日本小児アレルギー学会誌　第23巻第1号83～90，2009

小児領域の臨床試験と医薬品開発を促進するための海外の取り組み

土　田　　尚
国立成育医療センター　総合診療部

日本小児アレルギー学会
Japanese Society of Pediatric Allergy and Clinical Immunology

小児領域の臨床試験と医薬品開発を促進するための海外の取り組み

土田　尚
国立成育医療センター　総合診療部

Key words：小児領域の研究，適応外使用，治療上の孤児的状況，医薬品開発，臨床試験

略語：AIDS：Acquired Immune Deficiency Syndrome（エイズ・後天性免疫不全症候群），
BPCA：Best Pharmaceuticals for Children Act，CHMP：Committee for Medical Products for Human Use，
COMP：Committee for Orphan Medical Products，EMEA：European Medicines Agency（欧州医薬品庁），
EU：European Union（欧州連合），FDAAA：FDA Amendments Act of 2007，
FDAMA：FDA Administration Modernization Act（FDA 近代化法），
HIV：Human Immunodeficiency Virus（ヒト免疫不全ウイルス），
ICH：International Conference on Harmonization of Technical Requirments
for Registration of Pharmaceuticals for Human Use（日米 EU 医薬品規制調和国際会議），
NIH：National Institute of Health（米国国立衛生研究所），PAC：Pediatric Advisory Committee，
PDCO：Paediatric Committee，PEG：Paediatric Working Party，PIP：Paediratic Investigation Plan，
PMDA：Pharmaceuticals and Medical Devices Agency（医薬品医療機器総合機構），
PREA：Pediatric Research Equity Act，PUMA：Paediatric Use Marketing Authorisation，
SPC：Supplementary Protection Certificate（補足保護証明），
U.S.FDA：U.S. Food and Drug Administration（米国食品医薬品局）

和文抄録

医薬品の適応外使用問題はアレルギー分野に限らず，世界的な小児領域の問題のひとつとなっている．既に，1990年代から米国や欧州では，それらの解決に向けて，特に法制化を含めた取り組みが進んできた．この，決定的な契機は，米国での AIDS のこどもに対する抗 HIV 薬の必要性から，小児の臨床試験の重要性が強調されたということであったという．

いずれも基本的には飴と鞭という考え方であって，製薬企業に，小児領域の医薬品開発を義務付けるとともに，従った場合にはインセンティブを与えるという方策である．

米国では1997年の FDAMA が2002年の BPCA，2003年の PREA に再認され，さらに2007年の FDAAA によってより強化された．

EU では2007年に Paediatric Regulation が施行された．

これら方策により，欧米では確実に，小児領域の医薬品開発が促進されている．日本にはこのような，小児の臨床試験を推進していくような法律や規則はまだないが，小児科医が安心して診療に専心でき，こどもに最良の薬物療法が提供できるような，これら活動を進めていくための何らかの方策が必要であることに，もはや説明は不要である．

はじめに

「アレルギー治療薬の小児適正使用に向けて」の中で，ここでは，アレルギー治療薬も含めて，広く，小児領域の医薬品の適応外使用解決に向けて，海外，特に米国・欧州連合（European Union：EU）ではどのような取り組みがなされているのか，お話させていただきたいと思います．

まず，総論として，1．小児領域の医薬品開発と適応外使用について，次に，各論として，2．米国の場

合，3．EUの場合を，特により最近の出来事である，EUについては米国より詳しくお話させていただきます．さらに，これらを踏まえて，4．日本ではどのように考えていったらよいのか（4．は簡単に）ということについて，順を追ってまとめていきたいと思います．

1．小児領域の医薬品開発と適応外使用

【小児領域の医薬品適応外使用の実態】

適応外使用とはOff-Label Useのことですが，本来，薬事法に基づき承認された効能・効果以外，あるいは用法・用量以外で使用されることを指します．

小児領域の医薬品は歴史的にも，Therapeutic Orphan（治療上の孤児的状況の意）に置かれていると，1960年代に既にDr. Shirkeyが指摘をしています.[1] 10年近く前のお話ではありますが，日本でも，小児領域の日常臨床で使用されている医薬品で，小児に対する添付文書上の明確な用法・用量の記載のないものが約75%あり[2]，小児の用法・用量が添付文書に具体的に記載されているのは約20%，小児等における安全性が確立されていないとしているのは約40%であった[3]とする報告がありました.[4]

最近の正確なデータは持ち合わせていませんが，私たち小児科医が診療の中で，その必要性から，医薬品を適応外使用せざるを得ない状況が今も続いていることは，否定できるものではありません．

おそらく，小児領域は，全体の中で見れば，そのもの希少疾病と言えるものでしょうし，適応疾患の重篤性が高くても患者数が限られています.対象も新生児，乳児，幼児，小児及び思春期年齢と多様で幅広く，医薬品の剤形や薬物動態などでもきめ細かな対応が要求されますし，研究の同意にも十分な配慮を要することも，小児領域で適応外使用が行われている原因と言えましょう．小児領域の医薬品に関する世界的な問題として，この領域で臨床試験が計画・実施・評価され，その適応や用法・用量が確認された医薬品等が少ないと，少し前まで言われ続けてきていた訳ですが，それは前述した理由などによるものが大きかったでしょうし，ここから得られる利益もまた少なかったという現実があったと想像されます．

【小児領域の適正な薬物療法のために本来あるべき姿】

小児に最良の薬物療法を提供するためには，これは小児科医が安心して医薬品を使用できることでもあるのですが，使用されるべき医薬品については種々の情報収集がなされていて，予め安全性や有効性の評価がなされていることが絶対に必要です．そして，そうすることによって，小児科医が安心して診療に専心できることになるので，結局，小児科医にとっても，こどもにとっても，家族にとっても，安全な医療を提供・享受していくことに繋がります．

【欧米の小児領域の医薬品開発促進の契機】

これはよく言われていることのようですが，米国でも，小児領域での医薬品適応外使用状況は1990年代前半まで，現在の日本と大きく変わらない状況にあったということです．米国には，臨床試験等に対する臨床現場での理解があったこと，それまでにもそれぞれの施設で小児の臨床試験等の経験があったこと，小児の臨床試験等を推進することの必要性を学会や親の会から議会へ訴え続けていたことなどがあって，比較的短期間に組織立てて，小児の臨床試験等の推進体制が整ってきたということです.[5] また，米国ではエイズ（Acquired Immune Deficiency Syndrome: AIDS）のこどもに対する抗ヒト免疫不全ウイルス（Human Immunodeficiency Virus: HIV）薬などの医薬品の必要性から，小児の臨床試験の重要性が強調されてきたといった事情もあったようです.[6]

【規制当局と医薬品開発】

医薬品開発について，日本は米国やEUと，日米EU医薬品規制調和国際会議（International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use：ICH）という団体を組織しています．そして，これらの規制当局は，手短に言うと，それぞれ米国食品医薬品局（U.S. Food and Drug Administration：U.S.FDA），欧州医薬品庁（European Medicines Agency：EMEA）及び日本の厚生労働省（医薬品医療機器総合機構（Pharmaceuticals and Medical Devices Agency：PMDA）を含む）です．

米国やEUでは小児領域の医薬品開発を促進させるために，規制当局が中心になって，小児領域の臨床試験等を実施させるための仕組みをここ数年の間に次々と立法化させました．米国ではBest Pharmaceuticals for Children Act（BPCA）とPediatric Research Equity Act(PREA)が，EUではPaediatric Regulation

がこれに当たります．詳しくは後述しますが，ブロックバスター以外，BPCA下では自主的に小児の医薬品開発が実施されていくことが少なかったため，PREAを作ることになったということもあって，BPCAとPREAで，飴と鞭（carrot and stick）というように表現されることも多いようです．

煩雑になることを避けるために，以下では法律の細則には触れずに，概要の説明にとどめます．ご了承下さい．

2．米国の場合

【小児領域での臨床研試験等推進のための体制整備ー米国】

もともと米国では，1990年代から，小児領域の医薬品開発を促進させるための体制整備が進められていました．これらの仕組みの立法化に向けての背景やその内容，問題点などについてお話させていただきたいと思います．

1994 Pediatric Final Ruleは，添付文書の小児の項目をより充実させるためのFDAの通知でした．[7] 成人データが小児にも外挿できる場合には，成人データを用いて小児の評価をすることも可能であるとしたものですが，製薬企業にとって義務ではなかったために，この後承認された小児領域の医薬品数の増加はほとんどなかったようです．

米国でも小児領域での医薬品適応外使用が多かったために，1997年のFDA近代化法(FDA Administration Modernization Act: FDAMA）で，小児領域の医薬品開発に対する製薬企業へのインセンティブを与えるとされました．[8] 具体的にはFDAの発行するWritten Requestsへの対応を製薬企業が適正に行った場合には，その医薬品の市場独占期間を6ヵ月間延長するとするものです．

1998年にもFDAによるPediatric Final Ruleという動きがあり，FDAが製薬企業に小児の医薬品開発（臨床試験）を要求しましたが，これは製薬企業側に提訴され，最終的には無効判決が下り，結果，時限立法であったFDAMAが2002年のBPCAに再認されることになりました．

