HOT TOPICS

新生児医療の最前線

2007年8月に小児への適応拡大が承認された麻酔用鎮静薬フェンタニルについて，医師主導治験による適応拡大の経緯と臨床における使用にあたっての注意点を解説する．

医師主導治験によるフェンタニルクエン酸塩注射液の新生児・小児への適応拡大の経緯と臨床使用の注意点

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はじめに

今となってはもう，新しい話と言えるものではありませんが，ここでは，医師主導治験によるフェンタニルクエン酸塩注射液（以下，フェンタニル注射液）の新生児および小児への適応拡大の経緯と臨床での使用について，個人の見解を含めお話しさせていただこうと思います．おそらく，国立成育医療センター治験管理室長の中村秀文先生と共にこの医師主導治験におけるフェンタニル注射液治験調整医師を担当していたこと，また医薬品承認審査に係る審査官の経験があったことなどのため，この原稿を書く役目が私に回ってきたのだと思います．

医師をはじめとする医療提供者には，適応拡大に関する視点では，フェンタニル注射液がわが国で初めて医師主導治験によって承認された品目であることから，小児領域の医薬品適応外使用（off-label use）やその解決に向けての取り組み，取り組みの一つの方策としての医師主導治験，臨床試験推進という流れでとらえていただけると，小児領域の医薬品開発の理解の象徴であると考えていただけるでしょう．また臨床における使用に関する視点では，数十年にわたり日本を含む世界中で使用されてきた小児領域の一医薬品について，わが国で取ったドラスティックな対応やその後の臨床現場での使用の意味するところを酌むものとして読み進めていただけることを願っています．

小児領域の医薬品適応外使用とその解決に向けた取り組み

小児領域で使用される医薬品については，1960年代に既にDr. Shirkeyが，therapeutic orphan（治療上の孤児的状況）に置かれていると指摘しています[1]．そして現在に至るまで，医薬品の適応外使用などは世界的にも小児領域の問題の一つです．もちろん日本も例外ではありません[2]．なお，適応外使用とは，正しくは添付文書上に効能・効果や用法・用量が記載されていない内容で使用すること（狭義の「適応

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外使用」）ですが，広義には，海外で承認されていても国内に成分が存在しない場合の個人輸入による使用や，試薬や合成化合物の使用などの意味合いを指すこともあるので注意が必要です．

米国でエイズ（acquired immuno deficiency syndrome；AIDS）の子どもへの抗ヒト免疫不全ウイルス（human immunodeficiency virus；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ことなどもあって，1990年代から欧米ではこれらの解決に向けて，飴と鞭がその基本となる法制化（米国のBest Pharmaceuticals for Children Act；BPCA［2002年］[3]，Pediatric Research Equity Act；PREA［2003年］[4]，FDA Amendments Act of 2007［2007年］[5]や欧州のPaediatric Regulation［2007年］[6, 7]）を含めた取り組みが進んでいます[8]．日本にはまだこのような法律や規制はありません．再審査期間の延長や薬価の小児加算などは製薬企業へのインセンティブとなっているといった意見もあるようです．日本小児科学会薬事委員会による「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」（2004年）[9]や厚生労働省による小児薬物療法検討会議（2005年）[10]，未承認薬使用問題検討会議（2005年）[11]などの活動も適応外使用問題解決につながります．しかし，10年ほど前の調査ではありますが，国内の小児の日常臨床で使用される医薬品で添付文書上，小児に対する明確な用法・用量の記載がないものが約75％存在したという報告もあり[12]，これが昨今大きく改善されたことはないと言ってよいと思います．

フェンタニル注射液

フェンタニル注射液は，数十年にわたって世界的に使用されてきた医薬品です．日本でも，1972年に三共株式会社から販売が開始されました．2004年に，ドロペリドールとの併用などに限定されていたものが，いわゆる二課長通知[13]によって，全身麻酔，全身麻酔による鎮痛，局所麻酔における鎮痛の補助，激しい疼痛（術後疼痛，癌性疼痛など）に対する鎮痛に適応が拡大されました．しかしながら，細かい話はともかく，国内外の小児麻酔専門医が長い間，2歳以下の乳児や小児に使用し，その経験の蓄積は十分であると臨床現場で考えられていても，わが国の添付文書の「その安全性が確立されていないことから2歳以下の乳児・小児には禁忌」という記載はそのままで，これを外すという議論がなされたことはありませんでした．

添付文書に記載された禁忌は，警告（赤枠・文字も赤色）に続けて記載されるものであり，赤枠（文字は黒色）で囲まれています．添付文書上，この禁忌を外す，あるいは小児領域での効能・効果や用法・用量を記載するにはそれなりの根拠を示して，規制当局で認めてもらう必要があります．なぜ添付文書上の禁忌を外し，効能・効果や用法・用量をしっかりと記載した

いのかと言えば，そうすることによって患児（や家族）にとって安全とされるものとなり，医師もまた安心して使用できることにほかならないという考え方があるからです．最近は医療安全の文脈から語られることが多くなっているように思いますが，私はこのことはとても重要だと考え続けています．

医師主導治験とフェンタニル注射液

日本は資本主義国ですから，製薬企業の利益につながりにくいものを開発するプライオリティは高くありません．フェンタニル注射液は麻薬ですし，ましてや新生児や小児での使用となれば，当然，製薬企業にとって何らかのインセンティブが働かなければ，開発を進めていく動機はないに等しいということになるでしょう．しかし，医師の側には（もちろん患児や家族にとっても）小児領域での開発を進めたい理由があったことは前述したとおりです．

そのような折，2002年の薬事法改正で医師主導治験が実施可能となりました．これで製薬企業による治験ではなくても，医師や研究者が医薬品などの効能追加（多くは適応外使用解決）を目指す道筋が整えられたということになりました．

これが医師主導治験でフェンタニル注射液，特に小児での全身麻酔，全身麻酔における鎮痛の開発を進めていくことになった理由です．フェンタニル注射液の治験では日本医師会治験促進センターからの研究費をはじめとした補助を受けました[14]．なお，小児領域における医師主導治験の方法論の議論が十分でないところでのプロトコルのエンドポイントや用法・用量の取り決めなど，すなわち苦労ということになりますが，これらは長野県立こども病院の宮坂勝之先生が詳しく書いておられるので，ぜひそちらをお読みいただきたいと思います[15]．承認までの規制当局との幾多のやり取りを経て，2007年8月23日，フェンタニル注射液は国内医師主導治験では初めて，2歳以下での禁忌事項を外し，小児での承認を取得しました．

