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Cognitive function and behavioural status in paediatric heart and heart-lung transplant recipients: the Harefield experience

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Abstract

***Objective*—To assess the psychological impact of cardiac and cardiopulmonary transplantation on children.**

***Design*—Retrospective cross sectional study.**

***Setting*—One British centre performing paediatric heart and heart-lung transplant operations, four cardiac units in London, three London schools, two London health centres, and the dental department of a London children's hospital.**

***Subjects*—65 children who had been given heart or heart-lung transplants and two reference groups of 52 children who had had other types of cardiac surgery and 45 healthy children.**

***Main outcome measures*—Development, cognition, and behaviour at home and at school as assessed by measures with proved validity and reliability.**

***Results*—Developmental and cognitive measures indicated that children given transplants had significantly lower scores on several parameters, particularly in terms of development in children under 4½ years of age. Performance on all tests, however, was within the normal range. There were no significant differences in behavioural ratings between the transplant and reference groups, though problem behaviour at home was more prevalent in the transplant group.**

***Conclusions*—Though cognitive development may be within the normal range, there are adverse psychological effects associated with cardiac and cardiopulmonary transplantation. These data indicate the need for a controlled prospective study in which children and their families are seen before and at regular intervals after transplantation. Interventions should be developed that are tailored to the particular needs of this very specialised group of paediatric patients and their families.**

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Introduction

Cardiac transplantation and cardiopulmonary transplantation have become established treatments for end stage cardiac failure in adults,[1,2] but only recently have they been used to treat children with end stage heart or lung disease. Children with chronic illness are more likely to have severe psychological and social difficulties than their healthy peers,[3] but very little is known about psychological adjustment after heart or heart-lung transplantation.

Late follow up of children after heart transplantation showed that most had returned to activities appropriate for their age, including school, and that few were having cardiac related symptoms.[4-6] A further study of seven patients suggested that children can "adapt" to the experience of transplantation.[7] However, the numbers of patients in these studies were very small. Furthermore, most of them were of school age and were heart rather than heart-lung recipients. Cognitive impairment[8,9] and behavioural and emotional[10,11] disturbance have been reported in children who have had open heart surgery, particularly for cyanotic conditions. Adverse effects have also been reported in parents[12] and siblings[12,13] of children with congenital heart disease. Similar problems have been encountered after paediatric renal transplantation[14] and bone marrow transplantation.[15]

The objective of this study was to examine the behaviour and cognitive function of a group of children who had had heart or heart-lung transplantation and to compare them with another group of children who had had non-transplant cardiac surgery and a group of healthy, non-hospitalised children. This cross sectional study was designed to obtain preliminary observations on children after transplantation and to assess the practicality and acceptability of such studies to families and staff.

Subjects and methods

Patients—Inclusion criteria for the study were that the patients and their families spoke English as their first language, that they were domiciled in the United Kingdom or Irish Republic, that the patients were under 17 years of age, and that they attended Harefield Hospital for follow up. During October 1988 to

TABLE I—*Standard assessment instruments used in the three groups*

Assessment	Age range (years)	No of subjects: Heart and heart-lung transplantation	No of subjects: Other cardiac surgery	No of subjects: Normal	Test	Reference
Cognitive development	0-4·5	13	15	10	Ruth Griffiths mental development scales	16
	4·6-17·0	49	35	35	Short form IQ from British ability scales (BAS)	17
School attainment	5·0-14·5	35	31	30	Arithmetic (BAS)	17
					Reading (BAS)	17
					Schonell graded spelling test	18
Behaviour	3·0-5·0	3	8	7	Richman behaviour checklist	19
	5·0-17·0	41	30	31	Rutter A scales (behaviour at home)	20
	5·0-17·0	11	29	31	Rutter B scales (behaviour at school)	20

TABLE II—*Developmental scores at ages 0-4·5 years in the three groups. (Figures in parentheses are SD)*

