ORIGINAL ARTICLE

A cohort study of neurodevelopmental outcome in children with DiGeorge syndrome following cardiac surgery

M Maharasingam, I Östman-Smith, M G Pike

Arch Dis Child 2003;88:61–64

See end of article for authors' affiliations

Correspondence to:
Dr M G Pike, Department
of Paediatrics, John
Radcliffe Hospital,
Headington, Oxford
OX3 9DU, UK;
mandcpike@
compuserve.com

Accepted 1 August 2002

Aims: To examine whether the learning difficulties seen in a proportion of children with DGS are secondary to cardiac pathology and treatment, or a feature of the DGS phenotype.

Methods: Cohort study of all patients with DGS and coexisting cardiac lesions within a region. Ten children with 22q11 deletion were assigned two controls each, matched for age, sex, cardiac lesion, and preoperative hemodynamic status but without DGS. The neurodevelopmental status was evaluated with the Ruth Griffiths test for babies and young children.

Results: Children with the 22q11 deletion showed a wide range of developmental quotient (DQ; mean 71, 95% CI 47 to 95) and subscale scores, but these as a group were significantly lower than those of the control group (DQ 113, 95% CI 108 to 118). Four of the DGS children had DQs below 60. Hypocalcaemia, prolonged postoperative ventilation, and abnormal neurology perioperatively were associated with a low DQ.

Conclusions: A proportion of children with DGS have a very poor developmental outcome following cardiac surgery. This outcome is not attributable to the cardiac condition and its treatment alone, but represents either a pre-existing component of the syndrome or an interaction between the syndrome and its treatment.

DiGeorge syndrome (DGS) is characterised by a variable combination of facial dysmorphism, congenital heart defects, hypoparathyroidism, immune deficiency, and usually a deletion in chromosome 22q11.2. Neurodevelopmental disability has been identified in a proportion of these children.^{1–5} Neurological sequelae are also well recognised following cardiac surgery, especially with major defects such as arch anomalies, prolonged cardiopulmonary bypass time, and after periods of low perfusion pressure.^{6–7}

Early reports of DGS in the cardiovascular literature either did not comment on neurological outcome⁸ or simply indicated that neurodevelopmental sequelae are common.⁹ More recently, Wilson and colleagues¹ commented on the developmental status of 13 DGS patients: three were normal, five had mild to moderate impairment, and six severe learning difficulties. Of the six with severe learning difficulties, three had had significant hypoxic episodes around the time of cardiac surgery. Levy-Mozziconacci and colleagues² described the psychomotor development of nine of their patients; of these, five had developmental or speech delay, but the relation to the cardiac status of the individuals was not specified. Ryan and colleagues³ described 209/338 patients for whom developmental information was available as being normal or mild learning difficulties, and 60/338 as having moderate or severe learning difficulties; 75% of the total study group had congenital cardiac abnormalities but the relation of their developmental to their cardiac status was not explored. McDonald-McGinn and colleagues⁴ described the neurodevelopmental status of 95 of their cohort of 250 patients; of these 95, 28 were toddlers and 55 were of school age. Of the toddlers 21% were average, 32% were mildly delayed, and 47% were significantly delayed. Of the school age group, 13% were in the average range, 26% in the low average range, 35% in the borderline range, and 27% in the retarded range. Seventy four per cent of the children in this study had cardiac malformations, but the relation between congenital heart disease and neurodevelopmental status, or to underlying neurological malformation (which

was present in an unspecified number of patients) was not explored. Finally, Gerdes and colleagues⁵ found no association between mean developmental or language scores and the presence or absence of a cardiac anomaly in their preschool DGS study group, of whom 46% were identified as being significantly delayed.

The present study examines on a case-control basis whether neurological insults sustained as a result of cardiac pathology and surgery are the cause of the neurodevelopmental problems reported with DGS, or whether these are caused by the underlying genetic defect. A cohort of children with DGS, 22q11 deletion, and coexisting congenital heart disease referred to the Regional Centres for Clinical Genetics and for Paediatric Cardiology was compared for developmental status to children without features of DGS but matched for cardiac lesion and preoperative haemodynamic status.

