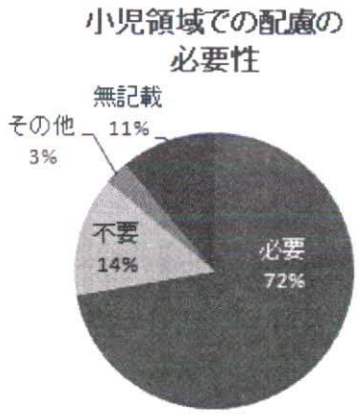
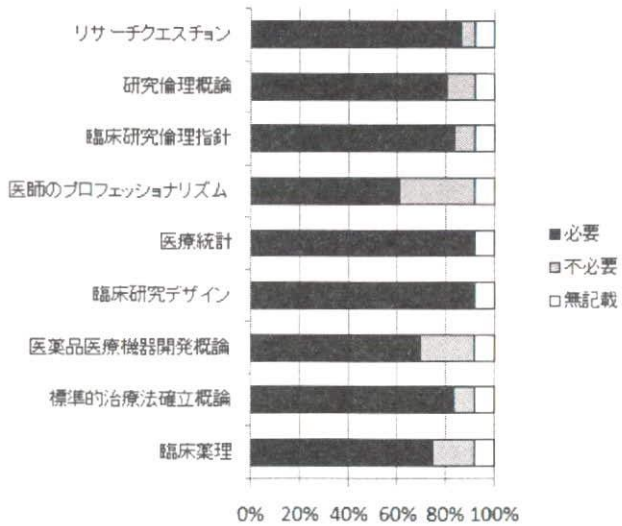


最後に、臨床研究を進めていくための教育プログラムの内容として、必要であるか否か問うた項目を示す。いずれも必要性は60%を超えるとの意見が多く（だいたい 80%超）、臨床研究を進めていくための教育プログラムとしてはこれらの章立てが必要であると考えられた。



この医療統計学セミナーは、臨床研究教育プログラム・パッケージで考えるところの医学生物統計の一形態の基本ともなるものであろう。今回、このような形態の講義・実習が、臨床研究に対する、経験年数の比較的浅い医師にとってはimprinting（刷り込み）、あるいは比較的経験を積んだ医師にとってはawareness（気づき）となっていること、そして何より、小児領域の臨床研究教育への要求になっていることが推察できた。

D. 考察

及び

E. 結論

質の高い臨床試験を適正に円滑に進めていくためには、GCPによる標準化ということの上に、プロジェクトマネジメントの考え方が必須である。

臨床試験のプロジェクトマネジメントを考察するに当たり、参加した国際医療福祉大学大学院の主催する乃木坂スクール「創薬育薬医療概論（CRA のための実践講座）」の中の「アウトソーシングの現状と利用の留意点－これからのモニター業務の実際と期待－」が参考になった。

臨床試験の流れの中で、医師が関わるべきであるのは、臨床データパッケージ（戦略立案のみならず、計画立案も含む）」、「安全性情報ハンドリング（の臨床的判断）」や「承認申請に係る部分（最終的な症例検討も含む）」であり、これは臨床試験に詳しい医師が中心となって、当該臨床試験に関係する（臨床）専門医も関与すべきである。特に、臨床試験のラショナーレを明確化し、その試験の位置付けをしっかりと研究者間で認識・共有できることが前提である。プロジェクトマネージャーは、その臨床試験が承認申請することを目的としているのであれば、臨床データパッケージ全体と、全体像からみた、その臨床試験の位置付けを十分論理的に考える必要がある。

その他の業務は医師でなく、専門の教育を受けたCRAが行う方がよいと考えられる。なぜなら、これらCRAが担った方がよいと思われ

る部分の業務については、その業務内容が臨床試験の種類によって極端に変わるものではなく、専門の教育を受けたCRAであれば、複数の小児領域の臨床試験を同時に取り扱うことが可能であると思われ、むしろ、それらによって蓄積されていく小児領域での経験による知見というものも積算されていき、貴重な財産となるはずのものであるからである。また、財産を散逸させないためにも、これらCRA業務を行う部署は臨床研究センター内に設置すべきである。