Parameter	Transplant mean (Tx)	Cardiac mean (C)	Normal mean (N)	95% Confidence interval for difference between Tx and C	95% Confidence interval for difference between Tx and N
Locomotor	90·7 (24·1)	96·9 (18·6)	117·8 (11·8)	−22·2 to 9·8	−44·4 to −9·8
Personal-social	97·6 (15·1)	99·4 (19·6)	117·4 (9·9)	−15·2 to 11·6	−31·2 to −8·3
Speech and hearing	95·6 (11·2)	100·4 (24·5)	121·0 (21·7)	−19·7 to 10·3	−39·8 to −10·9
Eye-hand coordination	96·1 (13·4)	99·3 (12·8)	114·2 (15·3)	−13·1 to 6·6	−30·6 to −5·6
Performance	96·4 (17·4)	107·9 (14·1)	119·4 (14·9)	−23·3 to 0·273	−37·3 to −8·7
Overall IQ	95·2 (12·9)	100·7 (16·1)	117·0 (12·7)	−16·7 to 5·7	−33·0 to −10·6

October 1991, 65 subjects met these criteria. All 65 families agreed to participate.

Reference groups—Two reference groups were studied. They were a consecutive series of 52 patients who had had conventional cardiac surgery over 24 months (mean age at assessment 6·2 years) and a group of 45 healthy children with no medical problems (mean age at assessment 8·2 years).[15] Selection criteria have been reported[15] and were comparable to those for the transplant group. The healthy subjects were recruited from local schools and health centres (n = 21) or from the dental department of Westminster Children's Hospital (n = 24) and were therefore resident in the Greater London area or home counties. The groups were comparable in social class distribution.

Measures used—Overall, measures were chosen which had proved validity and reliability and had previously successfully been applied to research in children (table I).[16-20] Three children in the transplant group were not tested for cognitive development because of neurological damage during or after transplantation. This was sustained as a result of cardiac arrest before establishing cardiopulmonary bypass in one case. The other two children had significant problems with cardiac output after surgery. These three children were assessed as being severely mentally handicapped. Two children in the conventional cardiac surgery group also were not tested because of neurological damage during open heart surgery. Response rates for completion of the behaviour questionnaires were 92% (60 children) in the transplant group, 96% (50) in the cardiac surgery group, and 93% (42) in the healthy group.

Parents' assessments—Parents were given a semi-structured interview, collecting information on demographic, social, and medical variables. Specific questions were asked about the amount of schooling missed and the child's previous medical history.

Clinicians' assessments—The cardiologists were asked to rate their patients' medical condition at the time of the assessment.

Statistical analysis—Developmental and cognitive measures were compared by one way analysis of variance. Scheffe's multiple comparison test was used to identify the source of any significant differences ($P < 0·05$) between the three groups, and performance of the heart and heart-lung recipients was compared by t test. Richman and Rutter scores (table I) were analysed by Kruskal-Wallis analysis of variance, and the numbers of children in each group obtaining scores above the cut off points on the Rutter scales were compared by χ^2 tests for κ independent samples. Owing to variations in the transplant group in the timing of the assessments after surgery, correlation coefficients (Pearson or Kendall's τ, as appropriate) were calculated to assess the degree of association between the cognitive or behavioural parameters and time since surgery.

Results

Forty one children had undergone heart transplantation, of whom 36 had an original diagnosis of cardiomyopathy, four congenital heart disease, and one Kawasaki disease. Twenty four children had received heart-lung transplants, of whom 14 had pulmonary vascular disease and 10 cystic fibrosis. The mean age at assessment was 9·4 years (range 0·6-16·6 years) and the mean time after transplantation at the time of assessment 10 months (range 3-25 months). There were 26 boys and 39 girls, and 50 (77%) came from intact, two parent families. Thirteen (20%) of the patients had had previous cardiothoracic surgery for their disease—primarily those with congenital heart disease—though all of the children had been in hospital at some stage before transplantation. Three heart-lung recipients had received a second transplant for chronic rejection, and a further patient was awaiting retransplantation. At the time of assessment no child was in hospital, though 12 (18%) patients were having problems with repeated infection or rejection episodes, or both.

