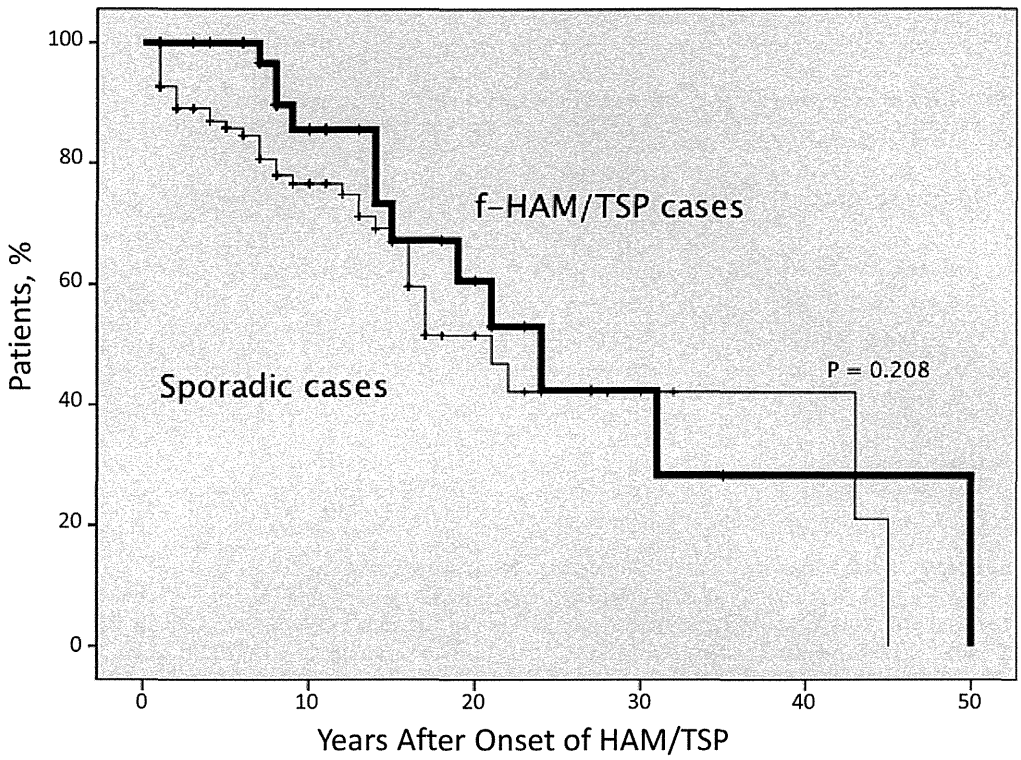

Figure 1. Kaplan–Meier estimates of the time from disease onset to assignment of motor disability scores of 6. In sporadic cases, more patients reached the score of six at an early stage; however, the difference was not significant. Approximately 30% of both f-HAM/TSP cases and sporadic cases needed a wheelchair in daily life in 15 years after onset and approximately 50% of patients from both groups needed a wheelchair in 20 years after onset.
doi:10.1371/journal.pone.0086144.g001

than in male. There was no significant difference between women and men in the age of onset (61.5 y.o.±12.6 vs. 62.7 y.o.±12.5), in the incidence of rapid progression (26.3% vs. 32.3%) and in MDG score (5.4 vs. 5.0; mean).

Discussion

We demonstrated that among 784 HAM/TSP patients, 40 (5.1%) had family members with the disease. The lifetime risk of developing HAM/TSP is 0.25% of HTLV-1 carriers in Japan

Table 1. Clinical features of f-HAM/TSP cases or sporadic cases of HAM/TSP.

	f-HAM/TSP cases (40 cases)	Sporadic cases (124 cases)	p value	p value†
Female ratio (%)	78.8% (7 males : 33 females)	66.4% (31 males : 93 females)	NS	
Age	55.6±13.0 (23–79)	61.8±12.5 (15–83)	**0.008**	
Age of onset	41.3±13.9 (14–65)	51.6±15.9 (13–78)	**<0.001**	**0.017**
Duration of illness (years)	14.3±11.4 (1–49)	10.2±9.6 (0–45)	**0.026**	**0.017**
Initial symptoms				
Gait disturbance	50.0%	52.4%	NS	
Urinary disturbance	32.5%	26.6%	NS	
Sensory disturbance	12.5%	14.5%	NS	
Others	5%	6.5%	NS	
Rapid disease progression	4 cases (10.0%)	35 cases (28.2%)	**0.019**	0.069
Motor disability score	4.0±2.0 (0–7)	4.9±1.5 (0–8)	**0.043**	**0.036**
Score more than 6	12 cases (30.0%)	38 cases (30.7%)	NS	
Time elapsed between onset and wheelchair use in daily life (years)	18.3±12.4 (7–50)	10.0±10.4 (1–45)	**0.025**	**0.020**

Data are presented as mean values ± s.d., (range),
†Adjusted for age and sex.
doi:10.1371/journal.pone.0086144.t001

Table 2. Laboratory findings of familial clusters or sporadic cases of HAM/TSP.

	f-HAM/TSP cases (40cases)	Sporadic cases (124 cases)	p value	p value†
Anti-HTLV-1 antibodies*				
Titer in Serum	20,787±31,004, N = 37	31,009±36,075, N = 109	NS	
Titer in CSF	2,310±11,741, N = 31	672±1,274, N = 111	NS	
Cerebrospinal fluid				
Cell number (/mm^3)	3.0±2.5, N = 25	5.7±10.0, N = 109	NS	
Protein (mg/dl)	29.9±9.4, N = 22	42.5±19.3, N = 109	**<0.001**	**0.007**
Neopterin (pmol/ml)	83.2±118.1, N = 18	38.3±56.8, N = 35	NS	
HTLV-1 proviral loads (Copies/10^4 PBMCs)	930±781, N = 32	968±1,746, N = 101	NS	

* Particle Aggregation Method.
Data are presented as mean values ± s.d., N = sample number,
†Adjusted for age and sex.
doi:10.1371/journal.pone.0086144.t002

[13]. Although clustering of familial adult T-cell lymphomas has been reported [8,9], to our knowledge the prevalence of familial clusters of HAM/TSP has not been described. A study in Peru showed that 30% of HAM/TSP patients have family members with paralytic neurological disorders, but the cause of paralysis was not evaluated [14]. In the present study, we included f-HAM/TSP diagnosed in medical institutions and excluded cases with a family history of neurological disorders. Thus, the actual incidence rates of f-HAM/TSP may be higher than those reported here. Interestingly, although HTLV-1 PVL has been associated with the development and clinical progression of HAM/TSP [15–17], there was no significant difference between f-HAM/TSP and sporadic cases in the present study. Because previous studies reported that HTLV-1 PVLs of asymptomatic carriers in relatives of HAM/TSP patients were higher than those in non-HAM-related asymptomatic carriers [6], relatives of HAM/TSP are believed to be at a higher risk of developing HAM/TSP. Interestingly, our data suggest that HAM/TSP patients aggregate in families and factors other than HTLV-1 PVLs may contribute to HAM/TSP.

Compared with sporadic HAM/TSP, the clinical characteristics of f-HAM/TSP have a younger age of onset and longer time elapsed between onset and wheelchair use in daily life. Although we were unable to identify the reason for earlier onset among f-HAM/TSP cases, one can speculate that mild symptoms, such as urinary and sensory disturbances, may be identified earlier by family members who are familiar with HAM/TSP symptoms. However, the present data show no difference in initial symptoms

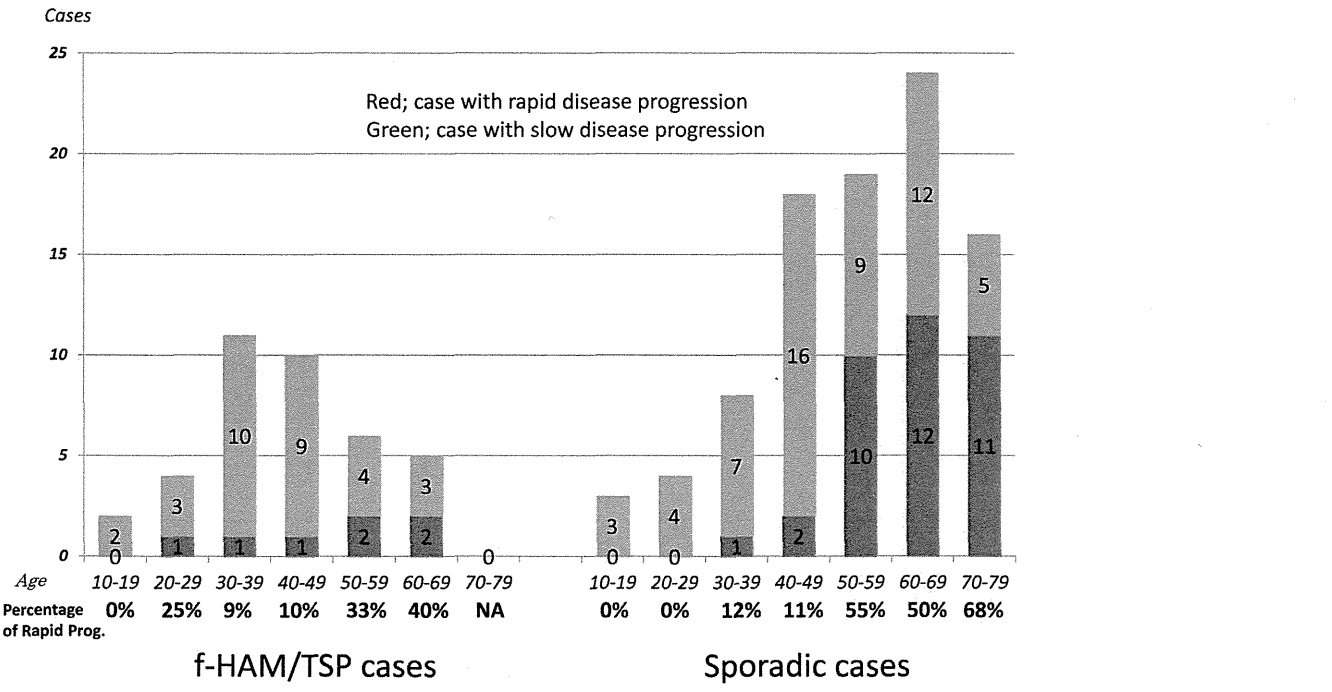

Figure 2. Age-specific proportions of rapid disease progression. The proportion of cases with rapid disease progression tended to increase with the older age of onset.
doi:10.1371/journal.pone.0086144.g002

Table 3. Clinical and laboratory findings of sporadic HAM/TSP with rapid/slow disease progression.

