CONGENITAL MALFORMATIONS

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INTRODUCTION

Improvements in standards of living combined with advances in perinatal medicine have contributed to congenital malformations becoming one of the major causes of infant mortality and morbidity. Since 1961 when Lenz described the association between thalidomide and limb defects there has been greater medical and public interest in the role of environmental factors in teratology. Heightened by the popular press, environmental pollution is now blamed for many otherwise unexplained malformations. The aim of this paper is to report the frequencies of different types of malformation, methods of documentation, and aetiologies.

FREQUENCY AND TYPE

The prevalence of a congenital malformation is the number of live plus stillbirths plus terminations reported with that malformation divided by the total number of births. The overall prevalence rate for all malformations is 25 – 30 per 1000 with 85% being reported in the first week of life.

Malformation	Liverpool Registry	Lancaster (1989 figures)
Neural Tube Defect/ Anencephaly	9.07	9.6
Hydrocephalus	2	3.2
Microcephaly	1.6	0
Cardiovascular system	23	16
Cleft lip/palate		
Gastro-intestinal tract	8.3	13
Genitalia (including hypospadias)	7.8	3.2
Urogenital	4.6	3.2
Limb	28	19
Chromosome	7.7	0

Table 1 – Rates of more common congenital malformations expressed as percentage of total number of malformations

Examples of the more common malformations are shown in Table 1. In Lancaster over the last five years there have been on average 20 major malformations annually presenting within the first seven days of life. This represents about 1% of all births, but if one were to include terminations, minor malformations and those presenting later in life then one would expect a figure of 2.5 – 3%. It is worthy of note that, in spite of terminations, these few infants are still responsible for up to 50% of first week deaths.

Because of non-standardisation in methods of reporting and failure to report more minor problems, overall prevalence rates vary considerably between different centres and, until a uniform system exists, cannot be used to compare prevalence rates between different parts of the country. It is, however, valid both to compare major abnormalities which are present at birth between centres and also to observe trends in a particular malformation in any one centre. Throughout the U.K. the prevalence of neural tube defects is falling (from 3.2 in 1960 to 1.25 in 1986 in Liverpool). This fall takes into account selective termination and is thought to be due to improved diet and more widespread use of iron, vitamin and folate supplements. There are, however, wide variations in the incidence of neural tube defects in different parts of the country and it is up to four times more common in Liverpool, Glasgow, South Wales and Dublin than in other parts. More detailed studies looking particularly at environmental factors are being performed.

METHODS OF DOCUMENTATION

The first widespread reporting system in this country was set up by the O.P.C.S. (Office of Population Census and Surveys) in 1964 following the thalidomide disaster. Statistics are collected from the Midwives Notification Certificate which is completed at birth and forwarded immediately to the O.P.C.S. The purpose is to provide an early warning system of any sudden increase in a specific malformation. The fast processing and publication of figures means that sudden changes are picked up quickly. A second advantage of this system is that nationwide coverage allows comparisons across the country. There are, however, disadvantages which make it a very inaccurate method of recording congenital malformations as a whole. Firstly, the midwives' diagnosis given at birth is often inaccurate; secondly, terminations for specific abnormalities are often not notified; thirdly, many malformations (e.g. congenital heart disease, bowel obstruction, metabolic disorder) are not apparent at birth, and finally, not all districts use the same methods of validation thus leading to lack of continuity across the country. O.P.C.S. is currently trying to improve this system.

Certain districts throughout the U.K. have set up their own reporting system and one of the best examples is in Liverpool where in 1960 a Congenital Malformations Registry was set up, which has now extended to include nine districts. In 1984 it became part of the EUROCAT Project (Concerted Action of the European Economic Communities for the epidemiological surveillance of congenital abnormalities), the aim of which is to monitor changes in the patterns of malformations and study possible aetiological factors in the population of a defined geographical area. It also provides a reliable baseline, monitoring any increase or decrease in a specific malformation. EUROCAT now has a

total of eighteen registers in nine E.E.C. countries. The Liverpool Registry also has a number of its own ongoing studies, e.g. malformations in infants of diabetic mothers, the effect of drugs taken by the mother in pregnancy, and offspring of malformed parents.

