分未満になるくらいにマスクフィッティングを行う．動作時に胸郭がうまく動いているか観察する．慣れてきたら，前述の様に装着時間を伸ばしていく[14]．短期間に，IPAP を 1 cmH_2O くらいずつ増やし，12 cmH_2O くらいまでは早期に増やすとよい．
（注：バクテリアフィルターを回路中に使用する際は、本稿の IPAP 値に 2 ～ 3cmH_2O 足して設定すること）

E. ALS における NPPV 維持と問題解決

1. 換気量維持の方法

IPAP 12 cmH_2O でしばらく患者の換気状態が安定していても，呼吸筋力の余力がなくなり，胸郭も硬くなると，換気量が不十分になり，呼吸不全が悪化する．夜間睡眠中に SpO_2 の低下がある場合や呼吸苦を感じる場合は IPAP を 1 cmH_2O ずつ増やして行く．16 cmH_2O 以上になると，圧が強すぎると感じる患者が増える．圧が高まるとマスクからのリーク量も増え，締め付けを強めるため皮膚トラブルが多くなる．そこで，日中には問題がない場合は，EncorePro®，DirectView[10] などの換気データの分析ソフトウエアを使い，SpO_2 と換気量の関係を評価するため，就寝中の装着時間，呼吸回数，一回換気量，分時換気量，リーク量などを確認する．夜間など特定状況でのみ換気量低下による SpO_2 の低下がおきる場合は，S/T モードから AVAPS（Average Volume Assured Pressure Support）モードに変更する[14]．このモードは，設定した換気量に至らないと自動的に IPAP を増やすモードである．たとえば，IPAP 16 cmH_2O で夜間のみ SpO_2 の低下がおきる場合，夜間の SpO_2 低下データと同時刻の一回換気量のデータを評価する．たとえば，SpO_2 が維持できる一回換気量の下限が 350ml であるならば，AVAPS の最低保障の換気量を 350ml と設定する．通常の IPAP は変えず，換気量が低下した時の最高の IPAP を 20 cmH_2O と設定すると，機械は一回換気量を 350ml に維持できるように IPAP 16 cmH_2O から 20 cmH_2O の間を動的に調整していく．必要な時のみ IPAP が徐々に増加するので，患者は楽で合理的である．

2. 機械的咳介助（MAC）の必要性

FVC の低下に対しては IPAP を増加することで対応可能だが，気道に痰などの分泌物があると，Bilevel PAP では有効な換気量に至らない．気道内分泌物をどうやって除去するかが重要である．CPF は気道内の痰などの分泌物のクリアランス（清浄化）能力を示す測定値である．最初は，CPF が低下しないように，呼吸理学療法を導入する．症例によるが CPF が 270L/ 分未満となったら，機械的咳介助（mechanically assisted cough: MAC）も導入することを検討する[15]．CoughAssist®（図 4）をマスクを介して，気道に陽圧（+40cmH_2O）を 2 秒ほど加えた後，瞬間的に陰圧（-40cmH_2O）を 2 秒程度加えることで咳のかわりになる強い呼気流量を発生させる．これを 4 回くらい繰り返し，同時に胸郭圧迫を加えると効果が高まる．その後，口腔から咽頭・喉頭の吸引をおこなう．痰や気道分泌物の除去効果をみながら繰り返す．最初は 1 日 1 セッション程度で慣れてもらい，気道内分泌物の多い場合は 1 日数回行う．上気道炎，肺炎の場合は抗生剤投与に MAC を繰り返すことで早期に治癒できることが多い．2010 年から在宅での保険が適応されている．

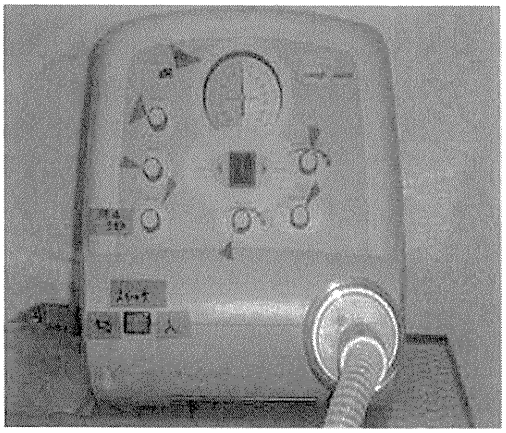

図 4：機械的咳介助を行う CoughAssist®

3. TPPV への移行

MAC の回数を増やしても十分に気道分泌物を除去できない場合は．気管切開による陽圧換気療法（TPPV）が必要となる[16]．TPPV では NPPV より容易に気道分泌物が除去できる．TPPV が必要となるもう一つの理由は，NPPV では IPAP を増加していくと体位変換でリークがおきやすくなり，車椅子乗車や坐位，立位という ADL 活動やリハビリテーションで低酸素血症を起こしやすくなるからである．24 時間 NPPV の場合は，日常生活動作でのマスクのずれで急変する危険性が増える．この時期になったら，安定した換気療法のために TPPV が必要となる．一方，デュシェンヌ型筋ジストロフィー患者の場合は，ALS と異なり喉頭・咽頭機能が保たれているため，NPPV ができなくても舌咽頭呼吸などを使い，短時間なら低酸素血症にならず日常生活動作が可能である．ALS 患者が NPPV から TPPV に移行するとほとんどの患者は，換気が安定し，ADL 制限もなくなり，良かったと感じる．ALS の進行期においては，NPPV は患者負担

とADL制限が多くなるので,患者・家族に対しては,NPPVが成功していれば,TPPVはより容易だと説明している.

Ⅳ. NPPV成功のための多専門職種ケア

A. 栄養療法とPEG

1. 栄養がALSの予後を決める－NSTの導入

最近の論文では,ALS患者の余命はBMI（body mass index）に依存することが報告された[3),17)]. また,NPPV継続の忍容性は栄養状態に依存している. このため栄養療法を適切におこなうために,多専門職種チームの中に栄養サポートチーム（nutrition support team: NST）を立ち上げる必要がある. 食形態を患者の嚥下機能に合わせ,むせず経口摂取が楽しく継続できる様にすべきである. 最近の研究では,ALSでは筋萎縮が進行中は代謝亢進状態にあることが分かってきた[18)]. このため,痩せによる栄養障害がこないように,栄養摂取量を増やす努力が病初期には必要である. 体重,BMIなどを参考に栄養摂取量を調整するが,筋萎縮にともなう体重の減少がどのくらい影響しているのか分析することは難しい. 二重標識水を使った測定がすすめられているが,個別の患者ごとに測定するまでには至っていない. 一方で,筋萎縮が高度になったら,栄養必要量は低下するが,摂取エネルギー量を低下させた場合は,微量元素やビタミンなどの栄養素の低下を来さないようにする.

2. PEGをNPPV導入前に造設する

ALSの呼吸不全と嚥下障害の出現する順序は患者によって異なるため,ALSのNPPV導入のタイミングとPEGのタイミングの判断は大変むずかしい[2),3)]. NPPVを導入して順調にみえていても,嚥下障害が進行し,栄養の摂取が経口から十分にできなくなる. 栄養障害のため,痩せが進行し衰弱してしまう. 経鼻経管栄養を開始しようとすると,挿入したチューブのために,マスクと皮膚の間からエアリークが発生し,エアリークを最小限にしようとしてマスクを締め付けることにより,チューブと皮膚の接着部位に褥瘡を形成し,NPPVの継続が阻害される. この時にPEGを作ることを患者が希望しても,%FVCが50%以下では経口の内視鏡操作による呼吸不全悪化の危険性が高く,PEGの造設をあきらめなくてはならない事態に遭遇する[3)]. この問題を回避するためには,ALS患者の場合はPEGをNPPV導入前に造設することが推奨される[2)].

3. NPPV後のPEG造設は可能か

ALS患者は,PEGがないと栄養障害のためNPPVの継続が難しくなる. 球麻痺で発症した方以外は,NPPVの導入時期は,経口摂取に不便を感じないことが多く,PEGの同意が得られにくいジレンマに遭遇する. NPPV前に,PEGがどうしてもできなかった場合は,呼吸不全がある場合は,鼻マスクによるNPPVを行いながら,経鼻内視鏡を経口挿入しPEGを作る検討をする. この方法は確立したが[19)],まだ普及していない. 患者が鼻マスクを使用できることが条件であり,術中はセデーションをせず,局所麻酔でPEGを造設する. 術中にIPAPを動的に増加させるコツが必要である. 海外ではRIG（radiologically inserted gastrostomy）が推奨されているが[2)],本邦での経験例はない. これは,経鼻内視鏡を使った上記の方法より,はるかに危険と思われる.

