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Congenital heart disease and associated malformations in children with cleft lip and palate in Pakistan

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SUMMARY. Children with cleft lip and palate often have other associated malformations. The reported incidence and types of associated malformations vary between different studies. There is a great paucity of literature on the subject from the region in general and none from Pakistan at all. The purpose of this study was to assess the frequency of associated malformations, particularly congenital heart disease, in children with cleft lip and palate presenting to the Aga Khan University (AKU) and Murshid Hospital (MH).

From 1st October 1999 to 31st March 2002, all children with cleft lip and palate who presented to AKU and MH were prospectively enrolled in the study group. Socio-demographic characteristics and a number of other variables were documented. All children underwent a thorough clinical examination and an echocardiogram as part of the study protocol.

123 children formed the study group. Thirty-five (29%) of these children were found to have associated malformations. The most common of these was congenital heart disease, which accounted for 51% of all associated malformations. Thirty percent of cleft palate children had associated anomalies while 27% of cleft lip, with or without cleft palate, children had associated anomalies.

There was a significant association between children born of a consanguineous marriage and the risk of associated malformations (p-value: 0.001). Consanguinity was present in 74% of children with associated anomalies as compared to 40% of children with no associated anomaly. Dysmorphic features and the presence of associated anomalies were also significantly associated (p-value: 0.009). Dysmorphic features were present in 46% of children with anomalies as compared to 21% of children with no associated anomaly. Fifty percent of children with associated anomalies had a low birth weight compared to 34% of children with no anomalies, but the difference was not statistically significant.

The presence of consanguinity in a child with dysmorphic features should raise the suspicion of an associated anomaly. The likelihood of this being a cardiac defect is high and should be ruled out with a thorough clinical examination, supplemented with an echocardiogram in certain cases.

Keywords: congenital heart disease, associated malformations, cleft lip and palate, consanguinity, dysmorphic features.

Introduction

Clefts of the lip and palate are the most frequent congenital malformations of the head and neck. The incidence is quoted at up to 2 per 1000 live births and has been found to be rising.[1] The incidence varies among different racial groups and is highest among Asians.[2]

The aetiology of cleft lip and palate is still largely an enigma and different results concerning environmental and genetic risk factors are obtained in different countries and regions.[3]

The association of cleft lip and palate and other congenital malformations has been well documented although the reported incidence varies from 1.5[4] to 63.4%.[5] It has not been established whether clefts are definitely related to specific types of other congenital malformations. Shprintzen[5] found malformations in the head and neck region to be the most common associated malformations; while Lilius[6] observed malformations of the extremities to be more common. Milerad[7] found congenital heart disease to be the most common, isolated, associated malformation; while Stoll[8] found a central nervous system anomaly to be the most common, single, other anomaly.

There is a great paucity of literature on associated malformations in cleft children from the region in general and none at all from Pakistan.

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Table 1 Associated malformations

congenital heart disease	18
Pierre Robin sequence	6
skeletal	6
urogenital	5
abdominal wall	5
multiple	5

Materials and methods

From 1st October 1999 to 31st March 2002, all children with cleft lip and palate who presented to the Aga Khan University and Murshid Hospital, were prospectively included in the study group. The former is a teaching hospital and tertiary care centre while the latter is a philanthropic welfare hospital located in an urban slum area of Karachi.

The variables registered for the study were age, gender, duration of gestation, birth weight, diagnosis and location of cleft, family history of clefts, known risk factors for clefting, consanguinity and associated malformations.

All children underwent a thorough clinical examination by a paediatric cardiologist. This was supplemented with an echocardiogram for all the children in the study group, irrespective of the findings at clinical examination.

A malformation was included if it required follow-up or treatment. A limitation of the study was the possibility that some children with syndromes may not be diagnosed, as we do not have the services of a clinical dysmorphology geneticist.

Statistical analysis

Data was entered in EPI Info version 6.04B. It was checked and verified for errors. We ran the basic frequencies in EPI Info and for univariate analysis. For multivariate analysis we used SPSS version 10. The statistical tests used were Chi square test for categorical data and student *t* test for continuous variables. Multiple logistic regression analysis was done using the Entered method with 95% confidence interval.