フェンタニル注射液の審査

医薬品の承認審査は，「薬学，医学，獣医学，理学，生物統計学などの専門課程を修了した審査員が，品質，薬理，薬物動態，毒性，臨床，生物統計を担当し，審査チームを形成して審査を行う．審査の過程では，外部専門家と専門協議を行い，より専門性の高い見地から審査することを目指している」と，その業務を行っている独立行政法人医薬品医療機器総合機構（以下，医薬品機構）のホームページにあります[16]．厚生労働大臣はこの審査の結果を考慮し，薬事・食品衛生審議会に諮問し答申を受け，承認の可否を判断することになっています．

審査の過程は，すべてではないですが，審査報告書にまとめられ，公開されています．フェンタニル注射液についても閲覧でき，審査の内

表　フェンタニルを小児におけるバランス麻酔または大量フェンタニル麻酔に用いる際の用法・用量

・麻酔導入時 フェンタニル注射薬として0.02～0.1mL/kg（フェンタニルとして1～5μg/kg）を緩徐に静注するか，またはブドウ糖液などに希釈して点滴静注する．大量フェンタニル麻酔に用いる場合は，通常，フェンタニル注射薬として2mL/kg（フェンタニルとして100μg/kg）まで投与できる．
・麻酔維持 フェンタニル注射薬として0.02～0.1mL/kg（フェンタニルとして1～5μg/kg）ずつ間欠的に静注するか，またはブドウ糖液などに希釈して点滴静注する．

（フェンタニル注射薬0.1mg「三共」・フェンタニル注射薬0.25mg「三共」の添付文書より一部改変）

容を垣間見ることができます[17]

実際には，医師主導治験に組み入れられ，血漿中濃度を測定できた乳児は数例でした．審査では，公表文献の結果も踏まえた上で，その安全性について，「低出生体重児を含む新生児や乳児では血漿中濃度や脳内移行性が高くなる可能性はあると考えられ，低出生体重児，新生児および乳児に対して自発呼吸下で投与する場合は低用量から開始し慎重投与が必要で，患者の状態を観察しながら適切に用量などを調節すべきである」とされました．もともと，臨床現場でも，フェンタニル注射液は呼吸抑制の程度を観察しながら麻酔科医の管理下で慎重に投与されていましたが，添付文書上でもしっかり注意が喚起されることとなりました．

用法・用量についても，医師主導治験に加え，国内外の成書，公表文献，ガイドラインなどからある程度コンセンサスの得られたところと判断されました．

ところが，審査の最後のほうで行われる専門協議で出た意見も参考にされ，新生児を対象としたバランス麻酔および大量フェンタニル麻酔の使用状況に関しては，製造販売後に統一的な方法で十分な情報を収集することが望ましく，製造販売後に当該患者における本剤の有効性および安全性について検討するという宿題が課せられました．

今回のフェンタニル注射液の新生児・小児への適応拡大は，わが国における医師主導治験としては，まだはじめの段階でした．最初のうちの医師主導治験となれば，以前からずっと臨床現場で使われていて，臨床現場での経験は豊富で，日本では適応取得ができていないとしても欧米をはじめ海外では適応取得できているような，今開発を進めたとしても製薬企業の直接の利益にはつながりにくい品目で実施される可能性が高く，事実，フェンタニル注射液もそうであったと想像されます．いろいろな点で，製薬企業にも相当の負担がかかったのではないでしょうか．

医薬品の審査を経験したことがあるからという訳ではないですが，臨床で広く使用されている医薬品に，医師主導治験によって効能を追加するという初めての事態に直面したのは研究者である医師や製薬企業ばかりでなく，規制当局たる厚生労働省や医薬品機構（含専門委員）も同じことでした．そういった意味から，フェンタニル注射液は，日本で最初に医師主導治験に

よって効能が追加された品目であり，その過程・結果はたいへん意義深いものであって，陰日向に多くの労苦が存在していたこと，今なお存在していることを忘れてはならないと思います．

フェンタニル注射液の臨床使用での注意点

臨床現場でフェンタニル注射液は当たり前のように使用されてきたので，もしかしたら中には，2007年8月まで新生児や小児に使われることが適応外使用であったとか，効能追加のためにこのような涙ぐましいプロジェクトが動いていたとか，あるいは「そもそも適応外使用って何？」という方がおられるかもしれません．

医薬品の承認審査を経験した小児科医としては，個人的には，有効性・安全性が確かめられた医薬品を日常臨床で使用するということは，患児や家族にとってはもちろんのこと，医師にとっても安心して診療に専心できることになりますので，ひいては医療安全につながるものと考えています．ですから，新生児科医，小児科医や小児麻酔科医をはじめとする医療提供者にも，このような文章を通じて，どれほど臨床現場での経験知が高いものであったとしても，安全で有効な薬を人々に届けるためにはきちんとした手続きが必要とされることや，そのために働く人々の存在があることを知っていただくのはとても重要であると思っています．

今や成人の世界では，剤形の違うフェンタニル製剤や複数のオピオイドをその特性によって使い分けていることは想像に難くありません．新生児を含む小児麻酔科臨床現場では，ずっと慣れ親しんできたと言えるフェンタニル注射液であっても，今まで述べてきたような事情を抱えている訳です．ですから，フェンタニル注射液であっても承認された効能・効果や用法・用量以外で使用すること，小児での安全性や有効性がその眼で確認されたとは言えないであろう剤形違いのフェンタニル製剤を使用することや他のオピオイドを特性によって使い分けるということは，子どもの世界ではまさしく適応外使用であって問題であると言わざるを得ません．医師の裁量の範囲として使用したい場合には，その旨をしっかり心に刻み，熟考し，必要な種々の措置を取った上で状況によって判断する，ということになるかもしれません．

おわりに

フェンタニル注射液が象徴であったと言えますが，日常臨床で頻用される医薬品などについては，添付文書に一度目を通してみてはいかがでしょうか．その使用が適応外であったことに新たに気付くこともあるかもしれません．医薬品などの添付文書については医薬品機構のホームページから簡単にアクセスすることができます[18]．

適応外使用問題解決を含み，使用されるべき医薬品は開発する方向で考えていかなくてはな

りません.

