Naiki M, Mizuno S, Yamada K, Yamada Y, Kimura R, Oshiro M, Okamoto N, Makita Y, Seishima M, Wakamatsu N. MBTPS2 mutation causes BRESEK/BRESHECK syndrome. Am J Med Genet A. 2011 Nov 21. doi: 10.1002/ajmg.a.34373. [Epub ahead of print]

2．学会発表

林　深、チアキ・ウエハラ　ダニエラ、長縄光代、井本逸勢、蒔田芳男、羽田　明、稲澤譲治　オリゴアレイ・SNPアレイを用いた先天異常疾患におけるゲノム異常評価とアレイポテンシャルの比較　第56回日本人類遺伝学会　2011.11.9-12. 千葉

蒔田芳男、副島英伸　Hemihypertrophyにおける11番染色体短腕BWS領域の異常について　第56回日本人類遺伝学会　2011.11.9-12. 千葉

柳久美子、要　匡、岡本信彦、塚原正人、黒澤健司、泉川良範、福嶋義光、蒔田芳男、近藤郁子、Altincik Ayca、水野誠司、伊藤靖典、成富研二　Aarskog-Scott症候群患児におけるFGD1変異（速報）　第56回日本人類遺伝学会　2011.11.9-12. 千葉

H．知的財産権の出願・登録状況

なし。

1．特許取得

なし。

2．実用新案登録

なし。

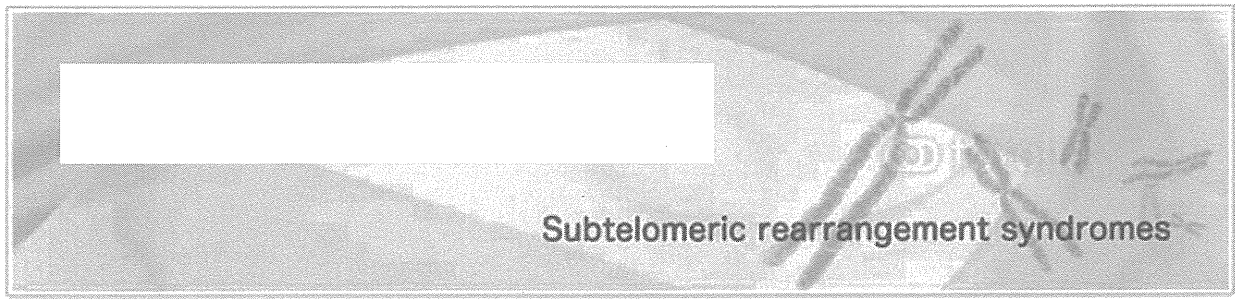
3．その他

特になし

Ⅲ．資料

サブテロメア微細構造異常症

Subtelomeric rearrangement syndromes



News & Topics

地方独立行政法人
神奈川県立病院機構
神奈川県立こども医療センター

公益社団法人
日本小児科学会

神奈川県立こども医療センター
遺伝科

ヤング・シンプソン症候群
の診断基準作成と実態把握に
関する研究

難病情報センター
Japan Intractable Diseases Information Center

〒232-8555　神奈川県横浜市南区六ツ川2-138-4　地方独立行政法人神奈川県立病院機構　神奈川県立こども医療センター遺伝科

Ⅳ．研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

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

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
Soneda A, Teruya H, Furuya N, Yoshihashi H, Enomoto K, Ishikawa A, Matsui K, Kurosawa K.	Proportion of malformations and genetic disorders among cases encountered at a high-care unit in a children's hospital.	Eur J Pediatr.	171	301-305	2012
Kurosawa K, Masuno M, Kuroki Y	Trens of occurrence of twin births in Japan.	Am J Med Genet Part A	158A	75-77	2012
Hirai N, Matsune K, O hashi H.	Craniofacial and oral featur es of Sotos syndrome: differ ences in patients with subm icroscopic deletion and muta tion of NSD1 gene	Am J Med G enet A.	155A	2933-9	2011
Shimizu K, Okamoto N, Miyake N, Taira K, Sa to Y, Matsuda K, Akim aru N, Ohashi H, Wak ui K, Fukushima Y, Ma tsumoto N, Kosho T.	Delineation of dermatan 4-O-sulfotransferase 1 deficient Ehlers-Danlos syndrome: observation of two additional patients and comprehensive review of 20 reported patients.	Am J Med G enet A	155A	1949-58	2011
Sakazume S, Ohashi H, Sasaki Y, Harada N, Nakanishi K, Sato H, Emi M, Endoh K, Sohma R, Kido Y, Nagai T, Kubota T.	Spread of X-chromosome inactivation into chromosome 15 is associated with Prader-Willi syndrome phenotype in a boy with a t(X;15)(p21.1;q11.2) translocation.	Hum Genet	131	121-30	2011
Okamoto N, Hatsukawa Y, Shimojima K, Yamamoto T.	Submicroscopic deletion in 7q31 encompassing CADPS2 and TSPAN12 in a child with autism spectrum disorder and PHPV.	Am J Med Genet A.	155A	1568-73	2011

Okamoto N, Tamura D, Nishimura G, Shimojima K, Yamamoto T.	Submicroscopic deletion of 12q13 including HOXC gene cluster with skeletal anomalies and global developmental delay.	Am J Med Genet A.	155A	2997-3001	2011
Naiki M, Mizuno S, Yamada K, Yamada Y, Kimura R, Oshiro M, Okamoto N, Makita Y, Seishima M, Wakamatsu N.	MBTPS2 mutation causes BRESEK/BRESHECK syndrome	Am J Med Genet A		Epub ahead of print	2011
Mizuno S, Fukushi D, Kimura R, Yamada K, Yamada Y, Kumagai T, Wakamatsu N	Clinical and genomic characterization of siblings with a distal duplication of chromosome 9q (9q34.1-qter)	Am J Med Genet A	155A	224-2280	2011
Liang JS, Shimojima K, Takayama R, Natsume J, Shichiji M, Hirasawa K, Imai K, Okanishi T, Mizuno S, Okumura A, Sugawara M, Ito T, Ikeda H, Takahashi Y, Oguni H, Imai K, Osawa M, Yamamoto T.	CDKL5 alterations lead to early epileptic encephalopathy in both genders.	Epilepsia	52(10):	1835-42	2011

Ⅴ．研究成果の刊行物・別刷

Eur J Pediatr (2012) 171:301–305
DOI 10.1007/s00431-011-1534-2

ORIGINAL PAPER

Proportion of malformations and genetic disorders among cases encountered at a high-care unit in a children's hospital

Akiko Soneda · Hideki Teruya · Noritaka Furuya · Hiroshi Yoshihashi · Keisuke Enomoto · Aki Ishikawa · Kiyoshi Matsui · Kenji Kurosawa

Received: 5 May 2011 / Accepted: 5 July 2011 / Published online: 16 July 2011

Abstract Genetic disorders and birth defects account for a high percentage of the admissions in children's hospitals. Congenital malformations and chromosomal abnormalities are the most common causes of infant mortality. So their effects pose serious problems for perinatal health care in Japan, where the infant mortality is very low. This paper describes the reasons for admissions and hospitalization at the high-care unit (HCU) of a major tertiary children's referral center in Japan. We retrospectively reviewed 900 admission charts for the period 2007–2008 and found that genetic disorders and malformations accounted for a significant proportion of the cases requiring admission to the HCU. Further, the rate of recurrent admission was higher for patients with genetic disorders and malformations than for those with acquired, non-genetic conditions. Over the past 30 years, admissions attributed to genetic disorders and malformations has consistently impacted on children's hospital and patients with genetic disorders and malformations form a large part of this facility. These results reflect improvements in medical care for patients with genetic disorders and malformations and further highlight the large proportion of cases with genetic disorders, for which highly specialized management is required. Moreover, this study emphasizes the need for involvement of clinical geneticists in HCUs at children's hospitals.

