

ORIGINAL ARTICLE

Survival of children born with congenital anomalies

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Aim: To describe the survival to age 5 years of children born with congenital anomalies.

Methods: Between 1980 and 1997, 6153 live born cases of congenital anomaly were diagnosed and registered by the population based Glasgow Register of Congenital Anomalies. They were retrospectively followed to assess their survival status from birth up to the age of 5 years.

Results: The proportions of all live born infants with congenital anomalies surviving to the end of the first week, and first and fifth year were 94%, 89%, and 88%, respectively. Survival to age 5, the end point of follow up, was significantly poorer for infants with chromosomal anomalies (48%) compared to neural tube defects (72%), respiratory system anomalies (74%), congenital heart disease (75%), nervous system anomalies (77%), and Down's syndrome (84%).

Conclusion: Although almost 90% of all live born infants with congenital anomalies survive to 5 years, there are notable variations in survival between anomaly types. Our findings should be useful for both clinicians and geneticists to assess the prognosis of congenital anomalies. This information is also important for affected families and for the planning of health care needs for this high risk population.

Congenital anomalies make an important contribution to infant mortality. They remain a leading cause of death among infants in many countries in the world.^{1–9} Epidemiologists have reported numerous investigations of the prevalence and aetiology of congenital anomalies, but analyses of mortality have tended to focus on the contribution of these disorders to perinatal and infant death rates rather than to the survival of affected infants.

Accurate quantification of the survival pattern of congenital anomalies is required for genetic counselling, clinical decision making in the antenatal and neonatal periods, and public health policy making. There are, however, relatively few published data on this topic. Leek¹⁰ observed that mortality varies with the type of anomaly, being highest among those with respiratory, cardiovascular, central nervous system, and genetic disorders. The survival of infants with chromosomal anomalies has been examined repeatedly. An Italian study,¹¹ for example, found that deaths in Down's syndrome babies were mainly due to cardiac and respiratory causes, and that poor survival was associated with high parity and advanced maternal age.

The development of ultrasound and other techniques for prenatal diagnosis will inevitably lead to a steadily increasing demand for evidence based estimates of the prognosis for infants born with a variety of congenital anomalies. As good quality epidemiological data are necessary to generate such information, we decided to utilise a long established British congenital anomaly register to describe the survival pattern of children born with congenital anomalies in the latter part of the twentieth century.

METHODS

Congenital anomalies refer to structural defects (congenital malformations, deformations, disruptions, and dysplasias), chromosomal abnormalities, inborn errors of metabolism, and hereditary disease present at birth.¹²

The source of data was the Glasgow Register of Congenital Anomalies (GRCA), a population based registry operated by the Greater Glasgow NHS Board. The GRCA was established in the early 1970s as an epidemiological surveillance system. It records standard information on all prenatally and postnatally diagnosed congenital anomalies in the offspring of mothers

resident within the boundaries of the Board. The register uses multiple sources of ascertainment and has no age limit for registration of cases. All notified anomalies are subjected to careful diagnostic validation by scrutiny of clinical and laboratory records. Anomalies are classified according to the ICD based coding of the British Paediatric Association Classification of Disease.¹³ Mortality data on children born with congenital anomalies are updated weekly by linking registry data with routine reports of immediate and underlying cause of death information that is sent to GRCA by the Registrar General for Scotland. Further information on the GRCA is available elsewhere.¹⁴

All cases (n = 6351) of live born congenital anomalies notified to the GRCA for the birth years 1980 to 1997 were included in the analysis. We retrospectively followed 6153 (97%) cases of live born anomaly on whom we had complete survival data from birth up to 5 years. Of these, 740 (12%) died, and 5413 (88%) were still alive at 5 years of age. No information was available on the remaining 198 (3%) cases, including 133 (2%) who had left Glasgow for elsewhere within the UK and 65 (1%) cases who moved abroad. They were then excluded from the study. We carried out a statistical comparison between cases lost to follow up and the study population to determine whether any particular type of anomaly was disproportionately represented in the cases lost to follow up.

Survival rates with 95% confidence intervals (CI) were calculated¹⁵ using the Kaplan-Meier method. Anomalies were analysed within selected groups as used by the EUROCAT network, of which the GRCA is part.¹² The log rank test was used to compare survival between groups of anomalies.