子どもに使用される可能性のある医薬品や医療機器について，きちんと安全性や有効性が適切に確認され，適正に臨床使用されることが当たり前に行われるしくみが早くでき，根付くことを願ってやみません.

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Clinical Investigation

Proposal of New Auxological Standards for Japanese Girls with Turner Syndrome

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Abstract. We recently published new reference growth charts for Japanese girls with Turner syndrome (TS) based on the cross-sectional data of 1,447 subjects beyond the secular trend of growth in Japan. This study was undertaken for their validation and, if necessary, modification before general application. For validation, 24 subjects who had data both at younger (≤5 yr) and older ages (≥13 yr) were used. We analyzed the concordance/discordance of their height standard deviation score (SDS) defined by the charts between the two age periods. For modification, the LMS method was used with 5,772 longitudinal measurements obtained both from the previously analyzed subjects and 118 newly recruited subjects who had been followed up at the National Center for Child Health and Development or Toranomon Hospital. Significant and critical discordance (mean difference, 1.95 SDS; 95% confidence interval (CI), 1.53–2.36; $p<0.0001$) was detected in height SDS. This prompted us to perform the modifications. A similar analysis using the modified charts revealed no significant discordance (mean difference, 0.27 SDS; 95%CI: −0.17 − 0.71; $p=0.22$). They seem more adequate for clinical applications for girls with TS born after 1970. New auxological standards for Japanese girls with TS were proposed.

Key words: Turner syndrome, growth chart, secular trend, LMS method

Introduction

Turner syndrome (TS) is the most common chromosomal disorder in females and affects about one in 1,500 to 2,500 live-born female infants (1). One of the most significant features of the syndrome is short stature. Untreated females are reported to be approximately 20 cm shorter than normal females within their respective populations (2). Growth patterns of

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girls with TS are different from normal populations mainly because of the short stature homeobox-containing gene on the X chromosome (SHOX) haploinsufficiency and their ovarian insufficiency. TS-specific growth curves have been published in various countries (3–5) including Japan (6), and they have been clinically used for evaluation of statural growth.

The currently used growth charts for Japanese girls with TS (6) were constructed with subjects whose body sizes had been obtained from questionnaires sent to their follow-up hospitals. Since we are dealing with three sets of charts in this article, these will be called "the current charts [1992]" to avoid confusion. The data consisted of 6,255 measurements from 705 girls who were born between 1955 and 1989 (median unknown). Given the year of publication, the adult height for them had to be derived from subjects born before 1972. The secular trend in adult height has reached a plateau since approximately 1990 in Japan (7). Judging from the birth-year range, the current charts [1992] were constructed with data from subjects whose majority were born before the adult height reached the plateau. For evaluation of the statural growth in girls with TS in clinical settings, use of these charts has probably become invalid. Therefore, we produced new clinical reference growth charts, which will be called "the new charts [2009]", based on cross-sectional data from 1,447 girls whose birth years ranged from 1970 to 2002, and after 1980 in 85.2%, following exclusion of measurements derived from those with presence of puberty at measurement, with previous growth promoting treatment or without cytogenetic evidence for TS (7, 8).

Though the new charts [2009] seem to be more adequate for evaluation of the growth of girls with TS born approximately after 1970 than the current charts [1992], they have some limitations derived mainly from selection bias. The analyzed data were obtained from those diagnosed as TS in medical institutions, which means that subjects who were not significantly smaller than normal populations are more easily missing. The heights of the majority of girls with TS usually drop below the 5th percentile for normal girls only after an age between two and five years (1). This implies that this kind of selection bias affects more severely in subjects younger than five years of age. In fact, relatively small girls in the TS population tended to undergo GH earlier, and relatively tall ones often suffered from short stature for many years before GH treatment (9). The purpose of this study is to validate the new charts [2009] especially focusing on the height standard under five years of age (validation study) and to modify them before their general application if necessary (modification study).

Subjects

The samples were newly obtained from medical records at the National Center for Child Health and Development (NCCHD) and Toranomon Hospital. In this study, TS was defined as a karyotype that contains a cell line of monosomy lacking at least a distal major part in the short arm of the X chromosome. Between January 1980 and December 2008, 205 girls with TS born after 1970 visited one of the two hospitals. Among them, we excluded subjects with clear evidence of spontaneous pubertal signs in their medical records (37 subjects) or who had already been employed in the previous study for constructing the new charts [2009] (50 subjects). Finally, remaining 118 subjects were included in the present study, and auxological data consisting of 1,703 measurements before start of growth promoting treatments were collected whenever possible (Hospital data, Fig. 1). The age at diagnosis in these subjects ranged from 0.75 to 23.25 with a median of 9.33 yr of age. The number of subjects that had auxological data under five years of age was 89. The birth years of subjects ranged from 1970 to 2008 (median, 1984), and 64.0% of the subjects were born after

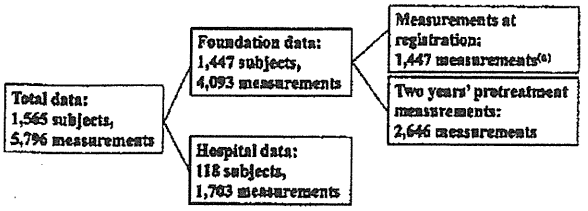

Fig. 1 Total data for construction of the new charts with modification [2010] (5,772 measurements). Twenty-four outliers from 5,796 measurements were excluded for the final analysis. The new charts [2009] were constructed using 1,447 measurements (a) (7).

1980. For the validation study, we sampled subjects who had data for both younger (≤5 yr) and older (≥13 yr) ages from Hospital data because we wanted to know whether the new charts [2009] could be used over the whole course of growth. Twenty-four of the 118 subjects were selected for this purpose.