B. リハビリテーションの考え方と方法

リハビリテーションを機能回復訓練と定義すると,ALSにおけるリハビリテーションの意味が分からなくなる. リハビリテーションとは本来,「復権（re-habilitate）」概念であり,どのような難病であっても,自分の身体を再度とらえなおし,障害とともに生きることを肯定できるように援助していく事を意味する.

理学療法的には,ALSの罹患筋には本来十分な休息が必要で,休息により機能が蘇ると考える. 一方で,あまり病的でない筋群には廃用症候群の予防が必要で,ストレッチやADL活動が重要である. ALS患者の筋には休息が必要な筋群と,運動が必要な筋群が混ざり合っていることが理学療法上の課題である. 十分な補助と運動を組み合わせる必要がある. 障害が進むと,筋力が低下するにもかかわらず,新たな運動パターンや器具などの学習が必要となるジレンマも課題となる. このため,ADL調整として,日常生活全体における身体動作の評価を行い,長時間過ごす椅子・クッション・背もたれ・テーブルやベッド・マットレス・枕などを最適化する. 作業療法的にbalanced forearm orthosis（BFO）やポータブルスプリングバランサー（PSB）を使い,重力に抗した筋力がなくても,遠位部の動作が可能ならば,上肢の自立度の改善を試みる. 日常生活の日課表を作り,最適な運動負荷を日常生活の中に組み入れると同時に,離床と臥床の援助をおこなう. 評価とプランニングは理学療法士,作業療法士などのリハビリスタッフと看護師が行い,日々の支援は看護師とヘルパーが行う.

C. 言語・非言語的コミュニケーションの充実

書字能力や発話能力が低下してくると,言語によ

るコミュニケーションの能率が低下する．それ以前に信頼関係を構築できれば最高である．ALSケアでは手，足，額，ほほなどに各種センサーを装着し，ナースコールの代用としたり，意思伝達装置を導入することが推奨されている．透明文字盤も含め，いろいろな方法を工夫すべきである．脳血流変化，脳波によるP300，視線入力なども検討されている．生活に直接関係する内容だけでなく，信頼関係の構築や楽しみのために，コミュニケーション時間を増やしていく必要がある．

ALSにどの程度，前頭側頭葉変性症が合併するかの頻度はまだ不明であるが，合併する場合には病初期にわかる事が多い．NPPVの導入前後に性格変化が分かったり，言語の意味が捉えにくくなったり，表出する言語内容が単純なものに限られてくることが，前頭側頭葉変性症の症状と考えられる．病識が乏しく，感情失禁なのか強制笑いか判断できないような症状を含む上位運動ニューロン症状を合併する場合もある．何れの場合も文字盤，スイッチによる言語的コミュニケーションは著しく難しくなる．この様な場合には，支援者は言語によるコミュニケーションに固執することはやめて，表情変化，感情，体調などを総合的にとらえるようなコミュニケーション方法に切り替えると，患者も家族も落ち着きを取り戻せる．前頭側頭葉変性症を合併するALSが，林らの言うTLS（totally locked-in state）に対応するのかどうかの結論はでていないが[20]，非言語的なコミュニケーションをいれてケアを行うと，患者・家族の状態は明らかに改善する．

D. 心理サポート：ナラティブ・アプローチとCBT

治らない病気に対応する方法として，前述のナラティブ・アプローチがある[21]．人のナラティブ（narrative）とは語られた言葉（ナラティブ・ディスクール）で作られるが，そこには何らかのストーリー（物語），すなわち事象（event）に対する自分自身の認識が含まれている．医療におけるナラティブ・アプローチとは，客観化された病気の治癒を目標とするのではなく，患者・家族のナラティブの改善を目標にケアを構築する方法の事である．プライマリケアから生まれたNBM（ナラティブに基づく医療）を筆頭に，社会構成主義，家族療法，構成主義心理療法などの流れがあるが，いずれも「人間とは，現実を単に心に映し出すだけでなく，それを構成しながら意味を作り出している動的な存在」という認識を基本としている．人は適切な支援さえあれば，治らないどんな病気でも，新たな人生の意味を再構成しながら生きていけると考える．ALSの包括的ケアで行なわれる心理アプローチはこのナラティブ・アプローチであり[7,22]，ALSの呼吸ケアにも必要なアプローチである．人工呼吸器を使い生きることを延命と考えるのも，一つのナラティブでしかないため，その捉え方を変えて，ナラティブを書き換えることができれば，延命ではなくQOLは向上すると考える．

慣れた心理療法士などは「認知行動療法（cognitive behavioural therapy: CBT）を取り入れている．行動レベルの異常は，患者の認識枠の異常に基づくという考えを基本的背景にもつCBTは，認識枠を再構成するための直接的な心理介入である．病とともに歩むとき，患者は自分の認識枠と周囲との関係性の両者を再構築しなければ生きづらくなる．患者自身でそれができるように非指示的にアプローチするのがナラティブ・アプローチであり[23]，それを意図的・指示的に心理介入する方法がCBTである[23,24]．本来は別個の考え方であるが，両者ともALSケアに有用である．

V．緩和ケアと難病ケア

A. 緩和ケア概念の誤解をとく

英連邦ではALSは緩和ケア対象疾患であるが，それはALS患者が安心して痛み無く死を迎えられるためのケアをしようという意味ではない．この緩和ケア概念は完全に誤解である[25]．緩和になるかどうかは状態や関係性によって決まるのであり，人工呼吸療法もPEGも患者・家族にとって緩和になるならば，適切に行なえると考えることが緩和ケアである．医療技術自体に「緩和」か「延命治療」かが定められているのではない．治癒困難な患者にとって症状コントロールのために必要な治療内容を「緩和（palliation）」と呼ぶのである．この意味では難病ケアと緩和ケアは同じである[7]．患者・家族が人生を放棄しようと悩んでいるとき，適切な緩和療法をおこない，支援し励ましていく．そのとき，患者・家族の心のギアは自然に切り替わっており，生命を支えられることへの不安感もないし，“無駄な延命治療にすがっている”わけでもない．緩和になっていれば，呼吸器の使用は，本来死んでいる人に対する「延命」という意味にならず，主体的な人生の歩みになっている．そうなると「法的に人工呼吸器は外せない」と患者・家族は考えなくなる．「人工呼吸器を外さないのは法や倫理の問題ではなく，私たちは苦労しても一緒に生きて行きたいし，お別れもしたくないから外さない」というナラティブに自然になっていく．

B. スピリチュアルケアの普遍性

スピリチュアルケアは，宗教的だと思われているが，誤解である．人は信仰の有無にかかわらず，それを必要とするからである．スピリチュアルケアとは，本来，どのような病気でも自らの「生を放棄せず（Do not abandon life）」，「生を肯定し（Affirm life）」再び生きられるようにサポートするケアの事である．この考え方は，英国のセントクリストファー・ホスピスの原点である[25]．喪失・絶望から心の復活・再生に向かうケアのことであり，身体の所有論を超えて，人の心が変化しながら，何らかの永遠性に至る道である．セントクリストファー・ホスピスでは最初，ピルグリムルームにキリストの三部作の油絵と十字架をおいていた．十字架刑を受けるイエス・キリストとALSやがんで苦しむ患者を重ね合わせ，復活と救いを考えた．その理念は今も変わっていないが，最近になり十字架とこの油絵はしまわれた[25]．彼らは，宗教的シンボルや典礼を使わなくても，スピリチュアルケアはできると自信をもったからである．人間が感じ悩むすべてを科学的に深められると考えるならば，スピリチュアルケアもまた科学することができる．これは科学の構成主義による見直しであるが，ナラティブ・アプローチも構成主義による心理療法の見直しでもある．

C. ALSケアにおける麻薬乱用への対処

全人的苦痛と訳される「total pain」は，緩和ケアで行なわれる全人的（holistic）ケアの文脈で，現代における緩和ケアの創始者，セントクリストファー・ホスピスの設立者であるシシリー・ソンダースが使った言葉である[25]．緩和ケアとは，麻薬だけで痛みなどの症状をコントロールしようとするのではなく，多様で細かな症状コントロール，麻薬以外の各種薬剤の使用，社会・心理的問題の解決，患者・家族のもつスピリチュアルニーズに対するケアによって，痛みなどの症状がとれ幸せになれるというケア概念である．各種のケア介入と麻薬の使用量は，実は逆比例している．イギリスには，医療用麻薬を多く使うほど良い緩和ケアだという考え方はない．我が国では，オピオイド（麻薬様物質）をALSの症状緩和に使う事についての混乱と緩和ケア概念の誤解がおきている[25]．