One of the major difficulties experienced by any registry is in obtaining notifications of all affected infants. Of 577 malformations in the Liverpool Region detected in 1984 only 28% had been reported to the O.P.C.S. The majority of notifications (32%) were notified to the registry via 'special clinics', with the remainder coming from Health Visitors, still-birth and death notifications, hospital discharge summaries and biochemistry laboratories. The message must be, therefore, that unless a district is extremely diligent with many 'secondary' searches, then notifications will be incomplete. A second difficulty is in deciding how much information to include on the notification form. The Liverpool form includes details of parental age, occupation, address, state of health, details of current pregnancy and previous pregnancies. Other information which may be of value but which is not sought includes previous occupations, previous addresses (from childhood) and similar details from grandparents.

Until 1989 the only reporting system in Lancaster was through the O.P.C.S. During 1987 (the year following Chernobyl) there was an impression (both by medical and nursing staff and the Manchester referral centre) of an increase in the number of major malformations. Because of inadequate statistics from previous years it was not possible to confirm this suspicion. Although the chances of a second Chernobyl were minimal, the local population was concerned at the nuclear plants in Heysham and Sellafield. After much research work a Congenital Malformations Registry was set up in Lancaster as a satellite from the Liverpool Registry. Registration commenced in January 1989. Details of all malformations are now sent quarterly to Liverpool, where it is analysed and stored on computer. After two years on the scheme a baseline has now been established and any sudden increase in malformations will be apparent.

Because of the importance of having defined geographical boundaries the register includes only those infants living in the Lancaster District, i.e. not those in South Cumbria, Yorkshire and Fylde. As in other districts the major problem is in the reporting of all infants particularly those who have not been on the S.C.B.U. or whose malformation is only detected after discharge home.

Table 1 shows registration details for the first year of the scheme. Since that time there have been improved notification methods for selective terminations for abnormality, for antenatally diagnosed conditions, for congenital heart defects and renal abnormalities. Notification is still poor for talipes, late dislocated hip, hypospadias and all congenital problems presenting outside the neonatal period*.

**I would be extremely grateful if G.P.s/C.M.O.s/ consultants in other specialities could inform me of any children in these categories born since January 1989 who may have escaped my notice.*

AETIOLOGY

Congenital malformations can be divided into those of simple genetic origin (i.e. a single mutant gene), those due to interaction between genetic and other factors, chromosomal, environmental and unknown. The last group is the largest, accounting for up to 60% of all malformations. Examples and incidences for each of these categories are shown in Table 2.

Aetiology	Incidence (expressed as % of all malformations)	Examples
Monogenic inheritance	7.5	Cystic fibrosis Haemophilia
Hereditary and other factors	20	Neural tube defects Congenital heart defects
Chromosomal	6	Down's syndrome (70%)
Environmental		
(a) Maternal infection	2.5	Rubella, CMV, toxoplasma, H.I.V.
(b) Maternal illness	1.5	Diabetes (9% of offspring) Maternal P.K.U.
(c) Maternal ingestion/ inhalation		Alcohol Cigarette Phenytoin (7.3% of offspring) Oral anticoagulants Mercury Irradiation
Unknown	60	

Table 2 – Aetiologies of different congenital malformations

Single mutant genes – both dominant and recessive, autosomal and gonadal – account for approximately 7.5% of congenital malformations. Recent advances in gene mapping now raise the possibility of antenatal diagnosis and selective termination of affected infants. This technique would, of course, only be applicable to the 'at risk' family and to those parents willing to have a termination. Autosomal recessive conditions, unless there were a previously affected infant, would be missed. Other major drawbacks of any antenatal diagnostic procedure are that the test is not infallible – false positives and false negatives occur in even the best of diagnostic centres, and secondly, the 'test' will only look for one specific abnormality and will not protect the foetus from every other type of malformation.