For establishment of new modified charts, which will be called "the new charts with modification [2010]", we utilized both the above-mentioned data and the data of subjects included in the previous study (7, 8). The samples in the previous study were obtained from a database compiled by the Foundation for Growth Science, Japan. In the database, three years' successive height data were available in many subjects, and we were able to collect auxological data consisting of 4,093 measurements (Foundation data, Fig. 1). In total, 5,796 measurements from 1,565 subjects were obtained for the modification study (Fig. 1). The data were cleaned in several stages. Bivariate plots of height and weight were used to identify gross disproportion. Data points were scrutinized, going back to the source data if necessary, and scriptural errors were corrected. In case a value was deemed highly unlikely (more than 5 SDS from the mean), the point was deleted even if there was no evidence of a scriptural error. In the course of the above data cleaning, 24 data were excluded because of highly unlikely measurements. The remaining data, 5,772 measurements from 1,565 subjects (their birth years are distributed from 1970 to 2006 with a median of 1985), were analyzed for the modification study. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Growth velocity (GV) was calculated as the annual height difference between two longitudinal measurements if the time interval of the data was between 0.5 and 1.5 yr. Perinatal information and their parents' height were collected wherever possible. Birth length is 46.8 ± 2.7 cm (n=723), birth weight was 2.68 ± 0.44 kg (n=1,423) and target height was 158.0 ± 4.2 cm (n=1,366), which was very similar to the average adult height for Japanese females (157.9 cm) in 1990 (10). Target height was calculated by the formula fitted for the Japanese before the secular trend had reached a plateau (11). These auxological data were consistent with the previous study. Use of the retrospective data was approved by the medical ethics committees of the NCCHD.

Methods

The collected longitudinal height data (Hospital data) were calculated to age-specific standard deviation scores (SDS) using the new charts [2009]. We hypothesized that the height SDS values in infancy and early childhood defined by the new charts [2009] would be larger than those of the same subject at older ages if the new charts [2009] had significant bias in which shorter subjects were more preferentially included in the younger ages. To elucidate this hypothesis, longitudinal changes of height SDS values were investigated. The data of the twenty-four above-mentioned subjects were plotted in the new charts [2009], and the difference between the initial and later SDS value was compared (validation study). The initial SDS values meant the earliest data of the subjects, and the later values meant their last data.

To establish the new charts with modification

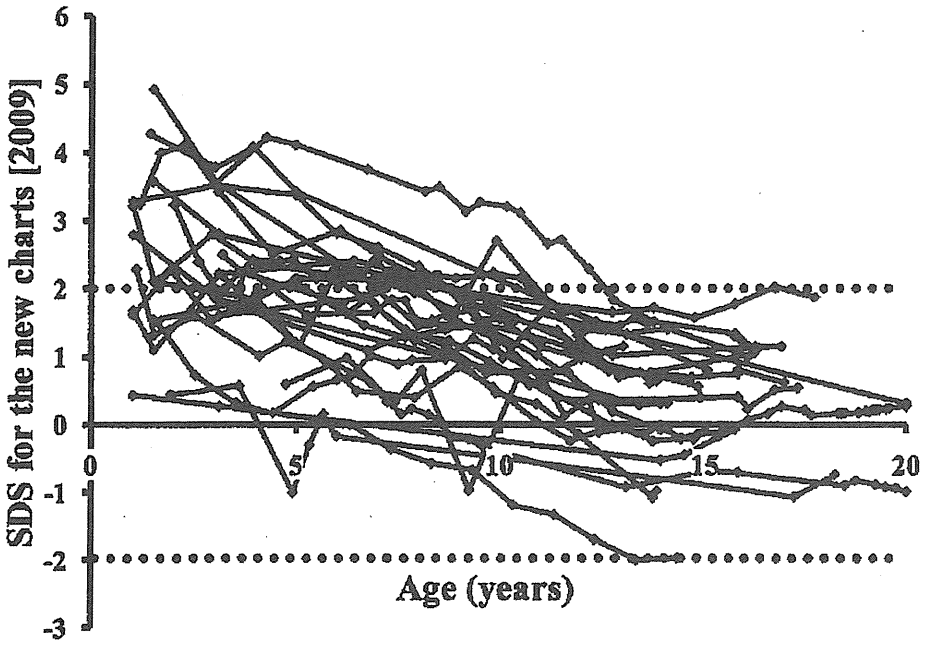

Fig. 2 Changes of longitudinal height SDS defined by the new charts [2009] (7) in the 24 subjects who had long-term data for early childhood (≤5 yr) through adolescence (≥13 yr).

[2010], the LMS method (12) was used with both Foundation and Hospital data (modification study). This assumes that the data can be transformed to normality by a suitable power transformation (L) and that the distribution is then summarized by the median (M) and coefficient of variation (S). The values of L, M and S are constrained to change smoothly with age, and fitted values can be used to construct any required centile curves. Using penalized likelihood, three curves (L, M and S) can be fitted as cubic splines by non-linear regression, and the extent of smoothing was controlled by equivalent degrees of freedom. Fitting and smoothing were done with lmsChartMaker Pro ver.2.3 (Medical Research Council, London, UK).

For statistical analysis in validation study, comparisons of difference in height SDS values between younger (≤5 yr) and older (≥13 yr) ages were assessed by paired *t*-test. To investigate the height difference between 45,X and non-45,X karyotypes, analysis of covariance (ANCOVA) was used with covariates of age and age-karyotype interaction. These analyses were performed using JMP 6.0.3 (SAS Institute Inc., Cary, NC, USA), and a p value less than 0.05 was considered statistically significant.

Results

Longitudinal height SDS values of the 24 subjects in the validation study are plotted in Fig. 2. They increased to even above +2 SDS in many cases as age decreased. The initial SDS value was significantly and critically bigger than the later one (mean difference, 1.95; 95% confidence interval (CI), 1.53–2.36; $p<0.0001$). We considered that these mean differences of approximately two channels in the growth chart were not acceptable for clinical applications, as the projected adult heights in infancy would be

Table 1 Age distribution of the numbers of measurements for constructing the new charts with modification [2010]

Age (yr)	Height*	Weight/ BMI/ WFH	Growth velocity
0	338 (1)	319	58
1	240 (9)	181	133
2	208 (14)	122	153
3	364 (41)	199	205
4	376 (74)	189	234
5	393 (104)	214	251
6	447 (105)	227	240
7	469 (104)	207	294
8	477 (113)	202	329
9	557 (152)	242	347
10	511 (160)	231	341
11	413 (168)	230	248
12	308 (131)	179	177
13	209 (75)	107	139
14	163 (68)	89	95
15	117 (52)	67	72
16	82 (38)	49	43
17	42 (22)	27	24
18	21 (11)	18	10
19	14 (2)	14	4
20+	23 (3)	23	5
Total	5,772 (1,447)	3,136	3,402

*Numbers in parentheses indicate those analyzed for constructing the new charts [2009] (7).

significantly and seriously higher than their actual heights. Therefore, modification of the charts was considered to be essential.