χ^2 tests were performed to try to assess changes in survival rates at one week, four weeks, and one year between three successive cohorts born in the time periods 1980–85, 1986–91, and 1992–97 respectively. This analysis was necessarily confined to all anomalies, as small numbers did not permit subdivision of the data.

RESULTS

Table 1 shows survival of the 6153 live born children with a diagnosis of congenital anomaly. The median survival time for all ascertained cases who died was 11 days (95% CI: 8 to 14). The shortest median survival time for those who died was in

Table 1 Survival of congenital anomalies among cases who died from birth to 5 years of age (ranked in order of median survival time)

Congenital anomalies	Number of live births followed	Number of deaths between birth and age 5	Median survival time for those who died (days)	95% CI for median survival (days)
Cleft lip with/without palate	278	5	155	*
Eye anomalies	86	4	151	*
Metabolic defects	352	25	70	4 to 293
Anomalies of limb	1051	12	43	3 to 253
Nervous system anomalies (excluding neural tube defects)	211	51	31	11 to 174
Neural tube defects	144	40	3	1 to 27
Congenital heart disease	1069	255	22	14 to 30
Digestive system anomalies	997	34	18	6 to 99
Integument anomalies	106	4	9	*
Chromosomal anomalies (excluding Down's syndrome)	102	53	6	4 to 34
Down's syndrome	210	33	100	72 to 205
Other anomalies	343	55	2	1 to 18
Urogenital tract and kidney anomalies	618	69	1	0.5 to 1
Musculoskeletal and connective tissue anomalies	462	78	1	1 to 7
Respiratory system anomalies	85	22	1	0.5 to 36
Ear anomalies	39	0	-	*
Total congenital anomalies	6153	740	11	8 to 14

*There must be at least six observations for calculation of confidence interval for median.

cases with urogenital tract and kidney anomalies (1 day, 95% CI: 0.5 to 1), musculoskeletal and connective tissue anomalies (1 day, 95% CI: 1 to 7), and respiratory system anomalies (1 day, 95% CI: 0.5 to 36). In contrast, children with Down's syndrome who died had the longest median survival time (100 days, 95% CI: 72 to 205). The median survival time for those who died from digestive system anomalies, congenital heart disease, and nervous system anomalies ranged from 18 to 31 days.

Table 2 and fig 1 present the cumulative proportion of live born children with congenital anomalies surviving from the first week to five years. The proportions of all live born infants with congenital anomalies surviving up to the first week, and to 1 and 5 years of age, were 94%, 89%, and 88%, respectively.

Infants with chromosomal anomalies were found to have the poorest prognosis compared to other groups of anomalies. Survival at the end point of follow up was poorer for children with (all) chromosomal anomalies (48%) compared to neural tube defects (72%, $p = 0.0002$), respiratory system anomalies (74%, $p = 0.0005$), congenital heart disease (75%, $p < 0.0001$), nervous system anomalies (77%, $p < 0.0001$), and Down's syndrome (84%, $p < 0.0001$).

To assess whether survival changed over time, three successive six-year time periods (1980–85, 1986–91, 1992–97) were compared in terms of proportions alive at the endpoint of three short follow up age intervals with complete data—that is, one week, four weeks, and one year. There was no statistically significant difference in survival rates over time. In the first time period (1980–85), the proportions alive at the end of one week, four weeks, and one year were 94.2%, 92.1%, and 88%, respectively. These proportions slightly increased to 94.9% ($p = 0.37$), 93.1% ($p = 0.25$), and 89.9% ($p = 0.35$), respectively in the last time period (1992–97).

A further statistical analysis was performed to compare between cases lost to follow up ($n = 198$) and the study population ($n = 6351$) to determine whether any particular type of anomaly was disproportionately represented in the cases lost to follow up. A statistical comparison between this group and the study population showed no significant difference in terms of type of anomaly ($p = 0.27$).

