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HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis: Semiautomatic Quantification of Spinal Cord Atrophy from 3-Dimensional MR Images

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Abstract

BACKGROUND—Human T-cell lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a disabling neurological disorder characterized by inflammatory changes in the spinal cord. We used a semiautomatic technique to quantify spinal cord volume from 3-dimensional MR images of patients with HAM/TSP.

METHODS—Five patients and 5 matched healthy volunteers (HVs) underwent MRI of the cervical and thoracic spinal cord at 1.5 T. Quantification of the spinal cord volume was obtained from 3-dimensional MR images using a semiautomatic technique based on level sets. An unpaired *t*-test was used to assess statistical significance.

RESULTS—Significant differences were found between mean spinal cord volume of HVs and HAM/TSP patients. The thoracic spinal cord volume was $14,050 \pm 981 \text{ mm}^3$ for HVs and $8,774 \pm 2,218 \text{ mm}^3$ for HAM/TSP patients ($P = .0079$), a reduction of 38%. The cervical spinal cord volume was $9,721 \pm 797 \text{ mm}^3$ for HVs and $6,589 \pm 897 \text{ mm}^3$ for HAM/TSP patients ($P = .0079$), a reduction of 32%. These results suggest that atrophy is evident throughout the spinal cord not routinely quantified.

CONCLUSIONS—Semiautomatic spinal cord volume quantification is a sensitive technique for quantifying the extent of spinal cord involvement in HAM/TSP.

Keywords

Spinal cord; HTLV-I; HAM/TSP; MRI; atrophy

Introduction

The human T-cell lymphotropic virus type I (HTLV-I) causes an inflammatory disorder of the central nervous system (CNS) termed HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) that affects approximately 1 in 30 individuals infected with the

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retrovirus HTLV-I.¹ HAM/TSP is a chronic myelopathy characterized by gait difficulty, urinary dysfunction, and paresthesias, with a progressive unremitting course resembling primary progressive multiple sclerosis. Spinal cord inflammatory infiltrates with demyelination, neuroaxonal degeneration, and reactive gliosis characterize the underlying pathology of HAM/TSP.² To date, no effective disease modifying therapy for HAM/TSP has been established, and the disease lacks a validated surrogate biomarker of disease activity.³

Brain alterations occurring in HTLV-I infected individuals often do not distinguish HTLV-I carriers from HAM/TSP.⁴ As previously reported by Griffith et al⁵ reductions in brain parenchymal fraction (BPF) do not occur frequently in patients with HAM/TSP when compared with age-/gender-matched healthy individuals. Spinal cord atrophy (volume loss) is detected by conventional MR imaging in up to a third of HAM/TSP subjects.^{6,7} The slowly progressive clinical course of typical HAM/TSP suggests that the detection of spinal cord atrophy may be possible within a time frame relevant to ongoing disease activity, but to date no study has established a clear relationship between cord atrophy and clinical disease.

We have used a semiautomated technique for accurate 3-dimensional (3D) quantification of spinal cord volume by MR imaging to capture the full extent of atrophy in CNS diseases with spinal cord involvement. Using 3D MRI spinal cord volume analysis, we detected significant volume loss not only in the thoracic cord, as previously reported, but also in the cervical cord in subjects with HAM/TSP compared to matched healthy volunteers (HVs). Our analysis of spinal cord volumes in individuals with HTLV-I infection including *definite* HAM/TSP, *possible* HAM/TSP, and *asymptomatic* carriers suggest that 3D MRI spinal cord volume analysis is a sensitive measure of CNS involvement in HTLV-I infection, and may be applicable to other progressive neurological diseases that involve the spinal cord.

