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

M Maharasingam, I Östman-Smith, M G Pike

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 Grifths 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. 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.

Early reports of DGS in the cardiovascular literature either did not comment on neurological outcome or simply indicated that neurodevelopmental sequelae are common. More recently, Wilson and colleagues 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 significant hypoxic episodes around the time of cardiac surgery. Levy-Mozziconacci and colleagues 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 colleagues 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 status to cardiac 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 study.

Abbreviations: DGS, DiGeorge syndrome; DQ, developmental quotient; FISH, fluorescence in situ hybridisation; VSD, ventricular septal defect
there was no correlation between overall developmental quo-
Examination of the control group alone (n = 20) shows that
results
The study, of whom 10 gave consent. Table 1 provides details about
the subjects with 22q11 deletion who died, or whose parents
died 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 a similar medical history
was selected; 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 fol-
lowing: presence of hypocalcaemia, immune deficits, type of
operation, duration of cardiopulmonary bypass, pre- and peri-
operative 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 dura-
tion 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, perform-
ance, gross motor, or personal-social subscale scores. Pro-
longed 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 signifi-
cance, and the effect of duration of ventilation approaches
significance for DQ and most subscale scores (p = 0.054 to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Children with 22q11 deletion who were not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td><strong>Procedure</strong></td>
</tr>
<tr>
<td>Died</td>
<td>PA, VSD, MAPCAs</td>
</tr>
<tr>
<td></td>
<td>PA, VSD, I branchial atresia, bronchomalacia</td>
</tr>
<tr>
<td></td>
<td>IAA, AS, hypoplastic aortic arch, VSD, PDA</td>
</tr>
<tr>
<td></td>
<td>IAA, AS, VSD</td>
</tr>
<tr>
<td>Declined participation</td>
<td>PA, VSD, MAPCAs</td>
</tr>
<tr>
<td></td>
<td>PA, VSD, MAPCAs</td>
</tr>
<tr>
<td></td>
<td>Truncus arteriosus, submucous cleft palate</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Diagnoses in cases and matched controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case no.</td>
<td>22q11 deletion</td>
</tr>
<tr>
<td>1</td>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>2</td>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>3</td>
<td>Truncus arteriosus</td>
</tr>
<tr>
<td>4</td>
<td>Truncus arteriosus</td>
</tr>
<tr>
<td>5</td>
<td>Interrupted aortic arch, VSD</td>
</tr>
<tr>
<td>6</td>
<td>Interrupted aortic arch, VSD</td>
</tr>
<tr>
<td>7</td>
<td>VSD</td>
</tr>
<tr>
<td>8</td>
<td>VSD + infundibular PS</td>
</tr>
<tr>
<td>9</td>
<td>Multiple VSDs</td>
</tr>
<tr>
<td>10</td>
<td>Small VSD (no surgery)</td>
</tr>
</tbody>
</table>

DORV, double outlet right ventricle; VSD, ventricular septal defect; ASD, atrial septal defect; BAV, bicuspid aortic valve.
DiGeorge syndrome following cardiac surgery

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Mean</th>
<th>Median</th>
<th>SE</th>
<th>SD</th>
<th>Range</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (days)</td>
<td>Controls</td>
<td>49</td>
<td>22</td>
<td>17</td>
<td>74</td>
<td>1-300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>27</td>
<td>25</td>
<td>16</td>
<td>51</td>
<td>1-150</td>
<td>0.1</td>
</tr>
<tr>
<td>Age at 1st operation (mth)</td>
<td>Controls</td>
<td>8.4</td>
<td>4.5</td>
<td>1.9</td>
<td>7.9</td>
<td>0.1-24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>5.1</td>
<td>3.5</td>
<td>1.9</td>
<td>5.3</td>
<td>0.1-16</td>
<td>0.26</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>Controls</td>
<td>84</td>
<td>80</td>
<td>8</td>
<td>33</td>
<td>40-165</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>81</td>
<td>73</td>
<td>12</td>
<td>33</td>
<td>40-130</td>
<td>0.79</td>
</tr>
<tr>
<td>Duration of ventilation (h)</td>
<td>Controls</td>
<td>42</td>
<td>24</td>
<td>8</td>
<td>35</td>
<td>3-120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>98</td>
<td>48</td>
<td>37</td>
<td>112</td>
<td>3-356</td>
<td>0.25</td>
</tr>
<tr>
<td>Age at testing (y)</td>
<td>Controls</td>
<td>4.4</td>
<td>4.1</td>
<td>0.5</td>
<td>2.1</td>
<td>1-7.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>3.6</td>
<td>3.4</td>
<td>0.7</td>
<td>2.2</td>
<td>0.5-7.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Calcium level (mmol/l)</td>
<td>Controls</td>
<td>2.46</td>
<td>2.46</td>
<td>0.01</td>
<td>0.06</td>
<td>2.34-2.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>2.22</td>
<td>2.41</td>
<td>0.10</td>
<td>0.33</td>
<td>1.64-2.53</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*pAll NS.

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

<table>
<thead>
<tr>
<th>DQ and subscales</th>
<th>Group</th>
<th>Mean</th>
<th>Median</th>
<th>SE</th>
<th>SD</th>
<th>Range</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ</td>
<td>Controls</td>
<td>113</td>
<td>118</td>
<td>2</td>
<td>10</td>
<td>81-127</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>71</td>
<td>86</td>
<td>11</td>
<td>54</td>
<td>3-110</td>
<td></td>
</tr>
<tr>
<td>Gross motor</td>
<td>Controls</td>
<td>107</td>
<td>108</td>
<td>3</td>
<td>12</td>
<td>81-131</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>74</td>
<td>90</td>
<td>10</td>
<td>32</td>
<td>0-108</td>
<td>0.001</td>
</tr>
<tr>
<td>Personal-social</td>
<td>Controls</td>
<td>109</td>
<td>109</td>
<td>3</td>
<td>12</td>
<td>74-129</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>72</td>
<td>90</td>
<td>11</td>
<td>34</td>
<td>6-108</td>
<td>0.0005</td>
</tr>
<tr>
<td>Speech and language</td>
<td>Controls</td>
<td>116</td>
<td>113</td>
<td>4</td>
<td>17</td>
<td>82-169</td>
<td></td>
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<tr>
<td></td>
<td>22q11</td>
<td>65</td>
<td>77</td>
<td>11</td>
<td>36</td>
<td>6-124</td>
<td>0.0004</td>
</tr>
<tr>
<td>Eye-hand coordination</td>
<td>Controls</td>
<td>113</td>
<td>111</td>
<td>3</td>
<td>13</td>
<td>92-138</td>
<td></td>
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<tr>
<td></td>
<td>22q11</td>
<td>73</td>
<td>84</td>
<td>11</td>
<td>33</td>
<td>6-115</td>
<td>0.0006</td>
</tr>
<tr>
<td>Performance</td>
<td>Controls</td>
<td>116</td>
<td>120</td>
<td>4</td>
<td>16</td>
<td>70-140</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11</td>
<td>69</td>
<td>83</td>
<td>11</td>
<td>34</td>
<td>0-106</td>
<td>0.0001</td>
</tr>
<tr>
<td>Practical reasoning</td>
<td>Controls</td>
<td>114</td>
<td>116</td>
<td>3</td>
<td>12</td>
<td>86-131</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22q11 (n=4)</td>
<td>73</td>
<td>93</td>
<td>25</td>
<td>49</td>
<td>0-108</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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. 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 colleagues (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. 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, 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.

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