DISCUSSION

Our study used a population based and systematically validated registry of congenital anomalies so that possible

Table 2 Cumulative percentages of live born children with congenital anomalies surviving to 5 years (ranked in order of cumulative percentages surviving to age 5)

Congenital anomalies	Cumulative percentages surviving (%)			
	1 week	4 weeks	1 year	5 years
Anomalies of limb	99.71	99.52	98.95	98.86
Cleft lip with/without palate	99.28	98.58	98.20	98.20
Digestive system anomalies	98.50	97.79	96.99	96.59
Integument anomalies	98.11	96.23	96.23	96.23
Eye anomalies	98.84	96.51	95.35	95.35
Metabolic defects	97.16	96.87	94.60	92.90
Urogenital tract and kidney anomalies	90.29	89.97	89.00	88.83
Other anomalies	89.50	88.92	84.84	83.97
Musculoskeletal and connective tissue anomalies	88.31	87.23	84.63	83.12
Nervous system anomalies (excluding neural tube defects)	90.99	87.68	81.99	77.25
Neural tube defects	82.64	77.78	72.22	71.53
Congenital heart disease	89.71	86.33	78.39	74.65
Respiratory system anomalies	82.35	81.18	75.29	74.12
Chromosomal anomalies (excluding Down's syndrome)	69.61	65.69	50.00	48.04
Down's syndrome	96.67	95.23	87.14	84.29
Total congenital anomalies	93.66	92.37	89.11	87.95

