Cleft deformities in Singapore: a population-based series 1993–2002

Tan K B L, Tan K H, Yeo G S H

ABSTRACT

Introduction: Cleft deformities, though non-lethal, receive much attention from parents and doctors alike because of their obvious physical disfigurement, social stigma and associated feeding and vocal articulation problems. There is also an association with chromosomal defects for certain cleft deformities. The aim of this study is to examine the incidence, demographic data and epidemiological trend of this condition over a ten-year period, and to compare our data with other local studies, as well as to examine the chromosomal defects associated with this condition.

Methods: Data of cleft deformity cases born during the period 1993–2002 was retrieved from the National Birth Defects Registry and analysed.

Results: There were a total of 859 cases of cleft deformities in the ten-year period 1993–2002, giving an overall incidence of 1.87 per 1,000 live births, with an increasing trend noted. Incidence was highest among the Chinese and lowest among the Indians. There were more males with cleft deformities compared with females. The risk of aneuploidy rose by about ten-fold in syndromic cleft cases, compared to non-syndromic cleft cases. There were two cases of Trisomy 21 in the non-syndromic cleft lip and palate group, giving an incidence of 1:133.

Conclusion: The race-specific and gender-specific differences in cleft incidence suggest genetic and environmental factors which warrant further studies. The increased risk of aneuploidy among syndromic clefts, as well as the finding of Trisomy 21 in non-syndromic cleft lip and palate cases suggest a need for karyotyping in these two groups of antenatally-diagnosed cleft deformities.

Keywords: aneuploidy risk, cleft deformity, cleft lip, cleft palate, non-syndromic cleft, Trisomy 21

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INTRODUCTION

Congenital malformations, both minor and major, have become one of the most important causes of perinatal morbidity and mortality in Singapore in recent years.[1] While major malformations, like congenital heart conditions and chromosomal abnormalities, receive much attention because of their high rates of mortality and morbidity, other minor malformations such as cleft deformities receive equal attention from parents because of their obvious physical disfigurement and consequent social stigma,[2,3] as well as problems in feeding and vocal articulation lasting beyond the infancy years. Children born with cleft deformities therefore require multidisciplinary care.[4]

There have been several local papers that studied the incidence and epidemiological patterns of cleft deformities in Singapore since the mid 1980s.[5-7] However, a review of these papers showed that the studies were hospital-based, and to date, there has been no population-based local study of cleft lip and palate deformities performed. Neither has there previously been an attempt to compare these hospital-based data with population-based data. The aim of this study was to look at the incidence, demographical data and epidemiological pattern of cleft deformities in Singapore over a ten-year period from 1993 to 2002, and to compare our data with those from other local hospital-based studies, as well as to examine the chromosomal defects associated with this condition.

METHODS

The method of data collection at the National Birth Defects Registry (NBDR) has been previously comprehensively described.[8] To ensure a high level of completeness of registration, the NBDR ascertainment is based on multiple sources comprising government bodies, and public and private medical centres which contribute to the collection of birth defect data. These include the Epidemiology and Disease Control Division of the Ministry of Health, the National Registry of Births and Deaths, as well as cytogenetic and histology laboratories, and nursery wards in both public and private hospitals in Singapore. To ensure a high quality of information provided to the Registry, NBDR staff actively follow-up any birth defect registration with health professionals and hospital records for incomplete, inconsistent and uncertain information.

Given the small size of the country, the multiple sources of ascertainment and strict quality control procedures, the ascertainment of birth defects (and in this case, cleft deformities) in Singapore is comprehensive and accurate. Using an in-house database software programme,

National Birth Defects Registry, Ministry of Health, c/o KK Women's and Children's Hospital, Level 7, Children's Tower, 100 Bukit Timah Road, Singapore 229899

Tan KBL, MBBS, GradDipCS
Research Fellow

Department of Maternal Foetal Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899

Tan KH, MMed, FRCOG, FAMS
Senior Consultant

Yeo GSH, MBBS, FRCOG, FAMS
Senior Consultant

Correspondence to:
Dr George Yeo Seow Heong
Tel: (65) 6394 1980,
Fax: (65) 6394 1984
Email: mfm93b@pacific.net.sg

Table I. Prevalence of cleft deformity cases by race (1993–2002).

Race	Total no. livebirths	Total no. cases	Prevalence per 1,000
Chinese	310,656	621	2.00
Malay	85,779	160	1.87
Indian	38,187	48	1.26
Others	25,910	30	1.16
Total	460,532	859	1.87

Table II. Type of cleft deformity (1993–2002).