Consanguinous marriages may give rise to autosomal recessive syndromes, in which case genetic counselling would be appropriate. It is, however, not uncommon to find that these particular families are prepared to accept the 1:4 recurrence risk and would certainly not consider termination.

The second major group of mixed hereditary and other factors may occur 'de novo' or with a positive family history, e.g. neural tube defect, congenital heart disease. The majority of open neural tube defects are now detected antenatally by means of alpha feto-protein measurement and ultrasound scanning, though false positives and negatives still occur. Regarding major congenital heart lesions, antenatal diagnosis by ultrasound can now be offered from certain centres, when there has been a previously affected infant. If the defect is confirmed, then the choice is either termination (for e.g. hypoplastic left heart) or delivery in a 'Cardiac Centre' if the condition is amenable to early surgery. In all these conditions referral for genetic counselling is appropriate, and empirical figures for recurrence risks will be given.

Chromosomal abnormalities account for 6% of congenital malformations. Studies on early abortuses of 5 – 12 weeks gestation suggest that the majority of affected foetuses

(particularly those with an abnormality incompatible with prolonged life) are aborted. Down's syndrome accounts for 70% of all live chromosome disorders. The prevalence rate has fallen over the last 20 years since screening and termination has been offered to all women over 36 years of age and to those with a previous chromosome disorder. However, as these two groups account for only about 25% of all cases of Down's syndrome, the impact of screening has not been as dramatic as on neural tube defects, where all women are offered screening.

A few major discoveries this century disproved the belief that the human embryo was protected from environmental causes of maldevelopment. Harmful effects of irradiation were described in 1920, rubella in 1941, and thalidomide in 1961. Rubella embryopathy is the best recognized of the infective embryopathies and the aim of the new immunization programme is to reduce the number of non-immunized girls reaching child-bearing age. It is disappointing to read several reports of affected infants being born to mothers who have either had the infection or been immunized earlier in life.

Cytomegalovirus (CMV) is a very common infection and approximately 3% of newborn infants have evidence of CMV, but fewer than 5% of these develop subsequent problems. As natural infection with CMV does not confer immunity, and more than one sibling may be affected by intra-uterine infection, immunization is not likely to be effective.

Infants of frank diabetic mothers (i.e. not including gestational diabetics) have a 9% risk of having an infant with a congenital malformation. Cardiovascular, neural tube and sacral defects are particularly common. There is good evidence that good diabetic control both before conception and in the early part of pregnancy reduces this risk.

Treatment of epilepsy during pregnancy is not easy. Carbamazepine is thought to be the safest drug, as both Phenytoin and Sodium Valproate are associated with recognizable syndromes. It has been suggested that maternal epilepsy, regardless of drugs, increases the risk of abnormality in the offspring. Alcohol is currently the commonest teratogen in this country, with about one in 500 infants being affected. The foetal alcohol syndrome consists of pre- and post-natal growth deficiency, microcephaly, and characteristic facies. It is likely that many cases are missed.

Specific environmental chemicals are frequently blamed for causing congenital malformations, but in the majority of instances the claim cannot be substantiated. An example occurred in Berlin in the months following the Chernobyl explosion, when there was a cluster of trisomy 21 births (10 cases compared with 2 expected). A special study was undertaken by the EUROCAT Registries and there was found to be no overall increase in the frequency of chromosomal abnormalities following the disaster. However in this and in similar clustering events it is hard to believe that the clustering has been purely a chance occurrence.

CONCLUSION

To conclude, the causes of the majority of congenital malformations are still unknown. As better treatments are being made available for all other neonatal problems, malformations are becoming an increasingly common cause of infant mortality and morbidity. In Lancaster they are responsible for up to 50% of first week deaths. It is, therefore, important, that more time, money, and effort be devoted to studying this major group of problems.