Short- and long-term outcome after fetal therapy for thoracic abnormalities

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Chapter 5

Long-term neurodevelopmental and respiratory outcome after fetal therapy for congenital thoracic malformations

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ABSTRACT

Introduction: The aim of this study is to evaluate long-term neurodevelopmental and respiratory outcome after fetal therapy for fetal pleural effusion, congenital cystic adenomatoid malformation and bronchopulmonary sequestration.

Methods: Children ≥18 months of age underwent an assessment of neurologic, motor, and cognitive development. Medical records were reviewed to determine respiratory outcome. Behavioral outcome was assessed using the Child Behavioral Checklist.

Results: Between 2001 and 2016, 63 fetuses with fetal hydrops secondary to thoracic abnormalities were treated at our center. Overall perinatal survival was 64% (40/63). Twenty-six children were included for follow-up (median age 55 months). Severe neurodevelopmental impairment (NDI) was detected in 15% (4/26). Three out of 4 children with severe NDI had associated causes contributing to the impairment. Overall adverse outcome, including perinatal mortality or NDI, was 55% (27/49). Fifteen percent (4/26) had severe respiratory sequelae. Parents did not report more behavioral problems than Dutch norms.

Discussion: Our results suggest that severe NDI in this specific high-risk cohort occurs in 15%, which is above the range of the incidence of NDI reported in case series treated with other fetal therapies (5–10%). Large multicenter studies and an international web-based registry are warranted to prospectively gather outcome data at fixed time points.

INTRODUCTION

Congenital thoracic malformations present in different forms prenatally. Fetal pleural effusion (FPE) presents as pleural fluid on prenatal ultrasound, probably due to leakage of lymphatic fluid in the pleural space(1, 2).

Congenital cystic (or pulmonary) adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS) present as cystic or solid lung masses. CCAMs are classified as being microcystic or macrocystic based on ultrasound appearance(3). A BPS is a solid lung mass characterised by an arterial feeding vessel originating from the systemic vasculature.

The outcome in FPE, CCAM and BPS is heterogeneous and varies from spontaneous resolution to severe fetal hydrops and perinatal death. Perinatal outcome is particularly poor in cases complicated by severe fetal hydrops. Perinatal survival rate in hydropic foetuses with FPE or CCAM ranges from 5 to 30%(4-8). Prenatal fetal intervention is therefore primarily indicated in cases with fetal hydrops and is associated with an increased survival rate up to 65%(4, 7). Fetal intervention for these lesions is aimed at permanently reducing the space occupying effect of the lesion and includes thoracoamniotic shunt placement in FPE and macrocystic CCAM and BPS with pleural effusion(8-10). BPS can also be treated by laser coagulation of the feeding vessel(11).

One of the concerns of the successful use of fetal therapy is that an increase in perinatal survival may be associated with an increase of children with long-term handicaps.

Long-term follow-up studies are lacking and counselling of parents prior to fetal interventions is limited to information on perinatal survival.

The aim of this study was to report on the long-term neurodevelopmental, behavioral and respiratory outcome after fetal therapy for congenital thoracic malformations including FPE, CCAM and BPS.

METHODS

In this observational cohort study we included all patients with FPE, CCAM or BPS treated with thoracoamniotic shunting or laser occlusion of the feeding vessel of BPS at our center between January 2001 and May 2016. The Leiden University Medical Center (LUMC) is the national referral center for invasive fetal therapy in the Netherlands. Patients throughout the Netherlands are referred to our center for these therapies.

The indication for fetal therapy was hydrops, defined as an accumulation of fluid in two or more compartments, including pleural effusion, skin edema, ascites, and/or pericardial effusion. For the purpose of this study we invited all families with their surviving children at least 16 months of age (corrected for prematurity) to participate

in this follow-up study. The study was approved by the ethics committee of the Leiden University Medical Center. Informed consent was obtained from all participating families.