Type	No. cases (%)
Cleft palate only	277 (32.2)
Cleft lip only	164 (19.1)
Cleft lip and palate	418 (48.7)
Total	859 (100)

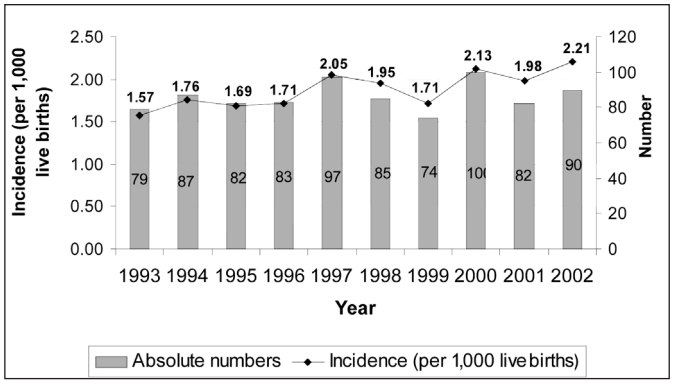

Fig. 1 Graph shows incidence of cleft deformities in relation to the number of live births during 1993–2002.

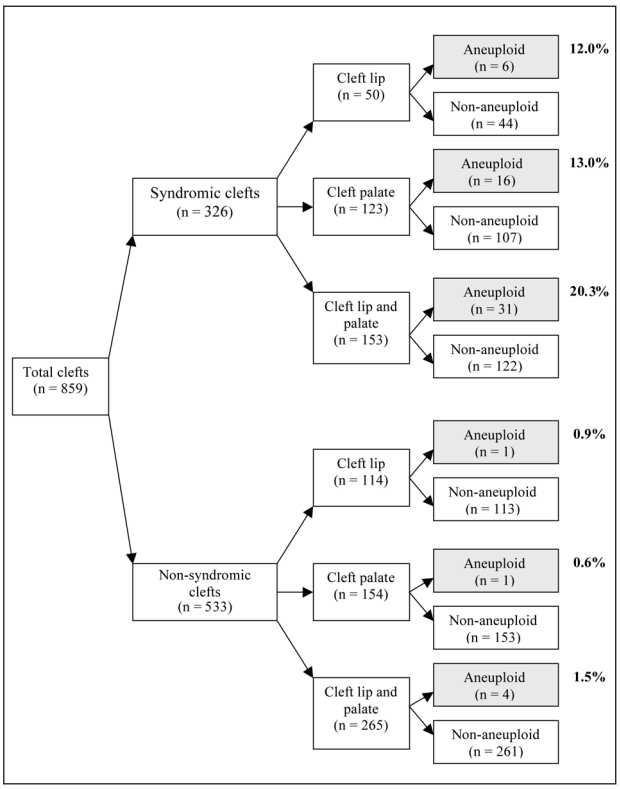

Fig. 2 Chart shows the case prevalence of aneuploidy among non-syndromic and syndromic clefts.

NBDR Version 1.0, developed with the Information Service Department of KK Women's and Children's Hospital, all notified cases of cleft deformities from 1993 to 2002 were extracted from the registry's database, and the data was then analysed. Care was taken to ensure confidentiality and anonymity of extracted and analysed data. The population denominators used in computing the rates per 1,000 live births shown in the tables were obtained from the Reports on Registration of Births and Deaths.[9]

RESULTS

Between 1993 and 2002, a total of 859 cases of cleft deformities were notified. In the same period, there were 460,532 live births, giving an overall incidence of 1.87 per 1,000 live births. An analysis of the trend over the ten-year period suggests an increase in incidence from 1.57 per 1,000 live births in 1993 to 2.21 per 1,000 live births in 2002 (Fig. 1). Of the 859 cases, 455 (53.0%) were male and 393 (45.8%) were female. 11 (1.3%) were of indeterminate gender. The race-specific incidence of cleft deformities was 1.87 per 1,000 live births and 2.00 per 1,000 live births in the Malay and Chinese populations, respectively, compared to 1.26 per 1,000 live births in the Indian population ($p = 0.02$ and 0.002, respectively) (Table I). There were 164 (19.1%) with cleft lip only, 277 (32.2%) with cleft palate only and 418 (48.7%) with combined cleft lip and palate (Table II). There were more males with cleft lip, and combined cleft lip and palate. More females were noted to have cleft palate only. Overall, there were more males with cleft deformities compared to females, with a ratio of 1.2:1 (Table III). There were 59 cleft cases (6.9%) associated with aneuploidy. 35/418 (8.4%) of combined cleft lip and palate had associated aneuploidy, compared to 17/277 (6.1%) of cleft palate, and 7/164 (4.3%) of cleft lip. The differences were, however, not statistically significant.

Further stratifying the cleft deformities into non-syndromic (not associated with other malformations)

Table III. Summary of cleft distribution pattern among the different races and sexes.