Materials and Methods

Subjects and Study Design

Five subjects with HAM/TSP and 5 age-, gender-, height-, and weight-matched HVs were included in this study. Clinical characteristics are summarized in Table 1. All subjects with HAM/TSP met criteria for *definite* HAM/TSP based on recently proposed ascertainment guideline.⁸ In addition, 4 subjects with serologically confirmed HTLV-I infection who did not meet criteria for *definite* HAM/TSP were included. Two subjects (HTLV1 and HTLV2) who denied complaints but demonstrated abnormalities on neurologic exam including mild spasticity and sensory changes were categorized as *possible* HAM/TSP, and 2 subjects (HTLV3 and HTLV4) who had no neurologic complaints with normal neurological exams were categorized as *asymptomatic* carriers. Disability scores including expanded disability status scale (EDSS) and Insituto de Pesquisa Clinica Evandro Chagas IPEC (IPEC) disability scale were determined for subjects with *definite* HAM/TSP. None of the subjects with HAM/TSP were “rapidly progressive” or showed T2 hyperintensity, gadolinium contrast enhancement, or swelling on cervical cord MRI.^{9,10} Written informed consent was obtained from all subjects and the study was approved by the NIH Institutional Review Board and HIPAA compliance was followed.

MR Image Acquisition

Each subject underwent a comprehensive spinal cord MRI examination on a 1.5 T whole-body scanner (GE Excite HDx, GE Healthcare, Waukesha, WI) using an 8-channel Cervico-Thoraco-Lumbar spine surface phased array coil (USA Instruments, Aurora, OH). Sagittal 2-dimensional fast spin-echo (FSE) T1, PD/T2-weighted and short tau inversion recovery (STIR), MR imaging sequences, as well as axial T2-weighted sequences of the cervical and thoracic spinal cord were acquired (Figs 1 and 2). In addition, a 3D 1 mm³ isotropic inversion recovery fast spoiled gradient recalled echo (3D IR-FSPGR) sequence was acquired and was used to perform the quantitative measurements. Acquisition parameters are summarized in Table 2. For the cervical spinal cord the acquisition field of view was 256 × 256 mm² while for the thoracic spinal cord it was 320 × 256 mm².

MR Image Processing and Analysis

Quantification of the spinal cord volume was performed on 3D T1-weighted (IR-FSPGR) MR images (Figs 3A and 4A) using a semiautomatic technique based on level sets.¹¹ The procedure is the same for both the cervical and thoracic spinal cord. The first step of this method is the bias field correction for correcting intensity variations in the image data due to the surface coil used. Second, anisotropic diffusion filtering is applied as a preprocessing filter to reduce noise and sharpen the anatomical boundaries in the images. Then based on the midsagittal, first and last slices the spinal cord volume boundaries are defined. The cervical spinal cord is constrained between the foramen magnum and the lower border of the C7 vertebral body and the thoracic spinal cord from the upper border of the T1 to the lower border of the T12 vertebral body, using a bounding box. Starting from the midsagittal image a coarse region of interest (ROI) is then placed and by means of a level set evolution is allowed to evolve (expand/contract) until the spinal cord boundary is found (Figs 3B and 4B) and extracted from the image (Figs 3C and 4C). The process is repeated for the parasagittal slices until all boundaries defining the spinal cord are found. From all the boundaries a 3D spinal cord surface for each segment is produced (Figs 3D and 4D), whose volume is then calculated. The whole procedure takes about 15 minutes of postprocessing time. As previously described¹¹ inter- and intraobserver variability for this technique was less than or equal to 3%. Also when compared to manual measurement/outlining, considered as ground truth, there was almost perfect correlation of $R^2 = .978$ making this technique suitable for clinical use.

HTLV-I Proviral Load

HTLV-I proviral load was determined by real-time polymerase chain reaction, as described previously.¹² The HTLV-I proviral DNA load was calculated by the following formula: copy number of HTLV-I (pX) per 100 cells = (copy number of pX)/(copy number of β -actin/2) × 100.

Statistical Analysis

Data were summarized as mean ± standard deviation. The Kolmogorov–Smirnov statistic was used to test for normality and the unpaired *t*-test or Mann–Whitney test was used to assess differences between groups as appropriate. Pearson correlation coefficient was

calculated to assess the relationship between spinal cord volumes and clinical parameters. Bonferroni correction was used for multiple comparisons. Statistical analysis was performed using Prism version 5 (GraphPad Software, Inc. La Jolla, CA).