なお，2002年，ICHの合意に基づき，その医薬品が小児にも使用されることが推定されるのであれば，成人で開発が行われている段階で，小児集団での開発計画を組み入れるべきであることが示されています．これは日本でもICH Topic E11として知られている内容です．[9,10]

【米国ーBPCA】

2002年のBPCA（飴の方）では，小児でもベネフィットをもたらすものであるのであれば，臨床試験を実施する必要があるということを柱として，製薬企業へのインセンティブとなる，優先審査の上，Written Requests対応を適正に行った小児の臨床試験に対する，市場独占期間の6ヵ月間延長が与えられることになりました．Written Requests対応を製薬企業が辞退した場合（パテントの切れたものや市場独占に当たらないものなど）の追加的な事項として，その場合には米国国立衛生研究所（National Institute of Health: NIH）に付託されることなども盛り込まれました．

その他，小児に関する事項の添付文書改訂での優先申請，FDA内にOffice of Pediatric Therapeutics（小児科治療学の部署の意．科学的・倫理的助言を与えることやFDAのPediatric Initiative促進に関する活動を行う）の設置，FDAに助言を与えるPediatric Advisory Committee（PAC．小児諮問委員会の意）の確立やインセンティブの付与された医薬品の安全性評価についても盛り込まれました．[11]

【米国ーPREA】

前述しましたが，BPCA（飴の方）下では自主的に小児の医薬品開発が実施されていくことが少なかったため，PREA（鞭の方）を作ることになったという経緯があったとされています．

2003年のPREAでは，成人と小児双方の疾患に対する医薬品の開発の場合，小児の臨床試験（Pediatric Plan）の実施を製薬企業に要請する権限がFDAに与えられることとなりました．簡単にはそれまでにFDAによって出された，Pediatric Ruleの法制化と考えてよいと思います．もちろん，小児の臨床試験が免除（Waiver）される場合や延期（Deferral）される場合があることについても触れられていました．[12]

米国では，これらの法律に従わなかった場合，特に罰則規定というものは存在しないようですが，小児の開発データが含まれていない場合の申請は，不正表示という扱いになることがあるとされているようです．

【米国ーFDA Amendments Act of 2007（FDAAA）】

BPCAとPREAもまた，2007年10月1日までの時

限立法でしたが，2007年９月にFDAAAの一部となり，さらに５年間の2012年までの時限立法として再認されることになりました．

ここでは，FDA内部にPediatric Review Committee（小児審査委員会の意）が設立されることとなり，Written Requests自体の審査，小児の臨床試験計画やや実施された小児の臨床試験の審査を行うことになっています．[13]

３．EUの場合

【小児領域での臨床研試験等推進のための体制整備－EU】

EUでも，その対応策は米国を追っていると思われるのですが，米国での轍を踏まぬような配慮がなされているように感じられます．

1997年のEMEAのEuropean Commission（欧州委員会）で，小児の医薬品開発については法律強化が必要であるという結論になりました．[14]

2001年，EMEA内にPaediatric Working Party（PEG．小児作業部会の意）が設置されました．PEGはCommittee for Medical Products for Human Use（CHMP．医薬品の科学的評価を担当する医薬品委員会の意）の作業部会として，小児薬理専門家や小児科専門医などから構成されています．CHMPの他の作業部会（安全対策部や品質保証部など）やCommittee for Orphan Medical Products（COMP．希少疾病に関する医薬品委員会の意）とも協力して活動することになっていて，後述しますが，Paediatric Regulationの制定にも貢献したということです．なお，PEGの活動は2007年７月より，Paediatric Committee（PDCO．小児委員会の意）に引き継がれています．

2002年，欧州委員会により，Better Medicines for Children（Proposed Regulatory Actions on Paediatric Medicinal Product）と呼ばれる諮問文書が発表されました．これこそ小児用医薬品規制措置案に他なりません．

2004年３月には，小児の臨床試験推進のための本格的な立法案が作成され，2004年12月，法律案として欧州委員会に諮ることが決定されました．

結局，2006年６月，Paediatric Regulationとして欧州委員会の採択を受け，2006年12月27日公布，翌2007年１月12日プレスリリース，１月26日より施行されています．[15]

【EU-Paediatric Regulation】

Paediatric Regulationの目的は，小児に使用される医薬品の研究や開発を奨励すること，小児の治療に使用される医薬品は必ず適正に臨床試験が実施されて承認されるようにすることや医薬品の小児での使用に関する情報を入手しやくすることにあるとされています．[16,17]

Paediatric Regulationもその根底には飴と鞭という考え方があると言えるでしょう．但し，EMEAではobligations and rewardsという言い方をしているようです．

【EU-Paediatric Regulation-Paetiatric Committee】

まず，Paediatric Regulationによって，EMEA内にPDCOが創られました．[18] PDCOは，EU加盟国や欧州経済領域加盟国からの小児科それぞれの分野の専門医20名強，CHMPのメンバー５名と患者やその家族の代表者など数名からなっていて，私が訪れた2008年９月のEMEA・PDCOでは，EMEAの事務局，これは小児チーム（CHMPにある審査部門とは別にSector of Paediatric and Orphan Drugsという部署があります．このうち，純粋にPDCOに協力する小児チームは，当時，小児科医６名を含む全11名で構成されていました．その他に秘書が５名配属されていました）と言ってよいと思いますが，これらを含めて60名強であったように記憶しています．

PDCOは１ヵ月に１回（１年で13回．どこかの月には２回開催されています），３日間ずつ予定されています．2008年９月は17日から19日までの３日間で，ほぼ朝から夜まで（途中休憩も少々あり），計20品目弱の審議がなされておりました．

PDCOは以下に示す，小児開発計画（Paediatric Investigation Plan: PIP）の審査の他にも，PIPの遵守や小児に関するデータの評価にも関与します．

【EU-Paediatric Regulation-Paediatric Investigation Plan】

Paediatric Regulationで製薬企業に課せられることになったPIPやそれらの免除（Waiver）・延期（Deferral）については，PDCOが評価（審査）と合意に責任を持つことになっています．[19] これはPIPが改訂されることになった場合でも同様です．

PIP提出後30日以内に，サマリーレポートが提出されることになります．

PDCO の Rapporteur（品目毎に決められます．他に Reviewer も決められます）は，EMEA の小児チームの協力を得て，PIP を審査し，PIP の審査開始60日以内に，PDCO としての意見を出します．PIP変更の場合には，改訂案提出後さらに60日以内に審査をすることになります．

PIP では剤形についても論じる必要があります．

PIP はだいたい成人の PK 試験終了までには提出することになっています．

また，PIP に対する助言は無料で受けることができます．

2008年11月頃のお話として，327品目（適応で言うと560適応）のうち，20%が Waiver を要求しているそうです．Waiver の対象リストもあって，肺がんやアルツハイマー病などがこれにあたります．

【EU-Paediatric Regulation-Incentives】

パテントのあるもの（いわゆる特許と欧州に特有の Supplementary Protection Certificate（SPC．補足保護証明）という特許の延長のような意味合いのもの（と考えてよいと思います）で保護されているもの）については，PIP どおりの小児の臨床試験が実施できていて，その結果が承認申請資料とされていることなどが守られていれば，小児の適応取得ができたかどうかに関わらず，製薬企業に SPC が６ヵ月延長されるというインセンティブが与えられることになります．

パテントの切れたものについては，小児の臨床試験の計画・実施は必須とはされていません．但し，小児の臨床試験の計画・実施をした場合には，Paediatric Use Marketing Authorisation（PUMA）という新しいインセンティブが与えられることになりました．PUMA 申請に使われた小児の開発のためのデータの保護が８年間されることと小児適応が取得されれば販売独占期間2年間が与えられることになります．[20]

希少疾病薬については，指定されている医薬品であれば10年間の販売独占期間が与えられることとなっていますが，小児の開発の要件が満たされていれば，さらに販売独占期間が２年間追加されることになります．

Paediatric Regulation では，小児の臨床試験データが含まれていれば，優先審査となります．

その他，Paediatric Regulation では，小児のデータが含まれない承認申請は受理されないこと，Paediatric Regulation に違反した場合には課金されることや名称や理由の公表がなされることになっています．

また，Paediatric Regulation では，小児の医薬品開発のための欧州ネットワークを始動・運営していくことが謳われています．

なお，米国の FDA と欧州の EMEA の小児チームどうしでの相互協力も既にはじまっていて，１ヵ月に１回，電話会議が開催されているということです．

重ねて申し上げることとなり，たいへん恐縮なのですが，煩雑になることを避けるために，以上，法律の細則には触れていません．必要な場合には，是非，法文そのものでご確認下さい．

４．日本ではどのように考えていったらよいのか

【日本ではどのように考えるのか】

ご存じのように，以上お話させていただきました欧米のような，小児領域の医薬品の適応外使用解決も目的とした，小児の臨床試験を推進していくような法律や規制は日本にはまだありません．再審査期間の延長や薬価の小児加算などは小児の医薬品開発に対する，製薬企業へのインセンティブという側面はあると言ってよいと思いますが，十分なものとは言えないでしょう．例えば，日本小児科学会薬事委員会も「小児科領域における適応外使用解決と治験推進のためのアクションプラン」[21]を策定し，厚生労働省では小児薬物療法検討会議[22]や未承認薬使用問題検討会議[23]を立ち上げ現在も活動中ですし，日本小児科学会分科会や厚生労働省の複数の班会議も小児の医薬品開発などに関して鋭意活動中です．[24] もちろんこれらもそれぞれ意味を持つ行いであると考えています．詳しい内容についてはそちらをご覧いただきたいと思います．