Type of disease progression	Rapid progression	Slow progression	p value
Female ratio (%)	71.4% (10 males : 25 females)	76.4% (21 males : 68 females)	NS
Age of onset	62.3±9.6, N = 35	47.4±15.9, N = 89	**<0.001**
Age of onset of f-HAM/TSP cases	60.5±3.7, N = 4	39.2±12.9, N = 36	**0.002**
Duration between onset and inability to walk alone (years)	1.5±0.9, N = 13	14.4±10.4, N = 25	**<0.001**
Anti-HTLV-1 antibodies*			
Titer in Serum	31,894±36,845, N = 34	30,608±35,965, N = 75	NS
Titer in CSF	1,251±1,800, N = 34	416±852, N = 77	**0.014**
Cerebrospinal fluid			
Cell number (/mm^3)	11.6±16.6, N = 34	3.2±3.5, N = 75	**<0.001**
Protein (mg/dl)	55.3±24.3, N = 34	36.7±13.0, N = 75	**<0.001**
Neopterin (pmol/ml)	74.9±107.9, N = 8	27.4±23.4, N = 27	0.255
HTLV-1 proviral loads (Copies/10^4 PBMCs)	370±327, N = 32	1,245±2,046, N = 69	**<0.001**

* Particle Aggregation Method.
Data are presented as mean values ± s.d., N = sample number.
doi:10.1371/journal.pone.0086144.t003

between f-HAM/TSP and sporadic cases. In all cases, the age of onset and initial symptoms of HAM/TSP were evaluated by the neurologists during hospitalization. Because inflammatory processes are less marked in f-HAM/TSP cases, as indicated by significantly lower protein levels in CSF, f-HAM/TSP cases may show slow progression of disease.

We need to discuss the possibility that the two groups compared represent different mode of HTLV transmission, i.e. vertical vs. sexual transmission. To clarify genetic backgrounds, sporadic HAM/TSP with seropositive carrier family members may be a more appropriate control, but are not available at present. The incidence of female cases showing no significant differences between f-HAM/TSP and sporadic cases, and between rapid and slow disease progression, might suggest less possibility of sporadic cases due to sexual transmission.

Although the subgroup of patients with rapid progression has not been clearly defined, previous studies suggest that rapid progression occurs in 10%–30% of all patients with HAM/TSP [12,14,16], and is associated with an older age of onset [14–16]. In the present study, the age of onset in patients with rapid progression was significantly older than that in patients with slow progression between f-HAM/TSP and sporadic cases, and the proportion of patients with rapid progression increased with the older age of onset (Figure 2). Among sporadic cases, cell numbers and protein levels in CSF were significantly higher in patients with rapid progression, suggesting that inflammation is more active in the spinal cords of patients with rapid progression and that cytotoxic T-lymphocyte (CTL) immune responses may be more intensive. Therefore, lower PVLs in PBMCs of patients with rapid disease progression may be attributed to the strong killing ability of the CTL. However, PVLs were higher in PBMCs of patients with HAM/TSP than in asymptomatic carriers [6]. In addition, the killing ability of CTLs in patients with HAM/TSP does not differ from that in asymptomatic carriers [18]. Hence, strong immune responses may be associated with the disease course. The onset of disease may require other factors that lead to strong immune responses. A late onset may also be associated with alterations of the immune function in HTLV-1-infected patients. Indeed, an increased age has been associated with autoimmune disorders, such as myasthenia gravis and rheumatoid arthritis, and may be partly explained by immune intolerance and accumulation of autoantibodies in older individuals [19,20].

In conclusion, we demonstrated that patients with HAM/TSP aggregate in some families. Compared with sporadic cases, the age of onset was younger and rates of disease progression were slower among familial cases, whereas HTLV-1 PVLs did not differ between f-HAM/TSP and sporadic groups. The present data suggest that factors other than HTLV-1 PVLs contribute to the disease course of HAM/TSP. Our data also suggested strong immune responses in the spinal cord of HAM/TSP patients with rapid progression. Further studies on HTLV-1, immune response to HTLV-1 and genetic factor in patients with rapid progression might provide new insights into HAM/TSP pathogenesis.

Acknowledgments

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Author Contributions

Conceived and designed the experiments: HT SI OW. Performed the experiments: SN EM. Analyzed the data: SN EM. Contributed reagents/materials/analysis tools: SN EM TM RK. Wrote the paper: SN EM.

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Doctor's Opinion

新たな医療の構築を地域で目指す
—病院のイノベーション・挑戦

国立病院機構新潟病院 副院長
中島 孝（神経内科医）

現代医療の科学モデルは根拠に基づく医療（ＥＢＭ）である。すなわち、臨床試験（治験）により何らかのアウトカムの改善が確率論的に証明された治療法を、インフォームド・コンセントの下で患者が自己決定し、多専門職種が協働するクリティカルパスにより、最短経路で安全かつ効率的な医療を提供するものである。しかし、このモデルは本当に正しいのだろうか？

現代ではこのモデルを使い、「健康」を目指す医療を頑張って行っても、病院を訪れる、高齢者、慢性疾患患者、進行期のがん患者、難病患者、認知症患者などは治らず、尊厳死論や医療の無駄議論などの混乱が起きている。「健康概念」による臨床アウトカム評価に基づくと、どんなに熱心に診療をしても、治らない患者は常に悪化評価される。これが医師や看護師の燃え尽き現象の原因となっており、その結果、その様な患者は十分に説明を受けた上で「死を選ぶ」か、「延命治療を選ぶ」か、自己決定すべきであり、自己決定能力がなくなる前に事前にそれを意思決定しておくべきという考えに至る。人は生まれたときに将来１００％治らない難病になり、死ぬことが定められているのは、自明であるにも関わらず死の自己決定の必要があるのだろうか。

現代医療では、この様な解決困難な問題が起きると、倫理問題や法的問題とするが、本来、混乱が起きないように、医療モデル自体を科学的に変更・改善すべきなのではないだろうか。

治せる病気は予防と早期治療原理で直ちに治し、残った治らない病気、進行期のがん、非がんの難病、慢性呼吸不全、認知症、慢性小児疾患、筋ジストロフィー、重症心身障害児者などに対しては、病気と共に歩む患者と家族を地域の中で支えていく原理を、新たな医療モデルとして、医学教育、研修に取り込み、病院で実践することが必要である。多専門職種でおこなう症状コントロールは、もちろん、さらに、新たな治療薬、医療機器を作りあげる研究・治験に取り組むべきである。その根底にあるのはどんな病気になっても、人が「今を生きる事」を放棄するのではなく、肯定して生きられるサポートを成功させる事である。小児から高齢者まで、どんな年齢にあっても、どんな病気と共にあっても、死を迎えるまで、人は変化し成長発達できるはずで、その中で、「喪失から再生へのケア」を実践すべきである。

当院ではこのため、臨床研修、卒後教育だけでなく、全職種が臨床研究を行っている。その頂点として、２０１３年３月から希少性難病に対する新規の医師主導治験を開始した。全職員に対する教育・研修プログラムを作るだけでなく、医師などは、常勤でありながら、地域の大学の大学院課程を履修できるようにした。既存のクリティカルパス、マニュアル、ガイドラインをコンプライアンス良く実践するだけでなく、新たな課題設定のもとで、それらを作り直していくために、大学院レベル以上の問題解決能力と学術能力が必要だからである。

この様なことを推進するためには、病院事業をどんな災害や危機からも強くし、患者と職員を同時に守ることが必須になる。病棟はすべて新築し直し、完全な免震病棟として、屋上階に非常用機械室を設置し、主要エネルギー源は重油でも都市ガスでもなく、液化石油ガスにした。診療情報の電子カルテ化の際に、情報ネットワークにおける設備の二重化だけでなく、サーバ、ネットワーク、端末に対して中央化無停電電源装置によるバックアップを行った。この様な徹底したサポートによって、常に、職員は患者・家族に笑顔で対応できる。

現代医療はＥＢＭの下で、集団において統計的有意な治療法のみを提供し、個別性を否定し、個人の満足が得られていない事が問題である。一方、現代において、イノベーションしようとしている医療の形は、新たな健康概念（BMJ2011）の下で、個人の生物学的・遺伝学的特性に基づくテーラーメード医療とナラティブ（語り）に基づく医療を合体させた「個人に基づく医療（Individual based Medicine）」である。どんな患者でも、どんな時にも、患者の主観的な臨床評価としての「患者の報告するアウトカム（ＰＲＯ：Patient reported outcome）」を向上できる医療を目指し、患者・家族と職員の両者の満足度を高められる病院を作り上げたいと思っている。是非、これに賛同する皆さん、医師と共に新たな医療を地域で構築し、実践したい。

12. ロボットスーツ HAL

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キーワード　ロボットスーツ　HAL　HAM　脊髄症　神経難病