For the modification study, Table 1 lists the number of subjects by age and origin of data. Table 2 summarizes the number of subjects according to their karyotypes. Heights in the 45,X subjects (n=463, 1,718 measurements) were a little but significantly taller than those in the non-45,X subjects (n=1,102, 4,054 measurements) (regression coefficient: 0.29±0.087 cm, $p<0.0001$). When we performed a similar analysis according to the assumed number of SHOX gene copies, the heights in the subjects whose SHOX gene copy was definitely determined single (n=1,256, 4,598 measurements) were significantly smaller than those in the remaining subjects (n=309, 1,174 measurements; regression coefficient: −0.92±0.11 cm, $p<0.0001$). As TS-specific growth curves published in various countries including Japan had been constructed with all karyotypes together, centile curves were fitted to the data all together using the LMS method.

For height and growth velocity (GV), the distributions were generally assumed to be normal, while for weight, BMI and weight for height (WFH), there was appreciable skewness, and the age-varying power transformations were adjusted for them. Clinical growth references for height, GV, weight, BMI and WFH are shown in Appendices, Figs. 1, 1, 2, 3 and 4, respectively. Appendix Table 1 provides values for the mean and standard deviation of height and GV by age. Appendix Table 2 provides values for L, M and

Table 2 Karyotypes of the 1,565 subjects recruited for construction of the new charts with modification [2010]

	Non-Mosaic	Number of subjects	Mosaic	Number of subjects
Aneuploidy	45,X	463	45,X/46,XX	96
			45,X/47,XXX	95
			45,X/46,XY	21
			45,X/46,XX/47,XXX	6
		463		218
Structural abnormality	46,X,i(Xq)	137	45,X/46,X,i(Xq)	329
	46,X,del(Xp)	61	45,X/46,X,del(Xp)	23
	46,X,r(X)	3	45,X/46,X,r(X)	119
	others	10	45,X/46,X,+mar	121
			others	81
		211		673
Total		674		891

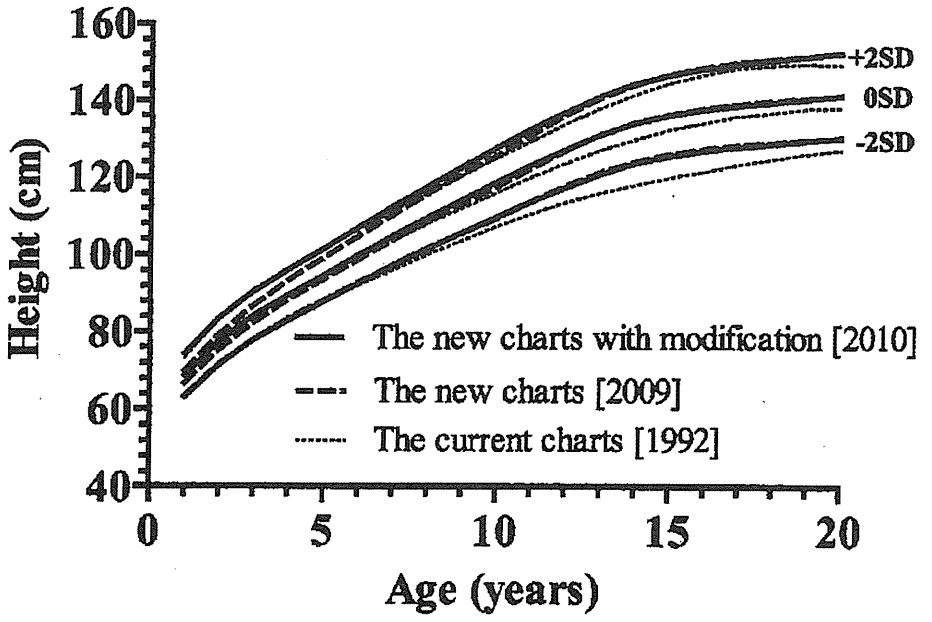

Fig. 3 Height charts for Japanese girls with Turner syndrome for comparison among the current charts [1992] (6), the new charts [2009] (7) and the new charts with modification [2010].

S of weight and BMI by age, and Appendix Table 3 shows each value of WFH by age. The new growth charts with modification [2010] for height are superimposed on both the new charts [2009] and the current charts [1992] in Fig. 3. The heights at older ages from the new charts with

modification [2010] are taller than those from the current charts [1992] and as tall as those from the new charts [2009]. On the other hand, the heights in younger ages from the new charts with modification [2010] are taller than those from the new charts [2009] and as tall as the current charts [1992]. The similar validation study as mentioned above with the new charts with modification [2010] revealed no significant difference (mean difference, 0.27; 95%CI: −0.17 − 0.71; p=0.22).

Discussions

Disease-specific growth charts are thought to be useful in predicting spontaneous growth pattern and can elucidate deviation due to additional disease (4, 13). Moreover, in the evaluation of growth promoting treatments, it is necessary to compare the growth pattern during treatment not only with that before treatment, but also with the spontaneous growth of untreated patients from the same population. The new growth charts [2009] had some limitations as discussed in a previously published paper (7). Briefly, in the previous study, the analyzed measurements were cross-sectional data obtained from the database at the start of GH treatment, and therefore, shorter subjects were more preferentially selected, especially at younger ages, because relatively short individuals with TS would be brought to the attention of a medical professional earlier and only individuals shorter than −2 SD would be registered for the eligible GH treatment. In this study, validation of the new charts [2009] was performed with longitudinal data (Hospital data), and we found significant and critical height SDS differences between younger (≤5 yr) and older ages (≥13 yr), indicating severe selection bias in the younger ages in the previous study. These significant differences were considered to be unacceptable in clinical practice for evaluation of height in TS and effects of growth promoting treatments. If the predicted adult height would be taller than the actual adult height by as much as 1.95 SDS, we could not evaluate growth promoting treatments. For example, in a Canadian randomized study (14), the effect of GH supplementation was additional gain of 1.3 SDS (95%CI, 1.1–1.5) for the TS-specific growth chart. Thus, the new charts [2009] were considered inappropriate for clinical practice, and modifications of the new charts were mandatory.