日常臨床に携わっている視点からも，あるいはきっと行政の視点からも，特に ICH での関係を考えてみても，おそらくは日本でも小児領域の医薬品開発を促進させるための何らかの取り決めが必要であることに，もはや説明は不要でしょう．但し，いつ，どのような内容のものをどのような形で提言していくのかについては，十分な検討を要するものであって，しかるべき時期に，しかるべき方法を選択することが重要であると考えています．

おわりに

こどもには，安全性や有効性の評価がしっかりとなされている医薬品を安心して使いたいと思います．そのためには，小児領域でも適正な臨床試験を推進していくことが大切です．小児科医として，安心して診療に専心できるよう，そして，安全な医療を提供できるよう，努めたいと願っています．

文　献

1）Shirkey HC. Editorial Comment. Therapeutic Orphans. J Pediatr. 1968; 2: 119-120.
2）厚生科学研究　厚生省医薬安全総合研究事業「小児薬物療法における医薬品の適正使用の問題点の把握及び対策に関する研究」－「小児薬物療法における処方実態調査と医薬品添付文書解析」平成12年度研究報告書（主任研究者：大西鐘壽，分担研究者：森田修之）
3）厚生科学研究　厚生省医薬安全総合研究事業「小児薬物療法における医薬品の適正使用の問題点の把握及び対策に関する研究」－「医薬品の添付文書における子どもに関する記載内容についてのアンケート調査」平成11年度研究報告書（主任研究者：大西鐘壽，分担研究者：森田修之）
4）厚生労働省科学研究費補助金　厚生労働科学特別研究事業　「「適応外使用」の対応に係る現状と今後のあり方に関する研究」－「「適応外使用」解決のための調査研究：小児科領域」平成16年度総括・分担研究報告書（主任研究者：黒川　清，分担研究者：土田　尚）
5）中村秀文．日本小児麻酔学会　第７回大会　教育セミナー２　「小児臨床薬理と治験」平成13年10月12日．
6）Murphy D. Pediatric trials. The Impact of U.S. Legislative and Regulatory Efforts. Applied Clinical Trials 2005; 14: 38-42.
7）Comments-Regulations: 1994 Pediatric Final Rule from the FDA Pediatric Drug Development. http://www.fda.gov/cder/pediatric/pediatric_rule1994.htm
8）Comments-BPCA/Pediatric Exclusivity: FDA Modernization Act: Section 111 from the FDA Pediatric Drug Development. http://www.fda.gov/cder/guidance/105-115.htm#SEC.%20111
9）ICH Topic E11 医薬品医療機器総合機構HPより．http://www.pmda.go.jp/ich/e/e11_00_12_15e.pdf
10）厚生省医薬安全局審査管理課長通知．小児集団における医薬品の臨床試験に関するガイダンスについて．（医薬審　第1334号．平成12年12月15日付）
11）Comments-BPCA from the FDA Pediatric Drug Development. http://www.fda.gov/cder/pediatric/PL107-109.pdf
12）Comments-PREA from the FDA Pediatric Drug Development. http://www.fda.gov/cder/pediatric/S-650-PREA.pdf
13）Comments-FDA Amendments Act of 2007 (FDAAA) from the FDA Pediatric Drug Development. http://www.fda.gov/oc/initiatives/HR3580.pdf
14）The European paediatric initiative: History of the Paediatric Regulation from the EMEA Medicines for children. http://www.emea.europa.eu/pdfs/human/paediatrics/1796704en.pdf
15）Medicines for Children from the European Commission Enterprise and Industry. http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/medchild_en.htm
16）Regulation (EC) No 1901/2006 from the Official Journal of the European Union. http://www.emea.europa.eu/htms/human/paediatrics/regulation.htm
17）Regulation (EC) No 1902/2006 from the Official Journal of the European Union. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf
18）Paediatric Committee from the EMEA Medicines for children. http://www.emea.europa.eu/htms/human/paediatrics/pdco.htm
19）Guidance for applicants-PIPs, waivers and modifications from the EMEA Medicines for children. http://www.emea.europa.eu/htms/human/paediatrics/pips.htm
20）Guidance for applicants-Paediatric-use marketing authorisations (PUMAs) from the EMEA Medicines for children. http://www.emea.europa.eu/htms/human/paediatrics/pumas.htm
21）日本小児科学会薬事委員会．小児科領域における適応外使用解決と治験推進のためのアクションプ

ラン（平成16年度）．日児誌　2004; 109: 76-77.
22）小児薬物療法検討会議　厚生労働省HPより．http://www.mhlw.go.jp/shingi/other.html#iyaku
23）未承認薬使用問題検討会議　厚生労働用HPより．http://www.mhlw.go.jp/shingi/other.html#iyaku
24）土田　尚．日本小児臨床薬理学会が目指すもの．日児雑　2007; 111: 959-966.

ACTIVITIES PROMOTING THE PEDIATRIC CLINICAl TRIALS AND THE DRUG DEVELOPMENT IN UNITED STATES AND EUROPEAN UNION

Nao Tsuchida

National Center for Child Health and Development
Department of General Pediatrics and Interdisciplinary Medicine

Abstract

Off-label use in children is common throughout the world and a key issue. Activities resolving these issues have been stepped forward in the U.S. and EU since the 1990s. It have been tried various expedients to achieve the purpose. Because of need for facilitating the development of pediatric trials of therapies for HIV, eventually the following laws were legislated. These are referred to children in whole or in part.

U.S.: FDA Modernization Act (1997)
Best Pharmaceuticals for Children Act (2002)
Pediatric Research Equity Act (2003)
FDA Amendments Act of 2007
EU: Paediatric Regulation (2007)

These approaches would promote the pediatric clinical trials and the drug development in the U.S. and EU. We have to work together cooperatively with the U.S. and EU.

Key words：Pediatric Research, Off-Label Use, Therapeutic Orphan, Drug Development, Clinical Trials

Endocrine Journal 2008, **55** (6), 1065–1070

Trends in Age and Anthropometric Data at Start of Growth Hormone Treatment for Girls with Turner Syndrome in Japan

TSUYOSHI ISOJIMA*, SUSUMU YOKOYA*,***, JUNKO ITO**,***, REIKO HORIKAWA*,*** AND TOSHIAKI TANAKA***,#

**Clinical Research Center, National Center for Child Health and Development, 2-10-1 Ohkura, Setagaya-ku, Tokyo, 157-8535, Japan*

***Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo, 105-8470, Japan*

****The Foundation for Growth Science, Japan, 5-1-16 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan*

#Tanaka Growth Clinic, 1-12-39 Taishidoh, Setagaya-ku, Tokyo, 154-0004, Japan

Abstract. The purpose of this study is to evaluate the trends in age and anthropometric data for girls with Turner syndrome (TS) at start of growth hormone (GH) treatment in Japan. The data for analysis were obtained from a retrospective cohort, the Foundation for Growth Science, Japan. We analyzed trends in starting age of GH treatment for girls with TS in Japan after dividing subjects (n = 1,478) into three registration periods: 1991–1994, 1995–1999 and 2000–2004. We also assessed the ratio of the subpopulation of subjects under five years of age. As results, the mean age (standard deviation (SD)) at start of GH treatment was significantly different among the three groups (10.95 (3.63), 10.15 (3.39) and 8.78 (3.61), $p<0.0001$). The proportion of the subjects under five years of age increased significantly over time (5.11%, 7.11% and 16.85%, $p<0.0001$). Mean (SD) height SD scores were also significantly different (–3.41 (0.87), –3.26 (0.81) and –3.17 (0.79), $p<0.0001$). However, the proportions of the karyotype of 45,X were not significantly different among the three groups ($p = 0.25$). We concluded that age and shortness at initiation of GH treatment had been improving over time. However, these favorable trends have not fully met the conditions recommended by international clinical guidelines for TS.

Key words: Turner syndrome, Growth hormone, Growth failure, Diagnosis delay

(*Endocrine Journal* **55**: 1065–1070, 2008)

TURNER syndrome (TS) is caused by a complete or partial absence of the second sex chromosome, and affects one in 2,000 to 5,000 live-born females [1]. One of the most significant features of the syndrome is short stature. Untreated adults are reported to be approximately 20 cm shorter than normal females within their respective populations [2]. Growth hormone (GH) has been used to accelerate growth, and has been known to increase adult height [3]. GH is usually introduced after a child's height falls below the fifth percentile for normal girls of the same age [4]. Though the optimal age for initiation of GH treatment has not been established [5], it is preferable not to start GH treatment later than five years of age, because the height of the majority of girls with TS usually drops below the fifth percentile of the normal girl growth curve between two and five years of age [1]. Many studies on GH treatment in girls with TS have established the importance of age at treatment initiation for long-term height gain [6–14]. Moreover, a recent study has shown that early GH treatment could normalize height in infants and toddlers with TS, and restoration of height close to the average would mitigate the potential detrimental effects of short stature during childhood and allow for age-appropriate initiation of feminization [15]. In Western countries, the age at ini-

Received: May 14, 2008
Accepted: August 7, 2008
Correspondence to: Tsuyoshi ISOJIMA, Clinical Research Center, National Center for Child Health and Development, 2-10-1 Ohkura, Setagaya-ku, Tokyo, 157-8535, Japan
Abbreviations TS: Turner syndrome, GH: Growth hormone, SDS: Standard deviation score, ANOVA: Analysis of variance

tiation of GH treatment has become younger [16, 17], although many patients with TS are left undiagnosed until mid-childhood, adolescence or even adulthood [17–20].