Demographics	Cleft pattern, no. (%)							
	Lip and palate		Lip		Cleft		Total	
	Yi et al[7]	PS	Yi et al[7]	PS	Yi et al[7]	PS	Yi et al[7]	PS
Gender								
Male	313	248	105	104	93	103	511	455
Female	233	160	103	59	137	174	473	393
Ratio	1.3:1	1.6:1	1.0:1	1.8:1	0.7:1	0.6:1	1.1:1	1.2:1
Total	546	408*	208	163@	230	277	984	848#
Race								
Chinese	446	302	161	121	171	198	778	621
	(81.7)	(72.3)	(77.4)	(73.8)	(74.3)	(71.6)	(79.1)	(72.3)
Malay	61	77	32	30	48	53	141	160
	(11.2)	(18.4)	(15.4)	(18.3)	(20.9)	(19.1)	(14.3)	(18.6)
Indian	29	21	11	5	9	22	49	48
	(5.3)	(5.0)	(5.3)	(3.0)	(3.9)	(7.9)	(5.0)	(5.6)
Others	10	18	4	8	2	4	16	30
	(1.8)	(4.3)	(1.9)	(4.9)	(0.9)	(1.4)	(1.6)	(3.5)

PS: present study
* total number of cases: 418, 10 cases of indeterminate gender
@ total number of cases: 164, 1 case of indeterminate gender
# total number of cases: 859, 11 cases of indeterminate gender

Table IV. Types of aneuploidy among syndromic and non-syndromic clefts.

	Total no. clefts	Types of aneuploidy					
		Total no.	Autosomal	Turner's syndrome	Trisomy 13	Trisomy 18	Trisomy 21
Syndromic clefts							
CL	50	6	2	0	3	1	0
CP	123	16	13	0	2	0	1
CLP	153	31	9	1	16	3	2
Total	326						
Non-syndromic clefts							
CL	114	1	0	0	1	0	0
CP	154	1	1	0	0	0	0
CLP	265	4	0	0	1	1	2
Total	533						

CL: lip only; CP: palate only; CLP: lip and palate

and syndromic (associated with other malformations) cases, there were 533 (62.0%) cases of non-syndromic cleft deformities and 326 (38.0%) cases of syndromic cleft deformities. Among the 533 non-syndromic cleft deformities, 0.9% (1/114) of cleft lip, 0.6% (1/154) of cleft palate and 1.5% (4/265) of combined cleft lip and palate cases were associated with aneuploidy, giving an overall aneuploidy rate of 1.1%. Among the 326 syndromic cleft deformities (associated with other structural deformities), 12.0% (6/50) of cleft lip cases, 13.0% (16/123) of cleft palate cases and 20.3% (31/153) of combined cleft lip and palate cases were associated with aneuploidy, giving an overall aneuploidy rate of 16.3% (Fig. 2). The differences in the occurrence of aneuploidy between syndromic and non-syndromic cleft deformities are statistically significant ($p < 0.0001$). Among the six cases of aneuploidy associated with the 533 non-syndromic clefts, we found two cases of Trisomy 21 among the 265 cleft lip and palate group, giving an incidence of 1:133 in this sub-group (Table IV).

Out of a total of 859 cases, 59 (6.9%) were associated with chromosomal defects. Of these, 23/59 (39.0%) were associated with Trisomy 13 (Patau Syndrome), 5/59 (8.5%) were associated with Trisomy 18 (Edwards Syndrome), and 5/59 (8.5%) were associated with Trisomy 21 (Down Syndrome). Together, these three major chromosomal syndromes accounted for 56% of the associated chromosomal defects. The majority of these three syndromes (25/33) were associated with combined cleft lip and palate. Three out of 33 were associated with cleft palate. Five out of 33 were associated with cleft lip. Of the five cases of Trisomy 21, three cases had syndromic clefts (one cleft palate, two cleft lip and palate); and two cases had non-syndromic clefts (two cleft lip and palate) (Table IV).

DISCUSSION

We noted that from 1993 to 2002, there has been an increasing trend of cleft deformities in the population.

Table V. Comparison of previous studies and the current one.