Results

Subjects with *definite* HAM/TSP showed significantly lower spinal cord volumes compared to HVs (Figs 5 and 6). The mean thoracic cord volume for subjects with HAM/TSP was $8,774 \pm 2,218 \text{ mm}^3$ compared to $14,050 \pm 980 \text{ mm}^3$ for HVs, representing a 38% reduction in mean thoracic cord volume in subjects with HAM/TSP ($P = .0079$). Spinal cord atrophy was not limited to the thoracic cord. The mean cervical cord volume for subjects with HAM/TSP was $6,589 \pm 897 \text{ mm}^3$ compared to $9,721 \pm 797 \text{ mm}^3$ for HVs, representing a 32% reduction in mean cervical cord volume ($P = .0079$). The ratio of cervical to thoracic cord volumes for HAM/TSP was .78 compared to .69 for HVs, reflecting the relatively greater volume loss in the thoracic cord of subjects with HAM/TSP.

As a group, subjects with HTLV-I infection not meeting criteria for *definite* HAM/TSP showed a mean cervical cord volume of $9,075 \pm 2,095 \text{ mm}^3$ and a mean thoracic cord volume of $12,788 \pm 3,562 \text{ mm}^3$. Although these cord volumes did not differ significantly from those of HVs ($P = .56$ and $P = .9$, respectively), the range of individual spinal cord volumes (Figs 5 and 6) reflected the clinical heterogeneity of this group. The two *asymptomatic* carriers in this group showed thoracic cord volumes of $15,548 \text{ mm}^3$ and $15,362 \text{ mm}^3$, well within the range of HVs, whereas the two *possible* HAM/TSP subjects demonstrated lower thoracic cord volumes of $12,308 \text{ mm}^3$ and $7,933 \text{ mm}^3$ that were close to or within the cord volume range of *definite* HAM/TSP subjects. These results suggest that the 3D volumetric measurements of the spinal cord may be a highly informative indicator of CNS involvement associated with HTLV-I infection.

To examine whether the spinal cord volumes correlate with measures of disability, the relationship between spinal cord 3D volumetric measurements and clinical parameters such as disease duration, EDSS, and IPEC were analyzed. The correlation between cervical cord volume and disease duration in *definite* HAM/TSP was significant at the $P < .05$ level ($R^2 = .77$, $P = .049$; Pearson correlation), but was not statistically significant following correction for multiple comparisons. Otherwise no significant correlations were observed between spinal cord volumes and age, EDSS, or IPEC in this retrospective cross-sectional study.

Discussion

We have used a semiautomated technique for quantification of spinal cord volume from 3D MR images. Applied to subjects with HAM/TSP, an inflammatory myelopathy with a well-characterized progressive clinical course resembling primary progressive multiple sclerosis, we showed that spinal cord atrophy distinguishes subjects with HAM/TSP from HVs. Thoracic cord volumes were over one third lower, and cervical cord volumes were substantially reduced in subjects with HAM/TSP, demonstrating, for the first time by MRI, substantial volume loss in the HAM/TSP cervical cord. In individuals with HTLV-I

infection but not fulfilling ascertainment criteria for *definite* HAM/TSP, the current technique appears to be informative with respect to distinguishing those who are asymptomatic from those who demonstrate abnormalities on clinical examination. Thus the 3D MRI spinal cord volume quantification employed in this study is a sensitive tool for detecting spinal cord volume loss, and may be a sensitive indicator of CNS involvement in HTLV-I infection.

Previous studies to characterize spinal cord volume by MRI in HAM/TSP have relied on measurement of midthoracic cross-sectional area ratios as a surrogate for cord volume and have not shown a clear relationship between atrophy and disease progression.⁶ Although the 3D MRI quantification of spinal cord volume employed in this study captures the full extent of spinal cord involvement, spinal cord volumes did not correlate with measures of clinical disability such as EDSS and IPEC in this cross-sectional study of subjects with HAM/TSP. A positive correlation between cervical spine volume and disease duration was seen at the $P < .05$ significance level, but was not statistically significant following correction for multiple comparisons. One possible explanation for the lack of a strong correlation between spinal cord atrophy and clinical disability in this study is that variations in baseline (presymptomatic) spinal cord volumes could obscure such relationships in a cross-sectional study. We predict that a longitudinal study of spinal cord volumes is more likely to demonstrate correlations between atrophy and disability.

