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Magnetic resonance imaging for Human T-cell lymphotropic virus type 1 (HTLV-1) associated myelopathy/tropical spastic paraparesis patients: a systematic review

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ABSTRACT

Introduction: Human T-cell lymphotropic virus type 1 (HTLV-1) associated myelopathy/tropical spastic paraparesis is a chronic progressive neurologic disease which might be associated by brain and spinal cord atrophy and lesions. Here we systematically reviewed the brain and spinal cord abnormalities reported by using magnetic resonance imaging modality on HTLV-1 associated myelopathy/tropical spastic paraparesis patients.
Methods: PubMed was searched for all the relevant articles which used magnetic resonance imaging for patients with human HTLV-1 associated myelopathy/tropical spastic paraparesis disease. Included criteria were all the cohort and case series on with at least 10 patients. We had no time limitation for searched articles, but only English language articles were included in our systematic review. Exclusion criteria were none-English articles, case reports, articles with less than 10 patients, spastic paraparesis patients with unknown etiology, and patients with HTLVII.
Results: Total of 14 relevant articles were extracted after studying title, abstracts, and full text of the irrelevant articles. Only 2/14 articles, reported brain atrophy incidence. 5/14 articles studied the brain lesions prevalence. Spinal cord atrophy and lesions, each were studied in 6/14 articles.
Discussion: According to the extracted data, brain atrophy does not seem to happen frequently in patients with HTLV-1 associated myelopathy/tropical spastic paraparesis. None-specific brain lesions identified in articles are indicative of low specificity of magnetic resonance imaging technique despite its high sensitivity.
Conclusion: Prevalence of spinal cord lesions and atrophy in these patients might be due to the degenerative processes associated with aging phenomenon. Further larger studies in endemic areas can more accurately reveal the specificity of magnetic resonance imaging for these patients.

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Introduction

Human T cell leukemia/lymphoma virus type 1 (HTLV-1) was isolated in 1980, by National Institutes of Health, USA as the first oncoretrovirus in human. The relation between chronic myelopathy (tropical spastic paraparesis, TSP) with unknown etiology and this retrovirus was investigated as HTLV-1 associated myelopathy (HAM) in some tropical and inter-tropical areas including Caribbe-

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an region, South and Central Africa and India and proposed as the hybrid name HAM/TSP (1). Today considerable number of patients with HAM/TSP has been diagnosed in regions with high prevalence of HTLV1 including Japan, Jamaica, Trinidad, Martinique, several parts of South and Central America (Brazil, Peru, Colombia), Central and South Africa, and Iran. HAM/TSP is a chronic progressive neurologic disease that progresses slowly with different onset of initial signs and accounts for 0.2-3% of patients with HTLV-1. Various clinical characteristics and diagnostic symptoms have been reported for patients with HAM/TSP including lower extremity hyperreflexia and spasticity, sensory disturbances, urinary bladder and sexual complications, urinary incontinence, and peripheral sensory loss to light touch (2-4).

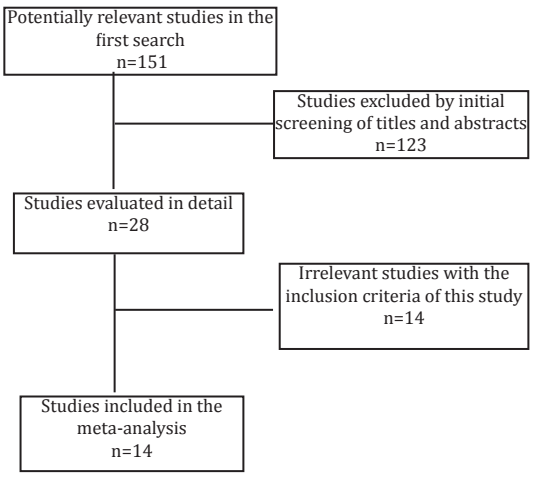
Magnetic resonance imaging has revealed high sensitivity for detecting and controlling patients with CNS complications. In HAM/TSP patients MRI has the ability to identify the level of brain and spinal cord abnormalities. In this study we systematically reviewed the diagnostic importance of MRI in patients with HAM/TSP.

Methods

Literature search strategy

We conducted the current systematic review based on the PRISMA guidelines (Figure1). PubMed was searched for relevant articles with the following search terms: (spastic paraparesis OR myelopathy) AND HTLV AND (magnetic resonance imaging OR MRI). The last search was done on December 2014. Title and abstract of the articles were studied and then irrelevant articles were omitted. Therefore the full text of the remaining articles was studied to detect any irrelevant article to our systematic review purpose. The reference list of the relevant articles was searched for reducing the possibility of missing relevant citations.