アメリカのEBMに基づくALSガイドラインにはALSのオピオイド使用は推奨されていないが[3)4)]，耐え難い呼吸困難感や体の痛みにより，ALS患者と家族がパニックになっている場合，オピオイド使用の検討が行われる[2]．しかし，実際の体の痛みは，ほとんど，理学療法や心理・社会的なサポート不足によるものが多い．また，呼吸困難感でパニック症状になる方のほとんどは，十分な多専門職種ケアが提供されておらず，患者・家族に不安感が高く，病気とともに生きていく事への恐怖心が基になっている．告知時点から適切なケアが行われなかったためであり，遅きに失したとしても十分に多専門職種ケアを提供することからケアを検討しなおすべきである．しかし，この時ケアチームは燃え尽きているか被害者的になっており，問題の根は深い．この悪循環を断ち切るために，症状コントロールに少量のオピオイドが役立つ場合は投与する．十分に多専門職種ケアを提供するという前提を無視すると，単にオピオイドの量を増量するだけになり，期待した効果が得られないと，裏切られた思いの患者・家族はパニックになって，さらに悪循環に陥るため大変危険である．

ケアの質を高めると同時に，薬物もオピオイドにこだわらず，抗うつ薬などの薬物療法も検討する．どうしても，オピオイドを使う場合には，エビデンスとして，呼吸困難感の緩和効果はモルヒネにのみあることを知っておくべきである．英国の十分なホスピスケアの環境の下では[26),27)]，モルヒネを低用量で長期に使うことで，ALS患者の生命予後をむしろ伸ばすと考えられている[28)]．一方で，短時間でモルヒネを増量していくと，薬理作用から自発呼吸抑制がおき死に至るし，別の副作用として，呼吸筋群の硬直や声門の閉鎖がおき，NPPVによるマスク換気ができなくなり，死に至る．このため，モルヒネを急激に高用量にしてはならない．合成モルヒネのフェンタニルはこの筋硬直作用がモルヒネよりも多いため，ALS患者に対し使用すべきではないという警告が出ている[29)]．

私たちの経験では，デュシェンヌ型筋ジストロフィーでは，心不全症状から強い呼吸困難感を呈する場合に，オピオイドは大変有用である．一方で，診断時から適切にケアされ，不安感の少ないALS患者は，呼吸器の使用・不使用に関わらず，少量の酸素投与を行うことがあっても，オピオイド投与が必要になる様な呼吸困難感が出現することはない．

Ⅵ. 医療・福祉制度を活用した多専門職種ケア

A. 在宅ケアカンファレンスでケア方針を共有

在宅ALSケアを行うためには，診療所，病院，訪問看護ステーション，ヘルパー事業所などが連携し，呼吸ケアのみならず，リハビリ介入，摂食・嚥下・栄養管理などの方法を検討する（**図1**）．医療保険だけでなく，障害者自立支援法と難病対策制度を利用する．40歳以上であれば介護保険制度も利

用する．診療所医師，病院医師，看護師，ケアマネジャー，MSW，保健師の中でリーダ役をだれかに担ってもらう．ヘルパー事業所も加えて定期的にケアカンファレンスを行い，情報を共有する．チームの共通方針は難病とともに生きる「人生（生）の肯定」であり，患者・家族がつらいことを理由に「人生（生）を放棄」しないように援助することである．患者・家族の気持ちを尊重することとは，患者・家族による「生の放棄」の意思を実行することではなく，患者・家族が「笑顔と楽しみ」を得られるように援助し，苦難においても心の余裕を取り戻し，振り返り，変化していける援助としていくことである．人は，法や倫理のために生きるのではなく，楽しいから，大切な人と別れたくないから生きるのである．「人生には意味と目的があり，それが無ければ生きる意味がない」というナラティブは混乱をまねきやすい．目標喪失が生きる意味の喪失になるからである．「人は意味や目的を授かって生まれたのではなく，生きていく中で，楽しみや目的が生まれるのが人生なのだ」というようなナラティブでケアを行う．

B. レスパイト入院の意味

定期的なレスパイト入院は，ALS在宅ケアには大変有用である．レスパイト入院は英国ホスピスで生まれた在宅支援の仕組みであり，医療専門職種は栄養，呼吸，身体障害の再評価や症状コントロールをする．ケア全般を振り返るためにカンファレンスを行う．患者・家族も医療専門職も今までの状況を振り返り，新たな気持ちで在宅ケアを再出発する．レスパイト（respite）入院を医療保険で行う際に，単なる息抜き入院にしないことが重要である．

C. 在宅を支援する療養介護事業

在宅生活が順調に見えても，家族の病気などで，限界に達したらどうなるのだろうかという不安は消えない．これが心理的負担になると，実際より病状が悪く感じられ，生きていく力が削がれてしまう．これを回避するためには，療養介護事業（障害者自立支援法）で終身入院が可能なことを説明する．この事業では障害区分6で気管切開人工呼吸療法をおこなっている患者に，入院医療と生活支援の両者が保証される．旧国立療養所の筋ジストロフィー病棟などがこれに対応しているが，新規にこの事業を導入する病院が増えている．ALSの入院生活が長期的に支えられるこの制度は安心感を生み出すため，患者・家族に伝えるべきである．障害者など一般病棟は在院日数制限の縛りがなく，長期入院できるように制度設計されているが，療養介護事業を平行して行っていない場合は生活支援員の配置がなく，生活支援が不十分なため，在宅生活と入院をキャッチボールの様に繰り返すとよい．

Ⅶ. まとめ

エビデンスに基づくALSの標準診療を反映したALS臨床評価指標アップデート（2009年）[3)-4)]では，リルテック内服，NPPV，PEG，多専門職種ケアの何れもが有用として推奨されている．一方，それらが実際の在宅ケアに十分に導入されていないことが問題である．その理由として，医療提供者側のスキル不足が考えられる．さらに，医療技術を提供する際のソフトパワーであるナラティブ・アプローチが十分活用されておらず，その前提となる，「難病と共に生きていく人生の肯定」を意識したケアができていない場合が多い．その様な状況下で患者・家族の喪失感，絶望感に直面するとすぐ担当者は混乱してしまう．患者の意思の尊重とは本来何なのかが分からなくなってしまうのである．この解決法を，本稿で詳細に論じ解説したので，参考にしていただければ幸いである．

謝辞：平成22年度難治性疾患克服研究事業「特定疾患患者の生活の質（ＱＯＬ）の向上に関する研究」の成果を紹介した．

文献

1) ALS治療ガイドライン作成小委員会．ALS治療ガイドライン [online]. Available at: http://www.neurology-jp.org/guidelinem/als_index.html.
2) Andersen PM, Borasio GD, Dengler R, et al. Good practice in the management of amyotrophic lateral sclerosis: clinical guidelines. An evidence-based review with good practice points. EALSC Working Group. Amyotroph Lateral Scler 2007;8:195-213.
3) Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2009;73:1218-1226.
4) Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: The care of the patient with amyotrophic lateral sclerosis:

multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2009;73:1227-1233.
5) de Carvalho M, Dengler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 2008;119:497-503.
6) Magnus T, Beck M, Giess R, Puls I, Naumann M, Toyka KV. Disease progression in amyotrophic lateral sclerosis: predictors of survival. Muscle Nerve 2002;25:709-714.
7) 中島孝．難病におけるQOL研究の展開．保健の科学 2009;51:83-92.
8) Van den Berg JP, Kalmijn S, Lindeman E, et al. Multidisciplinary ALS care improves quality of life in patients with ALS. Neurology 2005;65:1264-1267.
9) Radunovic A, Annane D, Jewitt K, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2009:CD004427.
10) 中島孝，小森哲夫．厚生労働省難治性疾患克服研究事業，「特定疾患患者の生活の質（QOL）の向上に関する研究」研究報告書分冊　筋萎縮性側索硬化症の包括的呼吸ケア指針ー呼吸理学療法と非侵襲陽圧換気療法（NPPV）第一部 [online]. Available at: http//:www.nanbyou.or.jp/pdf/2008als.pdf
11) Pinto A, de Carvalho M, Evangelista T, Lopes A, Sales-Luis L. Nocturnal pulse oximetry: a new approach to establish the appropriate time for non-invasive ventilation in ALS patients. Amyotroph Lateral Scler Other Motor Neuron Disord 2003;4:31-35.
12) Carratu P, Spicuzza L, Cassano A, et al. Early treatment with noninvasive positive pressure ventilation prolongs survival in Amyotrophic Lateral Sclerosis patients with nocturnal respiratory insufficiency. Orphanet J Rare Dis 2009;4:10.
13) Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol 2006;5:140-147.
14) 中島孝，川上英孝，伊藤博明．ALSへのNPPVの導入．Journal of clinical rehabilitation 2007;16:243-250.
15) Winck JC, Goncalves MR, Lourenco C, Viana P, Almeida J, Bach JR. Effects of mechanical insufflation-exsufflation on respiratory parameters for patients with chronic airway secretion encumbrance. Chest 2004;126:774-780.
16) Bach JR, Bianchi C, Aufiero E. Oximetry and indications for tracheotomy for amyotrophic lateral sclerosis. Chest 2004;126:1502-1507.
17) Marin B, Desport JC, Kajeu P, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. J Neurol Neurosurg Psychiatry 2010.
18. Bouteloup C, Desport JC, Clavelou P, et al. Hypermetabolism in ALS patients: an early and persistent phenomenon. J Neurol 2009;256:1236-1242.
19) 会田泉．ALSと筋ジス患者さんのNPPV導入後のPEGの実際例．難病と在宅ケア 2007;12:21-24.
20) Nishihira Y, Tan CF, Toyoshima Y, et al. Sporadic amyotrophic lateral sclerosis: Widespread multisystem degeneration with TDP-43 pathology in a patient after long-term survival on a respirator. Neuropathology 2009;29:689-696.
21) Gunaratnam Y, Oliviere D. Narrative and Stories in Health Care, Illness, dying, and bereavement. London: Oxford University Press, 2009.
22) 中島孝．ALS患者の在宅医療　QOL評価．Journal of Clinical Rehabilitation 2010;19:589-596.
23) マホーニー MJ, ed. 認知行動療法と構成主義心理療法　理論・研究そして実践．東京：金剛出版，2008.
24) Sage N, Sowden M, Chorlton E, Edeleanu A. CBT for chronic illness and palliative care: John Wiley and Sons Ltd, 2008.
25) 中島孝，白井良子．セントクリストファーホスピスから日本へ吹く風，ホスピス緩和ケアの誤解をとく．訪問看護と介護 2010;15:864-872.
26) Clemens KE, Klaschik E. Morphine in the management of dyspnoea in ALS. A pilot