	Five-year study[5] 1977–1981 (n = 450)		Ten-year study[7] 1985–1994 (n = 984)		Two-year study[6] 1986–1987 (n = 53)		Current ten-year study 1993–2002 (n = 859)	
	No. cleft (%)	R	No. cleft (%)	R*	No. cleft (%)	R#	No. cleft (%)	R@
Race		-						
Chinese	369 (82)		778 (79.1)	1.64	38 (71.7)	2.00	621 (72.3)	2.00
Malay	61 (13.6)	-	141 (14.3)	0.29	12 (22.6)	1.40	160 (18.6)	1.87
Indian	15 (3.3)	-	49 (5.0)	0.10	2 (3.7)	0.90	48 (5.6)	1.26
Others	5 (1.1)	-	16 (1.6)	0.04	-	-	30 (3.5)	1.16
Total	450 (100)	-	984 (100)	2.07	53 (100)	1.70	859 (100)	1.87

R: prevalence per 1,000 live births; %: percentage contributed by each ethnic group
* Calculated by taking the total live births (n = 474,542) delivered in the country in the period 1985–1994 as the denominator
# Calculated by taking the live births of each ethnic group delivered in the hospital in the period 1986–1987 as the denominator
@ Calculated by taking the live births of each ethnic group delivered in the country in the period 1993–2002 as the denominator

Whether this is a true increase over time or a reflection of a greater awareness of this condition and thus a higher notification rate to the National Registry, more studies should be done to evaluate this trend. We compared our incidence data with those of three previously-published local studies (Table V).[5-7] Fong et al's five-year hospital-based study looked at the percentage of clefts contributed by each ethnic group and showed that the incidence of cleft deformities followed a similar racial distribution with that of the nation, except for a lower incidence among the Indians.[5] Tan's rates in 1986–1987 were also hospital-based, and he concluded that Chinese had the highest incidence of cleft deformities, followed by Malays and Indians.[6] Yi et al concluded also that the Chinese had the highest cleft incidence and the Indians the lowest incidence among the three racial groups. This paper, however, used the total live births in the country as the denominator for calculating their rates, in contrast to the other two papers which used live births within each ethnic group as their denominators.[7] Regardless, all three studies showed the highest incidence among the Chinese population.

Our study similarly demonstrated that the Chinese population in Singapore has the highest incidence of cleft deformities, followed by the Malay population. The Indian population has the lowest incidence ($p = 0.002$). In another report from Malaysia, where these three main races are also present, the high incidence among the Chinese and the low incidence among the Indian populations had also been similarly demonstrated.[10] This predilection by the Chinese to have cleft deformities had also been previously shown by Vanderas in 1987[11] and Stevenson et al in 1966.[12] This suggests a possible genetic predisposition that should be further evaluated.

While Yi et al showed that there was a slight preponderance among males to have combined cleft lip and palate (1.3:1), and equal gender occurrence for cleft lip only,[7] our data suggests that both combined cleft lip and palate, and cleft lip have a much higher than the previously-reported proportion among males (1.6:1 and 1.8:1, respectively) (Table IV). We have similarly shown that the cleft palate-only group has a higher preponderance among females. These observations are consistent with those reported in other countries like Denmark,[13] Korea,[14] China,[15] UK (Glasgow),[16] and Puerto Rico.[17] The percentage of aneuploidy among the various non-syndromic cleft deformities varied from 0.6% to 1.5% in our series. However, the percentage rose ten-fold (12.0%–19.6%) when there were other associated structural defects. In other words, a syndromic cleft deformity had a ten-fold increased chance of having a chromosomal defect compared to a non-syndromic cleft deformity. There is thus a need, in terms of antenatal diagnosis, to look for associated structural defects in cases of antenatally-diagnosed cleft deformities, as it will significantly increase the risk of chromosomal abnormalities. Although this increase may also be likely due to the higher aneuploidy risk associated with certain malformations like cardiac defects and central nervous system defects, it illustrates the need for karyotyping in syndromic cleft cases. Various authors in the past have highlighted an increased risk of chromosomal abnormalities (in particular Trisomy 21) even in cases of non-syndromic cleft deformities.[18,19] Our findings similarly suggest an increased likelihood of Trisomy 21 even in non-syndromic cleft deformities, in particular cleft lip and palate which had an incidence of 1:133.

In conclusion, this is the first population-based study of cleft deformities in Singapore to date. There appears to be an increasing trend of cleft deformities in the period of study from 1993 to 2002, with a definite racial predilection among the Chinese and Malay populations, compared to the Indian population, suggesting possibly both genetic and environmental factors at play. This interplay of multifactorial causes is further suggested by males

being generally more likely to have cleft deformities, specifically cleft lip, and cleft lip and palate; whereas females, on the other hand, are more likely than males to have cleft palates. This study also showed a difference between non-syndromic and syndromic cleft deformities, with the latter having a more than ten-fold increased risk of aneuploidy. While there were no cases of Trisomy 21 among the non-syndromic cleft lip and non-syndromic cleft palate in our series, we found two cases of Trisomy 21 out of 265 non-syndromic cleft lip and palate cases. This may have a bearing on the obstetrician's decision and patient counselling for karyotyping in syndromic cleft deformities in general as well as non-syndromic cleft lip and palate cases.

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