A follow-up visit was performed at a minimum age of 18 months corrected for prematurity and included a neurologic examination according to Touwen(12) and an assessment of cognitive and motor development using the Bayley Scales of Infant and Toddler Development third edition (Bayley-III) in children between 21 and 36 months of age(13). Cognitive development of children between 3 and 7 years of age was tested with the Wechsler Preschool Primary Scale of Intelligence third edition (WPPSI-III) (14). Children at the age ≥ 7 years were tested with the Wechsler Intelligence Scale for Children third edition (WISC-III)(15). Both the WPPSI and WISC provide a Total IQ (TIQ) score including a Verbal IQ (VIQ) and a Performance IQ (PIQ). Bayley-III, WPPSI and WISC scores follow a normal distribution curve with a normed mean of 100 and a standard deviation (SD) of 15. A test score that is, a Bayley-III cognitive or motor composite score, WPPSI or WISC TIQ, VIQ or PIQ score, below 70 (< -2 SD) indicates severe delay and scores below 85 (< -1 SD) indicate mild-to-moderate delay. Children who could not be tested due to severe cognitive impairment were assigned a nominal score of 49 to reflect severe developmental delay.A trained psychologist (JMMvK), performed the psychometric tests in all children.

Cerebral palsy was defined according to the European CP Network and classified as spastic bilateral, spastic unilateral, dyskinetic (dystonic or choreo-athetotic), ataxic, or mixed.(16) Severity was classified according to the Gross Motor Function Classification System (GMFCS) for Cerebral Palsy(17). Minor neurological dysfunction (MND) was defined as a moderate abnormality of tone, posture and movement leading to only minor functional impairment or minor developmental delay(12).

The Achenbach's Child Behavior Checklist (CBCL) versions 1½–5 and 6–18 years(18, 19) was used to measure the occurrence of problem behavior. For the purpose of this study the Total problem scale, and the two broadband syndrome scales Internalizing (withdrawn, somatic complaints, anxious/depressed) and Externalizing (delinquent or rule-breaking, aggressive) behavior problems were used. T scores were computed from raw scores with higher scores on the syndrome scales indicating greater severity of problems. T scores of the normative sample have a mean of 50 ± SD 10. A clinical score in 10% of the children for the Total, Internalizing and Externalizing behavior problem scales (T score ≥ 64) served as cut-off points for comparison with Dutch normative data(19).

The primary outcome measure was a composite outcome termed severe neurodevelopmental impairment (NDI) including cerebral palsy (GMFCS II-V), cognitive or motor test score of less than 70, bilateral blindness, or bilateral deafness requiring amplification. Mild-to-moderate impairment was defined as MND, a cognitive or motor test score

< 85, mild hearing impairment, or mild visual impairment with good functional vision when corrected with glasses. An "overall adverse outcome" was calculated including perinatal mortality or severe NDI. Secondary outcomes included behavioral problem scores and respiratory outcome, including discharge on home oxygen and hospital readmissions for respiratory problems in the first 24 months after birth.

STATISTICAL ANALYSIS

All data were analysed using SPSS version 20.0 (IBM, Armonk, NY, USA). Categorical data are presented as numbers and percentages while continuous variables are presented as median with interquartile range (IQR). The percentages of children with a clinical CBCL score (T score ≥ 64) were compared with normative percentages (10% with clinical score) using a binomial test. The level of statistical significance for all analyses was set at $P < 0.05$.

RESULTS

In the study period 63 fetuses with thoracic abnormalities were treated antenatally. The antenatal and neonatal outcome of the 48 fetuses with FPE has been described earlier(20). A flowchart showing the derivation of all patients is shown in Figure 1.

Median gestational age at shunt placement or laser coagulation was 28.0 weeks (IQR 22.9-30.8 weeks). Fetal demise occurred in 16% (10/63) of pregnancies after the intervention. Eighty-four percent (53/63) of neonates were liveborn at a median gestational age of 33.9 weeks (IQR 30.5-36.5 weeks). Thirty percent (16/53) of liveborn neonates were born very preterm below a gestational age of 32 weeks. Seventy-five percent (40/53) of liveborn fetuses survived the neonatal period. Overall perinatal survival was 64% (40/63). Perinatal survival was 63% (31/48) in fetuses with FPE, 44% (4/9) in foetuses with CCAM and 83% (5/6) in foetuses with BPS.