The 52 children who had other types of cardiac surgery suffered from various congenital cyanotic and acyanotic disorders. Forty nine had had corrective surgery and three palliative surgery. Each patient was seen at a routine outpatient visit 12 months after surgery. A similar proportion of the transplant and cardiac surgery groups had been chronically ill since birth. Though all children in the cardiac surgery group had congenital heart disease, some had been essentially asymptomatic for much of their lives and were, in terms of physical limitations, comparable to many of the children in the transplant group with cardiomyopathy. At the time of assessment seven (13%) children in the cardiac surgery group were having ongoing medical problems.

The transplant and reference groups did not differ with respect to sex and social class distribution but the cardiac surgery group was significantly younger overall than the transplant group. However, when the children were grouped into age bands according to the age criteria of the developmental and cognitive tests[16,17] there were no significant differences in mean ages between the three groups in any age band.

DEVELOPMENT AT AGES 0-4·5 YEARS

In the transplant group all the mean subtest scores and the overall intelligence quotient (IQ) of the Ruth Griffiths scales were within the normal range according

to the standardised means for the test.[16] No comparisons could be made between the heart and heart-lung recipients because only one child in the group had undergone heart-lung transplantation. The transplant group had significantly lower scores than the healthy group on all developmental parameters, but the transplant and open heart surgery groups did not differ from one another (table II).

COGNITIVE ABILITY AT AGES 4·6-16·0 YEARS

The mean IQ of the 49 children in the transplant group was 99·0 (SD 14·5). Mean IQ scores on the attainments were arithmetic 94·8 (18·9), reading 98·2 (20·1), and spelling 86·5 (17·1). There were no significant differences in any of the cognitive or academic parameters between those children attending school and those not currently at school.

There were no significant differences between the heart and heart-lung recipients in overall IQ or school attainments, both groups falling within the normal range. The only significant difference between the two groups was in short term memory, in which the heart patients scored higher (mean 49·5 (SD 7·2) *v* 44·6 (7·2); 95% confidence interval of difference 0·744 to 9·03). There was no significant correlation between overall IQ and time since transplantation for the transplant group as a whole ($r=0·08$) or for the heart and heart-lung recipients as separate subgroups ($r=0·20$ and $r=0·17$ respectively).

On the British ability scales the transplant group performed at a lower level than the two reference groups in terms of individual subtest results (table III) and overall IQ (figure). Differences between the transplant and healthy groups were significant in the short term memory, non-verbal reasoning, and speed of information subtest results and between the transplant and cardiac groups in the short term memory result. The transplant group had a significantly lower mean overall IQ than either reference group (transplant group 99·0 (SD 14·5), cardiac group 109·9 (18·1), healthy group 111·2 (14·8); transplant and cardiac groups: 95% confidence interval 3·8 to 18·0; transplant and healthy groups 95% confidence interval 5·8 to 18·7).

On school attainments there were no significant differences between the transplant and reference groups in the arithmetic and reading parameters (figure). On spelling attainment the transplant group performed at a significantly lower level than the healthy group (transplant group mean 86·5 (SD 17·1), healthy group mean 100·3 (16·4); 95% confidence interval 5·4 to 22·4).

