

Epidemiology of facial clefting

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SUMMARY An analysis was performed of patients with facial clefts notified between 1960 and 1982 to the Liverpool Congenital Malformations Registry. From 1960–82 there were 325 727 births in the area surveyed and 544 cases of facial clefting were notified. When 88 patients with recognised syndromes and multiple congenital anomalies were excluded, the overall prevalence of facial clefts alone was 1.4 per 1000 total births. This group was then classified further into 137 cases of cleft lip alone, 166 cases of cleft lip and palate, and 153 cases of cleft palate alone. The prevalence of these groups per 1000 total births is 0.42, 0.51, and 0.47 respectively.

There were some fluctuations in annual prevalence with rises being observed in the mid and late 1960s and mid and late 1970s. There was a noticeable male predominance in the cleft lip and cleft lip and palate groups of 1.52:1 and 1.98:1 respectively, with a 1:1 ratio in the cleft palate group.

There were no significant differences in birthweight and mean maternal age in the three groups. In the cleft palate group, however, there was a significant trend towards an increase in the frequency of conception in the second half of the year. There was a maternal history of epilepsy in 4.4% of the cleft lip and 3% of the cleft lip and palate groups but only in 1 patient (0.6%) in the cleft palate group. The study illustrates the importance of environmental factors in the aetiology of facial clefting.

Facial clefts are among the most common congenital malformations and occur throughout the world. They are readily recognised at birth and usually easily classifiable. There is a strong genetic component in their aetiology but environmental factors have also been suggested, both from epidemiological and laboratory animal data.^{1–3} In addition to notification to the malformations registry, all facial clefts in the Mersey Regional Health Authority are referred for management to the Cleft Palate Unit at Alder Hey Children's Hospital. Consequently, ascertainment of livebirths with clefts should be complete. It was decided to analyse the epidemiology of cases registered in the Liverpool Congenital Malformations Registry since its establishment in 1960. This is, therefore, one of the longest longitudinal studies of the epidemiology of facial clefting that has been published.

Methods

Data on facial clefts, as well as other malformations, have been obtained over the past 23 years from multiple sources, including notifications from the

paediatric medical registrars in local maternity units, handicap registers kept by community child health departments, and minutes of perinatal death meetings. This information has been recorded onto a punch card system and more recently into the University of Liverpool's mainframe computer. The area covered by this registry originally consisted of Liverpool and Bootle. This was extended in 1979 to include the health authorities of Liverpool, Sefton North, Sefton South, St Helens and Knowsley, and Wirral. The data were supplemented by regular inspection of records from the Regional Cleft Palate Unit. Further information was obtained by recourse to the maternal and paediatric hospital case notes. Annual births were obtained from Mersey Regional Health Authority and also from the various district health authorities.

Results

Over the 23 years under review there were 325 727 births in the area surveyed, and 544 cases of facial clefting were ascertained. Where the facial clefting was associated with more than one other major

anomaly, whether or not the constellation of anomalies was part of a recognised syndrome, it led to the exclusion of 88 cases. In the 456 isolated facial clefts there were 137 cases of cleft lip alone, 166 of cleft lip and palate, and 153 cases of cleft palate alone (Table 1).

The very similar overall annual frequencies of the three types of facial clefts are shown in Table 2. There was a noticeable male predominance in patients with a cleft lip, particularly if a cleft palate was also present. Cleft palate alone was equally common in boys and girls.

Using three year moving averages there were some fluctuations in annual frequency over the 23 years (Fig. 1). A slight rise occurred in the mid and late 1960s and a more pronounced rise in the mid and late 1970s. All three types of facial clefts rose and fell synchronously.

There were no statistical differences between the three types of clefts regarding birthweight (mean for all types 3150 g) or maternal age (mean for all types 26.1 years).

Pooling cases over the 23 years by month of conception showed a trend which was significant at the 1% level towards an increased frequency in the latter half of the year in cleft palate alone (Fig. 2). This statistical significance, however, only held for girls. There were no seasonal trends in cases of cleft lip with or without cleft palate.

There was a maternal history of epilepsy in 4.4% of cases with cleft lip alone, 3% with cleft lip and palate, but in only one patient (0.6%) with cleft palate alone. No information was available on how many of the patients' fathers had epilepsy. Data on

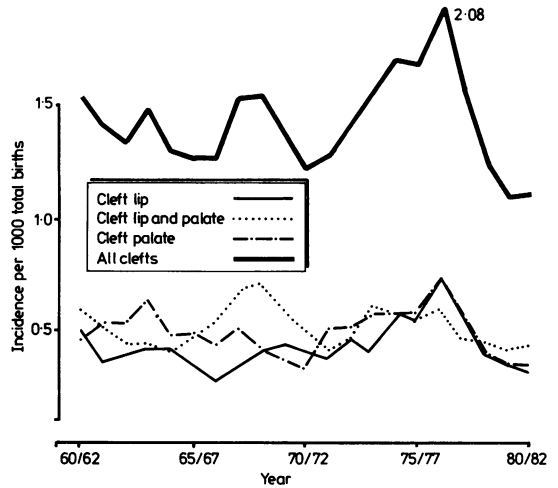


Fig. 1 Incidence of facial clefts by three year moving averages.