In this study, we modified the charts by utilizing both cross-sectional and longitudinal data because the most defective points of the new charts [2009] were derived from the fact that they were established from cross-sectional data which allowed severe selection bias. The data of relatively tall girls with TS were not included in infancy and childhood, especially for girls younger than five years of age. In total, 5,772 measurements from 1,565 subjects (their birth years are distributed from 1970 to 2006 with a median of 1985) were used. The amount of data analyzed in this study was sufficient, being comparable to amounts analyzed in construction of other TS-specific charts. All subjects were confirmed by chromosomal analyses to meet the definition of TS and were properly selected for analysis, excluding subjects who had undergone pubertal development or previous growth-promoting treatment or both. Furthermore, the similar validation study as mentioned above using the new charts with modification [2010] revealed no significant difference. The new charts with modification [2010] seem more adequate for clinical applications. We believe that these charts have been adequately and successfully produced taking these points into consideration.

Differences can be detected among the three charts (Fig. 3). For example, the adult heights from the current charts [1992], the new charts [2009] and the new charts with modification [2010] are 138.2 cm, 141.2 cm and 141.3 cm, respectively, when adult height is defined as the mean height at the age of 20 yr. These results

seem attributable to the secular trend observed during this same period in Japanese women, as discussed in a previous paper (7). On the other hand, the new charts with modification [2010] in childhood (≤5 yr) are different from the new charts [2009] but close to the current used charts [1992]. The standard heights of Japanese girls at three years of age in 1960, 1970, 1980, 1990 and 2000 were 90.7 cm, 93.0 cm, 93.9 cm, 94.0 cm and 93.7 cm, respectively (10), and at five years of age, they were 103.3 cm, 106.2 cm, 107.1 cm, 107.9 cm and 107.6 cm, respectively (10). This indicates that the secular trend in height at three and five years of age has reached almost a plateau in approximately 1980 in Japan, and children born in around 1975 and after have fairly constant heights at three or five years of age. Considering the current charts [1992] were established from 705 girls who were born between 1955 and 1989 (median unknown) and were published in 1992 (7), the average course in younger ages is likely lifted up by the subjects born after around 1975. Thus, it is reasonable that the secular trend is not detectable in younger ages between the current charts [1992] and the new charts with modification [2010], although we cannot completely deny minor contribution of selection bias which still remained after the modification process. Accordingly, we believe that the new charts with modification [2010] have been adequately produced and overcome both secular trends and selection bias at younger ages.

There are two limitations to the present study. The first one is the number of study samples. The number of the older children, especially over sixteen years, was small. This limitation is shared by all other recently established reference charts. It has become more difficult to obtain height data from subjects without accompanying growth-promoting treatment because GH treatment for girls with TS has become very common in many countries including Japan, and furthermore, its starting age has been decreasing (9). Despite this limitation, the adult height in this study is −3.3 SDS of the normal population (15) and is considered to be valid by comparison to adult height SDSs reported in other countries (−4.2 to −2.5 SDS) (2). The second limitation is that we do not know whether the subjects without puberty at younger ages in this study will or will not develop spontaneous puberty later. It has been reported that those with spontaneous puberty are significantly taller than those without puberty from 12 yr of age onward, although pubertal growth spurt does not seem to affect final adult height (5). Theoretically, two types of growth charts may be needed during the peripubertal period, but we produced one specific for girls without pubertal signs because of the limited number of pubertal subjects. However, when we plotted the data from all 144 subjects (107 subjects from Foundation data and 37 subjects from Hospital data) with pubertal development on the new charts with modification [2010], they were distributed within ± 2 SDS of the other subjects' data with only five exceptions (data not shown). This finding justifies the use of the new charts with modification [2010] for all girls with TS born after 1970 irrespective of later development of puberty.

In conclusion, we have proposed new auxological standards for Japanese girls with TS using 5,772 measurements from 1,565 subjects who did not present puberty. As these charts have overcome the issues of both secular trends and selection bias at younger ages as far as possible, they are expected to be widely used in various clinical settings and for research purposes.

Acknowledgement

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Appendices.