症例紹介

65歳，女性．10代に歩行障害で発症し，後にHAM（HTLV-1-associated myelopathy；HTLV-1関連脊髄症）と診断された．症状は，痙性歩行であり，徐々に進行し，最近はつかまり歩行がやっとであった．

冬期間，大雪のため，外出で歩行しなかったため，症状がさらに急速に悪化し，立位もできず，ほとんど寝たきりになり受診した．歩行改善が可能かどうか，精査とリハビリテーション（以下リハ）目的にて，X年3月13日，入院した．所見は両下肢の痙性が強く，痙性不全対麻痺だった．頻尿や便秘等の自律神経症状は強くなく，明らかな感覚障害を認めなかった．理学療法の歩行プログラムとして，移動型ホイストによる立位・歩行練習とロボットスーツHALを用いた歩行練習を導入した．

機器・用具の導入

(1) ホイスト，リフトシステムの導入

最初，平行棒，歩行器による歩行を検討したが，立位での不安，恐怖感や痙性のために足関節が十分に床につかない等の問題があり，安全な立位訓練のために，移動型ホイスト（mobile hoist）であるAll-in-One（http://www.healthcarelifting.com.au/products2_walker.php）を導入した．立位と歩行の恐怖心を緩和するために，免荷して，立位と歩行を試みた（図1a）．尖足歩行のパターンは変えられなかった．初日の10 m歩行は68.9秒で45歩であった．

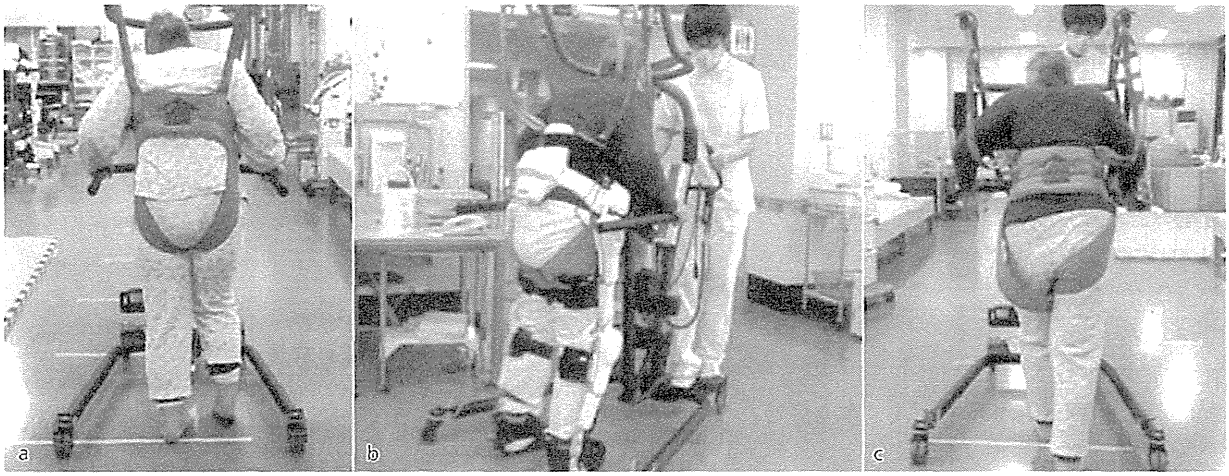
移動型ホイストは天井走行型ホイストと基本的機能は同じであるが，わが国ではほとんどの理学療法室は天井走行型のホイスト設備（http://www.liko.se/jp/international/Products/Overhead-Lifts/）を有していないため，移動型ホイストを利用する．移動型ホイストは設置保管場所が必要になる欠点があるが，歩行路を自由に設定でき，歩行の自由度が高まる点や，傾斜した歩行路を歩かせることができる利点がある．わが国では転倒の危険性がある立位，歩行訓練の際にも，ホイストがほとんど使われていないことが問題である．このため，立位・歩行訓練が十分にできていない．まず，移動型ホイストや天井走行型ホイストを標準的に導入する必要がある．

(2) HAL福祉用の導入

生体電位駆動型の装着型ロボットであるHAL（Hybrid Assistive Limb）は現在HAL福祉用が利用可能であり，当院ではホイストシステムで安全な立位を確保したうえで，歩行の再獲得練習に有効と考え導入を進めている．当院では，HAL福祉用の中で神経・筋疾患でも作動できる研究モデルHAL-HT01を使用している．

この症例にホイストで安全管理をし，本症例にも1回40分程度HALを用いた歩行練習を導入した（図1b）．HAL装着初日はHALに慣れてもら

■図1　ホイストとHALの導入



a）初日のホイスト装着歩行では，ホイストで免荷し，尖足歩行がやっとである．
b）移動型ホイストで安全管理し，HAL装着歩行練習を行った．
c）最終日の10 m歩行テストでは時間が短縮しただけでなく，脚の振り出しが改善し，痙性が低下し，足底も床に十分についている．

うため，単関節運動のみ実施したが，必ずしも，股・膝関節屈伸がスムースに行えず，本人より「ロボットが勝手に動いていうことをきかない」と言われ，さらに操作者も慣れておらず，装着，設定に時間がかかり疲労感を起こさせた．翌日の10 m歩行は16.3秒，25歩だった．

2日目は単関節運動，立ち上がり，歩行を実施した．装着時間の短縮，トルク・バランス設定の見直しにより，前回よりはるかに良好な関節運動が可能となり，立ち上がり，歩行練習を行うことが可能となった．いずれの動作でも，患者からは「楽に体が動く」「ロボットが手伝ってくれる」といったような感想が聞かれた．装着中の歩行は下肢を振り出すことが可能となった．取り外し後に単関節運動や足踏みテストを行ったところ，装着前と比較しスムースな運動が可能であり，即時効果が見られた．

3日目は単関節運動，立ち上がり，歩行を実施．前回同様，良好な関節運動が可能で，歩行練習を中心に行った．HALを用いての歩行練習後の歩行は歩幅の増大が認められた．

4日目は単関節運動を中心に実施し，異常波形が出現し，意図しない運動が起きるため，歩行練習は行わなかった．

5日目は単関節運動，立ち上がり，歩行練習を行った．装着直後に，前回の異常波形がみられたが，休息により消失し，歩行練習を中心に行った．直後の10 m歩行は15.4秒，22歩だった．翌日の10 m歩行は11.9秒，21歩とさらに改善を認めた．

(3) HAL歩行練習の評価結果のまとめ

急激な増悪で，歩行不能な状態になったHAM患者が16日間の入院中にHALを用いて5回の歩行練習プログラムを行ったところ，毎回著しい改善を示し，最終日には自立的な歩行を再獲得することができた．ホイストで安全管理したうえでの10 m歩行での必要時間は68.9秒から最終日の11.9秒と飛躍的に改善した．歩行パターンでは痙性の要素が著しく改善していた(図1c)．

(4) HAL使用の注意点

今回，副作用を全く認めなかった．HAL福祉用は医療機関，福祉施設，HAL-Fit等で利用されているが，重大な副作用の報告はない．現在，HAL医療モデル(HAL-HN01)に対する治験において厳密な有害事象を評価中である．

基本的にHALは安全使用研修を済ませ，使用経験のある指導者とともに医学的な判断のもとで使用すれば安全な使用ができる．しかし，歩行不安定症が対象であるため，転倒によるけがの予防

が最も重要で，両上肢の筋力が十分にあり平行棒内で理学療法士とともに使う場合を除き，原則的にホイストやリフトシステムを併用し転倒予防する．下腿フレームや大腿フレーム長が体に適合していないと，圧迫部の局所痛や下肢の疲れを引き起こすので，完全に適合させる．痛みが起きるとHALによる歩行改善効果は得られなくなる．生体電位電極による接触性皮膚炎もあり得るので注意する．

その他，歩行量が著しく少なかった方が急にHAL歩行プログラムを行うと，一過性の骨運動器の痛みが起き得る．もともと，変形性膝関節症，変形性股関節症，先天性股関節脱臼，変形性腰椎症や側弯症等の脊椎の変形がある場合はプログラムを工夫したり，疼痛や症状緩和のための理学療法を併用する等の対応が必要である．

(5) HAMの治療の概要とHAL歩行練習の位置づけ

HAMは脊髄症により，歩行障害，感覚障害，自律神経障害を引き起こす進行性の難病である．HAMはHTLV-1キャリア，ATLの分布と一致して分布(日本，カリブ海沿岸諸国，南アメリカ，アフリカ，南インド，イラン内陸部等と，移民を介してヨーロッパ諸国，アメリカ合衆国)しており，治療法の開発研究は世界的な課題である．日本では，HTLV-1抗体陽性者が生涯にHAMを発症する可能性は0.25%であり，HTLV-1感染の予防のために1986年11月より日赤血における抗HTLV-1抗体スクリーニングが開始され，2011年より母児間感染を防ぐための全妊婦を対象とするHTLV-1抗体検査が開始された．

HAMの治療のポイントは2つに分かれている．1つは脊髄の炎症の活動性のコントロールであり，インターフェロンα，副腎皮質ホルモンが使われるが，抗ウイルス療法(抗CCR4抗体を含む)が研究中である．2つめが脊髄症による運動症状コントロール・リハである．これは炎症の非活動期に重要であり，歩行リハ，痙性のコントロール，可能なら筋力増強と廃用性筋萎縮に対する治療を行う．