study. Eur J Neurol 2008;15:445-450.
27) O'Brien T, Kelly M, Saunders C. Motor neurone disease: a hospice perspective. BMJ 1992;304:471-473.
28) Oliver D. Opioid medication in the palliative care of motor neurone disease. Palliat Med 1998;12:113-115.
29) Zylicz Z, van Rijn-van der Plaat LL. Fentanyl may increase breathlessness in a patient with motor neuron disease. J Pain Symptom Manage 2006;32:199-200.

Neuroethics and QOL Perspectives of Cybernics Technology Enhancement or Palliation, towards Clinical Trial

Takashi Nakajima

Abstract. Medical applications of HAL are examined in their biomedical and ethical aspects. Locating HAL in the historical perspective and the present applications of man-machine hybrid technology to medical patients, I evaluate positive effects of HAL by examining a hypothesis that "appropriate assist is able to protect degenerative muscles, to keep muscle function longer and to prevent disused effect in healthier muscles.

Keywords Bioethics, Man-machine hybrid technology, HAL, QOL

1 Introduction

In the modern era, new technology expands to the extent of human biomedical function. It leads us to the use of new devices by which human function can be appropriately enhanced and assisted according to the user's intention. It leads us to the extent that the user does not intend to use these devices consciously. The hybrid system of wearable small computerized machines and man, has started to change the meaning of robotics, assistive technology, and medical therapeutics.

A prototype of HAL (Hybrid Assistive Limb), HAL-1 was developed based on cybernics technology in 1999.[1] The word, cybernics was coined from cybernetics, robotics, and informatics by Yoshiaki Sankai. After the development of cybernics, HAL has come to refer to an intelligent wearable robot that is able to estimate the wearer's motion intention in real time. This is achieved by means of measuring bioelectrical signals including the wearer's surface EMG, joint angles, and acceleration and force plate signals. Simultaneously HAL technology enhances the wearer's limbs movement with appropriate motor torque (Fig.1).[2] Its distinguished control mechanism consists of a hybrid of both "cybernic voluntary control" which is based on wearer's intention and "cybernic autonomous control" which is based on machine internal estimation.[2,3] Essentially HAL has an internal feed-forward control mechanism according to the wearer's intention. Limb movement, assistive torque, and secondary responses, such as spinal reflex and wearer's change of effort, are suitably adjusted simultaneously.

---

[1] Okamura J, Tanaka H, Sankai Y, EMG-based Prototype Powered. Assistive System for Walking Aid, *ASIAAR'99*. 1999:229-234.

[2] Suzuki K, Mito G, Kawamoto H, Hasegawa Y, Sankai Y, Intention-based walking support for paraplegia patients with Robot Suit HAL, *Advanced Robotics* 2007, 21(29):1441-1469.

[3] Hayashi T, Kawamoto H, Sankai Y: Control Method of Robot Suit HAL working as Operator's Muscle using Biological and Dynamical Information. In *IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS 2005): Aug 2-6 2005*; 2005:3455-3460

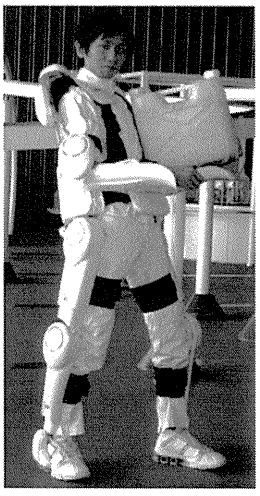

Fig. 1. HAL-5 supports the whole-body motion. A 20-kg load is carried on a single arm (2005).[2]

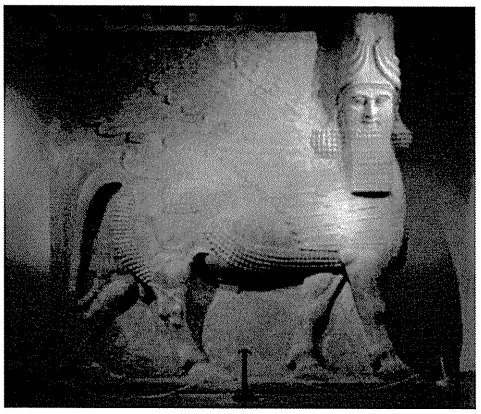

Fig. 2. The Assyrian Lamassu at the Oriental Institute Museum of the University of Chicago. http://en.wikipedia.org/wiki/Lamassu

In the context of HAL technology, the word "hybrid" also has another meaning referring to a self-regulating human-machine system such as a cybernetic organism or cyborg.[4] HAL can be categorized as both 1) a product of human enhancement technology for living and working in the extraordinary environments, and as 2) human assistive technology for better quality of lives for handicapped people.

In this article, the applications of HAL medical technologies are examined from biomedical and ethical perspectives. There will be many possible medical applications of a variety of HAL models including single leg models, upper limbs models, hand models, and biped models. Prior to using HAL models for medical applications, clinical trials are necessary. Clinical trials will significantly prove the efficacy and safety of the technology for potential patients.

Reviewing analogical stories or images of human-machine hybrids in history seems of great importance in order to conduct better clinical trials and to estimate HAL technology's efficacy in terms of Quality of life (QOL) measurement and other psycho-social effects in individuals and society.

2 Historical Perspectives of Man-machine Hybrid Technology

2.1 Assyrian Shedu

In the concept of a man-other beings hybrid that is analogous to HAL, the protective goddess Lamassu Assyrian Shedu (the late 8th century BC), is the oldest in history (Fig. 2). She has a human's head, an eagle's wings, a bull's legs, and a lion's body. Those components make the most

[4] Clynes ME, Kline NS: Cyborgs and Space. *Astronautics* 1960(September):29-33.

Fig. 3. Daedalus and Icarus in the Greek myths (Relief in the Villa Albani in Rome). http://en.wikipedia.org/wiki/File:Daedalus_und_Ikarus_MK1888.png

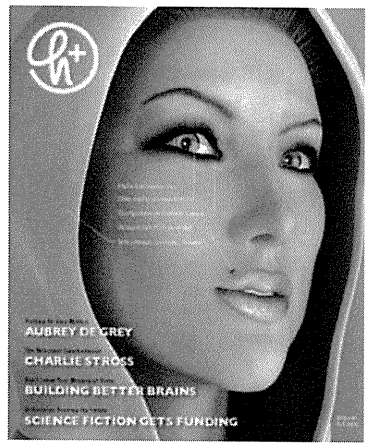

Fig. 4. The cover page of the 1st issue of Transhumanism magazine. http://hplusmagazine.com/magazine/

intellectual and physically strong servant goddess. She is often represented as a standing figure at the entrance of the throne room that introduces guests to another superior god. You can see this figure in famous museums around the world. This imaginary animal-human hybrid might have been made in response to the fundamental human desire to protect the beloved people, their property and culture.