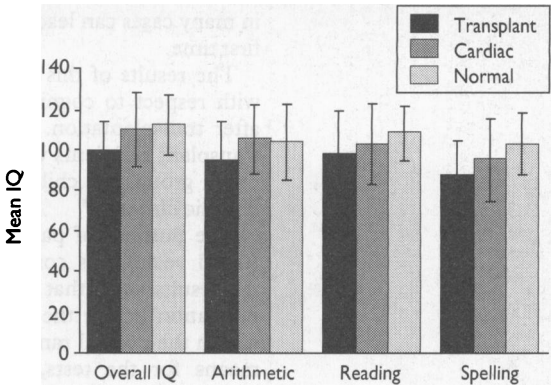
BEHAVIOUR AT HOME

On the Rutter A scales for behaviour at home 10 of 41 transplant recipients (24%) had significant problems. In seven cases behaviour was of the neurotic type.[20] Behaviour problems were more prevalent in the heart recipients (7/21; 33%) than in the heart-lung recipients (3/20; 15%) but this difference was not statistically significant. There was no significant correlation between the prevalence of behaviour problems and time since transplantation either in the total transplant group ($\tau=-0·005$) or in the heart ($\tau=-0·14$) and heart-lung ($\tau=-0·17$) recipients.

There were no significant differences between the transplant and reference groups in the prevalence of behaviour problems, though the proportion of children with a significant degree of problem behaviour was higher in both the transplant group (10/41; 24%) and cardiac group (5/30; 17%) than in the healthy group (2/31; 6%). Of those children with behaviour problems, a similar proportion in the transplant and cardiac groups had problems of a neurotic nature (seven of 10 and three of five respectively). There were no significant effects of age on the prevalence of behaviour problems in either the transplant or reference groups.

TABLE III—*Cognitive ability scores on subtests of British ability scales at ages 4·6-17·0 years in the three groups. (Figures in parentheses are SD)*

Parameter	Transplant mean (Tx)	Cardiac mean (C)	Normal mean (N)	95% Confidence interval for difference between Tx and C	95% Confidence interval for difference between Tx and N
Short term memory	47·2 (7·5)	56·3 (10·1)	55·3 (10·2)	−13·0 to −5·3	−12·0 to −4·3
Retrieval of knowledge	54·2 (11·8)	53·6 (10·6)	51·6 (6·4)	−8·0 to 9·2	−5·6 to 10·9
Non-verbal reasoning	49·6 (8·9)	54·0 (9·9)	55·7 (8·8)	−8·7 to −0·06	−10·1 to −2·1
Verbal reasoning	49·8 (8·8)	54·5 (9·6)	53·7 (8·1)	−8·9 to −0·4	−7·7 to −0·03
Speed of information	50·1 (11·6)	54·9 (13·6)	59·8 (11·2)	−12·5 to 2·8	−15·7 to −3·7



Mean overall IQ and school attainment scores in the three groups. Bars are SD

BEHAVIOUR AT SCHOOL

At the time of assessment only 15 (30%) of the 50 children in the transplant group eligible for school were attending, of whom 12 were at full time normal school, two were at school part time, and one was at a special school. Most of the children who were not attending school were less than six months after transplantation, but in 10 cases medical problems persisting more than six months after surgery had prevented the child's return. Two further children were physically well enough to attend but were not doing so for psychological reasons. Both were heart recipients. Though they had had a good medical outcome from transplantation, they had severe adjustment problems.

None of the transplant recipients who had returned to school were rated as having a significant degree of problem behaviour. The prevalence of problem behaviour was lower in the transplant group than in the cardiac (6/29; 21%) and healthy (2/31; 6%) groups, though not significantly so.

Discussion

Heart and heart-lung transplant operations are major surgical procedures. Transplant recipients require intensive medical support and must adhere to a strict medical follow up programme and drug regimen. Though potentially life saving, transplantation is a high risk procedure and as such is performed only when no other treatment is available. The patients are often chronically ill and many have had prolonged periods in hospital and numerous medical and surgical procedures. Their quality of life and life expectancy before transplantation are extremely poor. Though there is a dramatic improvement in the clinical condition of most patients after transplantation, regular hospital visits are necessary and there is inevitably concern and uncertainty about the future. Both the patient and his or her family must adjust to the fact that the child is no longer chronically sick and

in many cases can lead a normal life, sometimes for the first time.