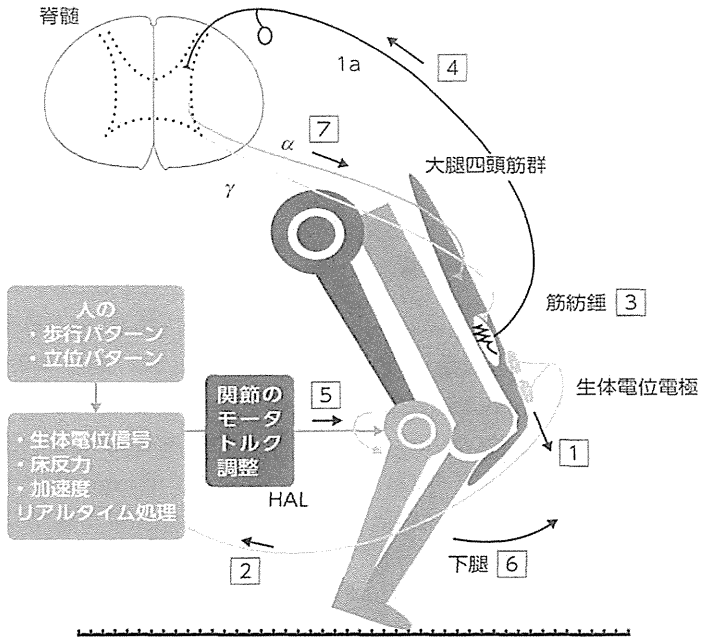
HAMの歩行機能の回復プログラムに関する研究はされてこなかった．今回の症例のように，痙性歩行に対してはHALによる歩行練習により痙性が軽減できる可能性があり，歩行パターンを想起実行できない状態に対してもHALによる歩行練習で再学習が可能と思われる．さらに，廃用症候群(廃用性筋萎縮)もHALとホイストを使った歩行練習で治療可能と考えられる．このようなプログラムがHAMの非活動期に有効と思われるが，炎症を抑制し，さらなる機能回復を目指すために，HALによる歩行練習プログラムと抗ウイルス薬，抗体薬，抗炎症薬とのcombined therapy(複合療法)を検討すべきである．

医療機器としてのHALの臨床応用について

筑波大学のシステム工学者の山海は1991年から，Cybernetics, Mechatronics, Informaticsを融合したサイバニクス(Cybernics)技術を用いて，人とリアルタイムに情報を交換し人を助ける装着型ロボットの開発を行ってきた．人の表面筋電図等の生体電位と装着ロボット内の内部センサーにより測定される加速度，関節角度，床反力情報を情報処理しリアルタイムに必要なモータトルクを発生させ，必要な筋群をアシストし，随意運動を増強する生体電位駆動型の装着型ロボットとして完成させ，HAL(Hybrid Assistive Limb)と命名した．HALの運動制御は機械と生体の一体的な運動を目標とするHybrid control mechanism(ハイブリッドメカニズム)であり[1]，装着者の運動意図に基づき制御するCVC(Cybernic Voluntary Control)と記録された起立，歩行等のパターンを参照し，HAL自身が自律制御を行うCAC(Cybernic Autonomous Control)が組み合わさっている．他に，装着者がHALの各関節の重さを感じないようにCIC(Cybernic Impedance Control)が使われている．

これにより，【脳→脊髄→運動神経→筋骨格系→HAL】および【HAL→筋骨格系→運動神経→脊髄→脳】という，脳・神経系とHALとの間でインタラクティブなバイオフィードバックが構成される(iBF；interactive Biofeedback仮説，山

■ 図2　HALと生体との一体的な運動



1歩行時に下腿を振り出すと，下腿の重みで大腿四頭筋群が伸張すると同時に，2随意運動としての大腿四頭筋群由来の生体電位入力が入る．3同時に1の大腿四頭筋群の伸張に伴い，筋紡錘の信号が変化する．4その結果，1aにより脊髄にフィードバックされ伸張反射を起こそうとする．5一方で，HAL内部のリアルタイムの処理により，モータで筋緊張が緩まる方向に調整する．6一体となったモータトルクと筋緊張により下腿の振り出しは継続されるが，7大腿四頭筋群への随意的な運動意図は弱まらないまま，伸張反射は低下する．

海嘉之による)と考えられている．このメカニズムは装着者の運動意思によって，HALが駆動すると骨格筋内の筋紡錘の緊張が低下し，Ia求心性ニューロンの信号変化が起き，骨格筋の伸張反射が低下する．その際に，随意運動に対応する生体電位が減少すれば，HALの補助は減少し目的運動は停止してしまうが，実際には，筋緊張が低下し，伸展反射が低下したまま随意運動が低下しないフィードバックがかかる．筋緊張が抑制された状態での随意運動を反復することで過剰な筋緊張が低下するような運動学習になると考えられている(図2)．

HALは人の機能と構造を変える医療機器として使うことができ，その効果は，①神経可塑性の促進，②運動神経・筋の保護効果，③廃用性筋萎縮の治療として示されると思われる．

HALの医学応用に対しては，疾患や疾患群に合わせた開発研究と，医療機器としての承認のためには臨床試験(治験)が同時に必要となる[2-5]．2013年3月から厚生労働省難治性疾患等研究事業において，「希少性神経・筋難病疾患の進行抑制治療効果を得るための新たな医療機器，生体電位等で随意コントロールされた下肢装着型補助ロボット(HAL-HN01)に関する医師主導治験―短期効果としての歩行改善効果に対する無作為化比較対照クロスオーバー試験(NCY-3001試験)：治験調整医師 中島 孝」が10施設の共同で行われている．

HALと薬剤との複合治療の可能性

脳，脊髄，神経，筋の領域では，根治療法として開発された薬だけでは運動機能の回復は望めない．運動機能を改善するためには，大脳・小脳・

脊髄・神経・筋の連携した運動再学習が必要で，その際にHALを使用することが重要である．つまり，薬剤，遺伝子治療，幹細胞，iPS細胞等とHALとの複合治療で有効性を高めることが最終的な目標といえる．デュシェンヌ型筋ジストロフィーのエキソンスキップ治療やポンペ病治療におけるERTとの複合治療が期待できる．

HAL下肢医療機器モデルが対象とする病態—歩行不安定症

HALの医療機器としての治療効果は疾患に基づいた歩行不安定症に対する改善効果や歩行機能の再獲得と考えている．歩行不安定症(walking instability)は新たに定義された概念であり，疾患，外傷，加齢にかかわらず，歩行が安定しない状態を指す(表)．ほとんど歩行不能状態といえるものから，何とか歩けるものも含まれるが，歩行スピード，歩行持久力の低下だけでなく，転倒リスクも伴う病態である．歩行不安定症が悪化すると，歩行不能となるため，歩行再獲得のための治療が重要となる[4,5]．

歩行不安定症では，10 m移動する場合にも，つかまったり，介助を必要としたり，歩行器やホイスト等の補助具が必要となる．歩行不安定症の病変部位，病態，疾患を表に示した．HALを一定時間，定期的，間欠的に装着し歩行訓練プログラムを行うことで，HAL非装着時の歩行不安定症が改善することを証明することが，HALの医療機器としての主要なアウトカムである．

■表　歩行不安定症を引き起こす病変部位・病態・疾患

解剖学的病変部位
脳，脊髄，末梢神経，筋および骨運動器
病態
筋力低下・筋萎縮，歩行パターンの変化，下肢筋トーヌス異常(痙性または低下)，両下肢深部感覚障害，姿勢反射障害，小脳機能障害，両下肢運動神経障害，両下肢錐体外路障害，両下肢錐体路障害
疾患名
脊髄性筋萎縮症，筋ジストロフィー，遠位型ミオパチー，ALS等の神経・筋疾患，ギラン・バレー症候群，CIDP，CMT等の末梢神経障害，多発性硬化症，脊髄損傷，脊髄血管障害，脳血管障害，頭部外傷，脳腫瘍，脊髄小脳変性症やパーキンソン病等を含む神経変性疾患，脳の周産期障害，脳性麻痺，代謝異常症，中毒，HAMやポリオ等の脳・神経系の感染症

HALの治療概念と倫理・社会面を巡る研究

WHO憲章前文(1948年)において，健康とは単に疾患がないとか虚弱でないとかではなく，身体的，心理的，社会的に完全によい状態(well-being)と定義され，あらゆる治療はこの健康概念に基づいて行われている．2003年のアメリカ大統領生命倫理審議会報告—生命技術と幸福の追求で，Beyond therapyがテーマとなった[6]．Therapy(治療)とは正常に戻すこと，健康にすることであり，Beyond therapy(超治療)とは正常以上にすることで，増強(エンハンスメント)技術，願望実現医療，Euphenics(人体改造学)等がそこに含まれるとされた[7]．

HALによる治療はこの枠組みで分類すると，治療とすべきか，超治療とすべきなのかの問題が起きる．もし仮に，「超治療，人体改造は規制すべき」という立場から，「装着者の筋力を超える力をアシストする」ことを規制対象とすると，神経・筋疾患患者にその人の筋力を超えるアシストを行うことが規制対象とされ，HALを用いた治療が困難になるという問題がある．

しかし，2011年にBMJで「われわれはどのように健康を定義すべきか？」という論文が発表され，健康の定義の変更が議論されている[8]．WHOの完全なwell-being概念はもはや科学概念としての健康定義として使用不能であり，高齢化社会での慢性疾患の増加に対応できないとされた．BMJの新たな健康概念は，「社会的，身体的，感情的問題に直面したときに適応し自ら管理する能力」と定義しようとする．この定義に基づけば，治療とは，正常に戻せるかどうかではなく，疾患や障害に適応するための能力に対する支援そのものを意味することになり，HALはこの健康概念における治療に対応し，Euphenicsではない．

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ORIGINAL ARTICLE

Feasibility of Rehabilitation Training With a Newly Developed Wearable Robot for Patients With Limited Mobility

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Abstract

Objective: To investigate the feasibility of rehabilitation training with a new wearable robot.