PATIENTS AND METHODS

Children with DGS associated cardiac defects (truncus arteriosus, interrupted aortic arch, pulmonary atresia with ventricular septal defect (VSD), Fallot's with right aortic arch) and children with cardiac lesions associated with other features of DGS (typical dysmorphism, thymic aplasia, hypocalcaemia, family history of DGS) managed at the John Radcliffe Hospital were investigated for their 22q11 status. It was established from the Churchill Department of Clinical Genetics database and the John Radcliffe Hospital Paediatric Cardiology Database that a total of 17 children with the 22q11 mutation had been seen in the units over the period 1993–98. Of these, four had died at ages between 5 days and 2 years. Parents of the remaining 13 were invited to participate in the

Abbreviations: DGS, DiGeorge syndrome; DQ, developmental quotient; FISH, fluorescence in situ hybridisation; VSD, ventricular septal defect

Table 1 Children with 22q11 deletion who were not tested

Diagnosis	Procedure	Hypocalcaemia	Immune deficit	Status
<i>Died</i>				
PA, VSD, MAPCAs	No surgery	Not recorded	Yes	Died age 2 years
PA, VSD, L bronchial stenosis, bronchomalacia	Correction with conduit age 4 days	Yes	Yes	Died age 5 days
IAA, AS, hypoplastic asc. aorta, VSD, PDA	No surgery	Yes	Yes	Died age 4 months
IAA, AS, VSD	Correction age 7 days	Yes	Yes	Died age 4 months
<i>Declined participation</i>				
PA, VSD, MAPCAs	4 palliative shunt ops	Yes	No	Alive, learning difficulties
PA, VSD, MAPCAs	3 palliative shunt ops	No	No	Alive, mild right hemiplegia, learning difficulties
Truncus arteriosus, submucous cleft palate	Correction with conduit, age 6 weeks	Yes	No	Alive, dyspraxia and dysarthria, learning difficulties

PA, pulmonary atresia; VSD, ventricular septal defect; MAPCAs, multiple aortopulmonary collaterals; IAA, interrupted aortic arch; AS, aortic stenosis.

study, of whom 10 gave consent. Table 1 provides details about the subjects with 22q11 deletion who died, or whose parents declined for them to be tested.

The John Radcliffe Hospital paediatric cardiology database was used to identify two control cases for each 22q11 deletion child. The matching process was as follows: where possible (that is, for commoner lesions such as Fallot's tetralogy and VSD) the child of the same sex with the nearest date of birth to the index child and with an identical cardiac lesion was identified; where no such match was available, a child with a haemodynamically equivalent cardiac lesion and preoperative haemodynamic state, and requiring surgical repair of comparable duration and complexity, was identified (for example, interrupted aortic arch with VSD matched with coarctation with aortopulmonary window or coarctation with transposition of the great arteries). Table 2 shows clinical details of cases and controls. None of the controls have any dysmorphic features of DGS; some with cardiac lesions suggestive of DGS, or a family history of congenital heart disease, have been tested for the 22q11 deletion using fluorescence in situ hybridisation (FISH) and have been normal.

For each child the hospital notes were examined for the following: presence of hypocalcaemia, immune deficits, type of operation, duration of cardiopulmonary bypass, pre- and perioperative hypotensive and hypoxic episodes, perioperative neurological abnormality, and length of postoperative ventilation.

The neurodevelopmental status of the children was examined (MM) using the Ruth Griffiths Abilities of Babies and Young Children. This assessment was performed "open" to the 22q11 status of the children at the time of assessment, because there is no realistic way of blinding an experienced paediatrician to the dysmorphic features of DGS.