In summary, spinal cord volume quantification from 3D MR images detects cervical and thoracic spinal cord atrophy in subjects with HAM/TSP and shows promise as a clinically relevant tool in for quantifying the extent of spinal cord involvement in HAM/TSP. Longitudinal studies are needed to adequately assess whether spinal cord volume loss correlates with disability in HAM/TSP and monitoring of disease progression. The 3D MR imaging spinal cord volume quantification technique may be applicable in other progressive neurologic diseases that involve the spinal cord such as primary progressive multiple sclerosis.

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References

1. Orland JR, Engstrom J, Fridey J, et al. Prevalence and clinical features of HTLV neurologic disease in the HTLV Outcomes Study. *Neurology*. 2003; 61(11):1588–1594. [PubMed: 14663047]
2. Iwasaki Y. Pathology of chronic myelopathy associated with HTLV-I infection (HAM/TSP). *J Neurol Sci*. 1990; 96(1):103–123. [PubMed: 2351985]
3. Oh U, Jacobson S. Treatment of HTLV-I-associated myelopathy/tropical spastic paraparesis: toward rational targeted therapy. *Neurolog Clinics*. 2008; 26(3):781–797.
4. Morgan DJ, Caskey MF, Abbehussen C, et al. Brain magnetic resonance imaging white matter lesions are frequent in HTLV-I carriers and do not discriminate from HAM/TSP. *AIDS Res Hum Retroviruses*. 2007; 23(12):1499–1504. [PubMed: 18160007]
5. Griffith C, Bagnato F, Gupta S, et al. Brain volume measurements in patients with human T-cell lymphotropic virus-1-associated tropical spastic paraparesis. *J Neurovirol*. 2006; 12(5):349–355. [PubMed: 17065127]

6. Yukitake M, Takase Y, Nanri Y, et al. Incidence and clinical significances of human T-cell lymphotropic virus type I-associated myelopathy with T2 hyperintensity on spinal magnetic resonance images. *Inter Med (Tokyo, Japan)*. 2008; 47(21):1881–1886.
7. Milagres AC, Jorge ML, Marchiori PE, et al. Human T cell lymphotropic virus type 1-associated myelopathy in Sao Paulo, Brazil. Epidemiologic and clinical features of a university hospital cohort. *Neuroepidemiol*. 2002; 21(3):153–158.
8. De Castro-Costa CM, Araujo AQ, Barreto MM, et al. Proposal for diagnostic criteria of tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM). *AIDS Res Hum Retroviruses*. 2006; 22(10):931–935. [PubMed: 17067261]
9. Umehara F, Nagatomo S, Yoshishige K, et al. Chronic progressive cervical myelopathy with HTLV-I infection: variant form of HAM/TSP? *Neurology*. 2004; 63(7):1276–1280. [PubMed: 15477551]
10. Umehara F, Nose H, Saito M, et al. Abnormalities of spinal magnetic resonance images implicate clinical variability in human T-cell lymphotropic virus type I-associated myelopathy. *J Neurovirol*. 2007; 13(3):260–267. [PubMed: 17613716]
11. Evangelou, IEGA.; Ohayon, JM.; Cantor, FC., et al. A novel quantification method for cervical spinal cord volume in multiple sclerosis patients from 3D magnetic resonance images; American Academy of Neurology Annual Meeting; Chicago. Apr. 2008
12. Nagai M, Usuku K, Matsumoto W, et al. Analysis of HTLV-I proviral load in 202 HAM/TSP patients and 243 asymptomatic HTLV-I carriers: high proviral load strongly predisposes to HAM/TSP. *J Neurovirol*. 1998; 4(6):586–593. [PubMed: 10065900]

Fig 1.

Sagittal cervical spinal cord MR images of a HAM/TSP patient acquired with TR/TE/TI (A) T1-weighted (725/12), (B) PD (2700/9.0), (C) T2 (2700/112)-weighted and (D) STIR (5000/28/160). TR = repetition time, TE = echo time, TI = inversion time.