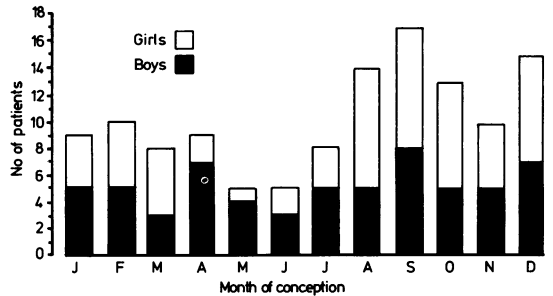


Fig. 2 Seasonal incidence of cleft palate in relation to conception 1960–82.

Table 1 Cases of facial clefting ascertained between 1960 and 1982

Cleft lip	137
Cleft lip and palate	166
Cleft palate	153
Pierre-Robin syndrome	27
Multiple congenital anomalies	38
Syndromes	23
Total	544

Table 2 Annual frequencies of the three types of facial clefts

	Frequency per 1000 total births	Sex ratio (boy:girl)
Cleft lip	0.42	1.52
Cleft lip and palate	0.51	1.98
Cleft palate	0.47	1.00

anticonvulsant treatment were not sufficiently reliable to determine whether the epilepsy, drug treatment in general, or a particular anticonvulsant was responsible for this association. Although there were twice the number of cases in the period 1971–82 (eight cases) compared with 1960–70 (four cases), this did not reach statistical significance (Fig. 3).

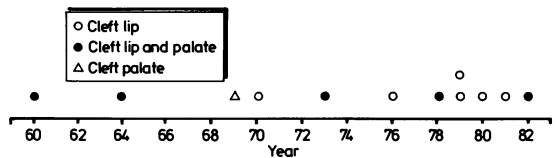


Fig. 3 Number of facial clefts born to epileptic mothers per year.

Discussion

We have shown that although the overall frequency of facial clefts is very similar to that of other surveys⁴⁻⁶ there were variations over the years, with increases towards the ends of each decade studied. If facial clefts were due exclusively to genetic influences one would expect very few changes in annual frequency unless there were, for instance, large changes in the genetic make up of the study population. Therefore, these annual variations in frequency could suggest the influence of environmental factors.

Our figures show a trend towards conception of babies with cleft palates in the second half of the year, but this trend was only statistically significant for girls. Seasonal variation would imply an environmental agent whose presence or effect varies through the year. Possible candidates would include climatic changes, infections, and dietary habits, all of which may vary through the year. Most other studies⁴⁻⁷ have not shown any seasonal variation for facial clefts, except for Edwards⁸ who showed a very highly significant trend for cleft lip babies in Birmingham to be born in the first half of the year with the highest incidence in March. The lack of correlation of other studies with our own might be explained by the presence of an environmental factor in Liverpool that is not present elsewhere. As this factor only seems to be operating in cleft palate alone, its effect must be apparent at about the 8th week after conception. The finding of sex specificity is unexplained.

The present study shows a strong link with maternal epilepsy in patients with cleft lip, with or without cleft palate, but not with cleft palate alone. Over the past 15 years other studies have shown that babies born to mothers with epilepsy have a two to threefold risk of a major congenital malformation.⁹⁻¹¹ The risk of facial clefting is especially high, being 10 times more likely than in a control population. This effect of maternal epilepsy might be due to a genetic link with epilepsy, the teratogenic influence of anticonvulsant drugs, or the effect of seizures during pregnancy.¹²⁻¹⁴ Although the latter seems unlikely,¹² it is possible that both a genetic link with epilepsy and the action of anticonvulsants may be factors. Our study was not able to unravel the two as our data on anticonvulsants taken in pregnancy are unreliable.

Of the anticonvulsants implicated in the pathogenesis of facial clefts, the hydantoin group, especially phenytoin, have been prominent.¹⁴ Over the past decade alternative drugs such as sodium valproate and carbamazepine, have been introduced. A recent community study of epilepsy¹⁵

showed, however, that phenobarbitone and phenytoin were still the most common drugs taken, although the popularity of the former had declined. Sodium valproate was the only other drug to have been taken in more than 10% of patients. We do not have data on anticonvulsant prescribing habits in Merseyside, but if they follow the same trends this may explain why the frequency of maternal epilepsy in babies with facial clefts did not fall over the two decades studied.

Although genetic influences are strong in the aetiology of facial clefts, we have shown that environmental factors are also important. Maternal epilepsy seems to be associated with cleft lip with or without palate, whereas seasonal factors effect cleft palate alone. The search for environmental factors is important as, if discovered, they might be amenable to prevention.

It is clear that prospective studies are necessary to elucidate the role of epilepsy and anticonvulsants in pregnancy in the aetiology of cleft lip. Retrospective analysis of drug histories is unreliable because notes are inadequate and no reliable evidence of compliance is available from past cases.

The data give a starting indication for planning health service resource requirements for this group of affected infants. Future resource allocation should take epidemiological data firmly into account.

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