Design: Before-after clinical intervention.

Setting: University hospital and private rehabilitation facilities.

Participants: A convenience sample of patients (N=38) with limited mobility. The underlying diseases were stroke (n=12), spinal cord injuries (n=8), musculoskeletal diseases (n=4), and other diseases (n=14).

Interventions: The patients received 90-minute training with a wearable robot twice per week for 8 weeks (16 sessions).

Main Outcome Measures: Functional ambulation was assessed with the 10-m walk test (10MWT) and the Timed Up & Go (TUG) test, and balance ability was assessed with the Berg Balance Scale (BBS). Both assessments were performed at baseline and after rehabilitation.

Results: Thirty-two patients completed 16 sessions of training with the wearable robot. The results of the 10MWT included significant improvements in gait speed, number of steps, and cadence. Although improvements were observed, as measured with the TUG test and BBS, the results were not statistically significant. No serious adverse events were observed during the training.

Conclusions: Eight weeks of rehabilitative training with the wearable robot (16 sessions of 90min) could be performed safely and effectively, even many years after the subjects received their diagnosis.

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Rehabilitation robotics emerged in the 1980s with the aim of using robotic technology to assist people with movement dysfunction.[1] Robotic devices have recently been developed for use in clinical settings. Tefertiller et al[2] reviewed 30 articles (14 randomized controlled trials, 16 nonrandomized controlled trials) that examined the effects of locomotor training with robotic assistance in patients after stroke, spinal cord injury (SCI), multiple sclerosis, traumatic brain injury, and Parkinson's disease. The review supports the conclusion that locomotor training with robotic assistance is beneficial for improving walking function in individuals after stroke and SCI.[2] The development of main gait training machines followed. These machines either involve an exoskeleton robotic device (eg, Lokomat, LOPES exoskeleton robot)[3,4] or a robotic device with foot-driven plates (eg, Gait Trainer GT I, Haptic Walker).[5,6] The exoskeleton robotic device is equipped with programmable drives or passive elements that flex the knees and hips during the swing phase, whereas with the other type of robotic device, the feet are placed on footplates, whose trajectories simulate the stance and swing phases. Other than robotic gait training and conventional therapy, another treatment

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approach involves treadmill training with partial body weight support.[7] However, this approach requires considerable involvement of a physical therapist, and generally, 3 therapists are required to induce movement of the paretic leg during the swing phase and to shift the patient's weight onto the stance limb.

The potentially positive common benefits of robotic gait training are that it involves repeatedly undergoing sufficient and accurate training for a prolonged period. Lokomat is the first robotic-driven gait orthosis with electromechanical drives to assist the walking movements of gait-impaired patients on a treadmill by supporting the body weight.[8,9] Husemann et al[10] compared a Lokomat group that received 30 minutes of robotic training with a control group that received 30 minutes of conventional physiotherapy. After 4 weeks of therapy, although there was no significant difference in walking ability between the groups, the walking ability in both groups as expressed by functional ambulation classification was significantly improved. The researchers reported that the Lokomat group demonstrated an advantage for robotic training over conventional physiotherapy in the improvement of gait abnormality and body tissue composition.[10] However, in a recent randomized controlled study[11] that compared robot-assisted locomotor training with therapist-assisted locomotor training in chronic stroke patients, the results indicated that greater improvements in speed and single limb stance time on the impaired leg were observed in subjects who received therapist-assisted locomotor training. Thus, the usefulness of robot-assisted rehabilitation is controversial.

The robot suit hybrid assistive limb (HAL)[12-15,a] is a new wearable robot that has a hybrid control system composed of 2 subsystems: cybernic voluntary control (CVC) and cybernic autonomous control (CAC) (fig 1). The HAL suit has power units and force-pressure sensors in the shoes. The power units consist of angular sensors and actuators on bilateral hip and knee joints. Muscle action potentials are detected through the electrodes on the anterior and posterior surface of the wearer's thigh. These various biologic signals are processed by a computer. The HAL suit can support the wearer's motion by adjusting the level and timing of the assistive torque provided to each joint according to the surface muscle action potential as well as the pressure sensors. The HAL suit can enhance the wearer's motion through the wearer's muscle action potential; thus, the HAL suit can appear as an actual motion. Therefore, if the wearer's muscle action potential varies, the wearer's motion varies, too. The HAL training, using muscle activity, has the potential to intensify the feedback by inducing an appropriate motion more strongly than standard robot training. Thus, after HAL training, patients with limited mobility will improve their walking abilities (gait speed, number of steps, cadence, or ability to transfer).

Few studies have been conducted to clarify the feasibility of rehabilitation with HAL. Only 1 preliminary study[16] has reported on the short-term effects of HAL on the walking pattern of stroke patients. The purpose of the present study was to investigate the feasibility of 16-session (8-wk) HAL rehabilitation training for patients with limited mobility.

List of abbreviations:

BBS	Berg Balance Scale
CAC	cybernic autonomous control
CVC	cybernic voluntary control
HAL	hybrid assistive limb
MADS	musculoskeletal ambulation disability symptom complex
SCI	spinal cord injury
10MWT	10-m walk test
TUG	Timed Up & Go

Methods

Study design

A quasiexperimental study was used, with measurements before and after the clinical intervention. The target population included patients with limitations in their walking (no matter the diagnosis, the time since the diagnosis, and the patient's age at diagnosis). The protocol of this study was approved by the Institutional Review Board of the University of Tsukuba Hospital and was registered with the UMIN Clinical Trials Registry. The clinical intervention was conducted at the University of Tsukuba Hospital and Cyberdyne, Inc, in Japan between January 2010 and March 2012. The patients included in this study were volunteers recruited through local newspaper advertisements or outpatients at the University of Tsukuba Hospital. They were informed about the aim and design of this study, and they subsequently provided written, informed consent. Informed consent was also obtained from the patient's guardian if the patient was younger than 20 years.

The inclusion criteria were (1) musculoskeletal ambulation disability symptom complex (MADS) or the underlying disorders of MADS, which is a condition newly defined in 2006 by Japanese medical societies[17]; (2) requiring physical assistance or assistive devices in at least 1 of the following daily activities: standing up, sitting down, and walking; (3) ability to understand an explanation of the study and to express consent or refusal; (4) body size that can fit in the robotic suit HAL (height range, 145–180cm; maximal body weight, 80kg); and (5) ability to undergo usual physical and occupational therapies. The exclusion criteria were the following: (1) inadequately controlled cardiovascular disorders; (2) inadequately controlled respiratory disorders; (3) intellectual impairments that limit the ability to understand instructions; (4) moderate to severe articular disorders, including contracture in the lower extremities; (5) moderate to severe involuntary movements, ataxia, or impairments of postural reflex in the trunk or the lower extremities; and (6) severe spasticity in the lower extremities.

Participants

Thirty-eight patients (25 men, 13 women) were enrolled in this study (24 outpatients, 14 volunteers through advertisements). The mean age ± SD of the 38 patients was 53.2±17.8 years (range, 18–81y). Table 1 summarizes their clinical characteristics. Their underlying diseases were stroke (10 men, 2 women), SCI (6 men, 2 women), musculoskeletal diseases (2 men, 2 women), and other diseases (Parkinson's disease, gonadotropin-dependent myopathy, limb-girdle muscular dystrophy, inclusion body myositis, traumatic brain injury, disuse syndrome secondary to malignant lymphoma, cerebral palsy, sequelae of poliomyelitis, and hypoxic-ischemic encephalopathy; 7 men, 7 women). Twenty patients were able to ambulate independently without any help (n=9) or with several assistive devices (T-cane, bilateral crutches, or lateral crutch) (n=11). Eleven patients were able to ambulate with several assistive devices and under supervision. Three patients required human assistance to ambulate at least 10m (cases 33, 34, 38), and the remaining 4 patients were unable to ambulate even

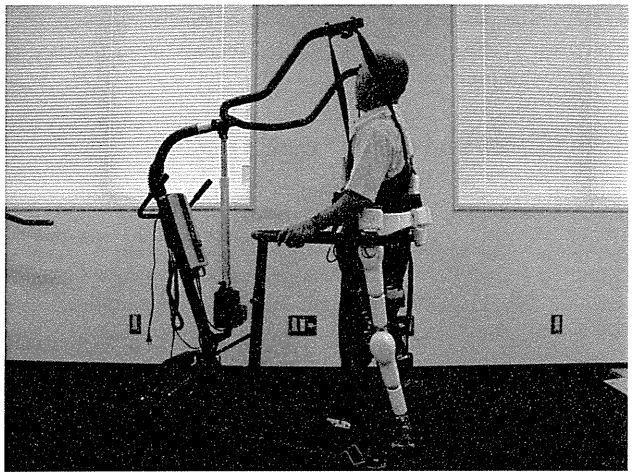

Fig 1 The robot suit HAL.

with assistive devices and human assistance (cases 8, 15, 17, 27). All the patients with stroke and SCI were in chronic stages.

Training program

HAL training was administered twice per week for 8 weeks (16 sessions). The 90-minute training sessions consisted of single-leg motion, a standing and sitting exercise, and walking on the ground with HAL. For safety reasons, a walking device (All-in-One Walking Trainer[b]) with a harness was used. Treadmill training with mild body-weight support (Unweighing System[c]) was also used for some patients. The HAL suit has a hybrid control system comprising the CVC and CAC. The CVC mode of the HAL suit can support the patient's voluntary motion according to the voluntary muscle activity and the assistive torque provided to each joint. The CAC mode provides physical support autonomously, based on output from force-pressure sensors in the shoes. This study mainly used the CVC mode, which allows the operator to adjust the degree of physical support to the patient's comfort and gradually reduce support as training progresses.

