

OMPHALOCELE: FROM DIAGNOSIS TO GROWTH AND DEVELOPMENT AT TWO YEARS OF AGE

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Running head:	Long-term follow-up in minor and giant omphalocele
Number of words in article:	2457
Number of tables:	1
Number of figures:	4
Number of references:	33
Number of words in abstract:	250

ABSTRACT

Objective To compare the prenatal frame of reference of omphalocele (i.e. survival of fetuses) with that after birth (i.e. survival of liveborn neonates), and to assess physical growth and neurodevelopment in children with minor or giant omphalocele up to two years of age.

Design We included fetuses and neonates diagnosed 2000-2012. Physical growth (SD scores, SDS) and mental and motor development at 12 and 24 months were analysed using general linear models, and outcomes were compared with reference norms. Giant omphalocele was defined as defect ≥ 5 cm, with liver protruding.

Results We included 145 fetuses and neonates. Of 126 (87%) who were diagnosed prenatally, 50 (40%) were liveborn, and 35 (28%) survived at least two years. Nineteen (13%) neonates were diagnosed after birth. Of the 69 liveborn neonates, 52 (75%) survived, and 42 children (81% of survivors) were followed longitudinally. At 24 months, mean [95% CI] height and weight SDS were significantly below 0 in both minor (height: -0.57 [-1.05, -0.09]; weight: -0.86 [-1.35, -0.37]) and giant omphalocele (height: -1.32 [-2.10, -0.54]; weight: -1.58 [-2.37, -0.79]). Mental development was comparable to reference norms in both groups. Motor function delay was found significantly more often in children with giant omphalocele (82%) than in those with minor omphalocele (21%, $p=0.002$).

Conclusions The prenatal and postnatal frame of reference of omphalocele differ considerably; a multidisciplinary approach in parental counselling is recommended. As many children with giant omphalocele had delayed motor development, we recommend close monitoring of these children and early referral to physical therapy.

Keywords: omphalocele, abdominal wall defect, outcome, follow-up, growth, neurodevelopment

INTRODUCTION

Omphalocele is a midline congenital abdominal wall defect (AWD) with an estimated prevalence of 3.38 per 10,000 pregnancies.(1) It is usually defined as 'giant' if the defect is ≥ 5 cm at birth, with the liver (partly) protruding.(2) Otherwise, it is called 'minor'.

Nowadays, over 90% of omphaloceles are diagnosed prenatally.(3) Isolated omphalocele, which presents approximately 20%, usually has a high survival rate of 90%.(4) Other fetuses, however, present with chromosomal abnormalities and/or associated congenital anomalies (non-isolated omphalocele)(4), which lead to a high prevalence of termination of pregnancy (TOP) and intra-uterine death (IUD).

Therefore, we hypothesize a striking difference between the frame of reference of prenatal specialists and that of paediatric surgeons and paediatricians.

Previous research on long-term outcome mainly focused on children with giant omphalocele,(5-7) or surprisingly did not differentiate between gastroschisis and omphalocele.(8-10) We expect normal growth and development in non-syndromic children with minor omphalocele, and delayed growth and motor development in those with giant omphalocele.

The aim of our study was to 1) compare the prenatal frame of reference of omphalocele with that after birth, and 2) assess physical growth and neurodevelopment in children with minor or giant omphalocele up to two years of age.

METHODS

Study population

We retrospectively analysed data of all fetuses and neonates diagnosed with omphalocele between 1 January 2000 and 31 December 2012 at the Erasmus Medical Centre-Sophia Children's Hospital Rotterdam. All parents of survivors were offered to enter their child in the longitudinal prospective follow-up programme for children with anatomical congenital anomalies treated in our hospital.(11) The Medical Ethical Review Board waived approval because data obtained during routine care were retrospectively analysed (MEC-2015-308).

