NE: Neurologic evaluation, NPE: Neuropsychological evaluation, SNB: Sural nerve biopsy, IA: Immunological assays, EPT: Electrophysiological tests, HPL: HTLV-I proviral load, FCA: Frequency of physical activity, NF: The number of falls,SE: Serological evaluation, DSS: Disability status scale, QSA: Quantitative spasticity assessment, PE: Physiatrist examination, MPI: Muscular power indexes.

DISCUSSION

It is long known that HTLV-1 is linked with numerous neurological disorders such as neuroinflammatory diseases(26). Studies showed that human immunoglobulin G (IgG) is localized to neurons in the brain of patients with HAM/TSP, while there is no evidence of such localization in normal brain; therefore, an antibody response is

developed in HAM/TSP patients that targets neurons, leading to autoimmune reactivity to the CNS(27).Also, it is revealed that inflammatory reaction in the spinal cord of patients with HAM/TSP could be responsible for bladder dysfunction as a common HTLV-1-associated neurological manifestation(28). Studies on natural history of HAM/TSP had provided new evidence on the incidence, prevalence, and progression of neurological disability in patients with HAM/TSP as well as HTLV-1 infected carriers (20). An increasing number of evidences suggested that wide range of neurologic disorders including myositis, peripheral neuropathy and bladder dysfunction are associated with HTLV-1 (29). Studies have also shown that amyotrophic lateral sclerosis, a progressive neurodegenerative disease, is associated with HTLV-1 myelopathy (30, 31).

On the other hand, many studies have shown that the incidence of neurological abnormalities is linked with HTLV-1 viral load. Hence, there may be correlation between neurological symptoms and HTLV-1 proviral loads in infected patients that may represent as an applicable biological marker of disease progression. According to findings, the frequency of peripheral neuropathy varies from insignificant rate to more 32 %(23). Medical examination, along with electrophysiological studies, as well assural nerve biopsy demonstrated that peripheral neuropathy may also occur in asymptomatic HTLV-1 infected patients in the absence of HAM/TSP. Studies show that HTLV-1 may actively involve in the pathogenesis of myeloneuropathy. Findings also demonstrated that elevated antibody level to HTLV-1 may be associated with mild sensory loss, bilateral extensor plantar responses, knee hyperreflexia, and other axonal and demyelinating neuropathies (32).

The major limitations of this survey included inadequate publications from different areas, since 10 of 11 included studies with 1320 studied populations had been conducted all on Brazilian patients. Hence, there may be risk of bias, since most of the extracted data are limited to only a specific population. Therefore, some comparative multicenter studies are required to be conducted on different populations in different geographical regions. However, the results of included studies showed that HTLV-1 is associated with risk of neurological abnormalities such as abnormal leg sensation, unusual mental status, neurogenic bowel and bladder dysfunction, leg and arm hyperreflexia, motor disability, cognitive deficits and peripheral neuropathy in both HAM/TSP patients and HTLV-1 carriers. Nevertheless, it is shown that the severity of neuropathy may vary with HTLV-1 viral load in infected patients.

CONCLUSION

The results of articles included in this survey showed that HTLV-1 may result in the incidence or exacerbation of various forms of neuropathy, particularly peripheral neuropathy. Also, findings showed that the severity of neuropathy may vary with HTLV-1 viral load in infected patients. Neurological evaluations along with electrophysiological and pathological studies showed that HTLV-I may play an important role in the pathogenesis of axonal and demyelinating neuropathy, leading to myeloneuropathy and peripheral neuropathy in both HAM/TSP patients and HTLV-1 carriers.

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