

# Long term behavioural outcome after neonatal arterial switch operation for transposition of the great arteries

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**Aims:** To evaluate behavioural outcome and quality of life in children aged 8–14 years after neonatal arterial switch operation for transposition of the great arteries.

**Methods:** Sixty children operated as neonates with combined deep hypothermic circulatory arrest and low flow cardiopulmonary bypass were evaluated at age 7.9–14.3 years by the Child Behaviour Checklist (CBCL) and the Inventory for the Assessment of the Quality of Life in Children and Adolescents (IQCL).

**Results:** Parent reported behavioural outcome on all CBCL problem and competence scores was worse, whereas quality of life on self reported IQCL scores was not reduced compared to the normal population. On multivariate analysis, severe preoperative hypoxia was related to parent reported social problems; peri- and postoperative cardiocirculatory insufficiency was associated with internalising, externalising, attention, and total behavioural problems. Reduced expressive language was associated with total behavioural problems, and poor academic achievement was related to parent reported deficits in school performance. Impaired neurological status and reduced endurance capacity both predicted self reported stress by illness.

**Conclusions:** The neonatal arterial switch operation with combined circulatory arrest and low flow bypass is associated with parent reported long term behavioural impairment, but not with self reported general reduction in quality of life. This discrepancy may be a result of different perception of illness. In our experience, increased risk of long term psychosocial maladjustment after neonatal corrective cardiac surgery is related to the presence of neurological impairment and reduced endurance capacity.

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The arterial switch operation (ASO) to correct transposition of the great arteries (TGA) has been widely accepted as the method of choice because of low perioperative and postoperative mortality and good midterm results with respect to outcome. Attention has been directed to neurological dysfunction and developmental sequelae accompanying neonatal cardiac surgery with its support techniques—continuous low flow cardiopulmonary bypass, either isolated or combined with cardiocirculatory arrest in deep hypothermia.<sup>1–5</sup> Long term behavioural outcome and quality of life have not been addressed so far in older children after uniform corrective cardiac surgery as neonates. Children with TGA are a group without any known prevalent risk of genetic abnormality with respect to morbidity of the central nervous system.<sup>6</sup>

Our aim was to evaluate long term behavioural and emotional development, and quality of life in school aged children eight to 14 years after neonatal ASO. Additionally we evaluated the influence of risk factors in preoperative, perioperative, and postoperative management and to what degree neurodevelopmental outcome is related to long term behavioural outcome and quality of life.

## METHODS

### Patient population

Between 1986 and 1992, 96 newborns with TGA underwent ASO. Mean birth weight was 3.5 kg (SD 0.5 kg). In 2000, at a mean age of 10.5 years (SD 1.6; range 7.9–14.3), we performed a follow up study of neurodevelopmental outcome,<sup>3</sup> cardiac health, and behavioural and emotional outcome.

The total study group consisted of 60 unselected children (group A, 78% of the survivors); 77% were male (mean age 10.7 years; SD 1.7) and 23% female (mean age 9.8 years; SD 1.1).

Participation was determined mainly by the distance of the family's residence from our institution. Non-participating patients were similar to participants with respect to age, sex, cardiac health, endurance capacity, neurodevelopmental status, and socioeconomic background, as assessed by questionnaires completed by their treating paediatricians and paediatric cardiologists.

A total of 73% of the study group had a simple TGA, 17% in addition a non-important ventricular septal defect (VSD), 3% a VSD closed during ASO, and 7% had coarctation of the aorta corrected during later infancy (5%) and at age 5 years (2%), respectively. At the time of evaluation, all patients, except six children with neurological disorders, had normal endurance capacity,<sup>7</sup> and none received any cardiac related medication. In order to compare the patients with a normal population, the 54 children (90% of the total group) without severe neurological disorder (cerebral palsy or notable global developmental delay needing continuous help and treatment in daily life) and with normal exercise capacity, were also considered as a separate subgroup (group B).

Socioeconomic status, evaluated according to the main breadwinner's profession,<sup>8</sup> was not different from that of a

**Abbreviations:** ASO, arterial switch operation; CBCL, Child Behaviour Checklist; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; IQCL, Inventory for the Assessment of the Quality of Life in Children and Adolescents; TGA, transposition of the great arteries; VSD, ventricular septal defect

normal population ( $p = 0.11$ ,  $\chi^2$  test). Neurodevelopmental or psychiatric diseases within the families were excluded by asking parents. Ten per cent of the patients attended a school for special education. Our study was approved by the Ethical Medical Committee of the Aachen University of Technology, and we obtained written informed consent of patients and parents.