Outcome measures

The feasibility of rehabilitation with HAL was assessed by the number of completers and the amount of time or the number of therapists needed to implement training. Patients were asked to report adverse events during the training period.

The primary outcomes were functional ambulation and balance ability. Functional ambulation was assessed with a 10-m walk test (10MWT) and a Timed Up & Go (TUG) test. In the 10MWT, patients were instructed to walk without wearing HAL on a flat surface at their self-selected, comfortable pace. Patients began to walk before they reached the starting line of the 10-m distance so that they could accelerate and attain a stable speed before the test. To calculate gait speed (m/s) as a primary outcome, the 10-m walking time was measured using a handheld stopwatch. In addition, the number of steps between the start and finish line was counted, and patient cadence was calculated from the walking time and number of steps. Patients were allowed to use their assistive device or lower limb orthosis, or both, as necessary. Each patient used the same assistive device or orthosis, or both, during the pre- and postintervention measurements. Therapists closely attended the patients during the 10MWT but did not provide physical assistance. For each measurement, the 10MWT was performed twice. The faster time of 2 trials was selected for analysis. In the TUG test, the following actions were timed: standing up from a standard-height chair, walking 3m, returning to the chair, and sitting down without HAL. Two trials (each turning clockwise and counterclockwise) were carried out for each measurement. Balance ability was assessed with the Berg Balance Scale (BBS), consisting of 14 tasks, as detailed by Berg et al.[18] Each task was scored on a scale ranging from 0 to 4 points (0 indicates inability to complete), and the total score was used as the index of balance ability. All primary outcomes were assessed at baseline and after completion of the 16 training sessions.

Statistical analysis

All parametric data are expressed as means with SDs. Paired *t* tests were used to evaluate differences between the baseline measurements and outcomes after the 16 sessions. Unpaired *t* tests were used to evaluate the differences in characteristics of those who completed 16 sessions and those who did not. An effect-size calculation (Cohen *d*) was used to assess the effect of the training. Pearson correlation coefficients were used to assess the relationship among outcome measures. Data were analyzed using IBM SPSS Statistics 18 software,[d] with the alphas level set at 5%.

Results

A typical 90-minute HAL training session proceeded as follows: assessment of blood pressure, resting heart rate, and walking pattern (10min); preparation of electrodes and putting on the HAL suit (5min); computer setup (5min); HAL training (60min, including resting time during computer operation); taking off the HAL suit and the electrodes (5min); and reassessment of walking pattern (5min). The net walking time was approximately 20 minutes. Typically, 2 therapists implemented the training: one supported the patient and the other operated the computer. All therapists and related staff had participated in a 3-hour training workshop conducted by the manufacturer to learn how to operate the HAL system.

Of the 38 patients (25 men, 13 women), 32 (21 men, 11 women) completed all 16 training sessions. The mean age ± SD of the 32 patients was 53.2±17.3 years (range, 18–81y). There was no statistically significant difference in age between those who completed training and those who did not (54.0±19.8y). It took 10.0±3.1 weeks (range, 8–21wk) to complete 16 sessions. Of the 6 patients who did not complete the 16 sessions, 2 (cases 15, 21) dropped out for medical reasons, and 4 (cases 1, 2, 29, 35) dropped out for personal reasons (difficulty visiting the hospital). One medical reason for dropout was low back pain that developed during the first training session (case 21); the patient withdrew consent at the third session. The other medical reason for dropout was a relapse (after the second session) of neuropathic pain caused by SCI (case 15); the patient withdrew consent at the fifth session. There were no serious training-related adverse events. One stroke patient (case 7) had knee pain (patellar tendinitis) at home after the 15th session but was able to complete the 16th session after 1 month of rest. Another patient with inclusion body myositis (case 31) developed knee

Table 1 Clinical characteristics of patients

Case No.	Age (y)	Sex	Diagnosis	Paralysis Type	Duration Since Disease	Ambulation	Assistive Device	Orthosis	Training	Duration of Training (wk)	Adverse Events
1	69	M	Stroke (cerebral infarcts)	Paraplegia	15y	Independently	T-cane	AFO	Dropout (personal reason)	ND	Nothing
2	61	M	Stroke (cerebral hemorrhage)	Paraplegia	14y8mo	Independently	T-cane	AFO	Dropout (personal reason)	ND	Nothing
3	65	M	Stroke (cerebral hemorrhage)	Hemiplegia	2y2mo	Supervision	Quad-cane	AFO	Complete	8	Nothing
4	37	F	Stroke (cerebral hemorrhage)	Quadriplegia	16y	Independently	NA	AFO	Complete	8	Nothing
5	72	M	Stroke (cerebral infarcts)	Hemiplegia	2y9mo	Supervision	T-cane	AFO	Complete	8	Nothing
6	54	M	Stroke (cerebral hemorrhage)	Hemiplegia	1y1mo	Supervision	T-cane	NA	Complete	8	Nothing
7	63	F	Stroke (cerebral hemorrhage)	Hemiplegia	1y6mo	Independently	T-cane	AFO	Complete	15	Knee pain (patellar tendinitis)
8	52	M	Stroke (cerebral hemorrhage)	Ataxia	2y2mo	NA	NA	NA	Complete	12	Nothing
9	74	M	Stroke (cerebral infarcts)	Hemiplegia	3y4mo	Independently	T-cane	AFO	Complete	9	Nothing
10	53	M	Stroke (subarachnoid hemorrhage, cerebral infarcts)	Hemiplegia	ND	Supervision	Pick-up walker	KAFO	Complete	9	Nothing
11	18	M	Stroke (moyamoya disease)	Hemiplegia	11y	Independently	NA	AFO	Complete	21	Nothing
12	64	M	Stroke (cerebral hemorrhage)	Hemiplegia	1y	Supervision	T-cane	AFO	Complete	8	Nothing
13	58	F	SCI (incomplete)	Quadriplegia	3y3mo	Supervision	Lateral crutch	KAFO	Complete	8	Nothing
14	69	M	SCI (incomplete)	Quadriplegia	1y3mo	Supervision	Pick-up walker	AFO	Complete	8	Nothing
15	43	M	SCI (incomplete)	Paraplegia	3y3mo	NA	NA	KAFO	Dropout (medical reason)	ND	Neuropathic pain after SCI
16	59	M	SCI (spina bifida)	Paraplegia	6y4mo	Supervision	T-cane	NA	Complete	8	Nothing
17	31	M	SCI (complete)	Paraplegia	3y	NA	NA	NA	Complete	10	Nothing
18	64	F	SCI (incomplete)	Quadriplegia	2y	Independently	T-cane	AFO	Complete	9	Nothing
19	54	M	SCI (central cervical cord injury)	Quadriplegia	5y	Supervision	T-cane	NA	Complete	12	Nothing
20	47	M	SCI (spinal dural arteriovenous fistula)	Paraplegia	1y1mo	Independently	Bilateral crutch	AFO	Complete	8	Nothing
21	74	F	Musculoskeletal disease (cervical spondylotic myelopathy)	Quadriplegia	ND	Independently	Bilateral crutch	NA	Dropout (medical reason)	ND	Low back pain
22	81	F	Musculoskeletal disease (OA knee)	NA	ND	Independently	NA	NA	Complete	10	Nothing
23	44	M	Musculoskeletal disease (OA knee)	NA	ND	Independently	NA	NA	Complete	11	Nothing
24	74	M	Musculoskeletal disease (OA knee)	NA	ND	Independently	NA	NA	Complete	10	Nothing
25	62	M	Parkinson's disease	NA	8y	Independently	NA	NA	Complete	11	Nothing

(*continued on next page*)

Table 1 (*continued*)

Case No.	Age (y)	Sex	Diagnosis	Paralysis Type	Duration Since Disease	Ambulation	Assistive Device	Orthosis	Training	Duration of Training (wk)	Adverse Events
26	72	F	Parkinson's disease	NA	7y8mo	Independently	Nothing	NA	Complete	9	Nothing
27	36	M	Gonadotropin-dependent myopathy	Paraplegia	19y	NA	NA	NA	Complete	8	Nothing
28	52	F	Limb-girdle muscular dystrophy	Quadriplegia	24y	Supervision	T-cane	NA	Complete	9	Nothing
29	57	F	Muscular dystrophy	NA	44y	Independently	NA	NA	Dropout (personal reason)	ND	Nothing
30	67	M	Limb-girdle muscular dystrophy	NA	28y	Independently	T-cane	NA	Complete	8	Nothing
31	73	M	Inclusion body myositis	NA	10y	Independently	T-cane	NA	Complete	10	Knee pain
32	24	M	Traumatic brain injury	Quadriplegia	17y1mo	Supervision	Walker	NA	Complete	8	Nothing
33	19	F	Traumatic brain injury	Quadriplegia	6y2mo	Assistance	Pick-up walker	KAFO	Complete	8	Nothing
34	29	F	Traumatic brain injury	Quadriplegia	10y7mo	Assistance	Pick-up walker	KAFO	Complete	9	Nothing
35	20	M	Disuse syndrome, secondary to malignant lymphoma	NA	3y9mo	Independently	T-cane	NA	Dropout (personal reason)	ND	Nothing
36	31	F	Cerebral palsy	Quadriplegia	30y10mo	Independently	Lateral crutch	NA	Complete	10	Nothing
37	55	M	Sequelae of poliomyelitis	Paraplegia	54y	Independently	Lateral crutch	NA	Complete	19	Nothing
38	48	F	Hypoxic-ischemic encephalopathy	Quadriplegia	2y	Assistance	NA	NA	Complete	12	Nothing

Abbreviations: AFO, ankle-foot orthosis; F, female; KAFO, knee-ankle-foot orthosis; M, male; NA, not applicable; ND, no data; OA, osteoarthritis.