Neurodevelopmental outcome:

Twenty-six children were included for long-term follow up at a median age of 55 months (range 21-130). Detailed information on the results can be found in Table 1, 2 and 3. The overall incidence of severe NDI in the children included for follow-up was 15% (4/26). For the 'overall adverse outcome' assessment, 49 fetuses were included. From the 63 fetuses that were treated antenatally, 10 children were excluded from analysis and in 4 cases (13%) parents gave no consent for testing (Fig. 1). Overall adverse outcome,

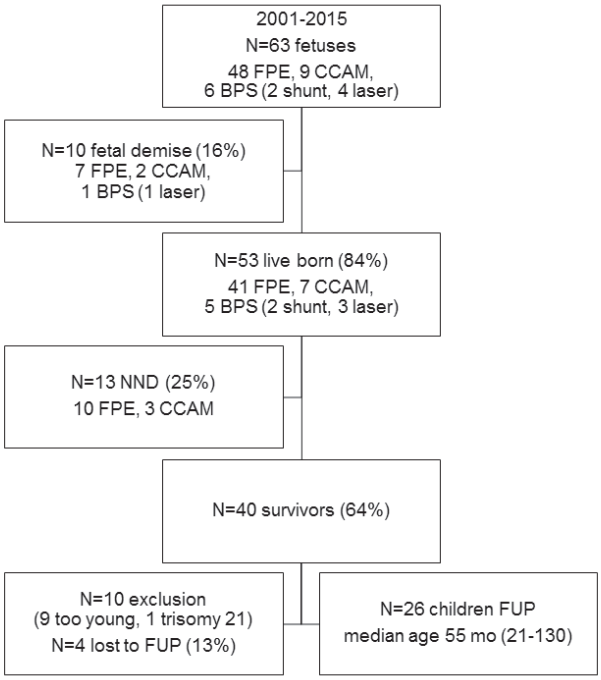

Figure 1. Flowchart showing the derivation of the study population.

including perinatal mortality (fetal demise (n=10) and neonatal death (n=13)) or long-term NDI (n=4), was 27/49 (55%).

Severe cognitive development, a score <70, was detected in 12% (3/26) of children and mild-to-moderate cognitive development <85 in 15% (4/26). Median cognitive score was 105 (range: 58-120), 102 (range: 86-118) and 87 (range: 47-103) according to Bayley-III (*n* = 8), WPPSI-III (*n* = 9) and WISC-III (*n* = 8) assessment, respectively. Overall, median cognitive score was 95 (range: 47-120). One child (case No. 15) had severe cognitive impairment and severe motor dysfunction due to congenital hypomyelinating neuropathy. She could not be assessed with formal psychometric testing and was assigned a test score of 49 in the database. Another child (case No. 19) moved with her family to another country where pediatric examinations showed age-appropriate motor and cognitive development. No score that is, a missing value, was assigned in the database. Nineteen percent (5/26) of children had mild motor dysfunction according to Touwen examination.

After birth, two children (cases No. 1 and No. 19) were diagnosed with Noonan syndrome. Case No. 1 presented with normal neurodevelopmental outcome at follow-up at age 6 years (WISC TIQ 96) and attends a regular school. Case No. 19 presented with severe cognitive and motor impairment at follow-up at 23 months of age. A tracheostomy has been placed due to severe respiratory failure probably because of Congenital

Table 1. Perinatal and long-term outcome of 20 cases of fetal pleural effusion treated with thoracoamniotic shunt placement

Case	GA at shunt placement, weeks	GA at birth, weeks	Mechanical ventilation	ICU stay, days	Age at FUP, months	Respiratory outcome		Motor development	Cognitive score	NDI	Behavioral problem
						Discharge home O2	Readmission <24 months				
1	33	33	yes	65	73	no	no	normal	95	no	no
2	18	39	yes	6	114	no	no	MND	103	no	no
3	30	34	yes	11	108	no	no	normal	84	no	no
4	32	33	yes	34	125	no	yes	normal	81	no	no
5	28	39	no	17	90	no	no	normal	78	no	yes
6	30	42	no	5	57	no	no	MND	107	no	no
7	33	33	yes	24	48	no	no	normal	86	no	no
8	25	37	no	9	29	no	no	normal	120	no	no
9	29	38	no	7	27	no	no	normal	105	no	no
10	24	28	yes	28	53	no	yes	normal	90	no	no
11	20	36	no	7	39	no	no	normal	118	no	no
12	20	38	no	7	37	no	yes	normal	102	no	no
13	34	36	no	22	25	no	no	normal	105	no	no
14	22	37	no	9	130	no	no	normal	92	no	NA
15	31	34	yes	114	88	yes	yes	neuropathy	49	yes	NA
16	21	29	yes	144	30	yes	yes	normal	105	no	no
17	31	33	yes	88	31	no	no	normal	95	no	no
18	32	34	yes	45	75	no	yes	normal	102	no	no
19	28	32	yes	282	23	yes	yes	severe	58	yes	no
20	31	36	no	12	21	no	no	severe	72	yes	NA
	29.5 (18-34)	35 (28-42)	11/20 (55%)	19,5 (6-144)	50,5 (21-130)	3/20 (15%)	7/20 (35%)	3/20 (15%)	95 (49-120)	3/20 (15%)	1/17 (6%)