Keywords Malformation · Genetic disease · High-care unit · Children's hospital · Mortality

Grant sponsor The Ministry of Health, Labor and Welfare, Japan

A. Soneda · N. Furuya · H. Yoshihashi · K. Enomoto · A. Ishikawa · K. Kurosawa (✉)
Division of Medical Genetics,
Kanagawa Children's Medical Center,
2-138-4 Mutsukawa, Minami-ward,
Yokohama 232-8555, Japan
e-mail: kkurosawa@kcmc.jp

H. Teruya
Division of Critical Care Medicine,
Kanagawa Children's Medical Center,
Yokohama, Japan

K. Matsui
Division of General Pediatrics,
Kanagawa Children's Medical Center,
Yokohama, Japan

H. Teruya
Department of Pediatrics, Yokohama Rosai Hospital,
Yokohama, Japan

K. Kurosawa
Clinical Research Institute, Kanagawa Children's Medical Center,
Yokohama, Japan

Introduction

Genetic disorders and birth defects account for a high percentage of the admissions to children's hospitals [4, 13]. In 2008 [5], the Ministry of Health, Labor and Welfare in Japan reported that congenital malformations, chromosomal abnormalities, and genetic diseases are the leading causes of death in children during the first year of life. As per that report, 999 infants under the age of 1 year died of congenital malformations and chromosomal abnormalities; this corresponds to 35.7% of the total number of deaths in this age group. Since 1985, congenital malformations and chromosomal abnormalities have remained the leading causes of infant mortality in Japan [5]. Indeed, in USA it

has been found that patients with genetic disorders had a greater need for hospital admission and were hospitalized for longer durations than were those without genetic disorders [14].

However, recent advances in treatment are likely to improve the survival of individuals with congenital malformations, which, in turn, is likely to increase the rates of readmission to pediatric intensive care units (PICUs) [16]. Several studies have assessed the role of genetic disorders in pediatric mortality and hospitalization [2, 6, 7, 16]. Congenital malformations and chromosomal abnormalities pose serious challenges for perinatal health care in this country, as they are the leading contributors to the infant mortality rate in Japan.

In this study, we assessed the reasons for admissions and hospitalization to the high-care unit (HCU) of a major tertiary children's referral center in Kanagawa Prefecture, Japan, and compared our findings to those of a study of this unit 30 years ago. To elucidate the impact and contribution of birth defects and genetic diseases on pediatric hospitalization, we studied the reason for hospitalization, underlying diagnoses, and duration of hospitalization in this children's hospital in Japan.

Materials and methods

Permission for the study was obtained from the Ethical Committee of our medical center.

We retrospectively analyzed the cases of children hospitalized at the HCU of Kanagawa Children's Medical Center (KCMC) between June 2007 and December 2008. KCMC is a major tertiary children's referral center for pediatric cardiology, surgery, and cancer cases and serves a large area in Kanagawa Prefecture, Japan. It has an institute for the severely handicapped, a PICU, a neonatal intensive care unit, and an HCU. In contrast to the PICU, which admits patients who have undergone cardiovascular or neurosurgery, the HCU specializes in pediatric patients with other acute conditions. All of the patients were included if they were admitted to the HCU from the emergency room, operating room, or inpatient ward. KCMC, with 419 beds, is the only specialized pediatric hospital in Kanagawa Prefecture, where the total number of births is 80,000 annually [8, 9]. About 8,500 patients (male/female, 1:1) were admitted to KCMC in 2007, and the average of hospital stay was 15.3 days.

We summarized and reviewed the medical charts of all patients admitted to the HCU. The charts and summaries were reviewed for age, sex, duration of hospitalization, underlying disease, and reason for admission. Subcategories were created for the underlying diseases and reason for admission.

The underlying disease was classified into two main categories: genetic conditions and acquired (non-genetic) conditions. Genetic conditions were considered to include chromosomal abnormalities, recognizable malformation and dysplasia, multiple malformations, isolated malformations (e.g., those related to the heart, central nervous system (CNS), and respiratory and gastrointestinal tracts), other single-gene defect-related conditions, mitochondrial diseases, and metabolic disorders (Table 1). All cases of chromosomal abnormalities and multiple malformations were examined using standard karyotyping. Cases of recognizable malformation/dysplasia were ascertained by clinical dysmorphologists (H.Y., N.F., and K.K.). Acquired conditions were considered to include perinatal complications, trauma, neoplasm, and sequelae of severe infectious conditions.

The reasons for admission were classified as problems of the respiratory system, CNS, heart, gastrointestinal tract, kidneys and urinary tract, infectious diseases, post-operative management, and unknown condition. Those cases that did not fall into these categories were placed into a category called "others."

Statistical analyses were performed to compare the duration of hospitalization and the age distribution, using StatView version 5.0 (SAS Institute, Inc; Cary, NY). Categorical data were reported as counts and percentages, and continuous data as mean (SD) or median values. Statistical differences for categorical variables were determined by using chi-squared analyses. Median differences were compared by Mann–Whitney U test.

Results

A total of 900 admissions, consisting of 687 individual cases with 200 recurrent admissions, were reviewed. Sixteen admissions were excluded from the study because of insufficient information regarding the underlying causes for admission.

The median age at admission was 3.5 years (range, 1 day–32.5 years), and the sex ratio was 1.36 (396 males and 291 females). The median lengths of hospitalization in the HCU were 4 days. Table 2 shows the distribution of the 884 admissions across the different categories of causes for admission. Most patients were admitted for common medical problems, including respiratory problems, post-operative management, and CNS problems. Of the 298 admissions for respiratory problems, most cases involved respiratory infection, including pneumonia and bronchitis. Admissions for post-operative management accounted for 30.7% cases (271 of 884 admissions), while CNS problems such as convulsions, encephalitis, and meningitis accounted for 16.3% (144 of 884 admissions).

Table 1 Definitions of categories

Category	Examples
Chromosomal syndromes	Down syndrome, trisomies 13 and 18, cri du chat syndrome, and Wolf–Hirschhorn syndrome
Recognizable malformation/dysplasia	22q11.2 deletion syndrome, CHARGE syndrome, and VATER association, Lowe syndrome, achondroplasia, Crouzon syndrome, Noonan syndrome, and Treacher–Collins syndrome
Multiple malformations	
Isolated malformations	
Congenital heart diseases	VSD ASD, AVSD, TGA, and DORV
Central nervous system malformations	Schistorrhachis, hydrocephalus, and meningoencephalocele
Gastrointestinal malformations	Diaphragmatic hernia, biliary atresia, and congenital intestinal obstruction
Respiratory system malformations	CCAM and tracheal stenosis
Other isolated malformations	Cleft palate and cleft lip
Single-gene defect	Metabolic diseases, spinal muscular atrophy, and spinocerebellar degeneration
Mitochondrion	

The classification of the underlying conditions of the 687 patients is shown in Table 3. In 13 cases, the data for identifying the underlying disease were insufficient (e.g., charts were missing). These cases were categorized as "unknown condition." Of the total 687 patients, 372 (54.1%) had genetic disorders and the remaining 302 (44.0%) had acquired conditions unrelated to genetic disorders, including perinatal complications, neoplasm, and trauma. Among the 372 patients with genetic disorders, 72 had chromosomal abnormalities, with Down syndrome (29 cases) being the most common underlying disorder. Seventy patients had recognizable malformations and dysplasia, with conditions such as osteogenesis imperfecta, 22q11.2 deletion syndromes, CHARGE syndrome, and VATER association. Multiple malformations with unrecognizable patterns were present in 38 cases while isolated malformations, including CNS malformation, congenital heart disease, and gastrointestinal malformation were present in 160 cases.

We also summarized the reasons for the total of 884 admissions, according to the underlying condition (genetic or acquired). Of these admissions, 200 were readmissions. Patients with genetic disorders and malformations had a greater tendency to be hospitalized repeatedly as compared with those with acquired conditions (Fig. 1). In both genetic and acquired condition categories, respiratory disease, post-operative management, and CNS problems were the major medical problems leading to admission.