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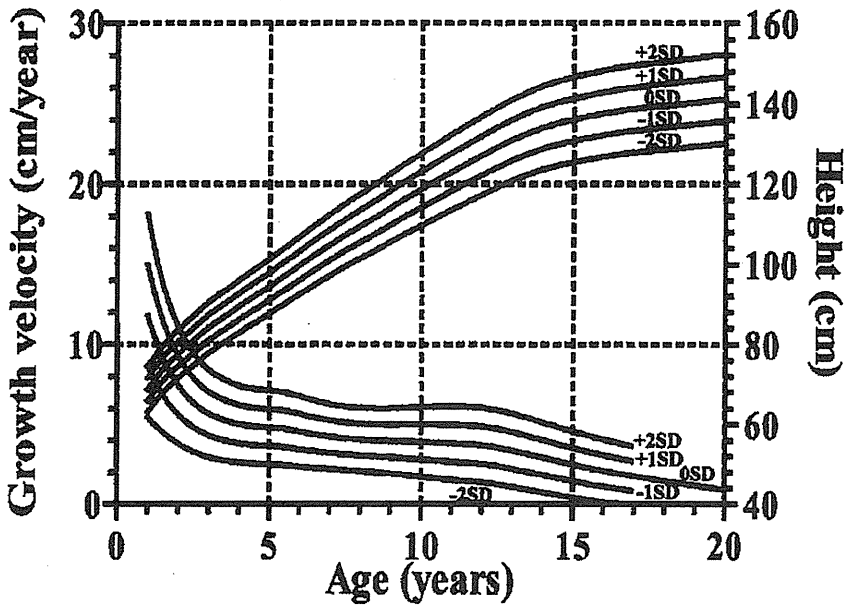
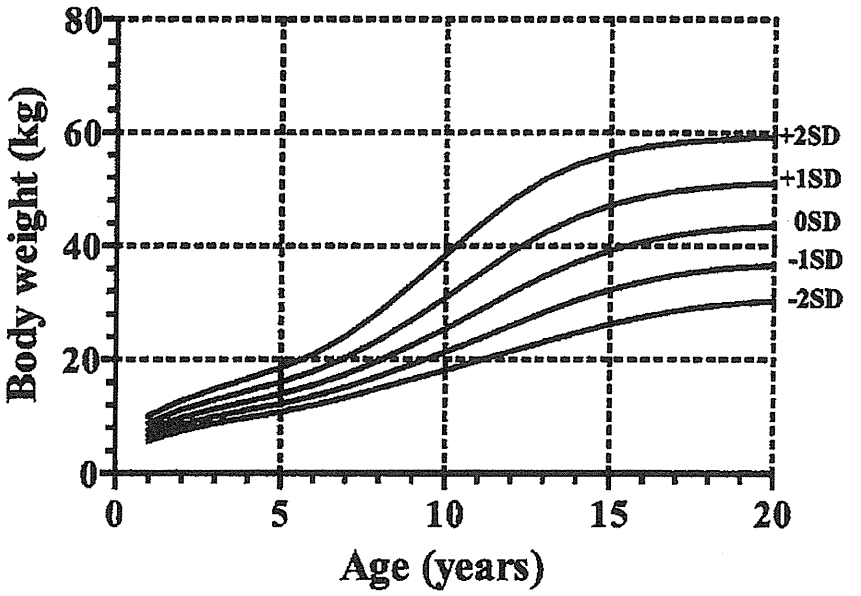
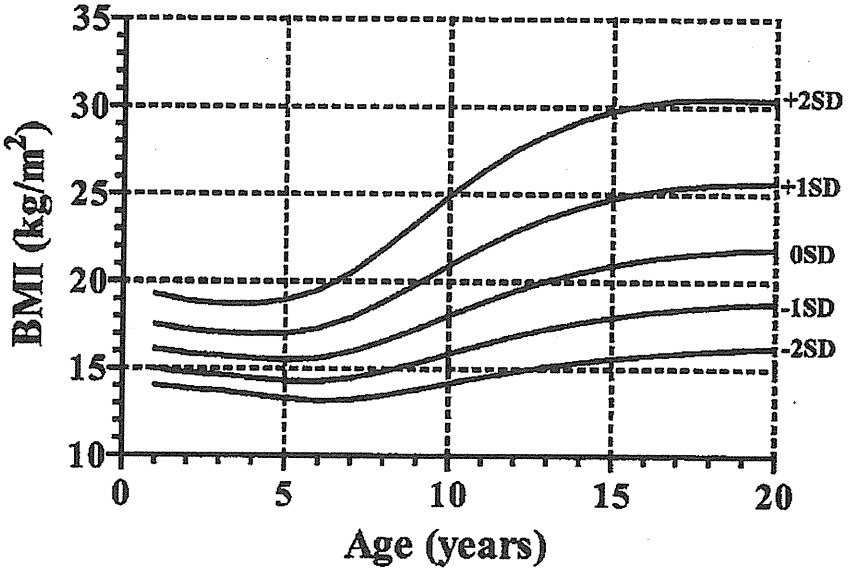


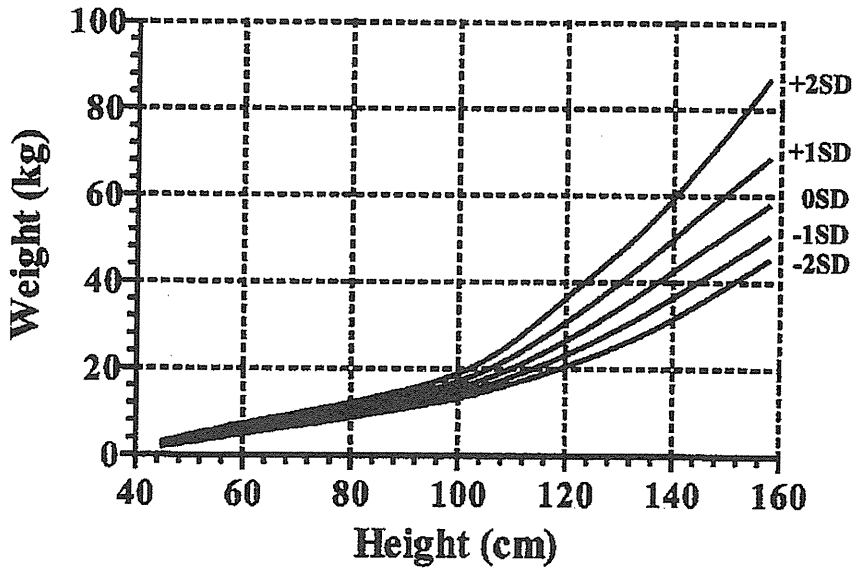
Appendix, Fig. 1
Height and growth velocity charts for Japanese girls with Turner syndrome.



Appendix, Fig. 2
Weight charts for Japanese girls with Turner syndrome. It should be noted that the intervals between the neighboring lines are not equal because of the skewed distribution of weight.



Appendix, Fig. 3
Body mass index (BMI) charts for Japanese girls with Turner syndrome. It should be noted that the intervals between the neighboring lines are not equal because of the skewed distribution of BMI.



Appendix, Fig. 4
Weight for height (WFH) charts for Japanese girls with Turner syndrome. It should be noted that the intervals between the neighboring lines are not equal because of the skewed distribution of WFH.