Statistical analysis was carried out using Statgraphics Plus and CIA software. A normal distribution could not be assumed for most variables and therefore the Mann-Whitney U test and the Wilcoxon rank sum test were used for intergroup comparisons and the comparisons of paired data respectively. Multivariate correlation analysis was used to identify factors correlating with intellectual outcome, and MANOVA was used to test for interaction between these factors, although the degrees of freedom only allowed two factors to be tested at a time. Local research ethics committee approval was obtained.

RESULTS

Examination of the control group alone ($n = 20$) shows that there was no correlation between overall developmental quo-

tient (DQ) and age at presentation, age at first operation, or age at testing. Duration of cardiopulmonary bypass and duration of ventilation were each negatively correlated with DQ ($r = -0.50$, $p = 0.03$; and $r = -0.74$, $p = 0.0005$ respectively). Duration of cardiopulmonary bypass was most significantly negatively correlated with speech and language ($r = -0.65$, $p = 0.005$) and practical reasoning ($r = -0.58$, $p = 0.02$), but showed no significant correlation with eye-hand, performance, gross motor, or personal-social subscale scores. Prolonged ventilation, a marker for a difficult postoperative course, shows a negative correlation with all the subscale scores except gross motor and personal-social ($r = -0.54$ to -0.82 , $p = 0.047$ to 0.006).

When the smaller DGS group was studied alone, the effect of duration of cardiopulmonary bypass does not reach significance, and the effect of duration of ventilation approaches significance for DQ and most subscale scores ($p = 0.054$ to

Table 2 Diagnoses in cases and matched controls

Case no.	22q11 deletion	Matched controls
1	Tetralogy of Fallot	Tetralogy of Fallot
2	Tetralogy of Fallot	Tetralogy of Fallot
3	Truncus arteriosus	Tetralogy of Fallot
4	Truncus arteriosus	Tetralogy of Fallot
5	Interrupted aortic arch, VSD	Truncus arteriosus DORV/Fallot
6	Interrupted aortic arch, VSD	Aortopulmonary window
7	VSD	Aortopulmonary window
8	VSD + infundibular PS	Transposition of great arteries + coarctation
9	Multiple VSDs	Coarctation, large VSD and BAV
10	Small VSD (no surgery)	His bundle tachycardia
		Aortopulmonary window + coarctation
		Aortopulmonary window + coarctation
		VSD
		VSD
		Tetralogy of Fallot
		Tetralogy of Fallot
		2 VSDs + ASD
		Musc. VSD + BAV
		Small VSD (no surgery)
		Small VSD (no surgery)

DORV, double outlet right ventricle; VSD, ventricular septal defect; ASD, atrial septal defect; BAV, bicuspid aortic valve.

Table 3 Clinical characteristics of DGS (n=10) and control (n=20) groups

Parameter	Group	Mean	Median	SE	SD	Range	p value*
Age at presentation (days)	Controls	49	22	17	74	1–300	0.1
	22q11	27	25	16	51	1–150	
Age at 1st operation (mth)	Controls	8.4	4.5	1.9	7.9	0.1–24	0.26
	22q11	5.1	3.5	1.9	5.3	0.1–16	
Bypass time (min)	Controls	84	80	8	33	40–165	0.79
	22q11	81	73	12	33	40–130	
Duration of ventilation (h)	Controls	42	24	8	35	3–120	0.25
	22q11	98	48	37	112	3–336	
Age at testing (y)	Controls	4.4	4.1	0.5	2.1	1–7.8	0.3
	22q11	3.6	3.4	0.7	2.2	0.5–7.5	
Calcium level (mmol/l)	Controls	2.46	2.46	0.01	0.06	2.34–2.58	0.08
	22q11	2.22	2.41	0.10	0.33	1.64–2.53	

*All NS.

0.059), but only achieves it for eye-hand ($r = -0.69$, $p = 0.038$) and practical reasoning ($r = -0.98$, $p = 0.016$).