We further compared age distribution and the lengths of hospitalization between the groups with genetic and acquired disorders (Table 4). The patients with genetic

Table 2 Medical problems for admission (N=884)

Causes for admission	Number	Percent
Respiratory problems	298	33.7
Post-operative management	271	30.7
CNS problems	144	16.3
Gastrointestinal problems	35	4.0
Cardiac diseases	23	2.6
Other infectious state	23	2.6
Examination	21	2.4
Kidney and urinary tract problems	14	1.6
Other	55	6.2
Total	884	100.0

Table 3 Classification of underlying diseases in 678 patients

Underlying diseases	Number	Percent
Genetic disorders and malformations (subtotal)	372	54.1
Chromosomal abnormalities	(72)	10.5
Recognizable malformation/dysplasia	(70)	10.2
Multiple malformations	(38)	5.5
Isolated malformations	(subtotal:160)	23.3
Central nervous system malformation	(71)	10.3
Congenital heart disease	(35)	5.1
Gastrointestinal malformation	(32)	4.7
Respiratory system malformation	(9)	1.3
Other isolated malformations	(13)	1.9
Single-gene defect	(26)	3.8
Mitochondrion	(6)	0.9
Acquired non-genetic conditions (subtotal)	302	44.0
Perinatal complications	(66)	9.6
Neoplasm	(38)	5.5
Trauma(non-accidental and accidental)	(27)	3.9
Infection	(16)	2.3
Other	(155)	22.6
Unknown	13	1.9
Total	687	100.0

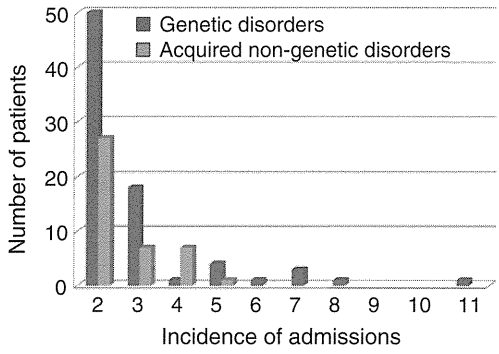


Fig. 1 Comparison of the incidence of admission between the groups with genetic disorders and acquired disorders. In both groups, a total of 200 patients were readmitted. The group with genetic disorders generally required frequent readmission

disorders were significantly younger than those with acquired conditions (median age, 2.0 vs. 4.9 years; $P<0.0001$). There is no significant difference in the length of hospitalization between the patients with genetic disorders and those with acquired conditions (median, 4 vs. 4 days; $P=0.26$), but some patients with genetic disorders had much longer hospitalization (mean, 13.0 vs. 7.0 days; $P=0.007$; range, 1–979 days). Among the reasons for admission, respiratory problems tended to have a longer duration of hospitalization for patients with genetic disorders than for those with acquired conditions (median, 7 vs. 5 days; $P=0.17$).

Discussion

Our study shows that genetic disorders and malformations account for a significant proportion of cases requiring admission to the HCU. Additionally, the rate of recurrent admission was higher among patients with genetic disorders and malformations than among those with acquired non-genetic conditions. This finding is in agreement with those of previous reports for other countries [4, 13].

Several studies from different countries have previously suggested that genetic conditions and malformations and the associated mortality and morbidity have a significant impact on the cost burden for society and the patients' families. Cunniff et al. reported that 19% of deaths in a PICU were in cases of heritable disorders [1]. Stevenson and Carey reported that the 34.4% of deaths in a children's hospital were due to malformations and genetic disorders [15]. On the basis of a population-based study, Yoon et al. reported that the overall rate of hospitalization was related to birth defects and genetic diseases, and varied with age and race/ethnicity [16]. McCandless et al. reported the enormous impact of genetic disease on inpatient pediatrics and the health care system in both admission rates and the total hospital charges [11]. These studies emphasize the importance of understanding the impact that genetic diseases have on mortality and healthcare strategies [15]. Furthermore, it is also clear that early recognition of the underlying disorders is necessary for optimal management of patients with genetic disorders.

Our study highlights another aspect related to the impact of genetic disorders and malformations. In 1981, Matsui et al. analyzed the cases of 18,736 children of total admission during 1975–1979 to KCMC and found that 44% had genetic disorders and malformations [10]. Although our study period and ward are limited to those in the HCU, the patients with genetic disorders and malformations had consistently significant impact in KCMC during the ensuing three decades. Further, it emphasizes that medical care for acute conditions and surgical procedures frequently requires highly specialized knowledge of unusual disease conditions and should be provided in consultation with specialists such as clinical geneticists.

Table 4 Comparison of patients with genetic disorder vs. acquired condition on ages at admission and lengths of stay

	Genetic disorders		Acquired conditions		
	Median (range)	*n*	Median (range)	*n*	*P*
Ages	2.0 years (1 day–27.0 years)	372*	4.9 years (9 days–32.5 years)	302*	<0.0001
Length of hospitalization (days)					
Respiratory problem	7 (1–979)	182	5 (1–97)	109	0.17
CNS	4 (1–54)	73	4 (1–207)	68	0.61
Cardiovascular	4 (2–11)	13	4 (2–24)	8	0.94
Gastrointestinal	5.5 (1–37)	22	5 (2–15)	12	0.60
Kidney and urinary tract	3 (2–12)	5	8 (2–12)	9	0.32
Sepsis	3.5 (2–9)	14	7 (2–20)	9	0.19
Post-operative care	2 (1–49)	174	2 (1–62)	93	0.18
Total	4 (1–979)	518	4 (1–207)	366	0.26

*For the patients who have recurrent admissions, the only first admission was calculated

Although the strategies for management of respiratory infection, by means of newly developed antibiotics and mechanical ventilators, and surgical intervention for infants with malformations, have improved, the general strategies for the medical treatment of genetic disorders and malformations remain to be clarified. Hall commented on the report by Yoon et al. [16] and emphasized the significance of basic research on the human genome and developmental genetics [3]. As shown in Table 2, genetic disorders and malformations include rare diseases, which, although uncommon, remain an important public-health issue and a challenge for the medical community [12].

Our study had the limitations of genetic studies and evaluation in cases with multiple malformations and other isolated malformations. The underlying conditions of most patients in this study were ascertained by clinical geneticists, but high-resolution genome analysis with arrays using comparative genomic hybridization was applied in only limited cases. Recently, research attention has focused to a large extent on rare genetic disorders and Mendelian diseases, because of their significant effect on human health, with the aim of identifying disease-related genetic variations. Re-evaluation and classification of underlying disorders, especially in the case of multiple congenital anomalies in undiagnosed patients, are required for further analysis.

Another limitation of our study is estimation of the financial burden of the group of patients with a genetic background. McCandless et al. showed that the disorders with genetic determinant account for 81% of the total hospital charges [11]. Their results are consistent with those of Hall et al. in 1978 [4]. Further analysis of financial burden in our study may provide useful information for improvement of health care systems.

In conclusion, we report here the proportion of genetic disorders and malformations among cases encountered at the HCU of a tertiary children's medical center in Japan. Over 30 years, the proportion of admissions attributed to genetic disorders and malformations has impact and currently accounts for more than half of admissions to this facility. These results firstly indicate improvements in medical care for patients with genetic disorders and malformations and further highlight the large proportion of cases with genetic disorders. As these cases require highly specialized management, the involvement of clinical geneticists in HCUs at children's hospitals is crucial. Eventually, a better fundamental understanding of genetic disorders and malformations may lead to further improvements in medical care and may reduce the impact of these conditions on the patients and their families.

Acknowledgments The authors are grateful to Dr. Hiroyuki Ida (Tokyo Jikei University) for his valuable comments. This research was supported in part by a grant-in-aid from the Ministry of Health, Labor and Welfare, Japan.

Conflict of interest The authors declare no conflict of interest.