Data are summarized as median (range) or percentage (n/N)

GA, gestational age; ICU, intensive care unit; FUP, follow-up; NDI, neurodevelopmental impairment; FPE, fetal pleural effusion; NA, not assessed; MND, minor neurologic dysfunction.

Table 2. Perinatal and long-term outcome of 4 cases of BPS treated with fetal therapy.

Case	Indication	Therapy	GA at therapy, weeks	GA at birth, weeks	Mechanical ventilation	ICU stay, days	Age at FUP, months	Respiratory outcome		Motor development	Cognitive score	NDI	Behavioral problem
								Discharge home O2	Readmission <24 months				
21	BPS	shunt	32	36	yes	7	31	no	no	normal	113	no	yes
22	BPS	laser	23	39	no	3	110	no	yes	normal	102	no	no
23	BPS	laser	29	41	no	0	61	no	no	normal	90	no	no
24	BPS	laser	25	38	no	4	48	no	no	normal	NA	no	NA
			27 (23-32)	38.5 (36-41)	¼ (25%)	3.5 (0-7)	54.5 (31-110)	0/4 (0%)	1/ 4 (25%)	0/4 (0%)	102 (90-113)	0/4 (0%)	1/3 (33%)

Data are summarized as median (range) or percentage (n/N)
GA, gestational age; ICU, intensive care unit; FUP, follow-up; NDI, neurodevelopmental impairment; NA, not assessed; MND, minor neurologic dysfunction.

Table 3. Perinatal and long-term outcome of 2 cases CCAM treated with thoracoamniotic shunt placement..

Case	Indication	Therapy	GA therapy	GA birth	Mechanical ventilation	ICU stay	Age FUP	Respiratory outcome		Motor development	Cognitive score	NDI	Behavior
								Discharge home O2	Readmission <24 months				
25	CCAM	shunt	23	38	no	7	109	no	no	MND	89	no	no
26	CCAM	shunt	22	26	yes	98	123	yes	no	MND	47	yes	no
			22.5 (22-23)	32 (26-38)	1 / 2 (50%)	52.5 (7-98)	55 55 (16-130)	1 / 2 (50%)	0/2 (0%)	0/2 (0%)	68 (47-89)	1 / 2 (50%)	0/2 (0%)

Data are summarized as median (range) or percentage (n/N)
GA, gestational age; ICU, intensive care unit; FUP, follow-up; NDI, neurodevelopmental impairment; NA, not assessed; CCAM, congenital cystic adenomatoid malformation; MND, minor neurologic dysfunction.

Pulmonary Lymphangiectasia (CPL) and a percutaneous endoscopic gastrostomy was performed to maintain nutrition. Recent ventilation tube insertion for both ears has resulted in better hearing that is, from a hearing loss of approximately 80 decibels to a loss less than 20-50 decibels. He attends a medical daycare facility. Twenty-seven percent (7/26) of children had mild visual impairment with good functional vision when corrected with glasses. Mild-to-moderate impairment, including MND, test scores below 85, and mild hearing and/or visual impairments, was present in 25% (9/26) of survivors.

Behavioral outcome:

Complete behavioral questionnaires were obtained from the parents of 85% (22/26) of children (n=1 ≤ 16 months of age and n=4 questionnaires not returned). According to the CBCL 1½-5 (*n* = 13), mean total problem score was 48.4 ± 12.2. Mean internalizing and externalizing problem scores were 46.6 ± 15.1 and 50.5 ± 10.0, respectively. According to the CBCL 6-18 (*n* = 9), mean scores were 56.67 ± 9.1, 51.4 ± 11.4 and 53.0 ± 11.8, respectively. T scores of the normative sample have a mean of 50 ± 10. Overall, behavioral problems within the clinical range were reported in 9% (2/22) of cases, with internalizing problems in 9% (2/22) and externalizing problems in 9% (2/22) of cases. No differences compared with normative percentages (10% with clinical score) were reported ($P > .05$).