### Surgical management and perfusion methods

ASO was performed following standardised deep hypothermic circulatory arrest (DHCA) and low flow cardiopulmonary bypass (CPB). The protocol of the bypass technique has been described previously.<sup>1</sup>

### Risk factors for outcome

We reviewed the notes for details of perioperative management, and the pre, peri-, and postoperative complications. In analysing the influence of risk factors on later behavioural and emotional outcome and on quality of life, a list of 13 variables, available in all patients, was considered. Definition and results for the total group A and for subgroup B are described in supplementary table 3 (available on the *ADC* website).

### Relation of neurodevelopmental and sociodemographic findings to outcome

The neurodevelopmental follow up examination consisted of standardised tests evaluating a broad spectrum of development. The results of eight definite assessment procedures, available in all patients, were related to behavioural and emotional outcome and on quality of life. Supplementary table 3 (available on the *ADC* website) presents definitions and results for the total group A and for subgroup B, together with socioeconomic status and age.

### Outcome variables

#### Child Behaviour Checklist (CBCL)

Parents (mother, 64%; father, 13%; or both together, 23%) were asked to complete the CBCL while their child underwent the follow up examination. Our ratings were based on the opinion of the child's main caregiver.

The Child Behaviour Checklist (CBCL/4–18),<sup>14</sup> German version,<sup>15</sup> is a psychological inventory designed to identify behavioural problems and deficient social competence among children aged 4–18 years “within the past six months” as reported by their parents. In the behaviour problem section, 113 questions are grouped to produce subscales such as withdrawn behaviour, somatic complaints, anxious/depressed behaviour, delinquent or aggressive behaviour, and social or attention problems. Three global scale scores (internalising, externalising, total behavioural problems) can be calculated from these symptom ratings. In the competence section, there are 27 questions about the child's activities, social involvement, school performance, as well as a composite scale (total competence).

The results of eight subscales of the CBCL (internalising, externalising, social, attention, total behavioural problems as well as social involvement, school performance, and total competence) were compared with published results in an age matched German population on which the German version of the test is based and correlated to the aforementioned risk factors for outcome (see supplementary table 3, available on the *ADC* website).

#### Inventory for the Assessment of the Quality of Life in Children and Adolescents (IQLC)

This assessment<sup>16,17</sup> was used to obtain standardised information from patients on nine items estimating subjective quality of life: school, family, other children, loneliness, health, humour/nerves, total quality of life, and, in addition (not comparable to normal children) stress from illness and stress from therapy. Rating scales comprise five values ranging from

1 (very good) to 5 (very bad) for each item. The results were compared to published results in a random sample of German pupils and correlated to the aforementioned risk factors for outcome (see supplementary table 3, available on the *ADC* website).

The neurodevelopmental and the psychosocial test batteries were administered uniformly to all children in the morning, taking 3–4 hours.

### Statistical analysis

Results are expressed as mean (SD), or as percentages. For comparison of mean values, *t* tests were applied, and for comparison of frequencies,  $\chi^2$  tests were administered at a level of significance of  $p < 0.05$ . For intergroup comparison of clinical variables, the non-parametric Mann-Whitney U test was used. The Spearman rank correlation coefficient was assessed for correlation of independent parameters. Alpha adjustment for repeated measures, calculated separately for each subgroup, was done according to Bonferroni-Holm. Probability values had explorative character with respect to selection of risk factors for multivariable analysis. For multivariable analysis of risk factors for behavioural outcome and quality of life, generalised linear models were performed for 11 continuous outcome variables, each with a cluster of independent risk factors which provided a level of significance of  $p < 0.1$  in corresponding explorative univariate analyses.

## RESULTS

### Behavioural outcome in comparison with normal children

In all children (group A), the CBCL provided significantly worse results compared to controls in all scales of assessment except attention problems (table 1). Internalising problems were represented mainly by the subscale “anxious/depressed” rather than by “somatic complaints” or “withdrawn behaviour”, whereas externalising problems reflected more aggressive rather than delinquent behaviour.