References

1. Cunniff C, Carmack JL, Kirby RS, Fiser DH (1995) Contribution of heritable disorders to mortality in the pediatric intensive care unit. Pediatrics 95:678–681
2. Garrison MM, Jeffries H, Christakis DA (2005) Risk of death for children with Down syndrome and sepsis. J Pediatr 147:748–752
3. Hall JG (1997) The impact of birth defects and genetic diseases. Arch Pediatr Adolesc Med 151:1082–1083
4. Hall JG, Poweres EK, McIlvaine RT, Ean VH (1978) The frequency and financial burden of genetic disease in a pediatric hospital. Am J Med Genet 1:417–436
5. Health and Welfare Statistics Association (2010) Mortality rate of infant. J Health Welfare Statist 57:63–65, in Japanese
6. Heron M, Sutton PD, Xu J, Vetura SJ, Strobino DM, Guyer B (2010) Annual summary of vital statistics: 2007. Pediatrics 125:4–15
7. Hudome SM, Kirby RS, Senner JW, Cunniff C (1994) Contribution of genetic disorders to neonatal mortality in a regional intensive care setting. Am J Perinatol 11:100–103
8. Kuroki Y, Konishi H (1984) Current status and perspectives in the Kanagawa Birth Defects Monitoring Program (KAMP). Cong Anom 24:385–393
9. Kurosawa K, Imaizumi K, Masuno M, Kuroki Y (1994) Epidemiology of limb-body wall complex in Japan. Am J Med Genet 51:143–146
10. Matsui I, Naito K, Hanawa Y et al (1981) Impact of the congenital birth defects on children's health care. J Jpn Pediatr Soc 85:889–897, in Japanese
11. McCandless SE, Brunger JW, Cassidy SB (2004) The burden of genetic disease on inpatient care in a children's hospital. Am J Hum Genet 74:121–127
12. Schieppati A, Henter J-I, Daina E, Aperia A (2008) Why rare diseases are an important medical and social issue. Lancet 371:2039–2041
13. Scriver CR, Neal JL, Saginur R, Clow A (1973) The frequency of genetic disease and congenital malformation among patients in a pediatric hospital. Can Med Assoc J 108:1111–1115
14. Sever L, Lynberg MC, Edmonds LD (1993) The impact of congenital malformations on public health. Teratology 48:547–549
15. Stevenson DA, Carey JC (2004) Contribution of malformations and genetic disorders to mortality in a children's hospital. Am J Med Genet 126A:393–397
16. Yoon PW, Olney RS, Khoury MJ, Sappenfield WM, Chavez GF, Taylor D (1997) Contribution of birth defects and genetic diseases to pediatric hospitalizations. Arch Pediatr Adolesc Med 151:1096–1103

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Trends in Occurrence of Twin Births in Japan

Kenji Kurosawa,[1]* Mitsuo Masuno,[2] and Yoshikazu Kuroki[2]

[1]Division of Medical Genetics, Kanagawa Children's Medical Center, Yokohama, Japan

[2]Kawasaki University of Medical Welfare, Kurashiki, Japan

Received 1 May 2011; Accepted 3 October 2011

The rise in the rate of multiple births since the 1980s is due to the effect of advanced maternal age and increased use of assisted reproductive technology (ART). To determine the trends of prevalence in twin births, we studied the data of a population-based birth defects monitoring system during 26 years in Kanagawa Prefecture, Japan. A total of 15,380 twins from 7,690 deliveries were ascertained from 990,978 births in the Kanagawa Birth Defects Monitoring Program (KAMP) during 1981–2008. From the start of KAMP in 1981, the incidence of twin births had been consistently increasing from 57.0 to 98.6 per 10,000 deliveries until 2003, but after this time, the incidence declined to 78.5 in 2007. While the rate of monozygotic twins has been stable (~40 per 10,000 deliveries) after 1990, that of dizygotic twins increased from 25.3 to 57.3 per 10,000 deliveries until 2002, and recovered to 40.1 in 2007. These results showed the most recent tendency of twin births and indicated that the single embryo transfer method can provide protection and reduction of perinatal risk caused by multiple births.

Key words: assisted reproductive technology (ART); twin; Kanagawa Birth Defects Monitoring Program (KAMP); zygosity

How to Cite this Article:
Kurosawa K, Masuno M, Kuroki Y. 2011. Trends in occurrence of twin births in Japan. Am J Med Genet Part A.

INTRODUCTION

Multiple births including twin births have several implications for maternal and child health care. Twin pregnancy is associated with an increased incidence of anomalies [Bahtiyar et al., 2007; Glinianaia et al., 2008; Hardin et al., 2009a], a higher risk of perinatal mortality, and preterm births with low birth weight [Helmerhorst et al., 2004; McDonald et al., 2005] compared with singleton pregnancy. A tendency for an increasing rate of twin delivery has been observed in 14 out of 16 countries in Europe, Canada, Australia, Singapore, and Hong Kong [Imaizumi 1998]. This tendency has also been observed in Japan [Imaizumi 2000]. The rise in the rate of multiple births is due to the effect of advanced maternal age and increased use of assisted reproductive technology (ART) [Bondel and Kaminski, 2002]. In the USA and Europe, between 20 and 30% of deliveries following ART are twin births compared with 1% following spontaneous conception [Andersen et al., 2008; Wright et al., 2008]. However, the rate of twin pregnancies in the USA has stabilized at 32 per 1,000 births in 2006 [Chauhan et al., 2010]. In Australia, recent data indicated that the proportion of twin deliveries decreased in 2006 [Wang et al., 2008].

To determine the trends of prevalence in twin births, we studied the data of a population-based birth defects monitoring system during 26 years between 1981 and 2008 in Kanagawa Prefecture, Japan. Kanagawa Prefecture, which is adjacent to Tokyo, includes Yokohama City with a total population 3,687,000. To investigate the effects of ART, we analyzed the data of twins according to the zygosity during the study period.

MATERIALS AND METHODS

A total of 15,380 twins from 7,690 deliveries were ascertained from 990,978 births in the Kanagawa Birth Defects Monitoring Program (KAMP). This program has been in operation since October 1981 as the first population-based monitoring system in Japan. Details of KAMP are described elsewhere [Kuroki et al., 1982; Kuroki and Konishi, 1984, 1992; Kuroki, 1988; Kurosawa et al., 1994; Yuan et al., 1995]. KAMP covers one-half of the total births (40,000 births annually) in Kanagawa Prefecture. All live births and stillbirths are screened for 44–48 marker malformations (only surface anomalies), arranged in 10–11 groups, and they are examined by general obstetricians or occasionally by general pediatricians within 7 days after birth. During the study period between 1981 and 2008, the KAMP was divided into four stages according to a minor modification in marker anomalies and registration systems. The first two stages, for 1981–1983 and 1984–1988, had total birth registration systems including all the malformed infants, normal

Grant sponsor: Ministry of Health, Labour and Welfare, Japan.
*Correspondence to:
Kenji Kurosawa, MD, PhD, Division of Medical Genetics, Kanagawa Children's Medical Center, 2-138-4 Mutsukawa, Minami-ku, Yokohama 232-8555, Japan. E-mail: kkurosawa@kcmc.jp
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.a.34362

infants, and all multiple births. However, in the last two stages, 1989–2000 and 2001–2008, all malformed infants as well as all multiple births were registered with two consecutive normal infants. Information on zygosity is not available in the KAMP, and therefore, we used Weinberg's differential rule for zygosity estimation [Fellman and Eriksson, 2006; Hardin et al., 2009b]. The incidence of twin births was defined as the number of twin pairs per total deliveries.

RESULTS

During the period of analysis, the incidence of malformed infants was 0.88% in live births and 17.24% in stillbirths. The sex ratio was 1.05. From the start of KAMP at 1981, the incidence of twin births had been consistently increasing from 57.0 to 98.6 per 10,000 deliveries until 2003 (Fig. 1). This tendency is consistent with the results of previous studies [Imaizumi, 1998, 2000]. The incidence of twin births peaked at 98.6 per 10,000 deliveries in 2003, but after this time, the incidence declined to 78.5 per 10,000 deliveries in 2007. The incidence of monozygotic twins fluctuated during the first 10 years, but after 1990 the incidence was stable at 40 per 10,000 deliveries. The incidence of dizygotic twins increased from 25.3 to 57.3 per 10,000 deliveries in 2002, but rapidly decreased to 40.1 in 2007, while the incidence of monozygotic twins was stable (Fig. 2). These results indicated that the incidence of twins is directly affected by the rate of dizygotic twins, and that the incidence of dizygotic twin births has already reached its peak, at least in the urban area of Japan.