Table 2 Functional ambulation and balance ability at baseline and after 16-session HAL training

Outcome Measurements	Baseline	After Training	Difference	*P*	n
10MWT					
Speed (m/s)	0.52±0.40	0.61±0.43	0.09 (0.05 to 0.14)	<.001	27
No. of steps	34.0±20.4	31.0±18.8	−3.0 (−4.9 to −1.0)	<.001	27
Cadence (steps/min)	74.3±34.1	81.1±32.9	6.8 (4.0 to 9.6)	<.001	27
TUG (s)	43.7±45.0	37.3±34.1	−6.4 (−13.0 to 0.2)	.057	26
BBS	33.6±16.9	35.5±16.3	1.9 (−0.1 to 3.9)	.059	32

NOTE. Values are mean ± SD, mean (95% confidence interval), or as otherwise indicated.

pain at home after an early session but was able to complete 16 sessions.

Outcome measures

Functional ambulation was not assessed for 5 patients at baseline because 3 were unable to ambulate with any assistance (cases 8, 17, 27), and the other 2 patients needed considerable human assistance to ambulate (cases 34, 38). The other 27 patients had significant improvements ($P<.05$) in gait speed, number of steps, and cadence after the 16-session HAL training (10MWT, table 2). Improvements in gait speed, number of steps, and cadence are defined as an increase, a decrease, and an increase in the respective parameters. The mean ± SD improvements and effect sizes (Cohen *d*) in gait speed, number of steps, and cadence were .09±.11m/s ($d=.82$), 3.0±4.9 steps ($d=.61$), and 6.8±7.1 steps/min ($d=.96$), respectively. Improvements in gait speed, steps, and cadence were observed in 25, 18, and 25 patients, respectively (figs 2–4). Worsened gait speed and cadence were observed in 2 patients (cases 28, 30). In regards to the number of steps, we observed no change in 8 patients (cases 3, 5, 16, 25, 28, 30, 33, 37) and increased steps in 1 (case 20). Correlation coefficients for gait speed with number of steps and with cadence were $r=.30$ (not significant) and $r=.73$ ($P<.01$), respectively. The effect sizes for gait speed in patients with stroke (n=9), SCI (n=6), musculoskeletal disease (n=3), and patients with other diseases (n=9) were 1.41, .78, 2.43, and .63, respectively. The results of the TUG test (n=26; case 10 was unable to perform the test) and the BBS (n=32) indicated improvement after the 16 training sessions, but these improvements were not statistically significant. The mean ± SD decrease (Cohen *d*) in the TUG test was 6.4±16.4 seconds ($d=.39$). Twenty-one of 26 patients were faster after training, and 5 patients were slower (cases 5, 13, 30, 31, 36) (fig 5). The mean ± SD increase (Cohen *d*) in BBS was 1.9±5.5 ($d=.35$). Nineteen of 32 patients had higher scores compared with baseline; no change was observed in 6 (cases 12, 17, 23, 27, 36, 37), and 7 had lower scores (cases 11, 16, 26, 30, 31, 32, 34) (fig 6).

Discussion

We investigated the feasibility of rehabilitation using a robot suit HAL. We demonstrated that HAL rehabilitation could be implemented safely and effectively. Although a few patients developed lumbar or knee pain during the training, no serious training-related adverse events occurred. Significant improvements in gait speed, number of steps, and cadence were observed, as assessed by the 10MWT. Improved TUG test and BBS results were also observed, but because of the small sample size of this pilot study, these improvements were not statistically significant. Overall, our results suggest that HAL rehabilitation has the potential to improve ambulation in patients with limited mobility.

Two patients (cases 15, 21) dropped out for medical reasons. One developed lumbar pain (case 21), and 1 had a relapse of neuropathic pain caused by SCI (case 15). Although it is unclear

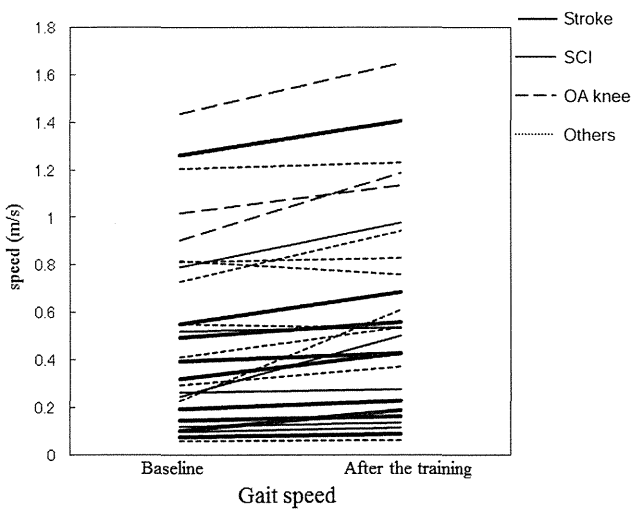

Fig 2 Change in 10MWT gait speed for 27 patients after HAL training. Abbreviation: OA, osteoarthritis.

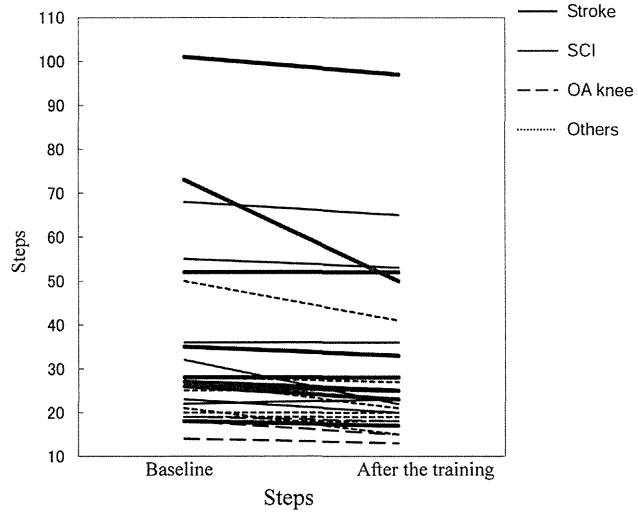

Fig 3 Change in number of steps during 10MWT for 27 patients after HAL training. Abbreviation: OA, osteoarthritis.

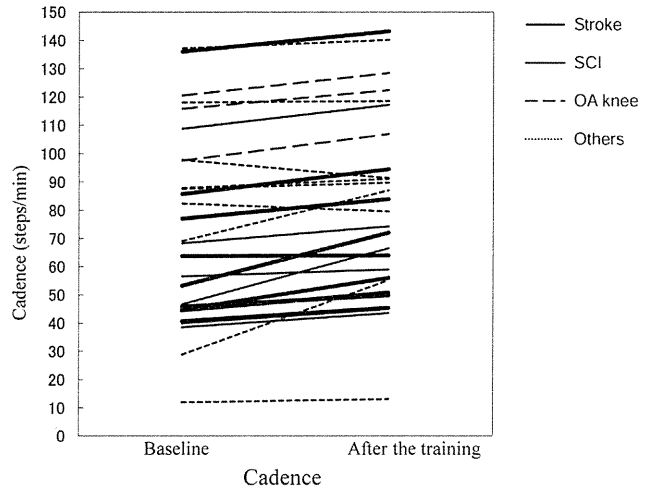

Fig 4 Change in 10MWT cadence for 27 patients after HAL training. Abbreviation: OA, osteoarthritis.

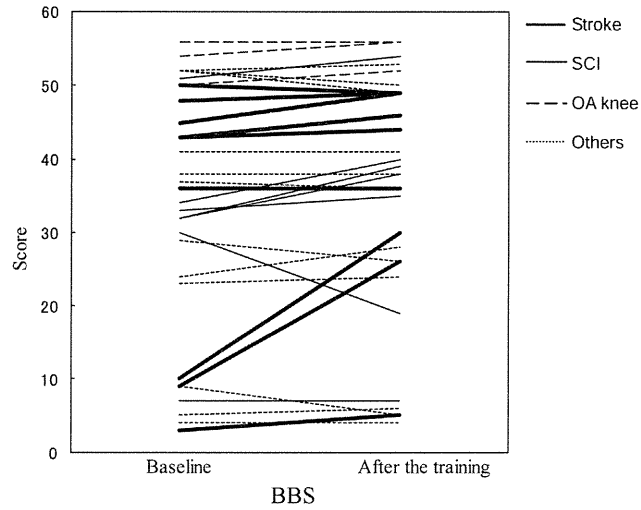

Fig 6 Change in BBS score for 32 patients after HAL training. Abbreviation: OA, osteoarthritis.

whether there was a causal relationship between HAL training and the pain that developed, the lumbar pain in case 21 had been persistent before the HAL training and even after the training ended, and the neuropathic pain in case 15 followed a previous pattern of symptom flares associated with seasonal change. Therefore, it is likely that HAL training did not directly cause the pain that developed in these 2 cases. Two other patients complained of knee pain during the training period, but this pain was not severe, and the patients were able to complete the training. Although, once again, direct causality is unclear, safe implementation of HAL rehabilitation requires adequate caution on the part of therapists and self-awareness on the part of patients who have lumbar and knee pain. Regarding feasibility, approximately 10 minutes was required for 2 to 3 therapists to put electrodes and the HAL suit on or take them off the patient. This procedure is a slight inconvenience to address but not a major obstacle to HAL rehabilitation.