In Japan, GH treatment for girls with TS was approved by the Ministry of Health and Welfare in 1991 only for those accompanying GH deficiency with short stature below –2 standard deviation score (SDS), and in 1999 for all girls whose height was below –2 SDS. As in other countries, we speculate that the initiation age of GH treatment appears to have become younger, and medical doctors feel that the degree of growth failure at the start of GH treatment has become less severe. However, no reports have verified this speculation with large cohort study data. In this study we evaluated the trends in age and anthropometric data of girls with TS in Japan at initiation of GH treatment using data collected at the Foundation for the Growth Science, Japan [21].

Subjects and Methods

Subjects

The subjects were obtained from a retrospective cohort, the Foundation for Growth Science, which has been controlling the use of GH through its registration system. The Foundation evaluates the candidate's eligibility for GH treatment according to certain diagnostic criteria for GH deficiency, TS and other pertinent disorders [21]. Physicians are encouraged to register each candidate for GH treatment at the Foundation using an application form which includes the candidate's pre-treatment anthropometric measurements, karyotypes (in the case of TS), presence or absence of puberty, and evidence of informed consent from each subject regarding the use of the data for scientific purposes.

Between 1991 and 2004, 1,867 girls were registered as TS subjects in this cohort, and 1,760 girls were judged to be eligible for GH treatment. These subjects comprise approximately two-thirds of all TS girls treated with GH in Japan, judging from the data compiled in medical aid programs for chronic pediatric diseases of specified categories in Japan [22, 23]. Although subjects with TS shorter than –2 SDS were approved for GH treatment in Japan, 24 subjects above –2 SDS were judged to be eligible on an individual basis. The diagnosis of TS was confirmed by reviewing all the reported karyotypes of cultured peripheral blood lymphocytes. In this study TS was defined as a karyotype which contains a monosomic cell line lacking at least a major portion of the distal part in the short arm of the X chromosome. Subjects having no evidence of such karyotypic features, or with a history of previous growth-promoting therapy such as GH or anabolic steroids or both were excluded. Two reasons are listed as to why GH treatment was introduced before registration: the first is that some subjects had participated in clinical studies for the governmental approval; the second is that some subjects had initially been treated for GH deficiency, and then reregistered with the Foundation after diagnosis of TS. In this study, we excluded all these subjects with prior growth-promoting therapy, because our aim was to study trends not only of age of GH initiation but also of the degree of growth retardation at start of GH treatment as girls with TS.

Methods

First of all, all subjects were analyzed for the difference between karyotypes of 45,X and non-45,X. In Belgium, a negative correlation was detected between age at diagnosis and height SDS for the normal population, which suggested delayed diagnosis of TS [24]. As our retrospective cohort did not contain ages at initial diagnosis, we studied the correlations between age at initiation of GH treatment (instead of age at initial diagnosis) and height SDS for the normal population or TS-specific population.

Many girls with TS who had been diagnosed well before the start of the study period appeared to have been registered in the first two years after the start of registration (1991), but registration numbers went down to relatively constant figures in the following two years. Thereafter, all the girls with TS shorter than –2 SDS irrespective of GH secretion status became eligible for GH treatment in November 1999. The subjects were therefore divided into three registration periods: 1991–1994, 1995–1999 and 2000–2004. We also analyzed the subpopulation of subjects under five years of age in each period to clarify the trend toward younger ages.

Statistical analysis

The results are expressed as the mean (SD), or by frequency and percent. Ages are also expressed as the median. Height SDS, TS-specific height SDS and body mass index (BMI) SDS were calculated by comparison with the Japanese 1990 growth reference [25], the currently used Japanese TS growth chart [26], and the Japanese BMI-for-age chart [27], respectively.

Comparisons of groups were assessed by one-way analysis of variance (ANOVA) or unpaired t-test for numeric variables, and chi-square test for categorical variables. When the result was significant, the differences between groups were subjected to two-by-two comparisons with post-hoc Bonferroni correction for multiple comparisons. Correlations were performed by Pearson's test. All analyses were made using JMP 6.0.3 (SAS Institute Inc., Cary, NC, USA) and P values less than 0.05 were considered statistically significant.

Results

In total, 282 subjects were excluded because of insufficient or inadequate cytogenetic basis of the diagnosis (24 subjects), previous growth-promoting treatment (255 subjects), and highly unlikely measurements (3 subjects). In the total of 255 subjects with previous growth-promoting treatment, the subjects in the three periods (*i.e.* 1991–1994, 1995–1999 and 2000–2004) are 163, 61 and 31 subjects, respectively. There were 217 subjects (85.1%) who had been treated with GH. The remaining 1,478 subjects formed the cohort of analysis. In the analysis of all subjects, neither age nor anthropometric indices were significantly different between 45,X and non-45,X subjects (Table 1). There was a strong negative correlation between age at initiation of GH treatment and height SDS for the normal population ($r = -0.36$, $p<0.0001$) (Fig. 1), and a strong positive correlation between age and TS-specific height SDS ($r = 0.36$, $p<0.0001$) (Fig. 2).

Table 2 summarizes the characteristics of girls with TS at initiation of GH treatment grouped by registration years. Mean ages (SD) in the three periods (*i.e.* 1991–1994, 1995–1999 and 2000–2004) were significantly different (10.95 (3.63), 10.15 (3.39) and 8.78 (3.61), $p<0.0001$). Means of height SDS for normal girls were also significantly different (–3.41 (0.87),

Table 1. Characteristics of girls with TS at initiation of GH treatment according to karyotype

	45,X (n = 422)	non-45,X (n = 1,056)	P value
Age (year)	10.07 (3.68) median: 10.25	10.22 (3.65) median: 10.42	0.46
Height SDS	–3.26 (0.87)	–3.32 (0.82)	0.17
TS Height SDS	0.35 (1.00)	0.30 (0.91)	0.36
BMI SDS	0.70 (1.15)	0.64 (1.22)	0.36

All the data are expressed as means (SD) unless otherwise indicated. P values refer to differences between groups as determined by unpaired t test. Height SDS indicates height SDS for normal girls; TS Height SDS, height SDS for girls with TS.

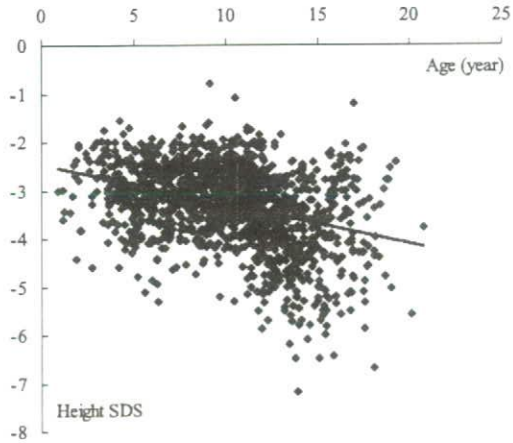

Fig. 1. Correlation between age at registration for GH treatment and height SDS for the normal population [25] ($r = -0.36$, $p<0.0001$). Although girls with TS shorter than –2 SDS receive approval for GH treatment in Japan, exceptional subjects above –2 SDS are judged eligible on an individual basis.

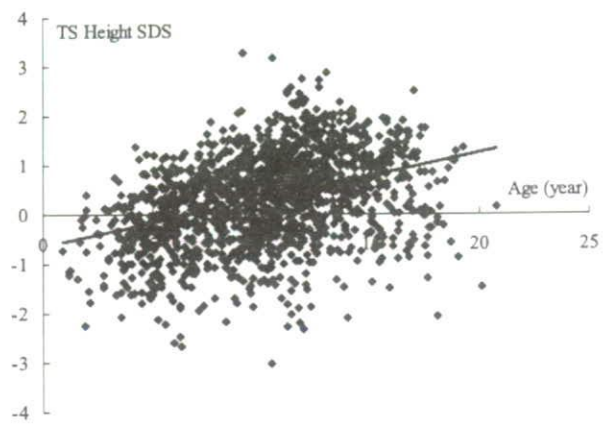

Fig. 2. Correlation between age at registration for GH treatment and height SDS for TS [26] ($r = 0.36$, $p<0.0001$).