Figure 1. PRISMA flowchart of the study



Study selection

No time limitation was inserted for the included articles but only English language articles entered in our systematic review. Inclusion criteria were all the case series and cohort studies which included at least 10 patients with recognized HAM/TSP disease and investigated the accuracy and efficacy of magnetic resonance imaging modality in detecting brain and spinal abnormalities. Exclusion criteria of our study were articles with less than 10 patients, patients with HTLV-II, patients with unknown causes TSP, HTLV-1/myelopathy, non-English articles, and case reports.

Data extraction

Data about authors, publication date, country, patient characteristics (age, sex, duration of the disease), and result of applying magnetic resonance imaging were extracted.

Outcome variable

We compared data obtained in each study regarding the brain lesions and atrophy level, location of the lesions, spinal cord lesions and atrophy level, relation between patients' age and disease progress, and the relation between patients' disease duration and the presence of brain and spinal lesions.

Data synthesis

We provided an evidence table involves all information abstracted from eligible studies. Results were organized based data obtained on brain and spinal cord lesions and level of atrophy, the association between incidence of observed abnormalities with patient's age and duration of disease.

Results

Search results

We identified a total of 151 articles in PubMed. We excluded all the non-relevant articles based on title, abstract, and eventually the full text. The remaining relevant articles were 14 in PubMed.

Description of the included studies

All the included articles were performed in United States, Canada, Brazil, Japan, United Kingdom, and Dominican Republic. The population size of the included studies ranged between 10-68 HAM/TSP patients. The mean disease duration of the patients ranged between 3-12 years.

Table 1 shows data extracted from included studies used MRI technique for HAM/TSP patients.

Discussion

Based on studies vast majority of HTLV-1 patients are asymptomatic, who are rarely evaluated especially in non-endemic regions. In some studies that

Table1. Data extracted from included studies used MRI technique for HAM/TSP patients