In subgroup B, problem scales and school performance provided similarly impaired results to group A, when compared to controls; social involvement and total competence scores, however, were not different (table 1).

### Quality of life in comparison with normal children

The IQLC, as completed by groups A and B, were not significantly different from results in controls. The item “health” was estimated as better than in controls for both groups (table 2).

### Associations between parents' estimate and self assessment

CBCL results were related to those of the IQLC for both groups. Significantly high correlations are highlighted in supplementary table 4, available on the *ADC* website.

In group A, parent reported social involvement and total competence (CBCL) were closely correlated to self reported performance at school (IQLC); parent reported internalising and total behavioural problems as well as deficits in social involvement and total competence (CBCL) correlated significantly with self reported contact problems with other children (IQLC); parent reported social problems (CBCL) showed a high correlation to self reported deficits in total quality of life (IQLC).

In subgroup B, correlations between parents' and children's estimates were even stronger: in addition, parent reported attention problems (CBCL) were associated with self reported contact problems with other children (IQLC); parent reported externalising and total behavioural problems (CBCL) correlated with self reported depressed humour and quality of life (IQLC).

**Table 1** Child Behaviour Checklist (CBCL) scores after ASO compared to normal children

CBCL assessed by parents	Score*	Frequency in normal children (%)†	Frequency in group A (%)‡	p value§	Frequency in group B (%)‡	p value§
Internalising problems	<60	84	65	0.0005	63	0.0003
	60–63	6	7		8	
	>63	10	28		29	
Externalising problems	<60	84	72	0.006	72	0.001
	60–63	6	17		16	
	>63	10	11		12	
Social problems	<67	95	89	0.0001	90	0.0001
	67–70	3	0		0	
	>70	2	11		10	
Attention problems	<67	95	87	0.05	86	0.03
	67–70	3	7		8	
	>70	2	6		6	
Total behavioural problems	<60	84	63	0.0001	61	0.0001
	60–63	6	7		6	
	>63	10	30		33	
Social involvement	<30	2	15	<0.0001	4	>0.2
	30–33	3	3		4	
	>33	95	82		92	
School performance	<30	2	8	0.0005	0	0.001
	30–33	3	10		14	
	>33	95	82		86	
Total competence	<30	2	15	<0.0001	4	>0.2
	30–33	3	2		0	
	>33	95	83		96	

\*Scores <60, <67, and >33, resp. = no problems; scores 60–63, 67–70, and 30–33, resp. = borderline problems; scores >63, >70, and <30 = striking problems. †n = 2856, according to Achenbach.<sup>14</sup>  
‡Group A: total group of 60 children; group B: subgroup of 54 children without severe neurological damage.  
§Calculated by comparison of frequencies versus normal children, p values uncorrected.

**Table 2** Inventory for the Assessment of the Quality of Life in Children and Adolescents (IQLC) scores after ASO compared to normal children

IQLC self assessment	Mean score (SD) in normal children*	Mean score (SD) in group A†	p value‡	Mean score (SD) in group B†	p value‡
School	2.02 (0.77)	2.08 (0.79)	>0.2	2.11 (0.78)	>0.2
Family	1.40 (0.57)	1.59 (0.75)	0.06	1.62 (0.77)	0.05
Other children	1.59 (0.80)	1.65 (0.68)	>0.2	1.59 (0.66)	>0.2
Loneliness	1.87 (0.92)	1.92 (0.86)	>0.2	1.94 (0.84)	>0.2
Health	1.93 (0.87)	1.47 (0.72)	0.002	1.41 (0.67)	0.0005
Humour/nerves	2.00 (0.71)	2.04 (0.72)	>0.2	2.06 (0.72)	>0.2
Total quality of life	1.62 (0.66)	1.64 (0.59)	>0.2	1.63 (0.57)	>0.2

\*n = 53, according to Mattejat *et al.*<sup>16</sup>

†Group A: total group of 60 children; group B: subgroup of 54 children without severe neurological damage; range of scores from 1 (very good) to 5 (very bad).

‡Calculated by comparison of mean values versus normal children.