Significant improvements in functional ambulation were observed, and the effect sizes (Cohen *d*) for gait speed, number of steps, and cadence were .82, .61, and .96, respectively. The correlation coefficient for gait speed with cadence was higher than

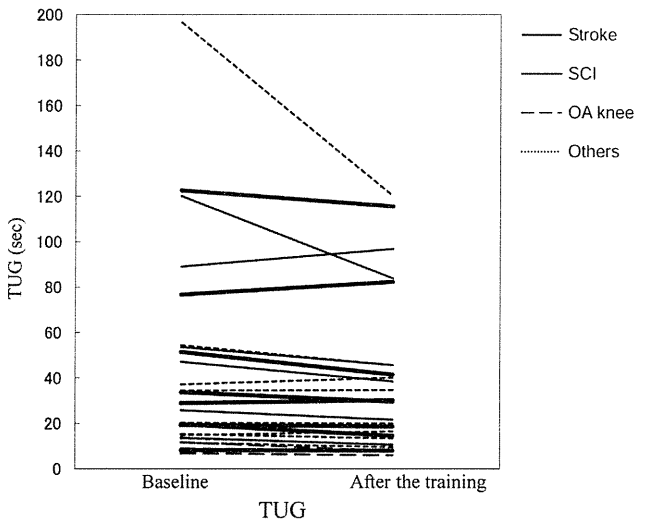

Fig 5 Change in TUG test results for 26 patients after HAL training. Abbreviation: OA, osteoarthritis.

that of gait speed with steps ($r=.73$ vs $r=.30$). Therefore, the improvement in gait speed with HAL training was mainly brought about by improvement in cadence. That is, HAL training improved stride frequency more than stride length. This finding is in agreement with that of a previous robotic training study.[19] The effect sizes for the TUG test and BBS were smaller than the effect sizes for the 10MWT. This result seems to occur because the TUG test and BBS involve complicated motions such as moving from sitting to standing, walking and returning, reaching forward, and alternating feet on each step. The effect sizes for gait speed in 9 patients with stroke and in 6 patients with SCI were large (1.41 and .78, respectively). Therefore, training effectiveness in patients with stroke and those with SCI can be expected. The effect size in 3 patients with musculoskeletal diseases was also large (2.43), but the number of patients was small. Therefore, further studies are needed. In this study, we recruited patients with a wide range of stroke and SCI severities. Future studies should examine the influence of the severity of stroke and SCI on the effectiveness of HAL rehabilitation.

Many recent studies have reported the efficacy of robot-assisted rehabilitation. It is very difficult to directly compare these studies and our study, because of differences in diseases, severity and duration of the disorder, robotic features, methods of intervention, and outcome measures.[20] Wirz et al[21] reported that after locomotor training with Lokomat, the 10MWT gait speed of 20 patients with chronic incomplete SCI increased by .11±.10m/s ($d=1.10$). The number of patients with SCI in our study was limited to 6, but our results also indicate the efficacy of HAL rehabilitation for these patients ($d=.78$). Hornby et al[11] reported that after robotic-assisted locomotor training, the gait speed in chronic stroke patients increased by .07±.07m/s ($d=1.0$). Our results also indicate the efficacy of HAL rehabilitation for 9 patients with chronic stroke ($d=1.41$). We conjectured that the mechanism of this recovery of functional ambulation was due to changes in plasticity in the spinal cord and supraspinal centers. Appropriate sensory inputs, such as maximum weight loading, facilitating proper trunk posture, and hip extension, are essential for maximizing functional recovery.[22] Our experience with HAL indicates that the HAL-induced motion might evoke the sensory input, which has a favorable feedback effect on the central nervous system for a recovery of locomotor function. In addition, even if a patient's condition were too severe for medical therapists to

provide adequate rehabilitation training, HAL might still make adequate training possible. HAL is a robotic device with potential rehabilitation applications that are dependent on the physical support it can provide.

Study limitations

This study was not a randomized controlled trial and could not compare the efficacy of HAL training with conventional rehabilitation. Second, long-term efficacy was not assessed after HAL training. Third, this study could not exclude observer bias and subject bias because the same staff implemented assessment and training, and approximately half of the patients were recruited through local newspaper advertisements. Finally, the statistical power was low because of the small number of patients with each disease.

Conclusions

This quasiexperimental study revealed the feasibility of HAL training for rehabilitating patients with limited mobility. This study has shown that it is possible to manage 8 weeks of rehabilitation with HAL training (16 sessions of 90min) safely and effectively, even with persons who received their diagnosis many years ago. After HAL training, significant improvements in gait speed, number of steps, and cadence were observed. Although improvements were observed in the TUG test and BBS, they were not statistically significant. There were no serious adverse events. Further studies are needed to compare the effectiveness of HAL training and conventional rehabilitation.

Suppliers

a. Cyberdyne Inc, D25-1, Gakuen Minami, Tsukuba, Ibaraki, Japan 305-0818.
b. ROPOX A/S, 221 Ringstedgade, Naestved, Denmark 4700.
c. Biodex Medical Systems Inc, 20 Ramsay Rd, Shirley, NY 11967.
d. SPSS, Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

Keywords

Feasibility studies; Mobility limitation; Orthopedic equipment; Rehabilitation; Robotics

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HTLV-1

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Glossary

Cytotoxic T cell A cytotoxic T cell belongs to a subgroup of T lymphocytes with CD8 receptor that are antigen- specific and capable of inducing the death of virus-infected somatic or tumor cells.

Gliosis Gliosis is the process of scarring in the central nervous system, caused by a proliferation of astrocytes.

Oligoclonal band Oligoclonal bands are bands of immunoglobulins that are seen when a blood serum (or plasma) or cerebrospinal fluid (CSF) is analyzed by protein electrophoresis. The presence of oligoclonal bands in CSF but not in blood serum (or plasma) means the production of immunoglobulins in central nervous system, that is, inflammation in the central nervous system.

Provirus A provirus is the form of the virus which is capable of being integrated into the chromosome of the host cell.

Spastic paraparesis Mild or moderate loss of motor function accompanied by spasticity in the extremities mainly caused by central nervous system (brain and spinal cord) diseases.

Human T-lymphotropic virus type-1 (HTLV-1) belongs to the *Deltaretrovirus* genus of the Orthoretrovirinae subfamily and infects 10–20 million people worldwide. HTLV-1 can be transmitted through sexual contact, intravenous drug use, and breastfeeding from mother to child. The infection is endemic in southwest Japan, the Caribbean, sub-Saharan Africa, South America, with smaller foci in Southeast Asia, South Africa, and northeastern Iran. HTLV-1 was initially isolated in 1980 from two T-cell lymphoblastoid cell lines and the blood of a patient originally thought to have a cutaneous T-cell lymphoma. It was the first human retrovirus ever associated with a human cancer. Three years before the isolation of HTLV-1, a Japanese group reported adult T-cell leukemia (ATL), a rare form of leukemia endemic to southwest Japan, as a distinct clinical entity. In 1981, the same group demonstrated that ATL was caused by a new human retrovirus originally termed 'ATLV'. Later, ATLV and HTLV have been shown to be identical, and a single name HTLV-1 has been adopted. In the mid-1980s, epidemiological data linked HTLV-1 infection with a chronic progressive neurological disease, which was termed 'tropical spastic paraparesis (TSP)' in the Caribbean and 'HTLV-1 associated myelopathy (HAM)' in Japan. HTLV-1-positive TSP and HAM were subsequently found to be clinically and pathologically identical and the disease was given a single designation as HAM/TSP. HTLV-1 can cause other chronic inflammatory diseases such as uveitis, arthropathy, pulmonary lymphocytic alveolitis, polymyositis, Sjögren syndrome, and infective dermatitis. Only approximately 2–3% of infected persons develop ATL and another 0.25–4% develop chronic inflammatory diseases, while the majority of infected individuals remain lifelong asymptomatic carriers (ACs). Thus, the viral, host, and environmental risk factors, as well as the host immune response against HTLV-1 infection, appear to regulate in the development of HTLV-1-associated diseases. For over two decades, the investigation of HTLV-1-mediated pathogenesis has focused on Tax, an HTLV-1-encoded viral oncoprotein. Tax activates many cellular genes by binding to groups of transcription factors and coactivators and is necessary and sufficient for cellular transformation. However, recent reports have identified another regulatory protein, HTLV-1 basic leucine zipper factor (HBZ), that plays a critical role in the development of ATL and HAM/TSP.

HTLV-1-Associated Diseases

Adult T-cell leukemia

ATL is a fatal malignancy of mature CD4+ T cells. It arises in only a small proportion of HTLV-1-infected people (1–5% of infected individuals) after long latency periods following primary infection. ATL shows diverse clinical features, but can be divided into four clinical subtypes: smoldering, chronic, lymphoma, and acute. Each subtype is directly correlated with the prognosis of patients: the smoldering and chronic types are indolent, while the acute and lymphoma types are aggressive and characterized by resistance to chemotherapy and poor prognosis. Development of ATL is characterized by infiltration of various tissues with circulating ATL cells, called 'flower cells', which have conspicuous lobulated nuclei. These cells cause further symptoms including lymphadenopathy, lytic bone lesions, skin involvement, hepatosplenomegaly, and hypercalcemia. Laboratory findings of ATL patients typically reveal a marked leukocytosis, hypercalcemia, high serum levels of lactate dehydrogenase (LDH), and a soluble form of interleukin-2 receptor (IL-2R). In cohort studies of HTLV-1 carriers, the risk factors for ATL appeared to include vertical infection (mother to child transmission), male gender, older age, and increasing numbers of abnormal lymphocytes. Since ATL occurs mainly in vertically infected individuals, but not in those who become infected later in life, the impairment of HTLV-1-specific T-cell responses caused by vertical HTLV-1 infection has been suggested as a possible cause of disease development. The HTLV-1-specific cytotoxic T-cell (CTL) responses from ATL patients are significantly lower than that of HAM/TSP patients. However, insufficient HTLV-1-specific T-cell responses might also occur during and after the onset of ATL. Although ATL has a poor prognosis, recent advances in its treatment have led to significant gains in response rates and