Table 2 Risk factors for congenital anomalies in patients with clefts

	Percentage of patients with congenital anomalies *(%)*	Odds ratio	*p-value*	Confidence interval
cleft patients with consanguinity[a]	74	4.34	0.001	2–11
cleft patients without consanguinity	40			
cleft patients with dysmorphic features[a]	46	3.28	0.009	1.3–8
cleft patients without dysmorphic features	21			

[a] Risk factors for congenital heart disease in patients with clefts.

Results

There were 123 children in the study group with 66 (54%) females and 57 (46%) males. Of these patients, 23 (19%) had cleft lip alone, 56 (45%) had an isolated cleft palate and 44 (36%) had both cleft lip and palate. Of 44 children with complete clefts, 36 (82%) were unilateral and 8 (18%) were bilateral cleft lip and palate. In children with cleft palate, there were 70% females and 30% males. In the children with cleft lip with or without cleft palate there were 60% males and 40% females.

Associated malformations

Thirty five (29%) children were found to have an associated malformation that required follow-up and/or treatment. In the group with malformations there were 49% males compared to 51% females, while there were 45% males and 55% females in the group without any associated defect. Six (26%) of the 23 children with isolated cleft lip, 17 (30%) of the 56 children with isolated cleft palate, and 12 (27%) of the 44 children with both cleft lip and palate had associated malformations.

Of the 35 children with associated defects, six (17%) had an isolated cleft lip, 17 (49%) had isolated cleft palate and 12 (34%) had both cleft lip and palate. Of the children with complete clefts, 11 (92%) were unilateral and one (8%) was bilateral.

The different organ systems affected by associated malformations are shown in Table 1. The commonest organ system affected was the cardiovascular system. Eighteen (51%) of the children with associated anomalies had congenital heart disease, confirmed with echocardiography. This represents a frequency of approximately 15% in the study group.

Of the children with clefts and associated malformations 50% had a low birth weight, while 34% had a low birth weight among the children with clefts and no associated malformations. Six percent of the children with associated malformations were born preterm while seven percent of the children without associated malformations were born preterm. Forty eight percent of the isolated cleft palate children had a low birth weight in contrast to 31% of the children with both cleft lip and palate. Fifty percent of the MH children had a low birth weight compared to 34% of the AKU children.

Consanguinity was present in 74% of the children with associated anomalies (*p*-value: 0.001) and this was of the first degree in 89% of them. In contrast, in children without associated anomalies consanguinity was present in 40% and this was of the first degree in 72%. There was no difference in consanguinity between children with isolated cleft palate (50%) and children with both cleft lip and palate (49%). Sixty three percent of the MH children gave a history of consanguinity compared to 44% of the AKU children.

Dysmorphic features were present in 46% of the children with associated anomalies and in 21% of the children without associated anomalies (p-value: 0.009). Forty six percent of the isolated cleft palate children had dysmorphic features while only 12% of the children with both cleft lip and palate had dysmorphic features. Twenty six percent of the MH children and 28% of the AKU children had dysmorphic features.

In children with associated anomalies, consanguinity and dysmorphic features were statistically significant variables, as shown in Table 2.

A family history of clefting was present in 23% of the children with associated anomalies and in 22% of the children without associated anomalies. Twenty five percent of the children with a cleft lip, with or without a cleft palate, had a family history of clefting compared to 20% of the cleft palate children. An antenatal drug history was present in 23% of the children with associated anomalies and 28% of the children with no anomalies. The commonest drug was the analgesic paracetamol with only one mother giving a history of anticonvulsant usage. There was no history of alcohol or tobacco intake in any of the mothers.

Discussion

There is little or no data on associated malformations in children with clefts from this region and none from the Indian subcontinent including Pakistan. There is, however, a high prevalence of birth defects in Pakistan quoted at 21% overall, out of which eight percent were thought to be severe.[9]

While the fact that this is a hospital-based study is a limiting factor, clefting is a condition that requires treatment in hospital and as such the study group is representative.

Looking at the literature on associated malformations in children with clefts, there is a wide variation apparent; hospital-based studies tend to report a higher frequency as compared to those relying on birth certificates. The exception to this rule is a hospital-based study from Singapore,[4] which reports an associated malformation rate of 1.5% among its cleft population. There is also some discrepancy in defining what constitutes a congenital defect. We have included all those defects that require treatment or follow-up, as has been the case with most mainstream studies that we came across.