Multiple analysis of variance was used to study the combined case and control groups. This shows a clear negative effect on DQ by the presence of the 22q11 deletion ($p = 0.004$), hypocalcaemia ($p = 0.009$), and immunodeficiency (in the form of quantitative or qualitative T cell abnormalities) ($p = 0.007$); the latter two features are confounded by their strong association with the 22q11 deletion. Abnormal neurological status perioperatively ($p = 0.035$), increasing cardiopulmonary bypass time ($p = 0.008$), and postoperative ventilation time ($p = 0.0003$) also had significant negative effects on DQ. The effects of these factors were independent of 22q11 deletion status.

Table 3 summarises the comparative clinical data for the 22q11 deletion group (n=10) and the matched controls (n = 20). There were no significant differences in age at presentation, age at first operation, duration of cardiopulmonary bypass, duration of postoperative ventilation, or age at testing. Hypocalcaemia and immune deficiency were, as expected, significantly more common in the group with 22q11 deletion ($p = 0.003$ and $p = 0.0002$ respectively). There was no difference in the incidence of perioperative acidosis (2/10 and 3/20 respectively).

When the neurodevelopmental outcome of the two groups was compared (table 4), the DGS group mean DQ score (71, 95% CI 47 to 95) was substantially lower than the mean DQ score of the controls (113, 95% CI 108 to 118; $p = 0.0001$). The DGS group scored significantly worse than controls for all Griffiths subscales (range $p = 0.0001$ to 0.01). It is of note that although six of the 10 DGS children had DQs within the normal range, scores were below 100 in four of the six, and that

the remaining four DGS children had a very poor neurodevelopmental outcome (DQs ranging from 3 to 56). The controls had DQs above 100 in all but two cases.

Two of the DGS group had particularly poor developmental outcomes (DQs 3 and 35). As these two subjects had had preoperative acidosis, preoperative hypocalcaemic fits and hypotension, and a particularly difficult postoperative course, the DGS group was also compared with the controls, with these subjects excluded. The statistically significant difference in DQ between DGS and control groups persisted when these two children were excluded from analysis.

There were four DGS children with both hypocalcaemia and perioperative fits. The two with preoperative seizures temporally associated with severe hypocalcaemia had DQs of 3 and 35, whereas the children who had brief postoperative seizures not coinciding with hypocalcaemia, had DQs of 91 and 110. No control children had pre- or perioperative fits. In both the total group ($p < 0.0001$) and within the DGS group ($p = 0.005$), hypocalcaemic fits were strongly correlated with a low DQ (correlation coefficient -0.81). It is notable that perioperative acidosis was strongly correlated with a low DQ in children with DGS ($p = 0.005$, correlation coefficient -0.81) but not in the control children ($p = 0.41$, correlation coefficient -0.20). In the case of two DGS children with DQs of 49 and 56, no predictive risk factors could be identified except the 22q11 deletion itself. Conversely there were several very sick infants with good outcomes among the controls; for example, a child who was hypotensive, acidotic, and profoundly hypoxic for 12 hours after coarctation repair, before proceeding to an emergency arterial switch operation requiring the longest bypass time in the study—165 minutes—had a DQ of 117.

Table 4 Griffiths developmental quotient (DQ) and subscale scores for DGS and control groups

DQ and subscales	Group	Mean	Median	SE	SD	Range	p value
DQ	Controls	113	115	2	10	81–127	0.0001
	22q11	71	86	11	54	3–110	
Gross motor	Controls	107	108	3	12	81–131	0.001
	22q11	74	90	10	32	0–108	
Personal-social	Controls	109	109	3	12	74–129	0.0005
	22q11	72	90	11	34	6–108	
Speech and language	Controls	116	113	4	17	82–169	0.0004
	22q11	65	77	11	36	6–124	
Eye-hand coordination	Controls	113	111	3	13	92–138	0.0006
	22q11	73	84	11	35	6–115	
Performance	Controls	116	120	4	16	70–140	0.0001
	22q11	69	83	11	34	0–106	
Practical reasoning	Controls n=18	114	116	3	12	86–131	0.01
	22q11- n=4	73	93	25	49	0–108	

DGS, n=10; and controls, n=20 unless otherwise stated.