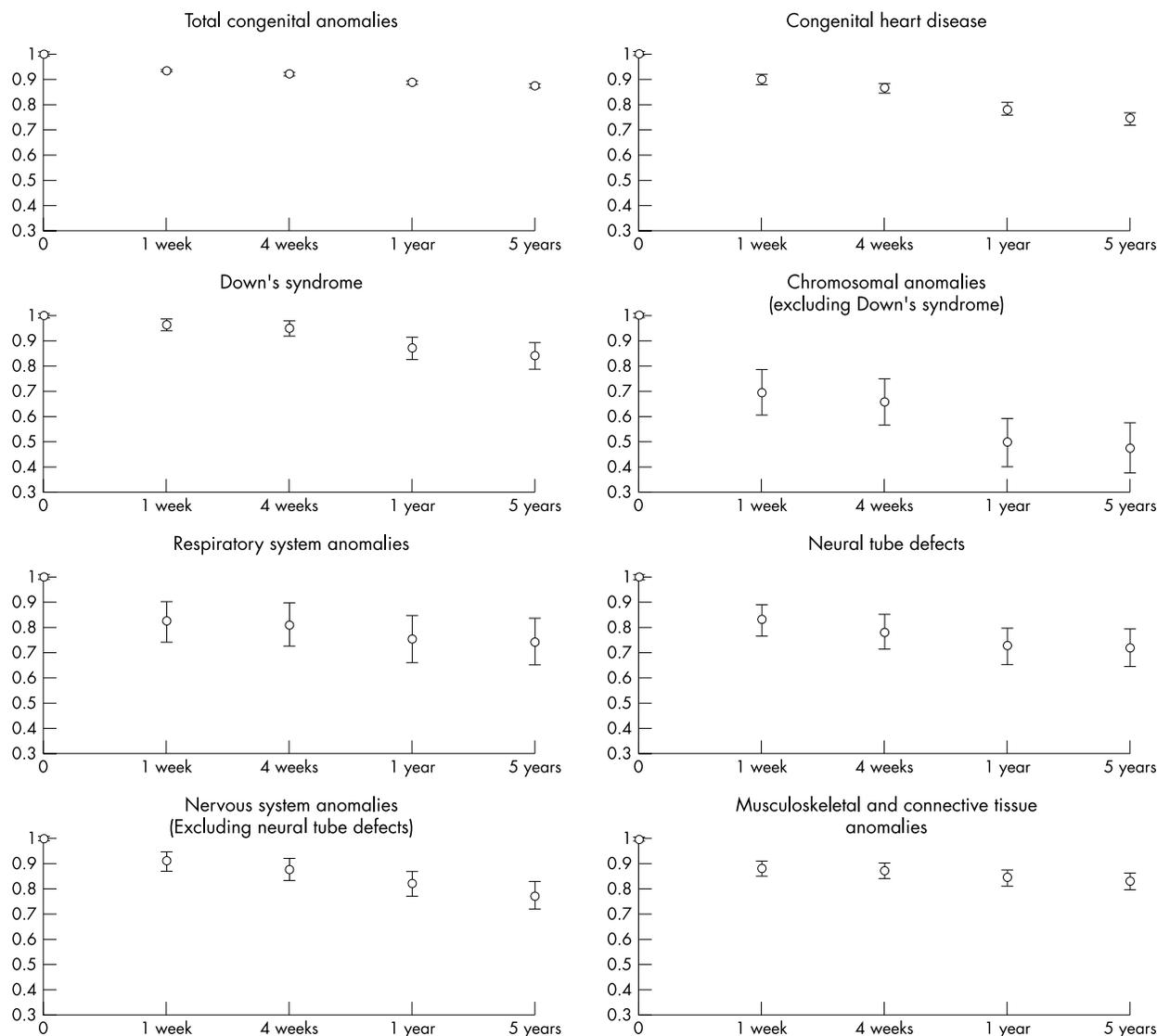


Figure 1 Survival of children with selected congenital anomalies (with 95% CI). x and y axes refer to "age at death" and "cumulative proportion surviving", respectively. Note that in some graphs, the large number of cases for total congenital anomalies results in extremely small confidence intervals, which are not properly visible.

sources of error in ascertainment were minimised. We were able to follow up 97% of the study cohort between birth and 5 years.

The study had, however, some limitations. First, in some groups of anomalies (cleft lip with/without palate, anomalies of eye, limb, and integument), few subjects died so that the results are based on very small numbers in these groups. Second, we lost 198 (3%) subjects as they had left the study area and we had no information about their current status. A statistical comparison between this group and the study population showed no difference in terms of type of anomaly, suggesting that there was unlikely to be selection bias. Finally, all registry data are subject to a degree of inaccuracy and underascertainment, although the GRCA is widely considered one of the best of its kind.

We found that almost 90% of all live born infants survived to at least 5 years, with notable variations in survival between anomaly types. Infants with chromosomal anomalies had the poorest prognosis.

In our study, the proportion of live born infants with Down's syndrome surviving to the first year was high (87%), much better than chromosomal anomalies as a whole, and

comparable with the proportions surviving in South America (74%),¹⁶ Ireland (88%),¹⁷ and Taiwan (94%).¹⁸

The survival of children with neural tube defects fell from 83% at the end of the first week to 72% at age 5 years. A Danish study reported 57% surviving to age 7 years.¹⁹ Adams *et al* reported that 57% of their cohort of infants with spina bifida in Atlanta, USA, survived one year or more.²⁰

The survival of infants with congenital heart disease to 1 year of age was similar in Glasgow (78%) to that reported from northern England (82%)²¹ and the Czech Republic (80%).²²

Although an improvement in the survival of congenital anomalies might have been expected over time given the likely improvements in medical care generally, and especially the ever more sophisticated techniques of surgical repair, we found no significant change in the survival of successive cohorts over the study period.

Because survival analysis of congenital anomaly births has rarely been performed, our findings should provide geneticists, obstetricians, and neonatologists a valuable source of data on the prognosis of anomalies in various age groups. Promoting the appropriate use of termination of pregnancy following prenatal diagnosis depends on professionals and parents having access to information to aid decision making.

This is particularly important for those anomalies that are known to be potentially lethal—including chromosomal anomalies, neural tube defects, respiratory system anomalies, congenital heart disease, and nervous system anomalies.

As we have described survival only up to age 5, we suggest that further outcome studies with longer follow up be carried out. Moreover, the paucity of published literature in this field suggests that further research is required to assess the quality of life and health care needs as well as the survival of such children.

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Looking for subgroups in the autistic spectrum

Subgroups within the autistic spectrum disorders may be definable on clinical, physiological, genetic, and pharmacological grounds. One possible subgroup has been suggested by a study in North Carolina (G Robert Delong and colleagues. *Developmental Medicine and Child Neurology* 2002;**44**:652–9).

They assessed response to the selective serotonin reuptake inhibitor, fluoxetine in 129 children aged 2–8 years with idiopathic autistic spectrum disorder. Twenty-two children (17%) had an excellent response (no longer autistic, able to participate in mainstream education though usually with special help). Sixty-seven (52%) had a good response (substantial benefit but still autistic and unable to participate in mainstream education) and 40 (31%) had a fair or poor response. Treatment response was analysed in relation to the child's clinical features and aspects of the family history in first or second degree relatives. Three features correlated strongly with an excellent or good response to fluoxetine; family history of major affective disorder (especially bipolar disorder), family history of high achievement (usually in science, mathematics, or computer science), and hyperlexia in the child.

These researchers propose that the combination of fluoxetine responsiveness, family history of major affective disorder, family history of high achievement, and hyperlexia in the child may define a subgroup within the autistic spectrum, possibly with a distinct genetic basis.