プロジェクトマネージャーは、臨床試験実施中は振り返り検討しながら、方向性をとりまとめ、適時に適確な指示を出し、研究参加医師、データマネージャー、CRCや医学生物学統計家との作業を横断的に調整できることが重要である。CRA中心に動いた方がよいと思われる部分についても、常に状況把握することが必要である。

国立成育医療センターの場合には、今後、研究と直接絡んだ治療などの開発、即ちトランスレーショナルリサーチというものも増えていくことであろうから、臨床研究センターのCRAにはCROとSMOの両面性を持つ必要があるであろう。

小児領域の多施設共同臨床試験を適正に円滑に遂行していくためには、プロジェクトマネージャーはもちろんのこと、小児領域の特殊性をよく理解し、製薬企業の治験にも精通したCRAやCRCなどの協力も保証された、系統的なプロジェクトマネジメント体制が確立されている上に、それらの有意義な運用が重要である。

これらの積み重ねが、近い将来、（国内）小児領域で臨床医がよりよい診断と治療を行うための、貴重な臨床試験方法論そのものとなろう。

F. 健康危険情報

該当する情報はない。

G. 研究発表

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3) 土田　尚．小児領域の医薬品開発や標準的治療法確立のための臨床試験．小児科診療 2009; 72; 651-658.

H. 知的財産権の出願・登録状況（予定を含む）

該当する事実・予定はない。

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研究成果の刊行に関する一覧表レイアウト

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Tsuyoshi Isojima, Susumu Yokoya, Junko Ito, Reiko Horikawa and Toshiaki Tanaka	Trend in Age and Anthropometric Data at Start of Growth Hormone Treatment for Girls with Turner Syndrome in Japan	Endocrine Journal	55 (6)	1065-1070	2008
Isojima T, Yokoya S, Ito J, Horikawa R, Tanaka T	Inconsistent determination of overweight by two anthropometric indices in girls with Turner syndrome	Acta Paediatrica	98	513-518	2009/04/09
Tsuyoshi Isojima, Susumu Yokoya, Junko Ito, Reiko Horikawa and Toshiaki Tanaka	New reference growth charts for Japanese girls with Turner syndrome	Pediatrics International	In press		
磯島豪，内木康博，堀川玲子，横谷進，田中敏章	小児における体格指数の検討　Body Mass Index (BMI) Zスコアと肥満度の相関　秋田県健常小児における検討	肥満研究	14 (2)	159-165	2008
土田　尚	小児領域の医薬品開発や標準的治療法確立のための臨床試験	小児科診療	72巻	651-658	2009
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研究成果の刊行物・別刷

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-

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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.

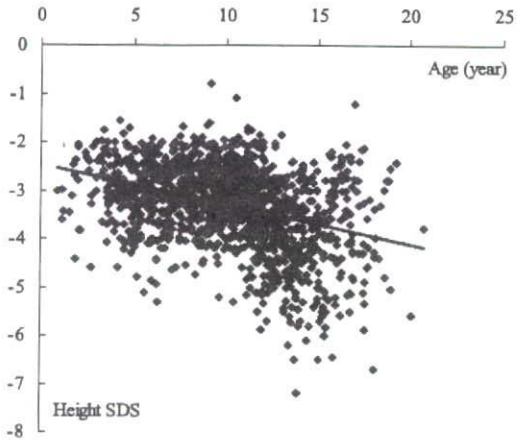

Fig. 1. Correlation between age at registration for GH treatment and height SDS for the normal population [25] ($r = -0.36$, $p<0.0001$). Although girls with TS shorter than –2 SDS receive approval for GH treatment in Japan, exceptional subjects above –2 SDS are judged eligible on an individual basis.