Fig 2.

Sagittal thoracic spinal cord MR images of a HAM/TSP patient acquired with TR/TE/TI (A) T1-weighted (725/12), (B) PD (2700/9.0), (C) T2 (2700/112)-weighted and (D) STIR (5000/28/160). TR = repetition time, TE = echo time, TI = inversion time.

Fig 3.

Cervical spinal cord volume quantification steps. (A) Sagittal 3D IR-FSPGR MR image (TR/TE/TI/FA, 7.8/3.2/450/20°) after surface coil intensity correction, (B) spinal cord boundary, (C) extracted binary mask, (D) 3D triangulated and rendered surface. TR = repetition time, TE = echo time, TI = inversion time, FA = flip angle.

Fig 4.

Thoracic spinal cord volume quantification steps. (A) Sagittal 3D IR-FSPGR MR image (TR/TE/TI/FA, 7.8/3.2/450/20°) after surface coil intensity correction, (B) spinal cord boundary, (C) extracted binary mask, (D) 3D triangulated and rendered surface. TR = repetition time, TE = echo time, TI = inversion time, FA = flip angle.

Fig 5.

Cervical spinal cord volumes in healthy volunteers (HV), subjects with HTLV-I infection not meeting criteria for definite HAM/TSP (HTLV) and subjects with definite HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).

Fig 6. Thoracic spinal cord volumes in healthy volunteers (HV), subjects with HTLV-I infection not meeting criteria for definite HAM/TSP (HTLV) and subjects with definite HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).

Table 1

Subject Clinical Characteristics and Spinal Cord Volumes

Subject ID	Age	Gender	Disease Duration (years)	Ascertainment	IPEC	EDSS	25FTW	HTLV-I Proviral Load	Cervical Spinal Cord Volume (mm ³)	Thoracic Spinal Cord Volume (mm ³)
HAM/TSP1	53	F	11	Definite	24	7.0	–	11.51	5,440	5,783
HAM/TSP2	58	F	11	Definite	9	3.0	5.8	11.03	6,598	10,878
HAM/TSP3	48	M	13	Definite	18	6.5	30.6	46.39	5,991	8,305
HAM/TSP4	49	F	4	Definite	24	6.5	25.7	11.00	7,334	11,060
HAM/TSP5	34	M	2	Definite	14	6.0	14.6	10.85	7,581	7,845
HTLV1	68	M	–	Possible	–	–	–	20.00	6,836	7,933
HTLV2	62	F	–	Possible	–	–	–	7.00	9,303	12,308
HTLV3	53	F	–	Asymptomatic	–	–	–	.07	8,337	15,548
HTLV4	48	M	–	Asymptomatic	–	–	–	.01	11,825	15,364
HV1	55	F	–	–	–	–	–	–	8,934	13,253
HV2	51	F	–	–	–	–	–	–	10,499	15,437
HV3	47	M	–	–	–	–	–	–	10,655	13,344
HV4	47	F	–	–	–	–	–	–	9,341	14,731
HV5	37	M	–	–	–	–	–	–	9,175	13,483

Table 2
Acquisition Parameters for MR Imaging Sequences for the Cervical and Thoracic Spinal Cord

MR Sequence	Plane	Field of View (mm)	Acquisition Matrix	Slice Thickness (mm)	Echo Train Length	Repetition Time (ms)	Echo Time (ms)	Inversion Time (ms)	No. of Signal Averages	Duration (min:sec)
2D FSE PD/T2-W	Sagittal	256	320 × 256	3.0	24	2,700	9.0/112	–	3	3:20
2D STIR	Sagittal	256	320 × 256	3.0	15	5,000	28	160	3	4:10
2D FSE T1-W	Sagittal	256	256 × 256	3.0	2	725	12	–	2	3:17
2D FSE T2-W	Axial	256	256 × 256	5.0	24	2,934	112	–	3	3:26
3D IR-FSPGR	Sagittal	256	256 × 256	1.0	–	7.8	3.2	450	2	8:10