The results of this study are generally encouraging with respect to cognitive performance and behaviour after transplantation. The short term findings in the transplant recipients were similar to those reported for other groups of children who have or have had a chronic illness.[14 15]

The number of patients in the younger age group (0-4·5 years) was comparatively small. Nevertheless, the results show that children who had cardiac transplantation before the age of 3 years were developing within the normal range according to the standardised means for the tests, though their develpment was significantly behind that of a group of healthy children. The lower mean subtest scores and overall IQ score obtained by the transplant and open heart surgery patients indicate that cardiac related problems by themselves have implications for early growth and development, which corroborates earlier findings.[8 10 21 22]

COGNITIVE DEVELOPMENT

In the absence of neurological damage, cognitive development in school age children who had had heart or heart-lung transplantation was within the normal range, though their scores were lower than those of a group of non-transplant cardiac surgery patients and a group of healthy children, particularly in short term memory tests. Differences between transplant and cardiac surgery groups may be related to the serious preoperative condition, prolonged hospitalisation, postoperative complications, and need for repeated hospital visits in the transplant group. A similar proportion of transplant recipients and non-transplant cardiac surgery patients were having medical problems at the time of the assessment, so the two groups were comparable in terms of their level of gross medical disability.

Initial diagnosis seemed to be a salient factor, rather than the type of surgical intervention. The open heart surgery group was predominantly children with acyanotic lesions, whereas the transplant group consisted of a higher proportion of children with cyanotic heart disease, for whom cognitive performance might be expected to be impaired.[9 23] There were also children with an initial diagnosis of cardiomyopathy or cystic fibrosis, which are not known to have any deleterious effect on brain development. Hence we must look at cognitive ability in terms of more specific diagnostic categories.

Owing to the retrospective nature of this study no preoperative measures were available to indicate whether IQ was lower before transplantation, but other studies of chronically ill children have found this to be so.[15] Transplant recipients had also missed substantially more schooling than the open heart surgery and normal groups, which is likely to influence their performance on academic attainments and contribute to their lower attainment scores. These lower levels of functioning on school attainments may also have been present before transplantation and could be related to problems in concentration that many of these children exhibited, manifested by the poor scores in the short term memory test.

Both the cardiac and normal groups seemed coincidentally to be "bright" samples, with 34·3% (12/35) of cardiac patients and 40·0% (14/35) of normal children obtaining an IQ score higher than one standard deviation above the mean, which was higher than the theoretically expected rate of 15·1%.[17] Another study, however, found a high mean IQ score for a sample of the normal population by using the British ability scales (mean IQ 112 (SD 13·4)),[24] which is consistent with our results.

BEHAVIOUR

Our results indicate that there are behaviour problems at home in preschool age children after transplantation, though the numbers of subjects on whom Richman behaviour checklist data were collected were too small for statistical analysis. Aspects of greatest concern to parents included temper tantrums, eating problems, sleeping difficulties, and anxiety, all similar to the problems mentioned by parents of the cardiac surgery and normal children. However, the frequency with which these problems were reported was higher in the transplant and cardiac surgery groups than in the healthy group.

In patients aged 5-17 years the Rutter A data indicated that the proportion with a significant degree of problem behaviour at home was higher than the expected 10% in the general population. In most cases the behaviour was classified as neurotic. From analysis of individual items on the scale, sleeping and eating difficulties, misery, irritability, and anxiety were particularly common. It was clear from interviews with the parents that the problems were related to adaptation after transplantation. For example, parents reported, "He worries about his health a lot and has become a hypochondriac. He answers back now and has a greater fear of needles"; "She seems to have undergone a personality change and now is withdrawn, introverted, and lonely."