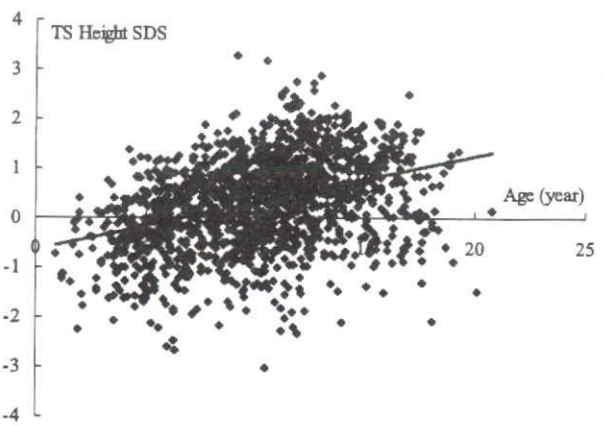

Fig. 2. Correlation between age at registration for GH treatment and height SDS for TS [26] ($r = 0.36$, $p<0.0001$).

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.

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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

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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

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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 pretreatment 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.

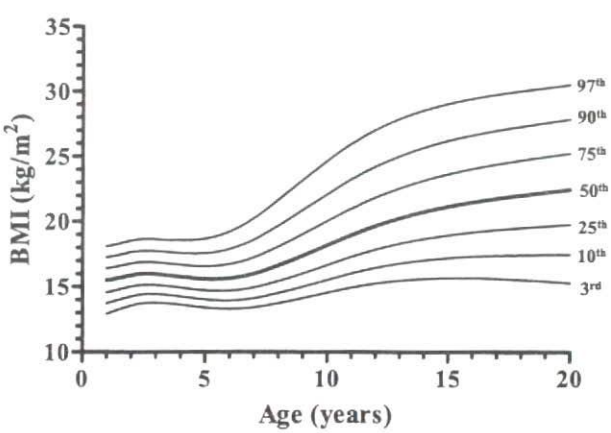

Figure 1 BMI chart for Japanese girls with Turner syndrome without puberty.

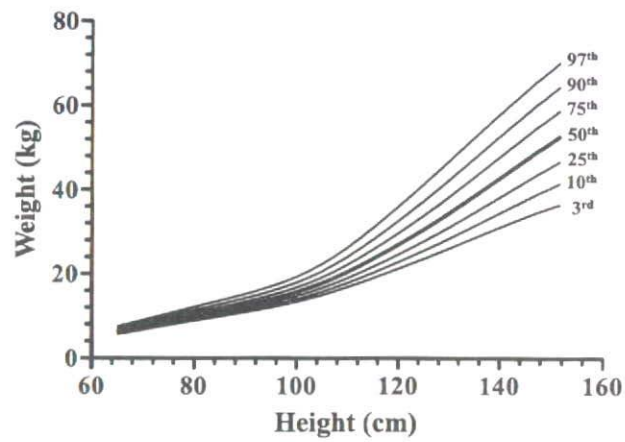

Figure 2 WFH chart for Japanese girls with Turner syndrome without puberty.

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

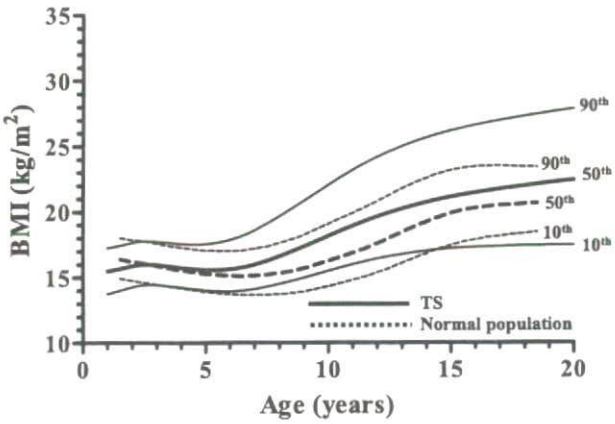

Figure 3 BMI chart for Japanese girls with Turner syndrome without puberty in comparison with normal population (20).