Table 2. Characteristics of girls with Turner syndrome at initiation of GH treatment grouped by registration years

	1991–1994 (n = 665)	1995–1999 (n = 451)	2000–2004 (n = 362)	Total (n = 1,478)	P value
45,X karyotype	204 (30.68%)	123 (27.27%)	95 (26.24%)	422 (28.55%)	0.25
Age (year)	10.95 (3.63) median: 11	10.15 (3.39)[a] median: 10.33	8.78 (3.61)[b,c] median: 8.79	10.18 (3.66) median: 10.33	<0.0001
Subjects under five years of age	34 (5.11%)	32 (7.11%)	61 (16.85%)[b,c]	127 (8.59%)	<0.0001
Height SDS	−3.41 (0.87)	−3.26 (0.81)[a']	−3.17 (0.79)[b]	−3.30 (0.84)	<0.0001
TS height SDS	0.34 (0.91)	0.37 (0.92)	0.21 (1.00)	0.32 (0.94)	0.032
BMI SDS	0.69 (1.20)	0.72 (1.18)	0.51 (1.21)[c']	0.65 (1.20)	0.023

P values refer to differences between groups as determined by ANOVA and chi-square test for numeric variables and categorical variables, respectively.

a: p = 0.0002 for 1991–1994 vs 1995–1999, a': p = 0.00027 for 1991–1994 vs 1995–1999, b; p<0.0001 for 1991–1994 vs 2000–2004, c; p<0.0001 for 1995–1999 vs 2000–2004, c'; p = 0.010 for 1995–1999 vs 2000–2004.

−3.26 (0.81) and −3.17 (0.79), p<0.0001). However, the proportions of the karyotype of 45,X in the three groups were not significantly different (p = 0.25). Post-hoc analysis between 1991–1994 and 2000–2004 revealed that the average age decreased significantly (p<0.0001), and that the height SDS for normal girls increased significantly (p<0.0001). Average age was also significantly different between subjects in 1995–1999 and those in 2000–2004 (p<0.0001), but height SDS for normal girls did not change significantly between the two groups (p = 0.12). Among all the 1,478 subjects, the number of subjects under five years of age was 127 (8.59%). The proportion in each group changed significantly by registration year group (5.11%, 7.11% and 16.85%, p<0.0001), and post-hoc analysis showed a significant increase in the proportion of subjects under five years of age (p<0.0001) (Table 2). When we performed the same analysis with 1,733 subjects including previous growth-promoting treatment, we obtained the same trends as the results from 1,478 subjects (data not shown).

Discussions

The age of girls with TS at initiation of GH treatment has been getting younger in Japan as evidenced by this retrospective large cohort (Table 2). Moreover, the proportion of subjects under five years of age has grown significantly over time. These trends are favorable for the better management of girls with TS. These desirable trends have also been observed in Western countries. From the Pharmacia and Upjohn International Database (KIGS) in the UK [16], the mean age of starting GH treatment has reduced from 10.4 in 1986 to 8.5 in 1996. The database of the Belgian Study Group for Pediatric Endocrinology [17] revealed that the median age at diagnosis was 11.2 years of age in 1991 and 6.6 in 2003. Taking both foreign and Japanese trends together, the age of GH initiation in Japan has come closer to that in Western countries.

We found a negative correlation between age and height SDS for the normal population (Fig. 1). This finding is conceivable, because girls with TS generally tend to lose height SDS as they grow. However, we also found a positive correlation between age and TS-specific height SDS (Fig. 2), suggesting that relatively small girls in the TS population tended to undergo GH earlier, and that relatively tall ones often suffered from short stature for many years before GH treatment. Regarding height SDS, it has been improving significantly when we compare subjects in 1991–1994 with those in 2000–2004. We do not think this improvement is not due to the character of the subjects on their GH secretion status. Girls with TS generally have a normal GH secretory pattern [3, 5], and their height does not differ irrespective of their GH secretory status [28]. Height SDS for the normal population was not significantly different between subjects in 1995–1999 and those in 2000–2004. Judging from the fact that mean height SDS at initiation in the most recent group (2000–2004) was −3.30 (0.84) in all subjects, and −2.98 (0.65) in subjects under five years of age, the majority of girls with TS initiated GH treatment only after their growth retardation had become serious. The most recent clinical practice guideline issued by the

Turner Syndrome Consensus Study Group recommends that the goal of growth-promoting therapies should be to attain normal height as early as possible, and that the diagnosis of TS should be considered in any female with unexplained growth failure or pubertal delay or any other stigmata such as edema of the hands or feet, nuchal fold, or left-sided cardiac anomalies [5]. Therefore, we have to conclude that the present situation in Japan concerning GH treatment for girls with TS is still not satisfactory for their optimal care.

In this study, no difference was detected in ages or all the anthropometric indices between 45,X and non-45,X karyotypes (Table 1). This finding was the same in the subgroup limited to subjects under five years of age (data not shown). According to reports from countries other than Japan, girls with 45,X karyotype are usually diagnosed earlier than girls with non-45,X karyotype because of their more typical and severe clinical manifestations [17–19, 29, 30]. One possible explanation is that diagnosis at infancy is not very common in Japan. However, further study is needed to uncover whether diagnosis delay exists in Japan, because this retrospective cohort study was not designed for epidemiological investigation and did not contain ages at initial diagnosis.

In conclusion, the age of girls with TS at initiation of GH treatment has been getting younger, and the proportion of subjects receiving GH treatment under five years of age has grown significantly. However, despite these favorable trends the situation of GH treatment for girls with TS in Japan has not reached the optimal levels recommended in clinical guidelines issued by the Turner Syndrome Consensus Study Group.

Acknowledgement

We wish to thank all the registered patients and physicians involved in this retrospective cohort. This study was partly supported by a grant from the Foundation for Growth Science, Japan.

References

1. Saenger P (1996) Turner's syndrome. *N Engl J Med* 335: 1749–1754.
2. Ranke MB, Grauer ML (1993) Adult height in Turner syndrome: results of multinational survey 1993. *Horm Res* 42: 90–94.
3. Baxter L, Bryant J, Cave CB, Milne R (2007) Recombinant growth hormone for children and adolescents with Turner syndrome. *Cochrane Database Syst Rev* Jan 24; (1): CD003887. Review.
4. Frías JL, Davenport ML, Committee on Genetics and Section on Endocrinology (2003) Health supervision for children with Turner syndrome. *Pediatrics* 111: 692–702.
5. Bondy CA for The Turner Syndrome Consensus Study Group (2007) Care of girls and women with Turner syndrome: a guideline of the Turner syndrome study group. *J Clin Endocrinol Metab* 92: 10–25.
6. Quigley CA, Crowe BJ, Anglin DG, Chipman JJ, The U.S. Turner syndrome study group (2002) Growth hormone and low dose estrogen in Turner syndrome: results of a United States multi-center trial to near-final height. *J Clin Endocrinol Metab* 87: 2033–2041.
7. Van Pareren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TCJ, Jansen M, Otten BJ, Hoorweg-Nijman JJG, Vulsma T, Stokvis-Brantsma WH, Rouwé CW, Reeser HM, Gerver WJ, Gosen JJ, Rongen-Westerlaken C, Drop SLS (2003) Final height in girls with Turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab* 88: 1119–1125.
8. Canadian Growth Hormone Advisory Committee (2005) Impact of growth hormone supplementation on adult height in Turner syndrome: results of the Canadean randomized control trial. *J Clin Endocrinol Metab* 90: 3360–3366.
9. Ranke MB, Partsch CJ, Lindberg A, Dörr HG, Bettendori M, Hauffa BP, Schwarz HP, Mehls O, Sander S, Stahnke N, Steinkamp H, Said E, Sippell W (2002) Adult height after GH therapy in 188 Ullrich-Turner syndrome patients: results of the German IGLU Follow-Up Study 2001. *Eur J Endocrinol* 147: 625–633.
10. Pasquino AM, Pucarelli I, Segni M, Tarani L, Calcaterra V, Larrizza D (2005) Adult height in sixty girls with Turner syndrome treated with growth hormone matched with an untreated group. *J Endocrinol Invest* 28: 350–356.
11. Soriano-Guillen L, Coste J, Ecosse E, Léger J, Tauber M, Cabrol S, Nicolino M, Brauner R, the StaTur Study Group, Chaussain JL, Carel JC (2005) Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. *J Clin Endocrinol*