Appendix Table 1 Mean and standard deviation (SD) of height and growth velocity for the Japanese girls with Turner syndrome

Height			Growth velocity		
Age (yr)	Mean	Standard deviation	Age (yr)	Mean	Standard deviation
1	68.79	2.83	1	11.79	3.17
1.5	73.82	2.95	1.5	9.14	2.31
2	77.62	3.03	2	7.43	1.81
2.5	81.04	3.10	2.5	6.34	1.52
3	84.25	3.17	3	5.68	1.36
3.5	86.93	3.23	3.5	5.29	1.26
4	89.56	3.29	4	5.02	1.20
4.5	92.10	3.35	4.5	4.88	1.17
5	94.66	3.42	5	4.82	1.16
5.5	97.25	3.50	5.5	4.74	1.14
6	99.86	3.59	6	4.57	1.10
6.5	102.44	3.69	6.5	4.39	1.06
7	104.96	3.80	7	4.24	1.02
7.5	107.35	3.91	7.5	4.14	1.00
8	109.63	4.02	8	4.07	1.00
8.5	111.89	4.13	8.5	4.01	1.01
9	114.27	4.25	9	3.97	1.03
9.5	116.58	4.37	9.5	3.94	1.06
10	118.82	4.48	10	3.91	1.10
10.5	121.00	4.59	10.5	3.87	1.13
11	123.14	4.70	11	3.83	1.15
11.5	125.19	4.79	11.5	3.78	1.17
12	127.25	4.89	12	3.71	1.18
12.5	129.26	4.98	12.5	3.57	1.17
13	131.12	5.07	13	3.39	1.15
13.5	132.74	5.15	13.5	3.17	1.13
14	134.13	5.21	14	2.94	1.10
14.5	135.24	5.26	14.5	2.72	1.07
15	136.13	5.31	15	2.50	1.04
15.5	136.91	5.34	15.5	2.29	1.02
16	137.64	5.38	16	2.09	0.99
16.5	138.25	5.40	16.5	1.92	0.96
17	138.76	5.43	17	1.75	
17.5	139.19	5.45	17.5	1.60	
18	139.51	5.46	18	1.46	
18.5	139.99	5.49	18.5	1.31	
19	140.44	5.51	19	1.18	
19.5	140.90	5.53	19.5	1.05	
20	141.34	5.55	20	0.93	

Appendix Table 2 LMS values of weight and body mass index (BMI) for the Japanese girls with Turner syndrome

Weight				Body mass index			
Age (yr)	L	M	S	Age (yr)	L	M	S
1	0.26	7.74	0.14	1	−1.51	16.14	0.08
1.5	0.09	8.90	0.14	1.5	−1.48	15.99	0.08
2	−0.04	9.83	0.13	2	−1.46	15.89	0.08
2.5	−0.14	10.65	0.13	2.5	−1.44	15.82	0.08
3	−0.23	11.38	0.13	3	−1.42	15.75	0.08
3.5	−0.30	12.03	0.13	3.5	−1.40	15.69	0.08
4	−0.37	12.66	0.13	4	−1.38	15.62	0.08
4.5	−0.43	13.29	0.13	4.5	−1.36	15.56	0.08
5	−0.48	13.95	0.13	5	−1.34	15.53	0.09
5.5	−0.54	14.67	0.14	5.5	−1.32	15.55	0.09
6	−0.59	15.47	0.14	6	−1.29	15.62	0.10
6.5	−0.64	16.38	0.14	6.5	−1.27	15.77	0.10
7	−0.68	17.43	0.15	7	−1.24	15.99	0.11
7.5	−0.71	18.60	0.15	7.5	−1.21	16.27	0.11
8	−0.72	19.86	0.16	8	−1.18	16.59	0.12
8.5	−0.72	21.17	0.16	8.5	−1.14	16.94	0.12
9	−0.69	22.54	0.17	9	−1.09	17.31	0.13
9.5	−0.63	23.96	0.18	9.5	−1.05	17.69	0.13
10	−0.56	25.45	0.18	10	−1.00	18.07	0.14
10.5	−0.47	26.99	0.19	10.5	−0.95	18.45	0.14
11	−0.37	28.57	0.20	11	−0.89	18.81	0.14
11.5	−0.27	30.17	0.20	11.5	−0.84	19.16	0.15
12	−0.17	31.74	0.20	12	−0.79	19.48	0.15
12.5	−0.07	33.25	0.20	12.5	−0.74	19.79	0.15
13	0.02	34.68	0.20	13	−0.70	20.07	0.16
13.5	0.10	36.01	0.20	13.5	−0.66	20.33	0.16
14	0.17	37.21	0.20	14	−0.62	20.56	0.16
14.5	0.23	38.30	0.19	14.5	−0.58	20.77	0.16
15	0.29	39.26	0.19	15	−0.55	20.97	0.16
15.5	0.33	40.11	0.19	15.5	−0.51	21.13	0.16
16	0.38	40.84	0.18	16	−0.48	21.28	0.16
16.5	0.41	41.46	0.18	16.5	−0.46	21.41	0.16
17	0.44	41.97	0.18	17	−0.43	21.51	0.16
17.5	0.46	42.40	0.17	17.5	−0.40	21.60	0.16
18	0.48	42.75	0.17	18	−0.38	21.68	0.16
18.5	0.50	43.03	0.17	18.5	−0.36	21.74	0.16
19	0.51	43.26	0.17	19	−0.34	21.79	0.16
19.5	0.52	43.43	0.17	19.5	−0.32	21.84	0.16
20	0.53	43.57	0.17	20	−0.30	21.87	0.16

Appendix Table 3
LMS values of weight for height (WFH) for the Japanese girls with Turner syndrome

	Weight for height		
Height (cm)	L	M	S
45	–0.60	2.39	0.12
50	–0.61	3.55	0.11
55	–0.63	4.72	0.10
60	–0.64	5.84	0.10
65	–0.66	6.90	0.09
70	–0.68	7.95	0.09
75	–0.70	9.01	0.08
80	–0.73	10.15	0.08
85	–0.76	11.36	0.08
90	–0.80	12.6	0.08
95	–0.85	13.94	0.08
100	–0.91	15.56	0.09
105	–0.98	17.61	0.10
110	–1.01	20.16	0.11
115	–0.95	23.16	0.13
120	–0.78	26.52	0.14
125	–0.54	30.14	0.15
130	–0.32	34.06	0.15
135	–0.23	38.24	0.16
140	–0.36	42.52	0.16
145	–0.66	46.82	0.16
150	–1.01	51.10	0.16
155	–1.36	55.37	0.15