Another, described as "moribund and anuric" after seven hours of intensive care trying to reverse a pH of 7.05, has a DQ of 104.

DISCUSSION

While this study is small and the matching process and developmental assessment were both "open", the group differences are very clear and indicate that abnormal neurodevelopmental status following cardiac surgery in DGS cannot be attributed to the cardiac disease and the effects of cardiac surgery per se. The three DGS children who refused to participate are all "statemented" as having special educational needs, and two of them have movement as well as cognitive difficulties; thus it seems unlikely that their reluctance to participate has biased our sample in favour of more severely affected children. If account is also taken of the 4/17 children with DGS who died at ages between 5 days and 2 years, all having complex congenital heart lesions recognised as associated with a high mortality, the poor overall prognosis of children with congenital heart disease associated with 22q11 deletion is underlined; in this regional cohort 8/17 subjects either died or have severe neurodevelopmental handicap (DQs 3 to 56), whereas in matched controls there was no child with a poor neurodevelopmental outcome.

A search for preoperative factors in the four DGS children with poor outcome which may distinguish them from the DGS children with a good outcome (that is, DQs between 81 and 110) revealed only two probable predictors—hypocalcaemic seizures ($p = 0.005$) and preoperative acidosis ($p = 0.005$). It would therefore seem reasonable to be cautious in predicting the neurodevelopmental outcome following cardiac surgery in children who have been identified as having the 22q11 deletion, particularly where these two risk factors are present. Perioperative seizures did not occur in control children in this study; while seizures in children undergoing cardiac surgery clearly occur for a variety of reasons, consideration should be given to the possibility of DGS in such children if this has not been excluded.

The reasons for the discrepancy in neurodevelopmental outcome in children matched for cardiac status, with and without the 22q11 deletion, merit further investigation. Abnormal developmental status has been identified in a variable proportion of children with DGS in a number of studies. In addition, structural brain abnormalities on imaging or at postmortem examination have been identified in some DGS children, of which some at least are congenital rather than acquired, although none have been explicitly associated with developmental outcome.^{3 4 10 11} It seems likely therefore that the developmental problems experienced by a proportion of DGS children after cardiac surgery are a function of their DGS and/or an interaction between this diagnosis and their cardiac condition, rendering them more susceptible to neurological sequelae. The findings of Gerdes and colleagues⁵ (although not a cohort or case-control study) would support the former of these two explanations. However, the finding in our cohort study that preoperative acidosis appears to have a more severe impact in children with DGS does suggest the possibility that the 22q11 deletion impairs the response to cardiovascular stress, perhaps more so when functional hypoparathyroidism with hypocalcaemia is present. The notion of an increased

CNS vulnerability of children with 22q11 deletion is also intriguing in the context of the high incidence of psychosis, particularly schizophrenia reported in adults with 22q11 deletion.¹² It may be that hypocalcaemia, together with immunodeficiency, are markers of a more significant chromosomal deletion and that it is the nature of this mutation which is responsible for the poorer developmental outcome. In any event it seems clear that the spectrum of developmental difficulties in this patient group cannot be laid exclusively at the feet of their cardiac illness.

Finally, this study emphasises the importance, commented on previously,^{13 14} of identifying pre-existing factors (such as DGS—identifiable by FISH within 72 hours) in any evaluation of developmental outcome following cardiac surgery. It is noteworthy, in this context, that those cardiac malformations considered high risk for neurological sequelae are also those associated with DGS. In the meantime it would seem sensible, given the gloomy outcome following hypocalcaemic fits in this study, to identify and treat hypocalcaemia aggressively in this group of patients.

ACKNOWLEDGEMENTS

Dr John Deeks MSc, Centre for Statistics in Medicine, Institute of Health Sciences, University of Oxford, is acknowledged for the design of the study.

Authors' affiliations

M Maharasingam, I Östman-Smith, M G Pike, Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

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