DISCUSSION

Our study found that during the last 20 years, the incidence of twin births increased from 57 to 98 per 10,000 deliveries, but after it reached a peak in 2003, it recovered to 78.5 per 10,000 deliveries in 2007. Our study demonstrated that the trend in twin births was affected by the incidence of dizygotic twins. The incidence of monozygotic twins was stable at 40 per 10,000 deliveries, while that of dizygotic twin births attained a peak in 2002 with 57.3 per 10,000 deliveries, and it declined to 40.1 after this time. To the best

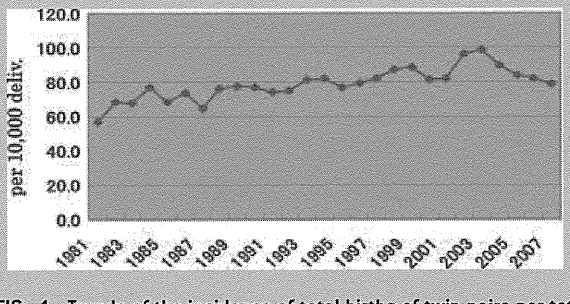


FIG. 1. Trends of the incidence of total births of twin pairs per total deliveries in Japan. The rate of twin births consistently increased from 57.0 per 10,000 deliveries in 1981 to 98.6 in 2003, but after this time, the rate recovered to that of the 1990s.

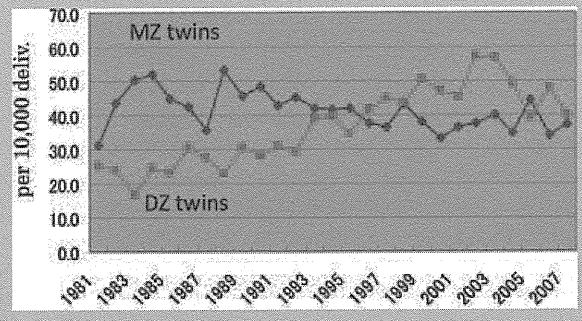


FIG. 2. Comparison of the rate of twin births between monozygotes and dizygotes. In the first 10 years, the fluctuation was remarkable in the rate of births in monozygotic twins for unknown reasons, but during the last 20 years, the rate was stable at approximately 40 per 10,000 deliveries. However, the rate of dizygotic twins consistently increased to reach a peak in 2003, and it then rapidly decreased.

of our knowledge, this is the first report describing the trends of a decrease in the rate of twin births in Japan. Because the rates of monozygotic twins are thought to be constant throughout the world, our results on the tendency of the rates of monozygotic twins have implication of the accuracy of the study. In the USA, between 1980 and 2006, the rate of twin pregnancies consistently increased from 18.9 to 32.1 per 1,000 births [Chauhan et al., 2010]. However, the rapid rise appeared to end in 2004 and the rate stabilized in 2006. A rise in the prevalence of twin births has also been observed in Austria, Finland, Norway, Sweden, Canada, Australia, Hong Kong, Israel, and Singapore [Imaizumi, 1997]. The rate of twin births in these countries stabilized between 2004 and 2006, and recent trends of a decreasing rate has been reported in some countries [Wang et al., 2008].

Clearly, the use of ART has contributed to the changes in the rate of twin pregnancies [Wright et al., 2008; Hansen et al., 2009]. ART twins have a greater risk of adverse perinatal outcome including preterm birth, low birth weight, and cerebral palsy compared with spontaneously conceived twins and singletons [Hansen et al., 2009]. The use of single embryo transfers reduces multiple birth rates and the risks of these adverse outcomes following ART. According to a report from the European Society of Human Reproduction and Embryology, compared with the number of cycles in 2003, fewer embryos were transferred in Germany in 2004, but there were still huge differences between countries [Andersen et al., 2008]. This transfer policy had a considerable impact in Belgium, Finland, Sweden, and several other countries [Andersen et al., 2008], and therefore, a reduced rate of twin births may be observed within a few years in these countries. In the case of Japan, the reduction of the rate was rapid, but a stable rate was not observed at the end of the study period. The rate of twin births may be stabilized when there is a balance between maternal age distribution in reproductive generation and establishment of technical standardization of single embryo transfer. Further analysis on the rates of multiple births based on the population-based monitoring system is required to determine the impact of ART.

ACKNOWLEDGMENTS

The authors are grateful to The Association of Obstetrics and Gynecology in Kanagawa Prefecture for participating in the KAMP, which made this work possible. This study was supported in part by a grant from the Ministry of Health, Labour and Welfare, Japan.

REFERENCES

Andersen AN, Goossens V, Ferraretti AP, Bhattacharya S, Felberbaum R, de Mouzon J, Nygren KG, The European IVF-monitoring (EIM) Consortium, for the European Society of Human Reproduction and Embryology (ESHRE). 2008. Assisted reproductive technology in Europe, 2004: Results generated from European resisters by ESHRE. Hum Reprod 23:756–771.

Bahtiyar MO, Dulay AT, Weeks BP, Freidman AH, Copel JA. 2007. Prevalence of congenital heart defects in monochorionic/diamniotic twin gestations: A systematic literature review. J Ultrasound Med 26:1491–1498.

Bondel B, Kaminski M. 2002. Trends in the occurrence, determinants, and consequences of multiple births. Semin Perinatol 26:239–249.

Chauhan SP, Scardo J, Hayes E, Abuhamad AZ, Berghella V. 2010. Twins: Prevalence, problems, and preterm births. Am J Obstet Gynecol 203: 305–315.

Fellman J, Eriksson AW. 2006. Weinberg's differential rule reconsidered. Hum Biol 78:253–275.

Glinianaia SV, Rankin J, Wright C. 2008. Congenital anomalies in twins: A register-based study. Human Reprod 23:1306–1311.

Hansen M, Colvin L, Petterson B, Kurinczuk JJ, de Klerk N, Bower C. 2009. Twins born following assisted reproductive technology: perinatal outcome and admission to hospital. Hum Reprod 24: 2321–2331.

Hardin J, Selvin S, Carmichael SL, Shaw GM. 2009a. The estimated probability of dizygotic twins: A comparison of two methods. Twin Res Hum Genet 12:79–85.

Hardin J, Carmichael SL, Selvin S, Lammer EJ, Shaw GM. 2009b. Increased prevalence of cardiovascular defects among 56,709 California twin pairs. Am J Med Genet Part A 149A:877–886.

Helmerhorst FM, Perquin DA, Donker D, Keise MJ. 2004. Perinatal outcome of singleton and twins after assisted conception: A systematic review of controlled studies. BMJ 328:261.

Imaizumi Y. 1997. Trends of twinning rates in ten countries, 1972–1996. Acta Genet Med Gemellol (Roma) 46:209–218.

Imaizumi Y. 1998. A comparative study of twinning and triplet rates in 17 countries, 1972–96. Acta Genet Med Gemellol (Roma) 47:101–114.

Imaizumi Y. 2000. Epidemiology of multiple births in Japan, 1951–1998. In: Yanaihara T, editor. Study on reproductive assisted medical service in Japan. Tokyo: Ministry of Health and Welfare of Japan. pp 776–793 (in Japanese).

Kuroki Y, Konishi H, Tsunoda A, Tadokoro F, Adachi K, Yagi S. 1982. A preliminary report on Kanagawa Birth Defects Monitoring Program (KAMP). Cong Anom 22:223–228.

Kuroki Y, Konishi H. 1984. Current status and perspectives in the Kanagawa Birth Defects Monitoring Program (KAMP). Cong Anom 24:385–393.

Kuroki Y. 1988. Monitoring of congenital anomalies. Cong Anom 28:S89–S99.

Kuroki Y, Konishi H. 1992. Monitoring of congenital anomalies in Japan. International Conference on Radiation Effects and Protection (Proceeding), Japan Atomic Energy Research Institute, pp 59-64.

Kurosawa K, Imaizumi K, Masuno M, Kuroki Y. 1994. Epidemiology of limb-body wall complex in Japan. Am J Med Genet 51:143–146.