2.2 Daedalus and Icarus in the Greek Myths

A second example is shown in the Greek mythology (Fig.3). The first innovative engineer Daedalus, built the labyrinth of Crete Islands in the Mediterranean Sea. When his son Icarus and he needed to flee from the labyrinth, he constructed wings made of wax and bird feathers. According to this Greek myth, Daedalus told Icarus not to fly high near the sun, as this would melt his waxed feather wings, causing him to fall down into the sea. However Icarus forgot his father's words, as flying high near the sun was easy and fun. As a consequence of these actions he fell into the sea and died.

What this Greek myth teaches us is the dualism in technology. People must consider these dual effects both before and also after the development of a machine. Enhancement biotechnology might also lead us towards danger. Although when used appropriately, like keeping Daedalus' words, the technology should be harmless.

2.3 Dreams of Euphenics and Transhumanism

A good example of the dualism of technology and science is observed in a new euphenics movement[5]. Euphenics looks useful for humankind; however it still has a danger of genetic

[5] Lederberg J: Molecular biology, eugenics and euphenics. *Nature* 1963, 198:428-429.

discrimination and racism such as that which was evident in the NAZI era. Transhumanism has been loosely defined[6] as follows: "it holds that current human nature is improvable through the use of applied science and other rational methods, which may make it possible to increase human health-span, extend our intellectual and physical capacities, and give us increased control over our own mental states and moods" (Fig.4). The final goal of the transhumanist is cause for concern because a man with enhanced intellectual and physical capacities may find it easy to control and rule ordinary inferior humankind. Moreover, transhumanists might find it difficult to pursue their personal happiness and to attain enlightenment.

If transhumanism technology can be utilized for improving patients' capability with intractable and incurable disease, the purpose of its technology will become completely different. Such enhancement technology can enable patients to survive longer and become much happier as well. If the patients are able to live a contented life in the community, using man-machine hybrid technology, the purpose of the technology can be beneficial. In this instance we do not have to think that human nature, which is transcendently given, has been changed by biotechnology. We can think that every lifeform including humankind is able to change itself dynamically in nature. The goal is not to restore a patient to their previous form, rather to provide assistive technology to enable them to live a contented life.

2.4 American President's Council Report on Bioethics in 2003

"Beyond Therapy: Biotechnology and the Pursuit of Happiness" was written in 2003 as a report of the President's Council on Bioethics.[7] In the report, "Beyond Therapy" biotechnologies were discussed for a variety of aims, including having better children, superior performance, ageless bodies and happy souls Man-machine hybrid technology might be also be considered as a kind of "beyond therapy", an enhancement and desire-driven therapy in their context. However if this technology is used not as therapy, but used for palliation and rehabilitation, it is feasible that the patients with intractable/incurable disease can be assisted in being self-affirmative. Moreover, they can be assisted in adapting to their environment, even if the patients are not able to be restored to "normal".

2.5 Is a Man-ventilator Hybrid Merely Life-prolonging Treatment or Palliation/Rehabilitation?

Amyotrophic lateral sclerosis (ALS) is a pan-ethnic progressive neuromuscular disease caused by the degeneration of motor neurons that control voluntary muscle movement, swallowing and respiration. Two per 100,000 of the population develop ALS each year. The patients will finally lose all the voluntary movements except for the eyes. Sooner or later they will need to use a ventilator to avoid hypoxemia induced by respiratory failure following respiratory muscle atrophy. There is a lot of confusion in caring for ALS around the world, although standard care for the

[6] Bostrom N: In defense of posthuman dignity. *Bioethics* 2005, 19(3):202-214.
[7] Beyond Therapy: Biotechnology and the Pursuit of Happiness
http://bioethics.georgetown.edu/pcbe/reports/beyondtherapy/index.html

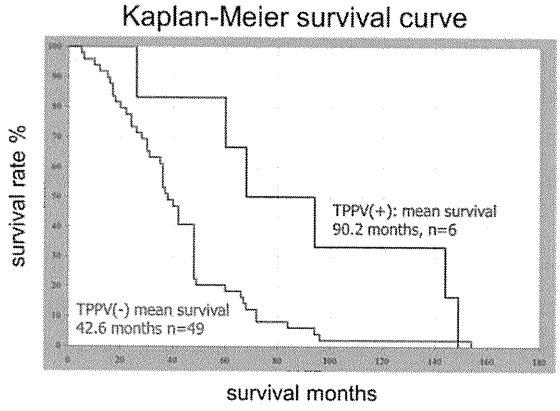

Fig. 5. Survival curve of ALS patients (Japanese data)[10]

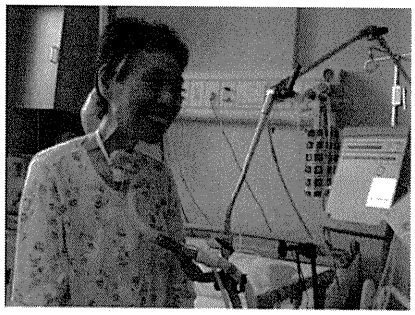

Fig. 6. Very nice facial appearance of the ALS patient living with ventilator machine.[10]

patients with ALS has been published.[8,9] In the Japanese Nanbyo (intractable / rare diseases) care system, approximately 15% of ALS patients choose tracheostomy positive pressure ventilation: TPPV.[10] Most patients usually start with non-invasive positive pressure ventilation: NPPV. NPPV cannot be continued long-term because glottic dysfunction always induces the obstruction of the air way with sputum.

In Fig. 5 our data shows that TPPV prolongs life for 4 years longer than non TPPV does. In general, people consider successful treatment to be treatment which restores a patient to their former state. Treatment which cannot achieve this goal, may be considered less successful or even worthless. In the perspective of palliative care and the Japanese 'Nanbyo' care system, if the patient cannot be restored to their former state by treatment, the goal of care is thought of differently. The goal of the care is thought of in terms that the patient with incurable disease identifies himself against in his new internal environment.

In the case of ALS, respiratory care including NPPV and TPPV prevents hypoxemia in patients. Hypoxemia induces secondary failure of many organs including skeletal muscles, respiratory muscles, the gastrointestinal system, the spinal cord and the brain. Prevention of hypoxemia might reduce the speed of the degeneration process of motor neurons. In addition to these life-saving benefits, the clinical data showed that ventilator support makes the patient happy (Fig. 6).

---

[8] Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, Kalra S, Katz JS, Mitsumoto H, Rosenfeld J *et al*: Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009, 73(15):1218-1226.

[9] Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, Kalra S, Katz JS, Mitsumoto H, Rosenfeld J *et al*: Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009, 73(15):1227-1233.

[10] Nakajima T: Individual ALS care in the Japanese 'Nanbyo' care model comparison with palliative care approaches in achieving best Quality of Life. *Amyotrophic Lateral Sclerosis* 2006(7):45-47.

3 Our Hypothesis towards Clinical Trials of HAL

3.1 HAL vs. BLEEX

As present there exists two completely different wearable robot models, the Berkeley lower extremity exoskeleton (BLEEX) and HAL. BLEEX is a human exoskeleton robot, which looks similar in appearance to HAL. The wearer of BLEEX can carry the payload easily because BLEEX supports its own weight and an external payload. The main application of BLEEX technology is likely to be in the enhancement of human motor function in extraordinary environments. It is easily applied to military purpose as well. In contrast, the main target of HAL is to improve people's life, especially in medical and welfare fields. The design of HAL is intended for both carers and patients. With these users in mind, HAL technology requires more research on safety and efficacy.

3.2 Our Hypothesis of Medical Application of HAL

Our likely hypothesis is that "appropriate assistance is able to protect degenerative muscles, to keep muscle function longer and to prevent disused effect in healthier muscles". In neuromuscular diseases, heterogeneity of muscle degeneration can be observed. Severely damaged muscles need to rest. In contrast, moderately affected muscles need assistance and healthier muscles need exercise. In Fig 7, muscle X-ray CT of the patient with Duchenne muscular dystrophy shows heterogeneity of affected muscles. If our hypothesis is correct, when the patient with neuromuscular disease wears HAL intermittently, severely damaged muscles can be protected and moderately affected muscles can be assisted. The additional benefit of this is that natural disease progression speed may be reduced. We can expect such disease modifying effects of HAL in patients with neuromuscular disease. HAL medical use could reduce the speed of declining muscle strength and disease progression. We must prove this hypothesis in future clinical trials.