There were differences in the types of behaviour problems manifested by the heart and heart-lung recipients, though these differences were not significant. In general, children with congenital heart disease and cystic fibrosis (the heart-lung group), who in many cases had been chronically ill for much of their lives, tended to cope better with the transplant and hospitalisation. They were used to dealing with illness, medical interventions, and enforced stay in hospital. In contrast, most heart recipients had an initial diagnosis of cardiomyopathy and many of them had had a fairly sudden onset of symptoms before transplantation. Some found it very difficult to accept that they needed a transplant and were extremely anxious, resentful, and aggressive after operation.

Comparison of the transplant and reference groups yielded no significant differences but both groups of hospitalised patients displayed a higher prevalence of problem behaviour than their healthy peers. The prevalence of problem behaviour in the transplant and open heart surgery groups corresponded to that found in other studies of chronically ill children.[25 26] Increased levels of anxiety, depression, and aggression postoperatively have also been found in paediatric kidney and bone marrow transplant recipients.[14 15 27]

The prevalence of problem behaviour at school was lower than that expected in the normal population (10%) and was also low compared with the reference groups. However, this must be interpreted with caution because of the small sample size. Teachers typically commented that the patients had adjusted well to their hospitalisation, and one explanation for the exceptionally low prevalence of problems in the transplant group is that the teachers' own feelings about the enormity of a transplant and their resulting perception of the children affected their responses. Many teachers seemed to regard children with transplants differently from other pupils, making allowances that they would not make for the child's peer group.

COMPARABILITY OF STUDY GROUPS

It would be preferable if the transplant and reference groups had been individually matched. In practice this is impossible, particularly in matching transplant and cardiac groups. The only significant difference between the three groups in any of the matching

Clinical implications

- Heart and heart-lung transplant operations are increasingly being used to treat children with end stage heart or lung disease
- The psychological impact of these procedures is not well documented
- In this series transplant recipients had significantly lower scores on cognitive and developmental parameters than children who had had other types of cardiac surgery or healthy children
- Transplant recipients had a higher prevalence of problem behaviour at home
- Adverse psychological effects are associated with heart and heart-lung transplantation in children and require further investigation and therapeutic intervention

criteria was in overall mean ages. Clinically, however, the difference in mean ages of the total groups is of little relevance with respect to psychological outcome and it is of far greater clinical significance to look at the patients within smaller age bands. When the groups were split into more meaningful age bands—according to the basis on which the tests were conducted—these differences were no longer significant. Also, there were no significant correlations between age and any of the outcome measures. A further source of variation within the transplant group concerned the length of time between transplantation and assessment, but there were no significant correlations between time since transplantation and any cognitive or behavioural parameters.

Conclusions

Our data, despite their limitations, provide indications of the behavioural and cognitive status of paediatric patients after heart and heart-lung transplantation. Our study was perceived positively by both families and staff, which was one of the objectives to be assessed. Despite the fact that patients were seen only once for a retrospective assessment, these preliminary observations indicate that there are important psychological effects associated with heart and heart-lung transplantation for children. A similar conclusion was also reached by Uzark and Crowley.[28]

The preliminary data emphasise the importance of conducting a controlled, prospective study including all family members, in which patients and their families are seen before and at regular intervals after transplantation. More detailed assessment of the child's emotional and behavioural status is necessary, and with larger numbers it will be possible to look more specifically at the influence of family, personality, and medical variables. Such a prospective study is now under way. It will enable us to ascertain whether the transplant group shows changes over time in psychosocial functioning and to look at how the children and their families compare, firstly, with other groups of chronically ill children having stressful and intrusive medical procedures and, secondly, with healthy children. Ultimately our data should allow the development of interventions tailored to the particular needs of this very specialised group of paediatric patients and families.

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Correction

Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes

An editorial error occurred in this paper by David R McCance and colleagues (21 May, pp 1323-8). In figure 4 the horizontal axis of the receiver operating curves should have been labelled 1 - specificity, not specificity as published.