McDonald S, Murphy K, Beyene J, Ohlsson A. 2005. Perinatal outcomes of in vitro fertilization twins: A systematic review and meta-analyses. Am J Obstet Gynecol 193:141–152.

Wang YA, Dean JH, Badgery-Parker T, Sullivan EA. 2008. Assisted reproduction technology in Australia and New Zealand 2006. Assisted reproduction technology series no. 12. AIHW cat. no. PER 43. Sydney: AIHW National Perinatal Statistics Unit.

Wright VC, Chang J, Jeng G, Chen M, Macaluso M. 2008. Assisted reproductive technology surveillance-united States, 2005. MMWR CDC Surveill Summ 56:1–22.

Yuan P, Okazaki I, Kuroki Y. 1995. Anal atresia: Effect of smoking and drinking habits during pregnancy. Jpn J Hum Genet 40:327–332.

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Craniofacial and Oral Features of Sotos Syndrome: Differences in Patients With Submicroscopic Deletion and Mutation of *NSD1* Gene

Norimitsu Hirai,[1]* Kensuke Matsune,[2] and Hirofumi Ohashi[3]

[1]Department of Pediatric Dentistry, Nihon University Graduate School of Dentistry at Matsudo, Chiba, Japan

[2]Department of Pediatric Dentistry, Nihon University School of Dentistry at Matsudo, Chiba, Japan

[3]Division of Medical Genetics, Saitama Children's Medical Center, Saitama, Japan

Received 7 October 2010; Accepted 22 January 2011

Sotos syndrome is a well-known overgrowth syndrome caused by haploinsufficiency of *NSD1* gene located at 5q35. There are two types of mutations that cause *NSD1* haploinsufficiency: mutations within the *NSD1* gene (mutation type) and a 5q35 submicroscopic deletion encompassing the entire *NSD1* gene (deletion type). We investigated detailed craniofacial, dental, and oral findings in five patients with deletion type, and three patients with mutation type Sotos syndrome. All eight patients had a high palate, excessive tooth wear, crowding, and all but one patient had hypodontia and deep bite. Hypodontia was exclusively observed in the second premolars, and there were no differences between the deletion and mutation types in the number of missing teeth. Another feature frequently seen in common with both types was maxillary recession. Findings seen more frequently and more pronounced in deletion-type than in mutation-type included mandibular recession, scissors or posterior cross bite, and small dental arch with labioclination of the maxillary central incisors. It is noteworthy that although either scissors bite or cross bite was present in all of the deletion-type patients, neither of these was observed in mutation-type patients. Other features seen in a few patients include enamel hypoplasia (two deletion patients), and ectopic tooth eruption (one deletion and one mutation patients). Our study suggests that Sotos syndrome patients should be observed closely for possible dental and oral complications especially for malocculusion in the deletion-type patients.

Key words: Sotos syndrome; *NSD1*; submicroscopic deletion; small dental arch; malocclusion; mandibular recession

How to Cite this Article:
Hirai N, Matsune K, Ohashi H. 2011. Craniofacial and oral features of Sotos syndrome: differences in patients with submicroscopic deletion and mutation of *NSD1* gene.
Am J Med Genet Part A 155:2933–2939.

INTRODUCTION

Sotos syndrome is a congenital genetic disorder characterized by overgrowth starting before birth, specific facial manifestations (macrocephaly, prominent forehead, hypertelorism, downslanting palpebral fissures, and pointed chin), advanced bone age, and developmental impairment. Since its initial description by Sotos et al. [1964] several hundred patients have been reported to date. It may be accompanied by a variety of complications, including cardiovascular, urinogenital, and ophthalmic malformations, skeletal abnormalities, and seizures. Dental and oral findings have been reported to include premature tooth eruption, hypodontia, enamel hypoplasia, excessive tooth wear, maxillary and mandibular recession, talon cusps, fused teeth, and expanded pulp cavity of deciduous teeth [Welbury and Fletcher, 1988; Cole and Hughes, 1994; Inokuchi et al., 2001; Gomes-Silva et al., 2006; Takei et al., 2007; Nishimura et al., 2008].

Kurotaki et al. [2002] reported that this syndrome is caused by haploinsufficiency of the *NSD1* nuclear receptor SET domain containing protein 1 gene located on 5q35. There are two main types that cause *NSD1* haploinsufficiency: mutations within the *NSD1* gene, and a submicroscopic deletion in the region that contains the *NSD1* gene (constant deletion of approximately 2.2 Mb including *NSD1* and around 20 neighboring genes) [Kurotaki et al., 2002]. Nagai et al. [2003] investigated differences in clinical manifestations between these two types, and reported

Grant sponsor: Ministry of Education, Culture, Sports, Science and Technology (MEXT); Grant number: 2008-2012; Grant sponsor: Ministry of Health, Labour and Welfare, Japan.

*Correspondence to:
Norimitsu Hirai, Department of Pediatric Dentistry, Nihon University Graduate School of Dentistry at Matsudo, 2-870-1 Sakaecho-Nishi, Matsudo, Chiba 271-8587, Japan. E-mail: hirai.norimitsu@nihon-u.ac.jp

Published online 19 October 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.a.33969

that major anomalies such as central nervous, cardiovascular, and urinogenital abnormalities are more common in the deletion-type. Their only reference to dental findings, however, stated that early tooth eruption occurred in both types with no significant difference.

The first detailed investigation of dental and oral findings seen in Sotos syndrome based on *NSD1* genetic diagnosis was carried out by Kotilainen et al. [2009]. They analyzed dental and oral findings from 13 patients with Sotos syndrome (all except one with the mutation type), including panoramic imaging, and reported the characteristic oral complications of Sotos syndrome, including hypodontia of the second premolars. We here report on the results of our investigation of detailed craniofacial, dental, and oral findings in five patients with deletion-type, and three patients with mutation-type Sotos syndrome.

MATERIALS AND METHODS

Patients

The eight patients comprised a group who underwent examination at Saitama Children's Medical Center. Five patients (three males, two females; age, 6–13 years) were identified as having a submicroscopic deletion on 5q35 including the *NSD1* gene, and three (all females; age, 6–10 years) were identified as having a mutation of the *NSD1* gene. Deletions were identified by fluorescence in situ hybridization (FISH) analysis of metaphase chromosomes from peripheral blood, using a total of seven bacterial artificial chromosome (BAC) clones comprising the BAC clone that includes the *NSD1* gene (RP11-99N22) together with those toward the centromere (RP11-880A16, RP11-690I8, RP11-991B23) and toward the telomere (RP11-147K7, RP11-452O4, and RP11-158F10). The results showed that the same ~2 Mb deletion was present in all five patients. Mutation analysis using genomic DNA extracted from peripheral blood was performed by polymerase chain reaction (PCR) and direct sequencing of all translated regions for exon 2–23. The results identified mutations generating premature termination in both Patients 6 and 7, comprising a five base deletion (2053–2057delAAGTA) and a base deletion (5431delC), respectively, and a missense mutation (4991G>C) in Patient 8. Details of clinical manifestations are shown in Table I. This study protocol was approved by the Ethics Committee of Saitama Children's Medical Center and proper informed consents were obtained from the legal guardians of the patients.