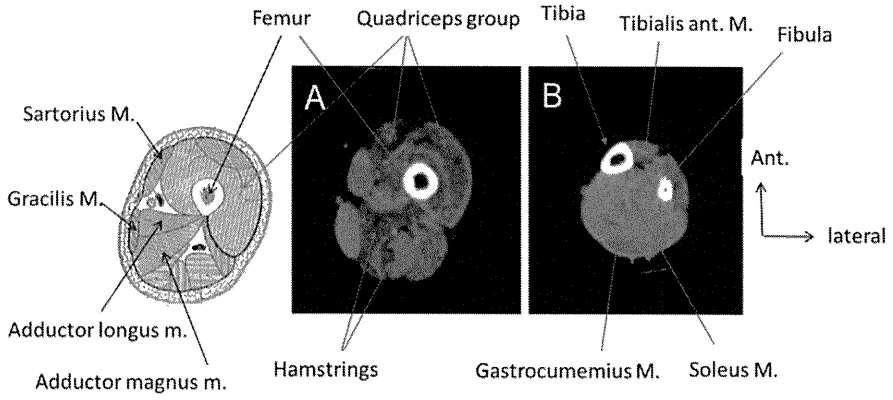

Fig. 7. X-ray CT of DMD patient at age 9 shows heterogeneous severity of affected muscle fibres in lower extremity. Hypodensity in muscle fibres shows fatty degeneration. Some muscle fibres including Sartorius, Gracilis, Gastrocunemius and Soleus M. are hypertrophic.

Preliminary studies in the University of Tsukuba and CYBERDYNE Inc. showed that a single leg HAL model may reduce the period of recovery for stroke patients in the acute phase. In the report a single leg HAL model for a patient with post-polio syndrome also compensates his leg function.[11, 12] Theoretically speaking, combination therapy with both intermittent HAL wearing and gene therapy such as exon skipping, that is planned in the near future, may have more efficacies in the Duchenne muscular dystrophy. Wearing HAL may augment the efficacy of commercially available enzyme replacement therapy (ERT) in the late onset of Pompe disease. Moreover, muscle decline speed might be alleviated by intermittent wearing of HAL in the neurogenic muscular diseases, including spinal muscular atrophy (SMA), spino-bulbar muscular atrophy (SBMA), amyotrophic lateral sclerosis (ALS), and Charcot-Marie-Tooth disease (CMT) as well. We are now starting to prepare for the clinical trials of the above diseases to prove the hypothesis.

3.3 Issues on Quality of Life and Patient Reported Outcomes

When we undergo clinical trials of HAL, issues on Quality of Life and patient reported outcomes (PRO) must be considered of great importance. When the WHOQOL scale was constructed to assess better health care intervention by the WHOQOL study group,[13] they summarized: "Quality of Life has been defined by the World Health Organization as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." However, in the fields of health care and health economics, there are tremendous misunderstandings in the concept of QOL. The main cause of the misunderstandings is that QOL is thought to be an indicator of humanity in their view. According to this misunderstanding, lower QOL means less humanity, that is, a patient living permanently with low QOL state does not have humanity. Loss of humanity or concept of normal human life could potentially lead patients to voluntary euthanasia or "dying with dignity". The question is raised, "Would you like to live longer, even if your QOL is the lowest?" People think the lowest QOL is a fixed value. Primarily, QOL is not a real entity, but an individual concept in mind (construct). Logically speaking, lower QOL perception of any patient can be changed by appropriate interventions if these can be provided properly.

To avoid the misunderstanding of QOL, the phrase, patient reported outcomes (PRO) has been recently used frequently in clinical trials instead of QOL.[14] The schedule for the evaluation of individual Quality of Life: SEIQoL, is the best representative of the instruments available for measuring PRO. SEIQoL also has a direct weighting version, SEIQoL-DW. In SEIQoL-DW,

---

[11] Kawamoto H, Taal S, Niniss H, Hayashi T, Kamibayashi K, Eguchi K, Sankai Y: Voluntary motion support control of Robot Suit HAL triggered by bioelectrical signal for hemiplegia. *Conf Proc IEEE Eng Med Biol Soc* 2010, 1:462-466.

[12] Shingu M, Eguchi K, Sankai Y: Substitution of motor function of polio survivors who have Permanent Paralysis of Limbs by using Cybernic Voluntary Control. In *International conference on Robotics and Biomimetics: December 19 -23 2009; Guilin,China*; 2009:504-509.

[13] Billington R: WHOQOL Annotated Bibliography. Edited by Department of Mental Health WHO. Geneva; 1999.

[14] Ring L, Hofer S, Heuston F, Harris D, O'Boyle CA: Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. *Health Qual Life Outcomes* 2005, 3:55.

respondents were first asked to nominate and describe the 5 areas of their lives (cues) that they consider to be the most important for their QOL. They were then asked to rate their current level of satisfaction/functioning on each cue. Finally, they were requested to indicate the relative importance of each cue. Calculations made from this data produced the SEIQOL Index. The SEIQOL Index score ranged from 0-100, where a higher score indicates better QOL.

In SEIQoL, QOL judgment is constructed from the assessment of functioning/satisfaction in individually important life domains and QOL is evaluated against ones own individual yardstick. Man is always interacting with his environment and self-evaluation such as his own QOL judgment is changing at the same time. Man-machine hybrid technology can be assessed in clinical trials using the SEIQoL perspective.

4 Conclusion

Robot Suit HAL has been developed on the basis of Cybernics, man-machine hybrid technology. In this article, perspectives of HAL medical applications are reviewed in the historical and philosophical standpoints which can overcome the previous arguments of euphenics and transhumanism. Every lifeform including humankind has the capability to change itself dynamically. When humankind applies HAL technology to patients with intractable and incurable disease, such application sounds appropriate even if the technology changes us. We will plan to conduct clinical trials to prove the hypothesis: "appropriate assistance is able to protect degenerative muscles, to keep muscle function longer and to prevent disused effect in healthier muscles." In this article, the misunderstandings of the QOL concept are discussed and methods to estimate clinically efficacy using QOL/PRO are also examined.

Acknowledgemens. I deeply appreciate Mr. Andrew P. Wood's help about reviewing the manuscript literally.

References

Okamura J, Tanaka H, Sankai Y: EMG-based Prototype Powered. Assistive System for Walking Aid. In *ASIAAR'99*. 1999:229-234.

Suzuki K, Mito G, Kawamoto H, Hasegawa Y, Sankai Y: Intention-based walking support for paraplegia patients with Robot Suit HAL *Advanced Robotics* 2007, 21(29):1441-1469.

Hayashi T, Kawamoto H, Sankai Y: Control Method of Robot Suit HAL working as Operator's Muscle using Biological and Dynamical Information. In *IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS 2005): Aug 2-6 2005*; 2005:3455-3460.

Clynes ME, Kline NS: Cyborgs and Space. *Astronautics* 1960(September):29-33.

Lederberg J: Molecular biology, eugenics and euphenics. *Nature* 1963, 198:428-429.

Bostrom N: In defense of posthuman dignity. *Bioethics* 2005, 19(3):202-214.

Beyond Therapy: Biotechnology and the Pursuit of Happiness
http://bioethics.georgetown.edu/pcbe/reports/beyondtherapy/index.html

Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, Kalra S, Katz JS, Mitsumoto H, Rosenfeld J *et al*: Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009, 73(15):1218-1226.

Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, Kalra S, Katz JS, Mitsumoto H, Rosenfeld J *et al*: Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009, 73(15):1227-1233.

Nakajima T: Individual ALS care in the Japanese 'Nanbyo' care model comparison with palliative care approaches in achieving best Quality of Life. *Amyotrophic Lateral Sclerosis* 2006(7):45-47.

Kawamoto H, Taal S, Niniss H, Hayashi T, Kamibayashi K, Eguchi K, Sankai Y: Voluntary motion support control of Robot Suit HAL triggered by bioelectrical signal for hemiplegia. *Conf Proc IEEE Eng Med Biol Soc* 2010, 1:462-466.

Shingu M, Eguchi K, Sankai Y: Substitution of motor function of polio survivors who have Permanent Paralysis of Limbs by using Cybernic Voluntary Control. In *International conference on Robotics and Biomimetics: December 19 -23 2009; Guilin,China*; 2009:504-509.

Billington R: WHOQOL Annotated Bibliography. Edited by Department of Mental Health WHO. Geneva; 1999.