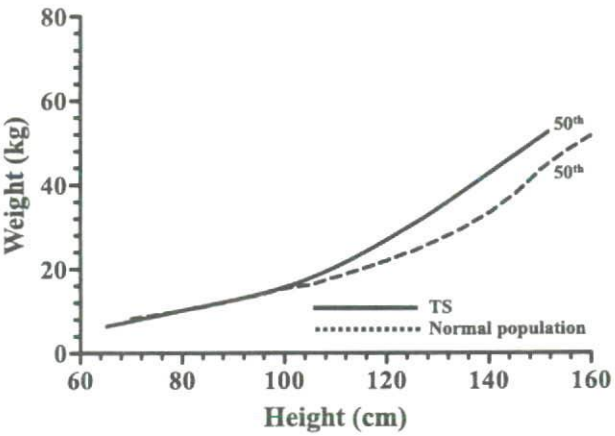

Figure 4 WFH chart for Japanese girls with Turner syndrome without puberty in comparison with normal population (17). Only the 50th percentile curves are shown, because WFH for the Japanese normal population has only values of the 50th percentile.

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.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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原著

小児における体格指数の検討：Body Mass Index(BMI)Zスコアと肥満度の相関

—秋田県健常小児における検討—

磯島　豪[*1,3]，内木　康博[*1]，堀川　玲子[*1,3]，横谷　進[*2,3]，田中　敏章[*3,4]

[*1]国立成育医療センター内分泌代謝科　[*2]国立成育医療センター第一専門診療部

[*3]国立成育医療センター臨床研究センター　[*4]たなか成長クリニック

索引用語：小児肥満，Body mass indey，肥満度，標準曲線

小児肥満判定に対する最適の体格指数は何かについての結論は，まだ出ていない．世界では，臨床研究や疫学研究にBody Mass Index(BMI)が，臨床に肥満度が多用されるが，日本では両方ともに肥満度が使用される傾向がある．理由の1つとして日本にBMIの標準曲線が存在しなかったことが挙げられるが，2006年にLMS法を用いて年齢ごとに正規化されたBMI標準曲線が報告された．今回の研究では，1975年4月より1976年3月の間に生まれ，6歳から17歳まで毎年1回身長・体重が秋田県で縦断的に測定された男子6,717人，女子6,926人を対象とした．BMI Zスコアと肥満度の相関を検討したところ，1歳ごとのすべての年齢で5次式にて有意で強い相関を認めた(男子R^2：0.946～0.998，女子R^2：0.907～0.995，すべて$p<0.0001$)．本研究により，2つの体格指数の有意で強い相関が認められたことから，BMI Zスコアは，肥満度と同様の意味で，臨床に使用できると考えられた．また，Benn Indexは，年齢とともに変化し，思春期ではべき数が3を超えていた．これは，思春期の肥満判定にローレル指数が使用されてきたことの合理性を示すことの1つであると考えられた．臨床現場では，小児科医は肥満判定にBMIを用いない傾向があると報告されているが，臨床研究や疫学研究では，世界的には，成人同様小児にもBMIを使用している．どちらが肥満判定に優れた体格指数であるかは不明であるが，本研究で示された2つの体格指数の良好な相関と，今後の肥満症についての予防や治療を含めた研究における成人との整合性を考え合わせると日本においても，少なくとも臨床研究や疫学研究には，BMIが積極的に使用されるべきであると考えられた．

はじめに

成人の肥満判定は主にBody Mass Index(BMI)で行われるが，小児肥満判定に対する最適の体格指数は，世界的に定まっていない[1]．成人の肥満判定は，肥満に伴う肥満症に関連した値からBMIによる基準値が定められ，日本では，25以上が肥満，22が理想値で

Correlation between body mass index z score and percent obesity in Japanese children in Akita prefecture

Tsuyoshi Isojima[*1,3], Yasuhiro Naiki[*1], Reiko Horikawa[*1,3], Susumu Yokoya[*2,3], Toshiaki Tanaka[*3,4]

[*1] Division of Endocrinology and Metabolism, National Center for Child Health and Development

[*2] Department of medical subspecialties , National Center for Child Health and Development

[*3] Clinical Research Center, National Center for Child Health and Development

[*4] Tanaka Growth Clinic