Metab 90: 5197–5204.
12. Reiter EO, Blethen SL, Baptista J, Price L. (2001) Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 86: 1936–1941.
13. Wasniewsla M, De Luca F, Bergamaschi R, Guarneri MP, Mazzanti L, Matarazzo P, Petri A, Crisafulli G, Salzano G, Lombardo F (2004) Early treatment with GH alone in Turner syndrome: prepubertal catch-up growth and waning effect. *Eur J Endocrinol* 151: 567–572.
14. Ranke MB, Lindberg A, Longás AF, Darendellier F, Albertsson-Wikland K, Dunger D, Cutfield WS, Tauber M, Wilton P, Wollmann HA, Reiter EO (2007) Major determinants of height development in Turner syndrome (TS) patients treated with GH: analysis of 987 patients from KIGS. *Pediatr Res* 67: 105–110.
15. Davenport ML, Crowe BJ, Travers SH, Rubin K, Ross JL, Fechner PY, Gunther DF, Liu C, Geffner ME, Thrailkill K, Huseman C, Zagar AJ, Quigley CA (2007) Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial. *J Clin Endocrinol Metab* 92: 3406–3416.
16. Betts PR, Butler GE, Donaldson MDC, Dunger DB, Johonston DI, Kelnar CJH, Krik J, Price DA, Wilton P (1999) A decade of growth hormone treatment in girls with Turner syndrome in the UK. UK KIGS Executive Group. *Arch Dis Child* 80: 221–225.
17. Massa G, Verlinde F, De Schepper J, Thomas M, Bourguignon JP, Craen M, de Zegher F, Francois I, Du Caju M, Maes M, Heinrichs C; the Belgian Study Group for Paediatric Endocrinology (2005) Trends in age at diagnosis of Turner syndrome. *Arch Dis Child* 90: 267–268.
18. Gravholt CH (2004) Epidemiological, endocrine and metabolic features in Turner syndrome. *Eur J Endocrinol* 151: 657–687.
19. Sävendahl L, Davenport ML (2000) Delayed diagnoses of Turner's syndrome: proposed guidelines for change. *J Pediatr* 137: 455–459.
20. Sybert VP, McCauley E (2004) Turner's syndrome. *N Engl J Med* 351: 1227–1238.
21. Tanaka T, Takano K, Hanew K, Nishi Y, Igarashi Y, Hirano T, Saito T, Tachibana K, Yokoya S, Fujieda K, Shimatsu A, Hizuka N, Tsushima T, Irie M (1998) Registration system for growth hormone(GH) treatment with standardized immunoreactive GH values in Japan. *Endocr J* 45: 459–465.
22. Gu YH, Kato T, Harada S, Sato Y, Kakee N (2008) Medical aid program for chronic pediatric diseases of specified categories in Japan: Current status and future prospects. *Pediatr Int* 50: 376–387.
23. Fujieda K (2004) Medical aid program for chronic pediatric disease of specified categories in Japan available online at: http: //www.pediatric-world.com/asahikawa/2007symaken/index.html Accessed June 23, 2008.
24. Massa G, Vanderschueren-Lodeweyckx M (1991) Age and height at diagnosis in Turner syndrome: influence of parental height. *Pediatrics* 88: 1148–1152.
25. Suwa S, Tachibana K (1993) Standard growth charts for height and weight of Japanese children from birth to 17 years based on a cross-sectional survey of national data. *Clin Pediatr Endocrinol* 2: 87–97.
26. Suwa S (1992) Standards for growth and growth velocity in Turner's syndrome. *Acta Paediatr Jpn* 34: 206–221.
27. Inokuchi M, Hasegawa T, Anzo M, Matsuo N (2006) Standardized centile curves of body mass index for Japanese children and adolescents based on the 1978–1981 national survey date. *Ann Hum Biol* 33: 444–453.
28. Tanaka T, Hibi I, Shizume K (1991) GH-secretion capacity in Turner syndrome and its relations to clinical characteristics and effect of GH treatment—a comparison with pituitary dwarfism—. *Folia Endocrinol* 67: 597–610 [in Japanese].
29. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH (2006) Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab* 91: 3897–3902.
30. Ostberg JE, Conway GS (2003) Adulthood in women with Turner syndrome. *Horm Res* 59: 211–221.

ACTA PÆDIATRICA
PROMOTING CHILD HEALTH

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Inconsistent determination of overweight by two anthropometric indices in girls with Turner syndrome

Tsuyoshi Isojima (isojima-t@ncchd.go.jp)[1], Susumu Yokoya[1,3], Junko Ito[2,3], Reiko Horikawa[1,3], Toshiaki Tanaka[3,4]

1.Clinical Research Center, National Center for Child Health and Development, Ohkura, Setagaya-ku, Tokyo, Japan
2.Toranomon Hospital, Toranomon, Minato-ku, Tokyo, Japan
3.The Foundation for Growth Science, Hongo, Bunkyo-ku, Tokyo, Japan
4.Tanaka Growth Clinic, Taishidoh, Setagaya-ku, Tokyo, Japan

Keywords
Body mass index, Obesity, Turner syndrome, Weight for height

Correspondence
Tsuyoshi Isojima, Clinical Research Center, National Center for Child Health and Development, 2-10-1 Ohkura, Setagaya-ku, Tokyo, 157-8535, Japan.
Tel: +81-3-3416-0181 |
Fax: +81-3-3416-2222 |
Email: isojima-t@ncchd.go.jp

Received
15 July 2008; revised 14 October 2008; accepted 17 October 2008.

DOI:10.1111/j.1651-2227.2008.01132.x

Abstract

Aim: To evaluate the prevalence of overweight in girls with Turner syndrome (TS) as classified by the two major anthropometric indices, body mass index (BMI) and weight-for-height (WFH) and to make growth reference charts of them for comparison with those of the normal population.

Method: The samples for analysis were obtained from a retrospective cohort. In total, 1447 girls' cross-sectional data were analysed. Subjects were divided into four groups by ages: group A (0–5.99 years), B (6–10.99 years), C (11–15.99 years) and D (16–20.99 years). The cut-off values of overweight by BMI and WFH were those of the 90th percentile and 120 percent, respectively and the prevalence was calculated. For constructing growth reference charts, the LMS method was used.

Results: The prevalence of overweight differed between the two indices. The proportions of the coincidental classification in all subjects, group A, B, C and D were 82.53%, 89.96%, 91.79%, 69.98% and 60.61%, respectively. These differences corresponded to the difference of age-dependent patterns of the two indices from those of the normal population, as judged from the growth charts constructed with all subjects.

Conclusion: A discrepancy in the prevalence of overweight as classified by BMI and WFH for girls with TS was detected.

INTRODUCTION

Turner syndrome (TS) is the most common chromosomal abnormality in females and affects about one in 1500 to 2500 live-born female infants (1). A cardinal clinical feature of TS is linear growth failure resulting in extreme short stature. Growth patterns of girls with TS are different from those of the normal population mainly because of haploinsufficiency of the short stature homeobox-containing gene on the X chromosome (SHOX) and ovarian insufficiency. Moreover, girls with TS are reported to frequently become overweight as they grow up (2–5). Many problems of females with TS in adult life are compounded by obesity (6). Therefore, it seems very important to pay attention to overweight in clinical practice.

There is a growing global epidemic of childhood obesity, with a large variation in secular trends across countries (7,8). At present, there is still no widely agreed standard for classifying overweight in children and adolescents (7). Previously, many researchers chose to use weight-for-height (WFH) for this purpose, especially for children under 10 years of age (7). In recent years, body mass index (BMI) has been more often accepted as a valid indirect measure of adipose tissue in both children and adolescents for survey purposes (9,10), although there are several reports that many pediatricians do not use BMI in clinical situations (11,12). For girls with TS, BMI is sometimes applied as one of the surrogate markers of adiposity (13,14). However, it is unknown whether BMI can be adequately used for this group of people whose growth patterns are different from the normal population.

In this study, we compared the prevalence of overweight determined by two major anthropometric indices, BMI and WFH, in girls with TS and made growth reference curves of both BMI and WFH to compare them with those of the normal population.

Abbreviations
TS, Turner syndrome; GH, growth hormone; BMI, body mass index; WFH, weight for height; SDS, standard deviation score; EDF, equivalent degrees of freedom.

METHODS

Population

The samples were obtained from a database registered at the Foundation for Growth Science, Japan. The Foundation has been controlling the use of growth hormone (GH) by its registration system in Japan through judging eligibility for GH treatment (15). Medical doctors are encouraged to have each candidate registered for GH treatment at the Foundation using an application form which includes his/her pre-treatment anthropometric measurements, karyotypes (in the case of TS), presence or absence of puberty and evidence of informed consent from each subject regarding the use of the data for scientific purposes.

Between 1991 and 2004, 1867 girls were registered as TS subjects in this cohort. The diagnosis of TS was confirmed by reviewing all the reported karyotypes of cultured peripheral blood lymphocytes. In this study, TS was defined as a karyotype, which contains a cell line of monosomy lacking at least a distal major part in the short arm of the X chromosome. Subjects having no evidence of such karyotypic features, missing a description regarding puberty status, with pubertal signs, with a history of previous growth-promoting therapy or whose age was over 20 were excluded.

Classification of overweight

Japan Society for the study of obesity recommends that children who have 120% or more of the standard weight are classified as overweight (16). WFH is one of the most available and useful standard weights in Japan (17). Therefore, in this study we calculated percent overweight using WFH. The calculation formula was 100 × (weight value − WFH)/WFH. With regard to BMI, the cut-off values of overweight in Japanese children have been reported to be those above the 90th percentile of normal standards (18,19). In this study, the values of the 90th percentile for normal Japanese sex-specific BMI-for-age (20) (which was established by the LMS method) were used for the cut-off values of overweight. BMI was calculated as weight in kilograms divided by square of height in meters.

Statistical analysis

Data were cleaned in several stages. Bivariate plots of height and weight were used to identify gross disproportions. Data points were scrutinized, going back to the source data if necessary and transcription errors were corrected. If a value was deemed highly unlikely (more than 5 standard deviation scores [SDS] from the mean), such a point was deleted, even in the absence of any evidence of a transcription error.

Populations were divided arbitrarily into four groups according to age: group A (age of 0–5.99 years), B (age of 6–10.99 years), C (age of 11–15.99 years) and D (age of 16–20.99 years). The anthropometric data were calculated to BMI and percent overweight if there were standard data of normal Japanese values corresponding to the same ages.