Author Country Year Reference	HAM/TSP Patients performing MRI	MRI	MRI findings
Liu **USA** **2014** **(5)**	N: 18 Mean age: 52yrs 11females/7males Mean DD: 11 yrs	SCCSA profiles for spinal cord atrophy evaluation	Entire length of cord was atrophic especially in cervical and thoracolumbar areas:N:100%
Vilchez **Dominican Republic** **2014** **(4)**	N: 10 Mean age: 58.3±7.8 yrs 8 females/2 males Mean DD: 11.9±8.4 yrs	SCCSA Diffusion tensor imaging (DTI) Transversal T2-weighted	Spinal cord atrophy:100% Focal spinal cord lesions in 6/10 patients (mostly bilateral localization) Focal small white matter lesions:100% (in centrum semiovale and periventricular)
Puccioni-Sohler **Brazil** **2012** **(6)**	N: 28 Median age: 52 yrs Median DD: 9.5 yrs	Brain and spinal cord T1and T2 weighted images	Hyperintense lesions:50% white matter lesions, and 11% cervical demyelination lesions Atrophy:14% in brain and 3.5% in spinal cord
Yukitake **Japan** **2008** **(7)**	N:38 Mean age: 59.1yrs 17 females/5 males Mean DD:8.3 yrs	SCCSA and T2-weighted images of MRI	Brain abnormalities: Normal: n=22, 57.9% Thoracic cord atrophy: n=13, 34.2% T2-hyperintensity: n=3, 7.9%
Morgan **Brazil** **2007** **(8)**	N: 10 Mean age:47 years 70% female Median DD: 3 yrs	T1 and T2 sequences	Cerebral WM lesions in 80% Median number of lesions: 5 Median lesion volume: 3.0 ml Lesion number, size or location was no different between carriers and HAM/TSP.
Griffith **USA** **2006** **(9)**	N:19 12 females/7 males Mean age: 49.3 ± 10.9 yrs Mean DD: 8.2 ± 5.5 yrs	T1 pre/postcontrast spin echo–weighted images (WIs) and T2WIs of the brain were obtained Conventional spinal cord MRI	Focal brain lesions: 9 (47.4%) Spinal focal lesions:3 (15.8%) 1/19 patients revealed significant brain parenchymal atrophy: volume reduction. WM lesions in periventricular and pyramidal tracts, and edema and swelling of spinal cord
Bagnato **USA** **2005** **(10)**	N:21 13 females/8 males Mean age: 48.0 (±13.1) Mean DD: 8.2 (±5.3)	Conventional brain and spinal cord magnetic resonance images	Nonspecific brain lesions: 11(52.4%) Spinal cord lesions: 3(14.3%)
Howard **Canada** **2003** **(11)**	N:12 8 females/4 males Median DD: 6yrs	Head, cervical and thoracic MRI	Servical cord abnormalities :4/8 (Hyper-intense signals and atrophy) Thoracic cord lesions:6/8 (hyperintense lesions and atrophy) Brain abnormalities: periventricular parts :8/10 WM:7/8 Brainstem1/10
Milargres **Brazil** **2002** **(12)**	N: 68 Female/male:1.5/1 Mean age at disease onset:43.2 yrs		Brain hyper-intense abnormalities in hemispheric areas in 32.7% of patients Spinal cord atrophy in 5.6%
Kuroda **Japan** **1995** **(13)**	36 22 females/14 males Mean age: 54 yrs	T1weighted and T2 weighted images	T2-hyperintens brain lesions in subcortical and deep WM of 30/32(84%) At least three lesions larger than 3 mm in diameter:2/36 No infratentorially lesions
Alcindor **USA** **1992** **(14)**	46 patients 32 females/14 males aged 17-81 yrs	T2- weighted cranial MRI	T2 hypeintense lesions:WM lesions in periventricular and subcortical areas of 32/40 patients Spinal cord atropy No abnormality in brain T1weghited images 9/32 abnormal spinal MRI
Rudge **UK** **1991** **(15)**	N:17 24females/3males Mean age:54 yrs Mean DD: 8.6 yrs	Brain and spinal MRI	Abnormal brain scan;75% 18% in brainstem 12% corpus striatum 65% WM 71% periventricular Normal Cervical cord scan Dorsal cord atrophy:60%
Kira **Japan** **1991** **(16)**	N:35 Mean age 50±9 yrs Mean DD : 12 yrs	Brain T2 weighted and T1 weighted MRI	Multiple deep and subcortical WM lesions in 66% of patients, followed by lesions in periventricular WM, and gray matter brain lesions were small to medium size and 3% large confluent lesions
Kira **Japan** **1988** **(17)**	N: 22 16females/6 males Mean age:47.8yrs Mean DD:10 yrs	T2and T1-weighted images of brain MRI,	Brain lesions:13(59%) mostly in subcortical and deep cerebral WM, only 6 patients had periventricular WM lesions

carriers were investigated with MRI, no significant atrophy and focal lesions were observed in this group of patients, so suggested further studies to reveal the importance of imaging parameters in detecting spinal cord involvement in HTLV1 carriers.

MRI findings

Brain atrophy

Only 2/14 included articles detected brain atrophy in HAM/TSP patients using MRI technique (6, 9). Based on these studies brain atrophy was observed in 4/28 and 1/19 patients of each articles. A recent study by Puccioni-Sohler et al, in 2012 proposed volume reduction, brain parenchymal reduction, widening of cortical sulci and fissures, ventricular enlargement, cerebellar atrophy with slight accentuation of cisternas, and sylvian and frontal regions convexity reduction. Based on these results brain atrophy symptoms does not seem to occur frequently in all HAN/TSP patients and studies with larger population are needed to investigate the prevalence of brain atrophy more accurately as a marker of HAM/TSP patients.

Brain lesions

Overall, 13/14 articles reported the incidence of brain hyperintense abnormalities in their patients mostly based on T2-weighted images with variable frequency of 52%-89% (4,6,10,12-17). Based on mentioned articles brain abnormalities of HAM/TSP patients are lesions in cerebral deep and subcortical white matter, periventricular areas, semioval centre, corona radiate, and also grey matter lesions and lacunar infarcts in basal ganglia. Periventcular parts of the brain white matter are suggested as major and preferred location of the detected lesions followed by subcortical white matter lesions (4,6,11,12,16). Based on literature, focal and non-specific identified brain lesions show that although MRI technique is highly sensitive to lesions but does not have high sensitivity for HAM/TSP patients (10). In one study it is suggested that the incidence of brain non-specific abnormalities might be the consequence of micro-degenerative process during aging phenomenon (6).