Ring L, Hofer S, Heuston F, Harris D, O'Boyle CA: Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. *Health Qual Life Outcomes* 2005, 3:55

ARTICLE IN PRESS

ELSEVIER

Brain & Development xxx (2011) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Spinocerebellar ataxias type 27 derived from a disruption of the fibroblast growth factor 14 gene with mimicking phenotype of paroxysmal non-kinesigenic dyskinesia

Keiko Shimojima [a], Akihisa Okumura [b], Jun Natsume [c], Kaori Aiba [d], Hirokazu Kurahashi [e], Tetsuo Kubota [f], Kenji Yokochi [g], Toshiyuki Yamamoto [a,*]

[a] *Tokyo Women's Medical University Institute for Integrated Medical Sciences, Tokyo, Japan*
[b] *Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan*
[c] *Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[d] *Department of Pediatrics, Toyohashi Municipal Hospital, Toyohashi, Japan*
[e] *Department of Pediatric Neurology, Aichi Prefectural Colony Central Hospital, Kasugai, Japan*
[f] *Department of Pediatrics, Anjo Kosei Hospital, Anjo, Japan*
[g] *Department of Pediatrics, Seirei-Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan*

Received 17 November 2010; received in revised form 27 April 2011; accepted 27 April 2011

Abstract

Many types of spinocerebellar ataxias (SCAs) manifest as progressive disorders with cerebellar involvement. SCA type 27 (SCA27) is a rare type of SCA caused by mutations in the fibroblast growth factor 14 gene (*FGF14*). *FGF14* disruption caused by a de novo reciprocal chromosomal translocation between chromosomes 13 and 21 was identified in a patient with the phenotype of paroxysmal non-kinesigenic dyskinesia (PNKD). This indicated genetic heterogeneity of PNKD, since 60% of the patients with PNKD exhibit mutations in another gene responsible for PNKD, the myofibrillogenesis regulator 1 gene (*MR-1*). We hypothesized that the remaining 40% of patients with PNKD may have *FGF14* mutations; therefore, the nucleotide sequences of *MR-1* and *FGF14* were analyzed in another six patients with PNKD, but no nucleotide alterations were observed in these genes for these patients. Further studies should be conducted on the phenotypic heterogeneity of *FGF14* mutations and/or haploinsufficiency in SCA27 and PNKD.

1. Introduction

Spinocerebellar ataxias (SCAs) are progressive disorders that manifest as cerebellar symptoms such as gait ataxia, stance ataxia, dysmetria and/or kinetic tremor in all four limbs, as well as oculomotor deficits (nystagmus and hypermetria/hypometria of saccades) [1]. SCAs exhibit genetic heterogeneity, and at least 29 types of SCAs have been recognized to date [2]. Most of the subtypes show autosomal dominant traits, while some show anticipation due to triplet repeats. Therefore, onset age depends not only on the genetic subtypes but also on the mutation types. Since SCAs cannot be diagnosed solely on the basis of clinical evaluation, knowledge of the family history is very important for diagnosis of SCAs. However, if the patient is a small child with negative family history, it is extremely difficult to arrive at a final diagnosis.

* Corresponding author. Address: Tokyo Women's Medical University Institute for Integrated Medical Sciences, 8-1 Kawada-cho, Shinjuku-ward, Tokyo 162-8666, Japan. Tel.: +81 3 3353 8111x24013; fax: +81 3 5269 7667.
E-mail address: toshiyuki.yamamoto@twmu.ac.jp (T. Yamamoto).

0387-7604/$ - see front matter © 2011 Published by Elsevier B.V. on behalf of The Japanese Society of Child Neurology.
doi:10.1016/j.braindev.2011.04.014

Please cite this article in press as: Shimojima K et al. Spinocerebellar ataxias type 27 derived from a disruption of the fibroblast growth factor 14 gene with mimicking phenotype of paroxysmal non-kinesigenic dyskinesia. Brain Dev (2011), doi:10.1016/j.braindev.2011.04.014

Table 1
Summary of FISH analyses.

Band	BAC probe	Start	End	Result	
13q14.11	RP11-13I8	41,402,236	41,593,291	Marker	
13q33.1	RP11-180C7	101,579,849	101,742,909	Normal	
	RP11-230O10	101,668,810	101,837,797	***Disruption***	Covering *FGF14*
	RP11-1005B17	101,752,504	101,933,396	Translocation	
	RP11-46I10	101,854,462	102,028,883	Translocation	
	RP11-29B2	102,007,252	102,165,732	Translocation	
	RP11-2L10	102,337,773	102,514,754	Translocation	
13q34	RP11-569D9	113,930,807	114,103,243	Translocation	
21q22.12	RP11-272A3	34,768,332	34,953,503	Marker	
21q22.13	RP11-105O24	37,717,328	37,872,927	Marker	
21q22.3	RP11-34P17	46,391,180	46,582,695	***Disruption***	
	RP11-71A7	46,607,929	46,756,333	Translocation	
	RP11-433E24	46,717,198	46,912,065	Translocation	

Genome location corresponds to the March 2006 human reference sequence (NCBI Build 36).

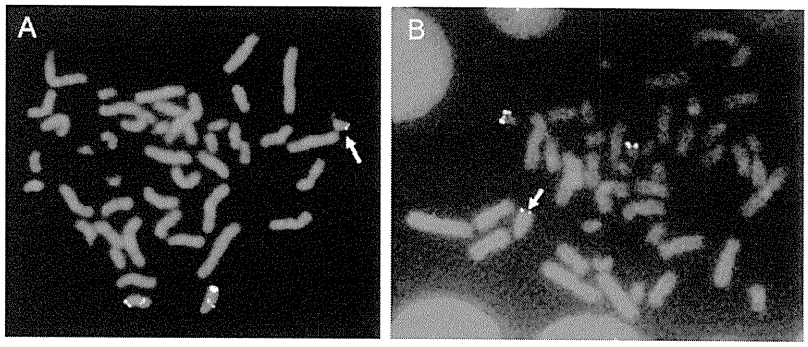

Fig. 1. Cytogenetic investigations for the breakpoints. (A) The one of the split signals of RP11-230O10 covering *FGF14* were identified on chromosome 21 (arrow). (B) The additional signals of RP11-34P17 located on 21q22.3 were identified on chromosome 13 (arrow).

We recently encountered a child who had paroxysmal non-kinesigenic dyskinesia (PNKD, MIM #118800) and exhibited a de novo reciprocal chromosomal translocation that caused a disruption in the fibroblast growth factor 14 gene (*FGF14*) responsible for SCA type 27 (SCA27, MIM #609307). In this study, we analyzed the responsible genes for PNKD including *FGF14* in other patients after obtaining permission from the ethical committee of our institution.

2. Case report

We encountered a boy (age, 3 years 9 months) who was referred to our institution for medical examination. He was born at 40 weeks of gestation, with a birth weight of 3370 g (75th–90th centile), height of 51 cm (75th–90th centile), and a head circumference of 32.5 cm (10th–25th centile). He underwent uneventful development until he was 8 months old. At this age, he started experiencing episodic attacks of muscle atonus and upward turning of both eyes; these episodes were triggered by intense crying and occurred several times a week. These episodes were diagnosed as breath-holding spells, and the patient underwent therapy with valproic acid and phenobarbital on increase in the frequency of these episodes. When the patient was admitted to the hospital, his stature was within normal limits for his age; his weight was 15.6 kg (50th–75th centile), height was 99.5 cm (50th–75th centile), and head circumference was 49.2 cm (25th–50th centile). Intermediate time of episodes, he did not exhibit any neurological symptoms except for hyperkinetic behaviors. Immediately after crying, the patient exhibited involuntary gross movements of the extremities, associated with choreic movements of the head and truncus. During these episodes, which usually lasted for approximately 5 min, he was alert and could reply when his name was called out. Laboratory tests, including routine blood and urine tests; radiological tests, including brain magnetic resonance imaging and magnetic resonance angiography; and electroencephalography yielded normal results. At the age of 6 years, the patient's development quotient was 67, as determined using the Tanaka-Binet Scale of Psychological Development; this

Please cite this article in press as: Shimojima K et al. Spinocerebellar ataxias type 27 derived from a disruption of the fibroblast growth factor 14 gene with mimicking phenotype of paroxysmal non-kinesigenic dyskinesia. Brain Dev (2011), doi:10.1016/j.braindev.2011.04.014