Oral and Dental Studies

Physical examination and dental cast studies were used to evaluate palatal morphology, tooth calcification, dental arches, occlusion, tooth size, and tooth eruption status. Panoramic and lateral cephalometric radiographs reconstructed from multi-detector row computed tomography (MDCT) were also used to evaluate the relationship of craniofacial, dental and skeletal structures, and hypodontia [Hirai et al., 2010; Yamauchi et al., 2010]. Crown and

TABLE I. Clinical Manifestations of Eight Patients With Sotos Syndrome

	Deletion type patients					Mutation type patients		
	1	2	3	4	5	6	7	8
Gender	M	F	F	M	M	F	F	F
Ages [years]	7	8	6	7	13	7	10	6
Overgrowth	–	–	–	–	–	+	+	+
Intellectual disability	Moderate	Moderate	Moderate	Moderate	Moderate	Mild	–	Mild
Seizure	–	+	–	+	–	–	+	–
Craniofacial features								
Macrocephaly	+	+	+	–	+	+	+	–
Prominent forehead	+	+	+	+	+	+	+	–
Hypertelorism	+	+	+	+	+	+	+	+
Downslanting palpebral fissures	+	+	+	+	+	+	+	+
Pointed chin	+	+	+	+	+	+	+	+
Strabismus	+	+	+	–	–	+	–	–
Skeletal anomaly								
Scoliosis	–	–	–	+	+	–	+	+
Pes planovalgus	+	+	+	+	+	+	–	+
Cardiovascular anomaly	AR	PDA	–	PDA, ASD, VSD	–	VSD, CoA	MR	–
Urogenital anomaly	Hydronephrosis, VUR	–	–	–	–	Urethrocele	Hydronephrosis, hydroureter	–
Others	Hearing loss	Myelomeningocele, umblical hernia	–	–	–	–	–	–

M, male; F, female; AR, aortic regurgitation; PDA, patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect, CoA, coarctation of aorta; MR, mitral regurgitation; VUR, vesicoureteral reflux; +, present; –, absent.

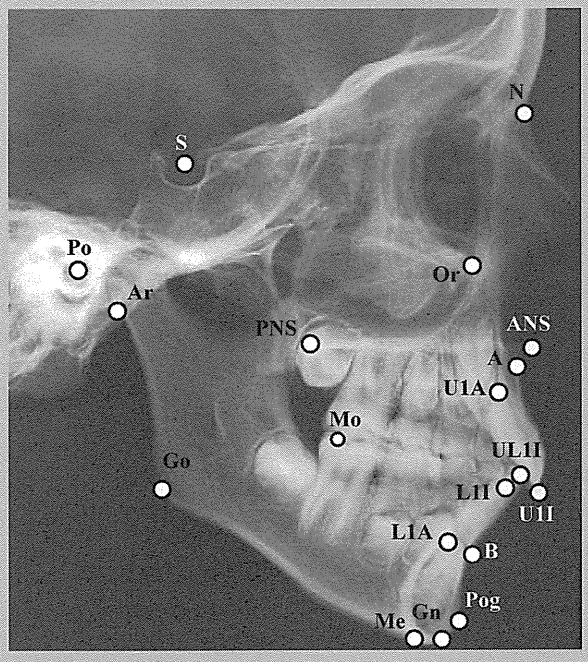


FIG. 1. Landmark points, angles, and lines used in cephalometoric analysis and profilogram. Landmarks: N, nasion; Or, orbitale; S, sella turcia; Po, porion; Ar, articulare; Go, gonion; Me, menton; Gn, gnathion; Pog, pogonion; A, A-point; B, B-point; ANS, anterior nasal spine; Mo, molar occlusion; U1A, upper central incisor root apex; U1I, upper central incisor edge; L1A, lower central incisor root apex; L1I, lower central incisor edge; UL1I, middle of U1I and L1I. Angles: convexity, N-A line to the A-Pog line; A-B plane, N-Pog line to the A-B line; SNA, S-N line to the N-A line; SNB, S-N line to the N-B line; facial angle, Po-Or line to the N-Pog line; SNP, S-N line to the N-Pog line; *y*-axis, Po-Or line to the S-Gn line; SN-S-Gn, S-N line to the S-Gn line; mandibular plane, Po-Or line to the Me-the lower border of the mandible line; gonial angle, Ar-the posterior border of the ramus of the mandible line to the Me-the lower border of the mandible line; GZN, S-N line to the Ar-the posterior border of the ramus of the mandible line; FH to SN, Po-or line to the S-N line; U-1 to FH plane, U1I-U1A line to the Po-or line; U-1 to SN plane, U1I-U1A line to the S-N line; L-1 to mandibular, L1I-L1A line to the Me-the lower border of the mandible; interincisal, U1I-U1A line to the L1I-L1A line; occlusal plane, Po-Or line to the Mo-UL1I line.

dental arch sizes were measured using a caliper with a resolution accuracy of 0.01 mm. Lateral cephalometric analysis was performed based on the method developed by Iizuka and Ishikawa [1957] (Fig. 1). All data in this study (tooth size, dental arch form size, and cephalometric findings) were compared with standard values for Japanese individuals [Otsubo, 1957; Otsubo et al., 1964].

RESULTS

Oral and dental anomalies noted in eight patients are summarized in Table II. All eight patients had a high palate, crowding, and excessive tooth wear. All but one (Patient 1 with *NSD1* deletion) had hypodontia exclusively in the second premolars. There were no differences between the deletion-type and mutation-types in the number of missing teeth (mean number of missing teeth was 2 in the deletion-type and 2.6 in the mutation-type) (Fig. 2). The results of cephalometric analysis showed that among the five deletion-type patients, maxillary and mandibular recession was present in three and maxillary recession alone in one, whereas among the three mutation-type patients maxillary and mandibular recession was present in one and maxillary recession alone in one. The deletion-type was regarded as having a stronger tendency for mandibular recession (Table III). In terms of occlusion, crowding was present in all patients, and deep bite was seen in all but one (Patient 2 with *NSD1* deletion). It is noteworthy that although either scissors bite (Patients 1, 3, and 4) or cross bite (Patients 2 and 5) was present in all of the deletion-type patients, neither of these was observed in mutation-type patients (Fig. 3).

Small dental arch was present in all the deletion-type patients and one mutation-type patient (Table IV). In terms of morphological categories of small dental arch, the maxilla exhibited a narrow dental arch with labioclination of the central incisors in all five deletion-type patients, with the mandible being saddle-shaped in three patients and U-shaped in two, while the mutation-type patient had U-shaped upper and lower dental arches (Fig. 4). In terms of tooth size, both microdontia and macrodontia were occasionally seen in both the deletion-type and mutation-types, but no characteristic findings were present in either type (data not shown). Enamel hypoplasia was present in two out of the five deletion-type patients (Patients 2 and 3), but was not present in the mutation-type. In addition, ectopic eruption of the first molar was present in one deletion-type patient (Patient 4, right mandibular) and one mutation-type patient (Patient 6, bilateral maxillary). Some representative photographs of oral and dental anomalies noted in patients studied are shown in Figure 5.

DISCUSSION

The oral manifestations observed in common with both deletion and mutation type Sotos syndrome patients noted here were a high palate, excessive tooth wear, recession of maxilla, deep bite, crowding, and hypodontia. Hypodontia has been previously described by several authors [Inokuchi et al., 2001; Callnan et al., 2006; Gomes-Silva et al., 2006; Nishimura et al., 2008]. Kotilainen et al. [2009] recently investigated 13 patients with Sotos syndrome (12 patients with *NSD1* mutations and one with *NSD1* deletion) and found one or more premolar teeth were absent in 9 out of 13 patients (8 out of 12 mutation patients and one deletion-type patient). Based on the observation that the deletion patient had the most severe phenotype of tooth agenesis, involving not only the second premolars and the third molars, but also one mandibular incisor, they noted the possibility that patient with the *NSD1* deletion had the most severe tooth agenesis. In our study, however, which included five deletion-type patients, although similar high rates of hypodontia were observed in both the deletion-type and mutation-type, we did not observe any difference in severity in either the deletion-type or mutation-type.

One noteworthy difference between the deletion-type and mutation-type was the fact that either scissors bite or cross bite

TABLE II. Oral and Dental Anomalies in Eight Patients

	Deletion type patients					Mutation type patients			Total	
Oral anomalies	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Deletion type**	**Mutation type**
High palate	+	+	+	+	+	+	+	+	5/5	3/3
Excessive tooth wear	+	+	+	+	+	+	+	+	5/5	3/3
Hypodontia	−	+	+	+	+	+	+	+	4/5	3/3
Maxillary recession	+	−	+	+	+	+	+	−	4/5	2/3
Mandibular recession	−	−	+	+	+	−	+	−	3/5	1/3
Malocclusion										
Scissors bite	+	−	+	+	−	−	−	−	3/5	0/3
Cross bite	−	+	−	−	+	−	−	−	2/5	0/3
Deep bite	+	−	+	+	+	+	+	+	4/5	3/3
Crowding	+	+	+	+	+	+	+	+	5/5	3/3
Small dental arch	+	+	+	+	+	−	+	−	5/5	1/3
Maxilla	N	N	N	N	N	U	U	U		
Mandibula	S	U	S	S	U	U	U	U		
Labioclination of maxillary central incisor	+	+	+	+	+	−	−	−	5/5	0/3
Enamel hypoplasia	−	+	+	−	−	−	−	−	2/5	0/3
Ectopic tooth eruption	−	−	−	+	−	+	−	−	1/5	1/3

N, narrow dental arch; U, U-shaped dental arch; S, saddle-shaped dental arch; +, present; −, absent.