Variables and definitions

Following prenatal detection of omphalocele, a prenatal specialist further examined the fetus to identify possible additional structural anomalies; karyotyping was offered in all fetuses. We classified additional anomalies by prognosis as follows: lethal (e.g. trisomy 18; anencephaly), very poor (e.g. congenital diaphragmatic hernia; large encephalocele) or uncertain (e.g. suspected intestinal atresia; congenital heart defect). Fetuses with isolated omphalocele were categorised according to the ratio of omphalocele circumference to abdominal circumference (OC/AC-ratio (<0.82 or ≥ 0.82) at their first prenatal ultrasound.(12)

All fetuses were delivered vaginally, unless obstetric reasons required otherwise. Neonates with a birth weight $<10^{\text{th}}$ centile of Dutch references curves were considered small for gestational age.(13) Neonates born <37 weeks' gestation were considered preterm. Socioeconomic status scores (population mean 0, SD 1) were based on postal codes.(14, 15)

After birth, the omphalocele was defined as 'giant' if the defect diameter was $\geq 5\text{cm}$ with liver protruding. All neonates were screened for multiple congenital anomalies (MCA); we documented those requiring surgery or multiple follow-up visits. Chronic lung disease was diagnosed in neonates who required supplemental oxygen for at least 28 days.(16)

We documented duration of initial mechanical ventilation, time to full enteral feeding (TFEF), presence of intestinal failure (i.e. TFEF ≥ 6 weeks), and length of initial hospital stay. If these exceeded two years, data were documented as 730 days.

Neonatal death was defined as death during the first 28 days of life, and infant death as death between 28 days and one year.

Physical growth and neurodevelopment

Height and weight had been measured at 12 and 24 months of age (corrected for preterm birth), and head circumference at 12 months of age. We calculated standard deviation scores (SDS) according to Dutch reference norms; -2 to $+2$ SD was considered normal range.(17) Mental and motor development had been assessed at 12 and 24 months using the Bayley Developmental Scales (BOS 2-30, Dutch version)(18) and, from December 2003, Bayley Scales of Infant Development-Second Edition (BSID-II-NL).(19) These scales

are interchangeable,(19) and provide a mental developmental index (MDI) and psychomotor developmental index (PDI) with a mean of 100 and SD of 15.(18, 19) Scores <55 are indicative of severe developmental delay; those were documented as 55. We excluded children with a confirmed syndrome influencing physical growth, neurodevelopment or both from the respective analysis.

Statistical analysis

Categorical variables are presented as number (%) and continuous variables as median (interquartile range, IQR). Prenatal, perinatal and postnatal characteristics of children with minor or giant omphalocele were compared using Fisher's exact tests for categorical data, and Mann-Whitney tests for continuous data. We used general linear models to analyse the course of height, weight and neurodevelopment over time. These models included type of defect (minor or giant), the time point (12 or 24 months) and their interaction term as independent variables. We used an unstructured error covariance matrix for the repeated measurements of each child to account for the within-subject correlations. The results are presented as estimated marginal means (i.e. the predicted values of the dependent variable, adjusted for covariates in the model) with their 95% confidence intervals (CI). A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS V.21.0.

RESULTS

We included 145 fetuses and neonates; 126 (87%) were diagnosed prenatally, 50 (40%) of them were liveborn. Nineteen (13%) neonates were diagnosed postnatally. Of all 69 liveborn neonates, 52 (75%) survived at least two years (Figure 1). Follow-up data of 42 (81%) children were analysed; all but three were seen at both time points (Figure 2). Prenatal, perinatal and postnatal characteristics of children who entered our follow-up programme did not significantly differ from those who did not (data not shown).