Among the three cleft types (cleft lip, cleft palate, and cleft lip and palate) the highest rate of associated malformations is with cleft palate. Thirty percent of the cleft palate children had associated malformations and 49% of the children with associated malformations had an isolated cleft palate. This is in keeping with other studies.[1] However, the tendency for bilateral complete cleft lip and palate to be associated with a higher frequency of associated malformations did not hold true in our series.

Fifty percent of the cleft children with associated malformations had a history of low birth weight compared to 34% of the cleft children without associated malformations. This difference did not hold true for prematurity; six percent of the children with associated malformations and seven percent of the children without associated malformations gave a history of being born preterm.

Stoll[10] found a significant association between clefting and consanguinity. In our study, consanguinity was present in 74% of the children with associated malformations as compared to 40% of the children without associated malformations. This was of the first degree in 89% of the former group and in 72% of the latter group. That there is a very high frequency of consanguinity among Muslims in general and Pakistanis in particular is a well documented fact.[11] Less clear is the exact relationship between consanguinity and the risk of congenital defects. There is some literature relating consanguinity to increased risk of mortality, in Pakistanis in early life, due to autosomal recessive diseases.[12] However, other studies do not support this association between consanguinity and birth defects, presumably on account of deleterious recessive genes having been 'bred out' over a period of time.[13] A recent comprehensive study from North America placed the added risk of cousin marriages resulting in birth defects at no more than two percentage points.[14]

Dysmorphic features were deemed to be present in 46% of the children with associated malformations as compared to 21% of the children with no associated malformations. The lack of a clinical dysmorphology geneticist is a limitation of the study as the possible inclusion of some unidentified syndromes makes comparison with other studies difficult. However, the strong association of dysmorphic features with associated malformations is of diagnostic significance. It should be of particular value, in the still all too common scenario in this part of the world, where individual practitioners rather than multidisciplinary teams look after cleft children.

Comparing AKU to MH reveals an associated malformation rate of 34% in the AKU children and 16% in the MH children. This difference is possibly due to the tertiary care status of AKU. Only 34% of the AKU children were thought to have a low birth weight as compared to 50% of the MH children. Forty four percent of the AKU children were products of a consanguineous marriage in contrast to 63% of the MH children. These differences could well be explained by the socio-economic differences between the two groups.

Among the associated malformations congenital heart disease was by far the commonest associated malformation, present in 18 (51%) of the children with associated malformations. This represents a frequency of approximately 15% in the study group as a whole. The incidence of congenital heart disease in the general Pakistani population is 0.5–0.8%. Therefore the risk of congenital heart disease in cleft children is about 23 times that of the general population. Milerad[7] found congenital heart disease to be 16 times more frequent in cleft children compared to the general Swedish population. Stoll[8] found congenital heart disease to be five times more common in cleft children compared to the general French population. However, these two studies employed clinical examination alone, and not echocardiography, when determining the frequency of congenital heart disease in their cleft population.

Table 3 Congenital heart disease

atrial septal defect	7
ventricular septal defect	3
patent ductus arteriosus	3
valvular heart disease	2
restrictive heart disease	2
left ventricular hypertrophy	1

The commonest defect in our study was ASD followed by VSD as shown in Table 3. Milerad[7] and Stoll[8] found VSD to be the commonest heart defect. Wyse[15] found defects in cleft patients to be predominantly conotruncal and most patients with clefting and congenital heart disease had additional abnormalities.

Correlating the findings at clinical examination by an experienced paediatric cardiologist and echocardiography, showed that in approximately 85% of the cases the clinical examination provided the complete diagnosis. Cardiac anomalies, picked up solely on echocardiography, were as a rule small defects that escaped clinical detection.

Conclusion

The significantly increased risk of associated malformations, particularly congenital heart disease, in children with clefts needs to be highlighted and disseminated to all health professionals involved in looking after children with clefts. It is important that there should be close liaison between the plastic surgeon and the paediatrician. These children need to be screened prior to surgery, especially if surgery is being considered in the neonatal period when clinical examination alone may not pick up congenital heart defects. The presence of dysmorphic features in a cleft lip or palate child, born of a consanguineous union, should raise suspicion of an associated malformation. This combination of findings in an infant may well merit an echocardiogram to evaluate the heart and specifically rule out congenital heart disease.

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