### Influences of risk factors on behavioural outcome and quality of life

On univariate analysis, six of 13 perioperative risk factors (preoperative hypoxia, durations of DHCA, CPB, and core cooling, cardiocirculatory insufficiency, resuscitation events) and all 10 neurodevelopmental and sociodemographic findings (see supplementary table 3, available on the *ADC* website) were correlated with CBCL and/or IQLC scores at a significance level of  $p < 0.1$ .

Multivariate analysis was performed for both groups. In the generalised linear models of multivariate analysis, 11 dependent behavioural and quality of life outcome parameters were considered. The model was able to confirm nine variables as independent risk factors with respect to psychosocial outcome (see supplementary table 5, available on the *ADC* website). In group A, *severe preoperative hypoxia* predicted social problems and deficits in social involvement. *Longer duration of DHCA* was associated with deficits in social involvement, and *longer duration of CPB* with reduced quality of life. The presence of *perioperative and postoperative cardiocirculatory insufficiency* predicted internalising and externalising problems, and attention problems and total behavioural problems. *Impaired neurological*

*status and impaired endurance capacity* both predicted stress by illness. *Reduced acquired abilities* were associated with deficits in school performance. *Reduced expressive language* was found to predict total behavioural problems and was weakly associated with deficits in school performance. Finally, *age at testing (puberty)* negatively influenced the subscales externalising problems and social involvement, and was weakly associated with attention problems.

In subgroup B, independent risk factors for psychosocial outcome, as indicated by additional underlined p values in supplementary table 5 (available on the *ADC* website), were less frequent than in group A. The influence of *peri- and postoperative cardiocirculatory insufficiency*, *impaired neurological status*, *impaired endurance capacity*, *reduced acquired abilities* and *reduced expressive language* was less, because these factors were fewer or absent in this subgroup (see supplementary table 3, available on the *ADC* website).

### DISCUSSION

Corrective surgery in the neonate offers the prospect of a life that may differ minimally from that of healthy children.

Therefore, from the cardiological point of view, children after neonatal ASO for TGA represent a uniform group of patients with excellent health<sup>18–20</sup> are particularly appropriate for study of long term psychosocial outcome.

### Behavioural outcome and quality of life in comparison to normal children

We assessed their clinically relevant behavioural problems in a standardised manner including self and parental reports.

Two divergent main findings emerged. Firstly, children with and without neurological disorders were described by their parents as highly behaviourally disturbed (when compared to the normal population). Contrary to these parental ratings, children in both groups described themselves as well adjusted and satisfied with their life.

The significantly higher total behavioural problem score in our sample was mainly owing to raised scores on the subscale anxious/depressed and aggressive behaviour, indicating that both internalising and externalising behaviour problems were prevalent. Additionally, both groups were described as less school competent although they had normal intelligence. This might indicate that these children had lower academic achievement than the control population. Reduced social competence, however, was clearly associated with the presence of neurological damage.

The results of the CBCL are concordant with those of two follow up studies using standardised inventories,<sup>21–22</sup> where poor psychosocial development has been reported; more optimistic outcomes, however, have recently been found in another investigation.<sup>23</sup>

Behavioural problems in chronically ill children have been investigated previously,<sup>24–25</sup> suggesting a prevalence of 15–25% of behavioural disorders in children with chronic illnesses, compared to 7–12% in the normal population.<sup>24–26</sup> If illnesses involving the central nervous system were considered, behaviour disturbances were found to be even more frequent.<sup>24–27</sup>

The high prevalence of externalising and internalising problems is surprising, because these children, especially those without severe neurological damage, had a life experience little different from healthy children: normal physical resilience, no pain, no medication with potential side effects, no special diet, and cardiological examinations only once or twice a year. Therefore, we consider the reported behavioural problems in our sample are most probably related to parental perceptions and attitudes or indirect illness related factors. De Maso and colleagues<sup>28</sup> have shown that maternal perceptions are much more potent predictors of emotional adjustment of children with congenital heart disease than objective measures of illness severity. Thus, physicians need to be aware of parents' concerns to anticipate and address those concerns.<sup>29</sup>

In contrast to parental ratings, the normal self reports by children indicate that either they did not have any behaviour problems, were not sufficiently aware of them, or denied them. The fact that the total group describe a better health satisfaction than the normative sample may suggest that denial mechanisms might have contributed to the positive self report outcome.

