

Etiology Of Cleft Lip And Palate

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EVERY thirty seconds, 2 congenitally malformed human babies are born. Cleft lips and palate are one of the most common of all congenital deformities in human beings.

INCIDENCE

Reports from various countries suggest that the incidence at birth has been rising from 1 per 1000 in the first one third of this century to between 1.5 and 2 per 1000 during the last decade. In the absence of any reliable data and lack of registration of all births, in our country it is not possible for us to confirm this; but it is true that we are treating many more cases at much earlier ages, than we had done a decade back. It is difficult to compare figures from different times in different countries, but in Denmark, where all patients with cleft lip and palate are registered, Fogh Anderson (1961, 1964) has reported a significant increase in incidence. The cause of the steadily increasing incidence of cleft formations at birth is not evident. Much work has to be done to assess whether it is genetically or non-genetically determined?

HEREDITY

The majority of congenital deformities in human beings are most probably due to a combination of exogenous environmental factors and a gene pattern predisposing to

malformations.

To day, heredity is regarded to be a very important factor in the etiology of facial clefts.

A statistical analysis of 703 Danish families 25 years ago (Fogh Anderson 1942) showed that typical cleft lip "CL" and cleft palate "CLP" which are both common in males belong to one genetic group, "CL"(P) with a positive history of clefts in about 2/5th of the families; whereas cleft palate (CP) alone which occurs more frequently in females is only factors in this type of isolated cleft. In atypical, rare clefts heredity is very unusual (Fogh Anderson 1965).

One apparent exception from this rule of genetic independancy of the two cleft groups exist in the case of accompanying fistula of the lower lip i.e., clefts lip and cleft palate alone are found in the same family in which the rare congenital lip fistula occurs as a typical dominant character.

The manner of inheritance is not clear. For cleft lip and palate, inheritance show a recessive character, but apparently dominance occurs, a "conditional dominance" with sex-limitation to males, possibly the genetic basis of cleft lip and palate is, in general, multicentric.

Observations by Fraser Roberts (1962) in 151 adult patients with cleft lip and palate indicate that affected females have

substantially more affected offspring than have affected males.

As regards cleft palate, though the number of inheritance is small, show simple dominance and sex limitation to females.

Irrespective of inadequate understanding of genetic mechanism and without knowledge of the proportion of environmentally determined cases, statistically worked out risk figures are of very great value to all concerned in the treatment and management of these congenital deformities. Based on Danish analysis of 703 cases (Fogh-Anderson 1942) and confirmed later by Fraser (1955) and Woolf (1963) the empirical risk figures: When both parents are normal and when child has cleft lip and palate, the risk of recurrence in subsequent children is about 4-5%, when one parent and one child are affected, the risk is about 3 times greater (13-14%).

The corresponding average figures for cleft palate are 2-3% and 14-17%, respectively.

In our series of consecutive 640 cases, genetic history is positive only in 94 cases, i.e., about 15%.

ENVIRONMENTAL FACTORS

Though "heredity" has a major role to play in the formation of facial cleft, it remains a fact that nearly 3/5th of cases of cleft lip and palate and 4/5th of the isolated cleft palates are "so called" solitary ultimately turn out to be hereditary by getting affected progeny.

A somewhat greater importance of environmental factors than previously accepted has been advanced during the recent years by several writers - based on the results

of animal experiments with vitamin deficient diets (Warkany & others).

American observations in human beings with or without supplemental vitamin intake (Lyndon Pees et al 1958; Conway, 1958) are very interesting, but are not yet statistically significant.

As regards geographical; seasonal and social distribution; parental age; birth order, etc., no convincing results in favour of exogenous influences have been published, except a slight increased parental age in some of the publications (Mac Mahon & Mekeown 1953, Rank and Thomson 1960; Frazer and Calnan 1961; Knox 1963).

MATERNAL AGE

Hagover reporting on 140,000 births observed that women gave birth between ages of 36 and 40 had twice as many and those over 40, had 3 times as many deformed children as did younger mothers. In a reported series, the first borns were affected three times more than other children.

We have seen quite a few cases in which the disparity of parental age has been quite pointed and significant. This may probably indicate the role of imbalance of a sexual hormones and will require much further study.

We have not been able to detect any discrimination in social strata in the causation of these anomalies.

A lower incidence of cleft deformities, however, have been reported in the coloured population than the whites, by some American observers (Davis 1924; Segin and Stark 1961). To indicate a racial difference would require much more systemic and detailed study involving larger elements of

population of diverse races in different parts of the world.