Spinal cord atrophy

According to our identified articles, only 5/14 articles investigated individuals with advanced HAM/TSP disease revealed the spinal cord atrophy in HAM/TSP patients, which is detected as thinning and diameter reduction of the cervical spine and the proximal portion of the dorsal medulla, atrophic of thoracic cord (5,6,11,12,15). Puccioni-Sohler et al suggested that incidence of both cerebral and spinal cord atrophy might be due to degeneration of parenchymal (6). In another study the 5.6% of 86 patients showed spinal cord atrophy in T2-wighted sagittal images and suggested that spinal cord atrophy was significantly prominent in patients with longer duration of disease (12). Liu et al in 2014 proposed thoracolumbar cord as the main involved part of cord in HAM/TSP patients by specifically evaluating spinal cord cross sectional areas (SCCSA) a long it entire length as an indicator of atrophy(5). Based on high correlation between SCCSA and clinical measures of HAM/TSP patients, this index is proposed as an effective tool for estimating the atrophy level (5). Similar results obtained in another recent study by Vilchez et al showed thoracic cord atrophy in all 10 included HAM/TSP patients which was more intense in patients with longer duration of the disease (4).

Spinal cord lesions

HAM/TSP mostly involved thoracic parts of spinal cord. Analyzed extracted data showed that 6/14 included articles have demonstrated T2-hyperintense spinal cord lesions in HAM/TSP patients considered by MRI; these cord abnormalities were associated with transient and diffuse swelling of spinal cord in some cases (4,6,7,9-11). According to the mentioned articles, spinal cord lesions are mostly in thoracic level of cord.

Yukitake et al mentioned that 3/4 patients with spinal cord T2-hyperintense demyelinating lesions had advanced disability, pleocytosis, and high concentration of protein and blood-CSF barrier dysfunction and had to use wheelchair; the coincidence of acute inflammatory process and spinal cord lesions have been also mentioned by others(6,7). To obtain more accurate evaluation of spinal cord lesions, performing larger sample size studies on HAM/TSP patients are recommended.

Based on literature variable percent of cases have shown spinal cord atrophy in each study which might be due to different individual characteristics such as age, sex, disease duration, duration of symptoms.

Disease duration

The relation between disease duration and the presence of atrophy or brain and spinal lesions were investigated in some studies. The incidence rate of thoracic cord lesions and atrophy was significantly related with patients' disease duration in some included studies; this relation was not detected in patients with cervical cord lesions(4,5). Patients with white matter lesions have had longer duration of disease; more than 2 years (12,16,17). Thoracic cord atrophy has also shown significant association with HAM/TSP patients' duration of the disease. In two included studies no significant relation has been detected

between presence and location of brain lesions and disease duration (6,7).

Patients' age

According to some studies, increased age can be proposed as a risk factor of the higher incidence of white matter lesions in patients with HAM/TSP. Puccioni-Sohler et al suggested a relation between brain MRI T2-hyperintense lesions and micro-degenerative process middle aged or older patients which were mainly in periventricular parts (6). This correlation was also observed in some other studies (8). However Griffith et al did not obtain any statistically significant relation between brain volume and age of the HAM/TSP patients, they only observed significant brain reduction in one 39 years old patient with 2 years disease duration, among 19 patients (9). Kira et al conducted 2 different studies on HAM/TSP patients and obtained similar results with Griffith et al regarding the patients age at the time of examination and prevalence of WM lesions (16,17).

Blurring due to motion, lack of contrast between the cord and the cerebrospinal fluid, are proposed as the possible artifacts of the SCCSA profiles in MRI(5).

According to the extracted data of the included articles, it can be suggested to perform studies on HAM/TSP patients more in endemic areas to increase the number of patients and the accuracy and validity of results. In asymptomatic patients further studies are needed on asymptomatic HTLV1 patients to accurately reveal the prognostic and diagnostic validity of imaging parameters in carriers.

Conclusion

In HAM/TSP patients brain atrophy is not reported frequently, however brain lesions are more prevalent in these patients. Brain lesions and atrophy might progress in patients, so yearly longitudinal follow up of patients are needed to accurately identify the brain changes over time in these patients. It can be also suggested that due to none specific brain lesions observed in most of the studies, the conventional MRI can be suggested as a sensitive diagnostic tool, but not a highly specific in HAM/TSP patients. The MRI technique has shown high sensitivity in detecting abnormalities but lesions seen on the MRI images are not specifically indicative of HAM/TSP pathology and can be attributed to other subclinical pathologies. Non-specificity is observed among studies of MRI in HAM/TSP.

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Conflict of Interest

The authors declare no conflict of interest.

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