### Influences of risk factors on behavioural outcome and quality of life

We included significant neonatal risk factors and follow up neurodevelopmental findings in the same models of multivariate analysis in order to identify the strongest influencing variables on psychosocial outcome.

Besides chronic low arterial oxygen saturation in children with lesions such as TGA, episodes of particularly severe preoperative hypoxia in some of our patients had a negative impact on later social competence, presumably related to either cerebral motor disturbance (four patients) or general

developmental retardation (three patients), but even in the subgroup of children without severe neurological disorder and with normal exercise capacity, this factor is still prevalent.

Vital organ support during cardiac surgery in our institution includes a combination of low flow CPB, deep hypothermia, and DHCA. DHCA leads to prolonged complete cerebral ischaemia, including impairment of cerebral metabolism and vascular autoregulation. The risks of low flow CPB comprise exposure to cerebral embolic injury, cerebral hypoperfusion, and global inflammatory response continuing into the postoperative period.<sup>30</sup> Longer duration of DHCA was associated with reduced social involvement and total competence: this association was even stronger in patients without severe neurological damage than in the total cohort, in keeping with a recent similar description by Utens and colleagues.<sup>23</sup> The relation of prolonged duration of CPB to reduced total quality of life, however, might have been supported by two outliers with low self esteem (paralysed children).

The risk of brain injury is from disturbances in post-bypass cerebral perfusion, intrinsic vasoregulation, and cardiocirculatory function.<sup>30</sup> In our study, cardiocirculatory insufficiency was an independent risk factor for internalising problems as anxiety and depression, externalising problems such as delinquent and aggressive behaviour, as well as attention problems. This may be owing to a direct effect, as deficits in perioperative cerebral perfusion predominantly exert negative influences on vulnerable brain regions such as the frontal brain lobes, hippocampus, and cerebellum.<sup>31–33</sup>

Impaired neurological status and reduced endurance capacity predicted increased stress from illness as assessed by the children themselves. As in other studies, patients with cerebral palsy, ataxia, and/or global developmental delay reported particularly poor self esteem and health related quality of life,<sup>34–35</sup> and problems such as anxiety and depression.<sup>22–26–37</sup> The inverse relation between cardiac function and behavioural problems, as seen for example in children after atrial repair of TGA,<sup>22–27–38</sup> seems to be predominantly mediated by the awareness of physical impairment. This is underlined by our observation that in the subgroup without severe neurological damage, but with slight neurological and motor disorders, health related quality of life was not influenced by their neurological problems.

While cognitive function assessed by formal intelligence testing was no different from controls and was not correlated with behavioural outcome, we found, as did another report after neonatal ASO,<sup>22</sup> lower academic achievement (acquired abilities: learning and knowledge). Deficits in expressive language which was impaired in our cohort<sup>3</sup> and another,<sup>5</sup> were associated with increasing total behavioural problems. Reduced verbal expressiveness can be followed by psychiatric symptoms.<sup>39</sup> Acquired abilities and expressive language, both normal among the children without severe neurological damage, did not influence psychosocial outcome in this subgroup.

### Limitations

Both the CBCL and IQLC inventories are subjective rating scales and we did not conduct a standardised psychiatric or neuropsychological assessment. The lack of concordance between both measures would have been better interpreted if further proxy raters, such as teachers, had been involved. In addition, we did not investigate maternal mental state, known to potentially bias assessment of children's health.<sup>40</sup> A few children additionally had coarctation repaired, and parents' and patients' assessment might have been influenced by this second operation.

### Conclusions

Parent assessed long term behavioural and emotional impairment after neonatal arterial switch operation with combined deep hypothermic circulatory arrest and low flow cardiopulmonary bypass is more prevalent than in controls. Health



related quality of life, as assessed by the patients themselves, is mainly dependent on somatic state and endurance capacity, and is not generally reduced. Neurological and motor impairment and reduced exercise capacity are significantly related to the occurrence of psychiatric disorders. We emphasise the need to improve pre-, peri-, and postoperative management in neonatal corrective surgery. Furthermore, assessing behavioural problems in these children and being aware of parents' illness related concerns might be helpful for early identification of children at risk for psychiatric disorder.

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Supplementary tables 3–5 can be viewed on the ADC website [www.archdischild.com]

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