Respiratory outcome:

Fifteen percent (4/26) of children still received oxygen therapy at discharge from the hospital. One child (case No. 15) was born at 29 weeks' gestation and was diagnosed with a severe neuropathy. One child (case No. 19) was diagnosed with Noonan syndrome after birth and appeared to suffer from CPL requiring long-term ventilation through a tracheostomy. The two other children requiring home oxygen were born premature at a gestational age of 26 and 29 weeks. Thirty-one percent (8/26) of children was readmitted to the hospital for respiratory problems (mainly respiratory tract infections) after discharge home and within 24 months after birth.

DISCUSSION

In this study we evaluated the long-term outcome in survivors after fetal therapy for fetal thoracic malformations including FPE, CCAM, and BPS. Overall adverse outcome, including perinatal mortality or severe long-term impairment was high (55%) but was mainly due to a relative high risk of perinatal death. Severe NDI in long-term survivors was detected in 15%. Mild-to- moderate impairment was present in 25% of survivors.

Compared with normative data, the parents of the children did not report more behavioral problems.

This is the first detailed analysis of a relatively large cohort of long-term survivors after fetal interventions for FPE, CCAM and BPS. We employed standardized psychometric tests in all children performed by a certified child psychologist. Importantly, the lost to follow-up rate was low (13%), reducing the risk of selection bias.

To date, only one long-term follow-up study reporting on the respiratory outcome has been published. Caserio et al. report on respiratory morbidity in a group of 15 survivors after congenital chylothorax(7). They found recurrent respiratory infections and signs of asthma in 27% of survivors. However, not all patients received fetal treatment, and some of the survivors were diagnosed with chylothorax only postnatally. In our study, we did not record the percentage of children with respiratory infections or signs of asthma as we think these parameters are not specific for respiratory problems in this selective population of children. However, some children (15%) had severe respiratory sequelae, with the need of home oxygen therapy after hospital discharge. This appeared to be related to premature birth, CPL and severe demyelinating neuropathy. Unfortunately, we do not have the facilities to perform lung function testing in children below age 5 years in our hospital. Lung function testing would have been a more objective measure to quantify respiratory outcome in this population.

Neurodevelopmental outcome in children treated with fetal therapy for fetal pleural effusion or congenital thoracic abnormalities has not been reported before. Our results suggest that long-term NDI in this specific high-risk cohort occurs in 15% of survivors, which is above the range of the incidence of NDI reported in case series treated with other fetal therapies (5-10%)(21-24). The rate of NDI in children treated with intrauterine transfusion (IUT) for alloimmune hemolytic disease was reported in 5%(21). In children treated with fetoscopic laser surgery for twin-twin transfusion syndrome (TTTS), long-term NDI occurs in 10% in most recent series(25). NDI has been reported in 7% of children treated with selective reduction in complicated monochorionic twin pregnancies(22). In most studies, prematurity and severe neonatal morbidity were identified as potential risk factors for NDI. Unfortunately, in this study, the sample size was too small to perform a risk factor analysis which would allow results to be adjusted for, e.g., the underlying cause of hydrops and prematurity. In addition, three out of four children with severe NDI had associated causes contributing to the impairment, that is, hypomyelinating neuropathy, Noonan syndrome, and NAA10-gene mutation. These associated anomalies might therefore contribute more to this relatively high rate of NDI than the thoracic abnormality and/or the associated hydrops.

Care should be taken when interpreting our results. In our cohort, different techniques were used depending on different clinical factors and the indications for intervention varied. Therefore, our study group is relative inhomogeneous and difficult to compare

to other studies. Furthermore, the interpretation of our results is limited by the lack of an appropriate control group. It would be interesting to assess long-term neurodevelopment in all children who have had fetal hydrops, whether or not they received fetal therapy. The most important limitation is the relatively small sample size which is inherent with the rarity of the disease and the fetal intervention. To reach reliable conclusions, large multicentre studies are warranted and an international web-based registry should be installed to prospectively gather outcome data in this high-risk group of children. It is important to continuously assess the neurodevelopment of the children, at fixed time points, e.g., at 2, 5, and 8 years, using standardized psychometric tests with increasing reliability of results with increasing age of the children. Only then, parents with an hydropic fetus with thoracic abnormalities can be accurately counselled including not only information on survival, but most importantly also with reliable information on long-term outcome in case of survival.

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