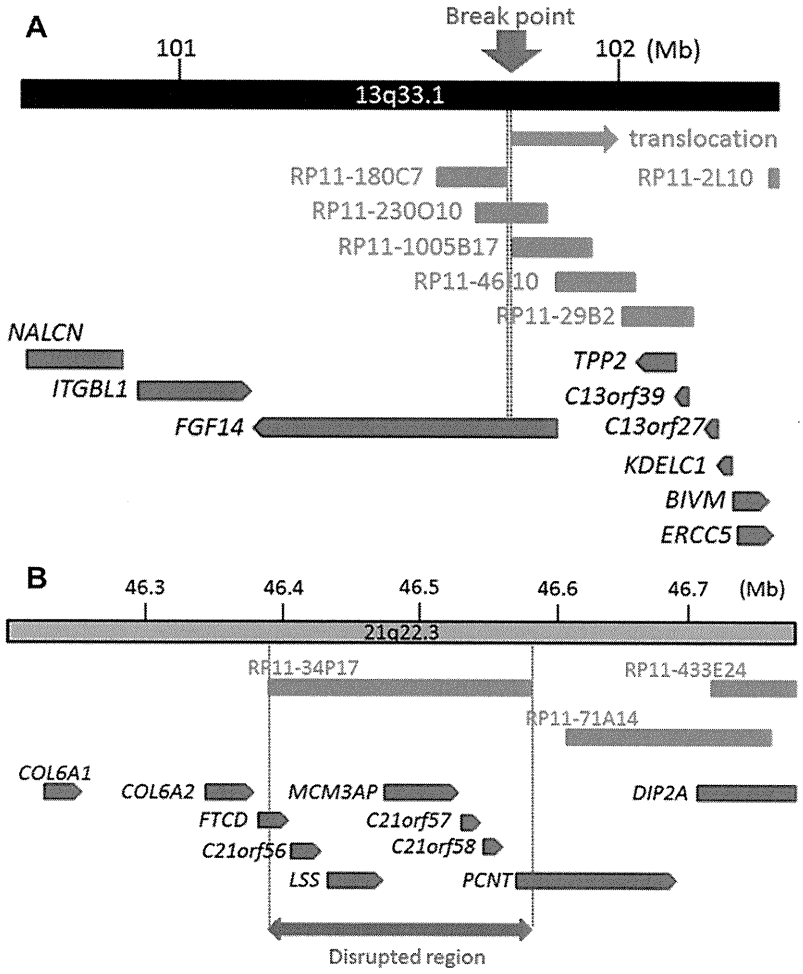

Fig. 2. Physical maps around the breakpoints of translocation. (A) Although RP11-230O10 is disrupted, RP11-180C7 and RP11-1005B17 are not disrupted. This indicates that the break point of this region is narrowed into 10-kb region covering *FGF14*. (B) The disrupted BAC clone, RP11-34P17, includes seven known genes. However, these seven genes do not show any functional relevance to the patient's neurological findings. Rectangles and pentagons indicate the locations of the BAC clones and the known genes, respectively. Italic symbols indicate the name of the genes.

value indicated mild mental retardation [3]. He graduated from a special educational school and is now 19 years old. Conventional chromosomal analysis detected the presence of a reciprocal translocation with the karyotype 46,XY,t(13;21)(q32;q22.3). Since his parents showed normal karyotypes, the patient's translocation was considered as a de novo translocation.

Fluorescent *in situ* hybridization (FISH) analysis was performed to investigate the breakpoints of the translocation, according to a previously described method [4]. BAC clones used as the probes were selected from the suspected breakpoints using UCSC genome browser (http://www.genome.ucsc.edu) (Table 1). Although one of the signals of RP11-230O10 was split into chromosome 21 (Fig. 1A), the neighboring two BAC clones were not disrupted. Thus, the breakpoint was narrowed into 10-kb region of chr13:101,742,909–101,752,504 which disrupted *FGF14* (Fig. 2A). Similarly, the breakpoint on chromosome 21 within the 21q22.3 band was determined on the region of RP11-34P17 (Fig. 1B), which included seven known genes with no functional relevance to the patient's neurological findings (Fig. 2B). From these evidences, we concluded that the phenotype observed in this patient could be attributable to the breakage of *FGF14*.

The myofibrillogenesis regulator 1 gene (*MR-1*) is known to be responsible for PNKD [5]; therefore, we analyzed the nucleotide sequences of *MR-1* and *FGF14* for this patient by using the standard polymerase chain reaction (PCR)-direct sequencing method with primers designed using web-based PRIMER 3 software (Supplementary Table S1), and there was no nucleotide alteration in this patient. Then, we participated in the cohort study using DNA samples obtained from the other six children (two males and four females from five families, age 3–16 years old) who were diagnosed as

Please cite this article in press as: Shimojima K et al. Spinocerebellar ataxias type 27 derived from a disruption of the fibroblast growth factor 14 gene with mimicking phenotype of paroxysmal non-kinesigenic dyskinesia. Brain Dev (2011), doi:10.1016/j.braindev.2011.04.014

having PNKD based on the reported description [6]. The result showed no nucleotide alteration in *MR-1* and *FGF14*.

3. Discussion

Our patient started exhibiting episodic involuntary movements when he was 8 months old. Because his consciousness was not disturbed, these movements were considered as nonepileptic paroxysmal movements. Despite the lack of a family history of PNKD, we considered his clinical diagnosis as PNKD, which is an autosomal dominant hereditary movement disorder exhibiting involuntary movements, including chorea, ballismus, and dystonia with the onset age usually 1–12 years [7].

In this patient, a de novo reciprocal chromosomal translocation between chromosomes 13 and 20 was identified, and detailed cytogenetic analyses confirmed a disruption in *FGF14*, which is recognized as the cause of SCA27, since two *FGF14* mutations have been reported in large SCA families [8,9]. Therefore, the genetic diagnosis of this patient was confirmed as SCA27 not PNKD. It was hard to diagnose him as SCA27 before the genetic diagnosis, because SCAs generally show wide spectrum of clinical phenotypes and because this patient was a sporadic case and there was no family history [1].

Previous study reported a daughter and her mother who had the identical reciprocal translocation between chromosomes 5 and 13 [10]. In the family, the breakpoint on chromosome 13 disrupted *FGF14* same as our patient. Although the mother exhibited mental impairment and pes cavus, gait ataxia was observed only when she closed her eyes; this indicated very mild cerebellar involvement. In contrast, the daughter began to exhibit cerebellar dysfunctions with gait ataxia and tremor since the first year of life. She also exhibited dyskinetic jerky movements. These clinical features are similar to those observed in our patient. This evidence suggests that disruption or loss-of-function mutations in *FGF14* may be responsible for SCA27 but the disease penetrance would be less than 100%. In addition, phenotypic overlapping of PNKD and SCA27 is observed in this family and our patient.

PNKD exhibits genetic heterogeneity, because approximately 60% of patients with PNKD exhibit *MR-1* mutations [7], but the causative factors have not yet been identified for the remaining 40% of patients with PNKD. Therefore, we hypothesized that *FGF14* may be responsible for the remaining 40% of patients with PNKD and that this may be the reason of phenotypic overlapping of PNKD and SCA27. Based on this hypothesis, we analyzed the nucleotide sequences of *MR-1* and *FGF14* in six patients with PNKD, but there were no mutations. This result may be attributable to the small study population used in this study. Therefore, further studies are required to prove our hypothesis.

Conflict of interest

The all authors declare no conflict of interest.

Acknowledgment

Dr. Shimojima thanks Hayashi Memorial Foundation for Female Natural Scientists for the grant aid support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.braindev.2011.04.014.

References

[1] Manto MU. The wide spectrum of spinocerebellar ataxias (SCAs). Cerebellum 2005;4:2–6.
[2] Soong BW, Paulson HL. Spinocerebellar ataxias: an update. Curr Opin Neurol 2007;20:438–46.
[3] Koeda T, Takeshita K. Visuo-perceptual impairment and cerebral lesions in spastic diplegia with preterm birth. Brain Dev 1992;14:239–44.
[4] Shimojima K, Sugiura C, Takahashi H, Ikegami M, Takahashi Y, Ohno K, et al. Genomic copy number variations at 17p13.3 and epileptogenesis. Epilepsy Res 2010;89:303–9.
[5] Rainier S, Thomas D, Tokarz D, Ming L, Bui M, Plein E, et al. Myofibrillogenesis regulator 1 gene mutations cause paroxysmal dystonic choreoathetosis. Arch Neurol 2004;61:1025–9.
[6] van Rootselaar AF, van Westrum SS, Velis DN, Tijssen MA. The paroxysmal dyskinesias. Pract Neurol 2009;9:102–9.
[7] Bruno MK, Lee HY, Auburger GW, Friedman A, Nielsen JE, Lang AE, et al. Genotype–phenotype correlation of paroxysmal non-kinesigenic dyskinesia. Neurology 2007;68:1782–9.
[8] van Swieten JC, Brusse E, de Graaf BM, Krieger E, van de Graaf R, de Koning I, et al. A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia [corrected]. Am J Hum Genet 2003;72:191–9.
[9] Dalski A, Atici J, Kreuz FR, Hellenbroich Y, Schwinger E, Zuhlke C. Mutation analysis in the fibroblast growth factor 14 gene: frameshift mutation and polymorphisms in patients with inherited ataxias. Eur J Hum Genet 2005;13:118–20.
[10] Misceo D, Fannemel M, Baroy T, Roberto R, Tvedt B, Jaeger T, et al. SCA27 caused by a chromosome translocation: further delineation of the phenotype. Neurogenetics 2009;10:371–4.

Please cite this article in press as: Shimojima K et al. Spinocerebellar ataxias type 27 derived from a disruption of the fibroblast growth factor 14 gene with mimicking phenotype of paroxysmal non-kinesigenic dyskinesia. Brain Dev (2011), doi:10.1016/j.braindev.2011.04.014