Infections and other diseases in early pregnancy have been suspected as a teratogenic since the association between rubella and congenital malformations was discovered in 1941. Recently, measles, Asian influenza and other viral infections have been similarly incriminated.

Intra-uterine infection with the protozoon toxoplasma has been described by several authors to produce congenital malformations including cleft lip and palate. (Gabka 1954 etc.)

The recently proved larger incidence of malformations among children of diabetic mothers in connection with the increasing number of diabetic women who now a days bear children, may be at least one factor in the increased incidence of congenital deformities.

Quite recently, epilepsy has become a teratogenic suspect. Whether the disease itself or drug used in the disease are teratogenic, is difficult to say, without further investigation. (Janz & Fuch 1964).

Until the thalidomide era, no teratogenic drug in man, has been demonstrated apart from aminopterin, a folic acid antagonist which was responsible for multiple congenital malformations.

Amongst endocrine substances, cortisone is a well established experimental teratogen, producing cleft palate in almost 100% of certain genetic strains of mice. The data in humans is still very inadequate, but (Bongiovanni 1960; Popperl 1962). The possibility of maternal mental stress and strain in the first trimester of pregnancy as reported by

several workers, as an important aetiological environmental factor has to be borne in mind, also in the context of the corticosteroids being an important experimental teratogen.

Certain antihistaminics used as antiemetics in pregnancy has become suspect teratogens, following the observation that large dose of meclizine in animals were teratogenic in animals (King, 1963). In a recent presentation by Henz in 1966, 12 cases of cleft lip or palate were reported in 3,333 infants from mothers who had received Meclizine in early pregnancy i.e., an incidence about two times the expected number.

Some appetite reducing drugs (weight reducing) have been, also recently incriminated. In experimental teratology, excessive Vit. A has been known to produce multiple congenital deformities. Radiation and effects of nuclear fission are known teratogenic agents even in human beings and the increased incidence of congenital malformations in Nagasaki and Hiroshima following nuclear holocaust is still too recent in human memory to forget its lessons. This raises the question of advisability of avoiding exposures of even therapeutic radiations or even diagnostic radiology in expectant mothers in the first trimester of pregnancy.

It emphasises a fact of basic importance, that no new drugs or any drug or agent which is even remotely suspected to be teratogenic should ever be exhibited to expectant mothers, specially in the first trimester of pregnancy.

ASSOCIATION WITH OTHER NON-FACIAL CONGENITAL DEFORMITIES

Associated deformities like hydrocephalus, microphæmia; Treacher-collin syndrome; Spina Klippel Fiel Syndrome; polydactyl; syndactyl; congenital valvular diseases of heart; exomphalos and talipes have been observed.

In my series, we have observed association of one case of Klippel Fiel Syndrome with cleft palate; two cases of Treacher-collin syndrome with cleft palate; four cases of Polydactyly with cleft lip and palate; one case of syndactaly with cleft lip and palate, and one case of exomphalos with a congenital alveolar facial cleft.

Before concluding, I wish to pose the question, whether we are able to do anything in an attempt to prevent the occurrence of cleft formations in the future or even to reduce its incidence.

For this, careful surveillance of human births, rapid detection of danger signals and precise compilation of detailed histories of cases are essential.

We have got to learn everything we can of the mechanisms of normal and abnormal prenatal development. This will provide the only possible means of relating experimental teratogenesis to the prevention of such anomalies in human being.

Progress in the prevention of congenital malformations of all types will not be achieved till we find out more about the

exogenous environmental factors involved, and the means by which we may eliminate or counteract them.

Our hope lies in the adoption of a common research programme on an international basis through cooperation between geneticists pharmacologists; teratologists; plastic surgeons; gynaecologists and other specialists to throw more light on the above mentioned exogenous factors.

It may be worth considering whether a National Cleft Lip and Palate registry could be formed under the auspices of our association, the main object of which would be to:—

(a) Make an investigation into the average frequency of these congenital malformations in our country, by making it possible for all births to be registered through municipal corporation in urban areas and Gram Panchayats in villages.

(b) To investigate on the basis of sufficiently large material, fit for the purpose, the occurrence of malformations amongst relations of a large number of these congenitally deformed patients and the part hereditary plays in the etiology of congenital deformities.

(c) To investigate on the basis of experimental and statistical work, all suspected teratogenic agents and all suspected environment factors.

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