Reference growth charts were obtained by the LMS method (21). This assumes that the data can be transformed to normality by a suitable power transformation (L) and the distribution is then summarized by the median (M) and coefficient of variation (S). Using penalized likelihood, three curves (L, M and S) can be fitted as cubic splines by nonlinear regression and the extent of smoothing was controlled by equivalent degrees of freedom (EDF). Fitting and smoothing were done with lmsChartMaker Pro ver.2.3 (Medical Research Council, London, UK).

RESULTS

In total, 420 subjects were excluded because of insufficient or inadequate cytogenetic basis of diagnosis (31 subjects), presence of pubertal signs (107 subjects), lack of records about puberty (14 subjects), previous growth-promoting treatment (264 subjects), age over 20 (one subject) or highly unlikely measurements (three subjects). The remaining 1447 subjects were analysed for constructing reference curves. Table 1 lists the number of the subjects by age. It is to be noted that none of the data from the girls with TS was collected after GH administration. Their birth years ranged from 1970 to 2002 (median: 1985). Perinatal information and their parents' anthropometric measurements were collected whenever possible. Average birth length was 46.8 ± 2.7 cm (n = 633), birth weight 2.68 ± 0.44 kg (n = 1322) and target height 157.6 ± 7.2 cm (n = 1289), which was very similar to the average adult height for Japanese females (157.9 cm) in 1990 (22). Target height was calculated by the formula adjusted for Japanese before the secular trend had

Table 1 Age distribution

Age (years)	Number
0	1
1	9
2	14
3	41
4	74
5	104
6	105
7	104
8	113
9	152
10	160
11	168
12	131
13	75
14	68
15	52
16	38
17	22
18	11
19	2
20	3
Total	1447

Table 2 Karyotypes of 1447 subjects

	Non-mosaic	Number of subjects	Mosaic	Number of subjects
Aneuploidy	45,X	432	45,X/46,XX	87
			45,X/47,XXX	91
			45,X/46,XY	16
			45,X/46,XX/47,XXX	6
		432		200
Structural Abnormality	46,X,i(Xq)	128	45,X/46,X,i(Xq)	309
	46,X,del(Xp)	55	45,X/46,X,del(Xp)	22
	46,X,r(X)	3	45,X/46,X,r(X)	106
	Others	10	45,X/46,X, + mar	109
			Others	73
		196		619
Total		628		819

Table 3 Prevalence of overweight

Group	BMI (+)/ WFH (+)	BMI (−)/ WFH (+)	BMI (+)/ WFH (−)	BMI (−)/ WFH (−)	The number of the same classification /Total number	The number of the same classification* /Total number
A	9 (3.77%)	4 (1.67%)	20 (8.37%)	206 (86.19%)	215/239 (89.96%)	213/233 (91.42%)
B	184 (29.07%)	44 (6.95%)	8 (1.26%)	397 (67.72%)	581/ 633 (91.79%)	554/633 (87.52%)
C	176 (35.70%)	148 (30.02%)	0 (0%)	169 (34.28%)	345/ 493 (69.98%)	314/493 (63.69%)
D	16 (24.24%)	26 (39.39%)	0 (0%)	24 (36.36%)	40/66 (60.61%)	39/66 (59.09%)
All Subjects	385 (26.90%)	222 (15.51%)	28 (1.96%)	796 (55.63%)	1181/1431 (82.53%)	1120/1425 (78.60%)

Definition of each group is written in the text.

BMI (+) indicates overweight subjects defined by BMI; (−) no overweight subjects.

WFH (+) indicates overweight subjects defined by WFH; (−) no overweight subjects.

Numbers in parentheses show percentages of the total number in each group.

*Figures in this particular column indicate the same classification of overweight determined by BMI and WFH when International cut-off values of BMI (10) instead of Japanese cut-off values were used. It is of note that the numbers of the subjects analysed are different, because International cut-off values can be obtained only for girls older than two years of age.

reached a plateau (23). Table 2 summarizes the number of the subjects grouped by karyotypes.

BMI-for-age can be obtained for girls older than 1.5 years of age, and WFH can be given for the heights taller than 70 cm in Japan. Therefore, we could not have the 90th percentile value of BMI and/or percent overweight in 16 subjects. Finally, 1431 subjects were evaluated for the difference of prevalence of overweight between the two indices, BMI and WFH. Prevalence of overweight by the two definitions of each group is shown in Table 3.

Centile curves were fitted to the data all together using the LMS method. For both BMI and WFH there were appreciable skewness and the age-varying power transformation were adjusted for them. EDF for (L, M, S) of BMI and WFH are (3,7,4) with age transformed and (2,5,4) with age rescaled, respectively. Growth references for BMI and WFH are shown in Figures 1 and 2, respectively. These references are superimposed on those of the normal population in Figures 3 and 4.

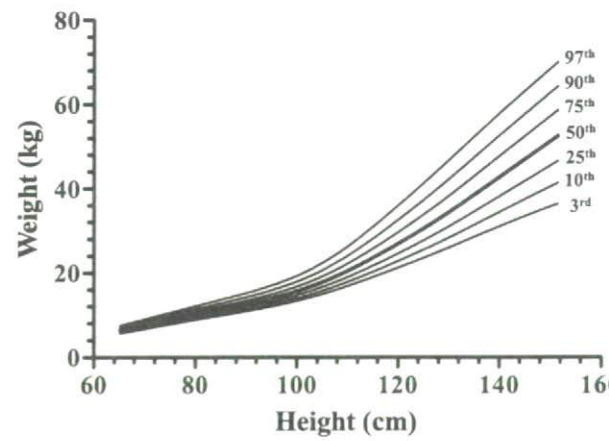

Figure 2 WFH chart for Japanese girls with Turner syndrome without puberty.

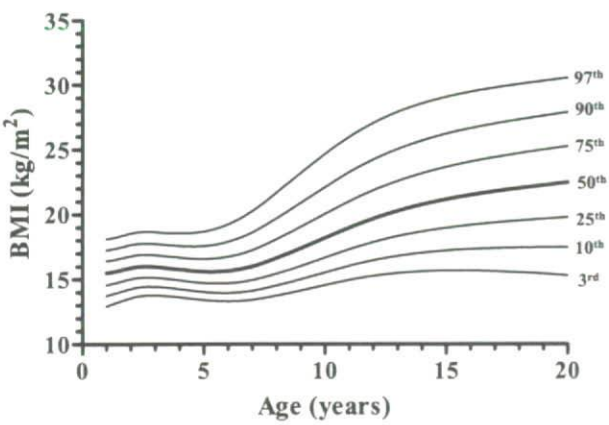

Figure 1 BMI chart for Japanese girls with Turner syndrome without puberty.

DISCUSSIONS

Evaluation of overweight is usually made with anthropometry for practical reasons. Among the various anthropometric indices, BMI is the most widely used both clinically and academically, especially after the International Obesity Task Force recommended BMI as a valid surrogate marker of adiposity (7). However, different measures and references have been used in each country for classification of overweight, as is the case in Japan, where percent overweight has been used in preference to BMI. It is also reported that in normal children aged 2–19 years, no differences were found between BMI and WFH in detecting overweight in terms of percentage body fat or total fat mass as determined by

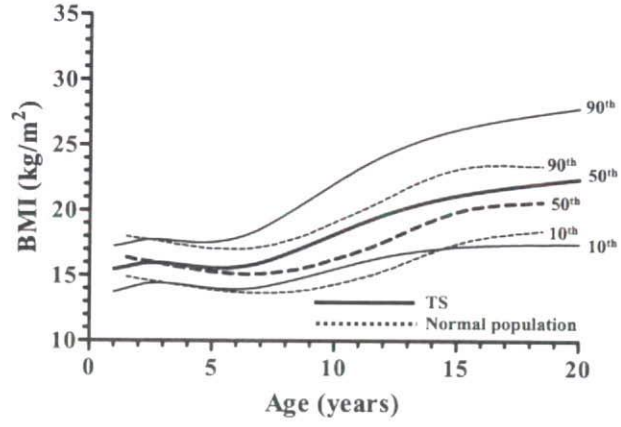

Figure 3 BMI chart for Japanese girls with Turner syndrome without puberty in comparison with normal population (20).