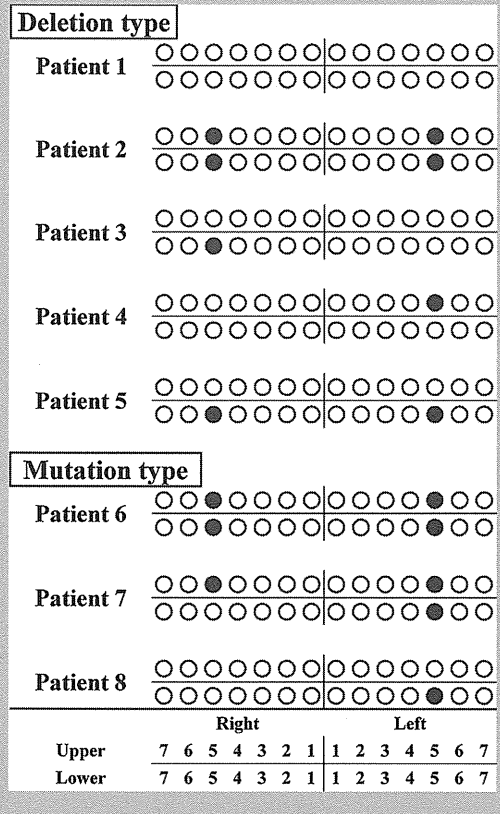


FIG. 2. Hypodontia in eight patients with Sotos syndrome. •, Congenitally missing teeth.

was observed in all deletion-type patients, whereas neither was present in the mutation-type. All of the deletion-type patients had small dental arches, and in terms of morphological categories, the maxilla exhibited a narrow dental arch with labioclination of the central incisors in all five deletion-type patients, with the mandible being saddle-shaped in three patients and U-shaped in two. Only one single mutation-type patient had small dental arches with both upper and lower dental arches being U-shaped. Narrowing of the dental arch is more pronounced in the narrow-shape and saddle-shape compared with the U-shape. It is possible that the degree of narrowing of the dental arch in the deletion-type and the misalignment in arch morphology between the maxilla and mandible causes scissors bite or cross bite.

In addition, maxillary and mandibular recession has also been reported as a dental manifestation of Sotos syndrome [Welbury and Fletcher, 1988; Takei et al., 2007]. In our results, there was a tendency toward maxillary and mandibular recession in the deletion-type and maxillary recession in the mutation-type. Based on these findings, there was a tendency for maxillary recession to occur in both the deletion-type and mutation-type, but there was also a tendency toward the occurrence of mandibular recession in the deletion-type. Taken in conjunction with the pronounced mandibular recession seen in the deletion-type on cephalometric analysis, mandibular malformations, including those of the dental arch, may be regarded as characteristic of the deletion-type. The cause is unknown, but in the deletion-type, minute genome imbalances, involving considerable number of genes other than the *NSD1* gene, may either: (1) directly cause deficient growth of the mandibular area; or (2) secondarily cause malocclusion or abnormal dental arch morphology as a result of dysfunction of the perioral muscles associated with more

TABLE III. Lateral Cephalometric Analysis With MDCT of Eight Patients

	Deletion type patients					Mutation type patients		
	1	2	3	4	5	6	7	8
Skeletal								
Covexity	−2.56	−1.05	−0.66	−1.80	−1.95	−4.56	−2.52	−2.94
A–B plane	−1.12	−3.96	1.68	−0.32	1.40	2.15	1.96	2.56
SNA	−2.54	1.24	−2.28	−3.45	−2.32	−2.69	−3.18	−1.63
SNB	−1.80	1.71	−3.31	−3.18	−2.84	−0.76	−2.29	−0.07
Facial angle	0.68	−3.23	−0.47	0.38	0.34	0.38	−1.55	1.43
SNP	−0.71	1.77	−1.76	−1.16	−0.63	0.02	−2.22	0.11
Y-axis	−0.50	−0.37	−0.38	−0.08	0.17	−0.36	1.29	−1.34
SN-S-Gn	3.08	−1.30	0.32	3.86	0.93	0.22	1.86	−0.30
Mandibular plane	1.29	1.05	−1.47	0.30	1.12	−0.58	1.98	−0.29
Gonial angle	6.24	−0.15	−4.06	−5.27	0.73	0.29	0.44	3.06
GZN	0.77	0.09	3.01	2.84	1.19	−0.37	1.52	−0.27
FH to SN	2.38	−1.15	0.71	2.55	0.98	0.52	0.97	1.37
Denture								
U-1 to FH plane	1.30	1.37	2.94	0.30	0.72	−0.47	0.50	0.69
U-1 to SN plane	0.51	1.87	2.56	−0.52	0.24	−0.64	−0.46	0.21
L-1 to mandibular	−2.24	−0.47	0.98	−1.47	−1.64	−2.39	−0.46	−1.93
Interincisal	−0.07	−1.07	−1.53	0.46	0.22	1.90	−0.83	0.71
Occlusal plane	−0.99	1.09	−0.76	−0.24	2.97	−1.37	1.35	−0.49

Unit, SD.

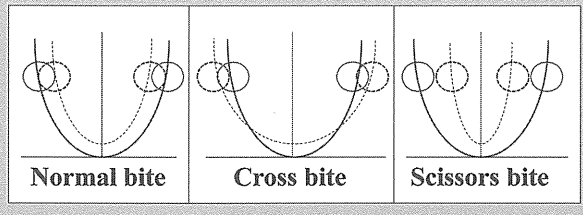


FIG. 3. Schematic representations of normal and abnormal occlusions. ——, Maxillary dental arch; - - - - - -, mandibular dental arch; ◯, maxillary first molar; ◯, mandibular first molar.

pronounced developmental impairment [Grabowski et al., 2007a,b; Stahl et al., 2007].

Enamel hypoplasia has also been reported as a dental manifestation of Sotos syndrome [Inokuchi et al., 2001]. Kotilainen et al. [2009] reported enamel hypoplasia in four out of 13 patients (all mutation type). In our study, enamel hypoplasia was present in two out of five deletion-type patients, but not in any mutation-type patients. Enamel hypoplasia is thought to be a common manifestation that can occasionally occur in both the deletion-type and mutation-type rather than a manifestation that is prone to occur in either type.

As mild to moderate intellectual disability is common in Sotos syndrome, conventional panoramic, and cephalometric studies

TABLE IV. Dental Arch Measurements in Eight Patients

	Deletion type patients					Mutation type patients		
	1	2	3	4	5	6	7	8
Maxillary								
W_c	−0.55	Deciduous	0.04	Deciduous	1.79	−1.75	0.61	−1.30
W_6	−3.76	−3.59	0.02	−4.18	−3.11	−1.73	−2.04	−1.76
L_{16}	2.68	1.33	2.88	1.02	−0.69	1.44	0.14	−1.36
Mandibular								
W_c	Deciduous	Deciduous	−1.00	Deciduous	−0.73	−1.81	−2.70	−0.30
W_6	−4.82	−2.51	−2.16	−4.45	−3.38	−1.57	−4.34	0.96
L_{16}	0.81	1.32	1.85	0.63	−3.40	0.20	−2.07	0.56

Unit, SD.
The W_c and W_6 represent the distance between the primary cuspids (the cuspids), and the first molars, respectively. The L_{16} represents the length from the mesial surface of the first molars to central point of incisors.