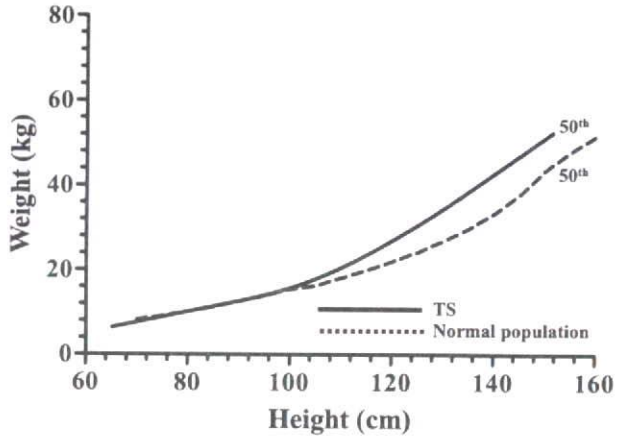

Figure 4 WFH chart for Japanese girls with Turner syndrome without puberty in comparison with normal population (17). Only the 50th percentile curves are shown, because WFH for the Japanese normal population has only values of the 50th percentile.

dual-energy X-ray absorptiometry (24). In this study, we found that in TS, percentages of overweight differed between the two methods and the ratio of discordance became larger with age (Table 3). Considering the consistency of the two indices in the normal population, it is surprising that more than 30% of subjects with TS older than 10 years of age were classified differently. When International cut-off values of BMI (10) instead of Japanese cut-off values were used for classification of overweight, we obtained the similar results (Table 3). These results indicate specific difficulty in defining overweight for girls with TS by anthropometric indices. The TS consensus study group recommends females with TS should aim to have a BMI less than 25 kg/m^2 in an updated clinical practice guideline (6). And the clinical report of the American Academy of Pediatrics states that diet and exercise for weight control should be discussed for girls with TS, because obesity may be a particular problem for them (25). Although it is reported that BMI is a good marker of obesity and associated cardiovascular risk in adult females with TS (26), it is still unknown whether or not BMI should be used as a surrogate marker of overweight for girls with TS in clinical practice. The answer to this question is beyond the scope of our present study. Nevertheless, discrepancies of classification of overweight by the two indices were shown in this study and therefore attention should be paid to the determination of overweight for girls with TS by anthropometric indices.

In an attempt to uncover the reason for the discrepancies discussed above, we thought that it would give us new insight to compare the growth patterns of the two indices between girls with TS and normal subjects. As the first step, we produced clinical reference charts of BMI and WFH for Japanese girls with TS who did not develop puberty, because these charts had not been produced before. They were constructed by the LMS method, which is thought to be one of the most widely applied approaches (27). In addition, diagnoses of all the subjects were confirmed by the definition of TS based on the chromosomal analyses and properly selected by excluding the cases of pubertal development and/or previous growth-promoting treatment. From this perspective, we believe that these charts have been adequately and successfully produced and can be used as appropriate standards in clinical practice. To our knowledge, these are the first charts of BMI and WFH for TS girls in an Asian population.

The newly constructed reference growth chart for BMI of girls with TS in comparison with that of the normal population (Fig. 3) shows that the difference of the 50th percentile values between girls with TS and the normal population increases towards approximately 11 years of age, and then tends to decrease with age. This phenomenon is also seen in another TS-specific BMI chart (5). It is of note that peak growth velocity of Japanese girls occurs around 11 years of age (28). This coincidence of the age may suggest that the different BMI growth pattern is associated with lack of puberty in TS girls. However, the difference cannot be explained only by pubertal development, because growth patterns of girls with TS differ from the normal population also in the prepubertal stage (2–5). In addition, when we investigated the appropriate power (p) of the weight/height^p index according to ages, the optimal value of p was not appreciably different from that in the normal girls (data not shown), which was approximately two in pre-school children, increased gradually to around three at age 11 and fell back to the level of two thereafter (29,30). As for the WFH reference, we find that WFH is quite normal below the height of 100 cm, but above 120 cm there is a more rapid increase of the WFH in TS girls (Fig. 4). This finding is consistent with observations, which have been reported in western countries (2,4,5). Through comparison of TS-specific reference growth charts for BMI and WFH with those of the normal population, we could illustrate the different degrees of distinction of growth patterns between girls with TS and normal girls in each index. Therefore, our finding of discrepancy in the prevalence of overweight as classified by the two indices for girls with TS probably corresponds to these differences of growth patterns

in the two indices from the normal population, although the nature of the differences remains unclear.

This study has two limitations. The first one is a selection bias. This retrospective cohort consists of those diagnosed as TS in medical institutes, which means that subjects who are not significantly smaller than the normal population are probably missing. More specifically, physicians do not usually register girls with TS if they are taller than −2SDS of the female standard, because the registry is primarily for candidates of GH treatment. It is of note that indication of GH for TS is limited to subjects shorter than −2SDS in Japan. The height of the majority of girls with TS usually drops below the fifth percentile of the normal girl growth curve only after an age between two and five years (1). This implies that a selection bias occurs more severely in subjects younger than approximately three years of age. Therefore, values under three years of age in the BMI reference chart for girls with TS are not very reliable. The second limitation is the fact that we cannot know which indices are better for identifying overweight for girls with TS from this study. Our present study only illustrated a discrepancy in the classification of overweight between the two indices, although medical practitioners are eager to know which index is better for evaluating weights in clinical settings. This research question needs to be answered. However, our study does not make any proposals, because there were no other clinical data on obesity than the anthropometric measurements in this retrospective cohort. Further investigation is needed to understand the characteristics of overweight of girls with TS in relation to obesity and metabolic syndrome in adulthood, and to develop an adequate anthropometric screening method for possible obesity in TS.

CONCLUSIONS

A discrepancy in the prevalence of overweight as classified by BMI and WFH for girls with TS was detected and it became larger with age. This specific discordance corresponded to the different degrees of distinction of growth patterns in two indices compared with the normal population. Careful interpretation of the anthropometric indices is essential for the determination of overweight for girls with TS. Further investigation is required to reveal a better method for evaluating obesity by anthropometric measurements.

ACKNOWLEDGEMENT

We wish to thank all the patients and doctors for the registration into this retrospective cohort. This study was partly supported by the grant from the Foundation for Growth Science, Japan.

CONFLICT OF INTEREST

The authors have no conflict of interest.

References

1. Saenger P. Turner's syndrome. *N Engl J med* 1996; 335: 1749–54.
2. Ranke MB, Pflüger H, Rosendahl W, Stubbe P, Enders H, Bierich JR, et al. Turner syndrome: spontaneous growth in 150 cases and review of the literature. *Eur J Pediatr* 1983; 141: 81–8.
3. Suwa S. Standards for growth and growth velocity in Turner's Syndrome. *Acta Paediatr Jpn* 1992; 34: 206–21.
4. Bernasconi S, Larizza D, Benso L, Volta C, Vannelli S, Milani S, et al. Turner's syndrome in Italy: familial characteristics, neonatal data, standards for birth weight and for height and weight from infancy to adulthood. *Acta Paediatr* 1994; 83: 292–8.
5. Rongen-Westerlaken C, Corel L, Broeck JVD, Massa G, Karlberg J, Albertsson-Wikland K, et al. Reference values for height, height velocity and weight in Turner's Syndrome. *Acta Paediatr* 1997; 86: 937–42.
6. Bondy CA for The Turner Syndrome Consensus Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner syndrome study group. *J Clin Endocrinol Metab* 2007; 92: 10–25.
7. Lobstein T, Baur L, Uauy R, IASO International Obesity TaskForce. Obesity in children and young people: crisis in public health. *Obes Rev* 2004; 5(Suppl 1): 4–104.
8. Janssen I, Katzmarzyk PT, Boyce WF, Vereecken C, Mulvihill C, Roberts C, et al. Health behavior in school-aged children obesity working group. Comparison of overweight and obesity prevalence in school-aged youth from 34 countries and their relationships with physical activity and dietary patterns. *Obes Rev* 2005; 6: 123–32.
9. Dietz WH, Robinson TN. Use of the body mass index (BMI) as a measure of overweight in children and adolescents. *J Pediatr* 1998; 132: 191–3.
10. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *Brit Med J* 2000; 320: 1240–3.
11. Voelker R. Improved use of BMI needed to screen children for overweight. *JAMA* 2007; 297: 2684–5.
12. Barlow SE, Dietz WH, Klish WJ, Trowbridge FL. Medical evaluation of overweight children and adolescents: reports from pediatricians, pediatric nurse practitioners, and registered dietitians. *Pediatrics* 2002; 110: 222–8.
13. Corel LJA, Van Den Broeck J, Rongen-Westerlaken C, Massa G, Wit JM. Body weight in children with Turner syndrome treated with growth hormone. *Int J Obesity* 1996; 20: 957–62.
14. Gravholt CH, Naeraa RW, Brixen K, Kastrup KW, Mosekilde L, Jøgensen JOL, et al. Short-term growth hormone treatment in girls with Turner syndrome decreases fat mass and insulin sensitivity: a randomized, double-blind, placebo-controlled, crossover study. *Pediatrics* 2002; 110: 889–96.
15. Tanaka T, Takano K, Hanew K, Nishi Y, Igarashi Y, Hirano T, et al. Registration system for growth hormone (GH) treatment with standardized immunoreactive GH values in Japan. *Endocr J* 1998; 45: 459–65.
16. Asayama K, Ohzeki T, Sugihara S, Ito K, Okada T, Tamai H, et al. Criteria for medical intervention in obese children: a new definition of 'obesity disease' in Japanese children. *Pediatr Int* 2003; 45: 642–6.
17. Ito Y, Fujieda K. Obesity (in Japanese). *Shoonikashinryo* 2003; 66: 1913–19.
18. Japan Society for the Study of Obesity. *Manual for the treatment of obesity disease in children (in Japanese)*. Tokyo, Ishiyaku Publishers Inc, 2004.
19. Guillaume M. Defining obesity in childhood: current practice. *Am J Clin Nutr* 1999; 70(Suppl 1): 126S–30S.
20. Inokuchi M, Hasegawa T, Anzo M, Matsuo N. Standardized centile curves of body mass index for Japanese children and