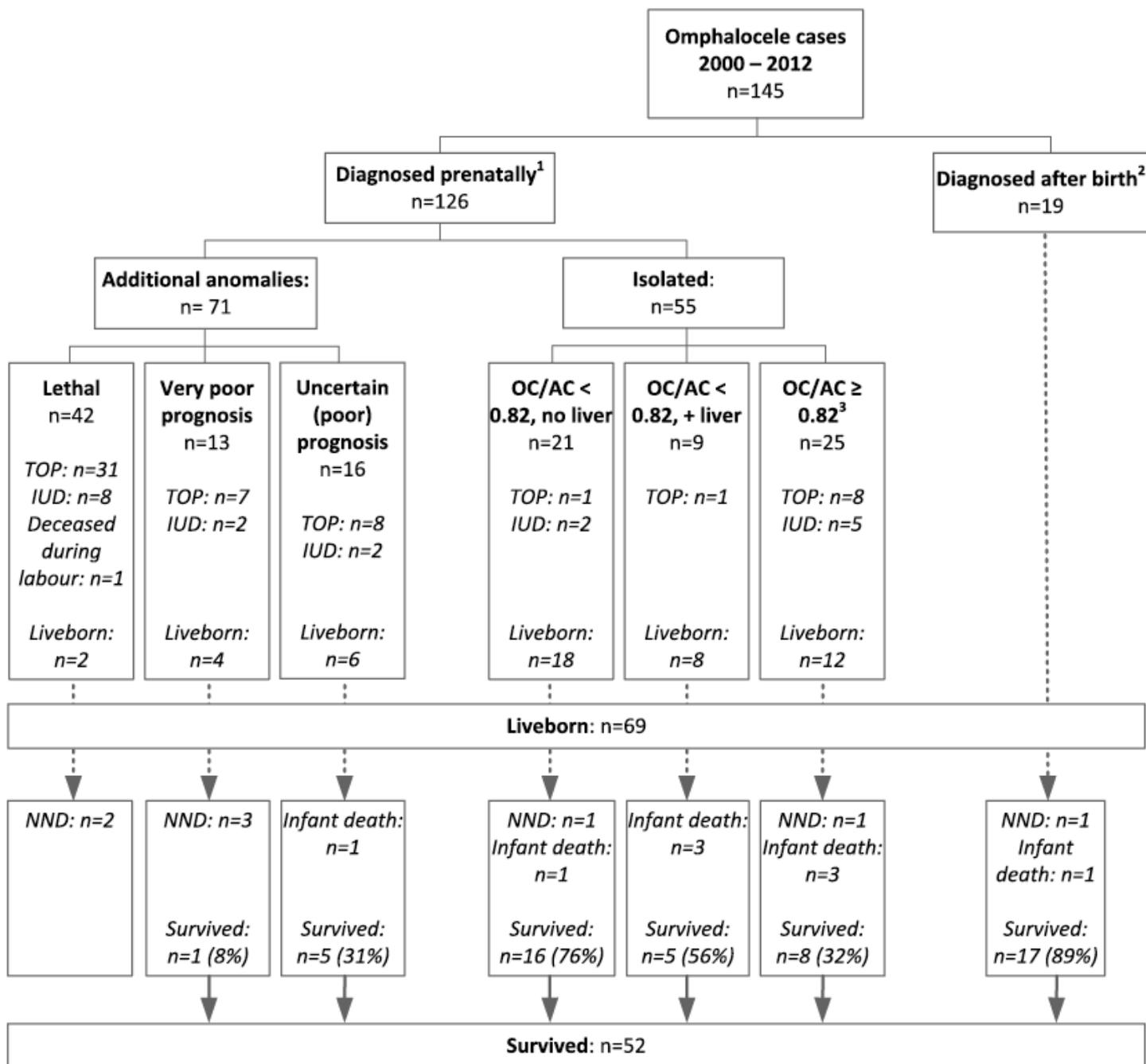


Figure 1. Flowchart of survival in all omphalocele fetuses and neonates

TOP: termination of pregnancy; IUD: intrauterine death; OC/AC: omphalocele circumference / abdominal circumference; NND: neonatal death. ¹ 2/126 were diagnosed late in pregnancy (1 at day of birth: MCA (suspected intestinal atresia), 1 at 34 weeks' gestation: isolated, but limited imaging due to severe polyhydramnios and maternal obesity); ² 1/19 prenatally diagnosed with gastroschisis instead of ruptured omphalocele; ³ Including one ruptured giant omphalocele, liver was included in 22/24 fetuses (1 unknown).

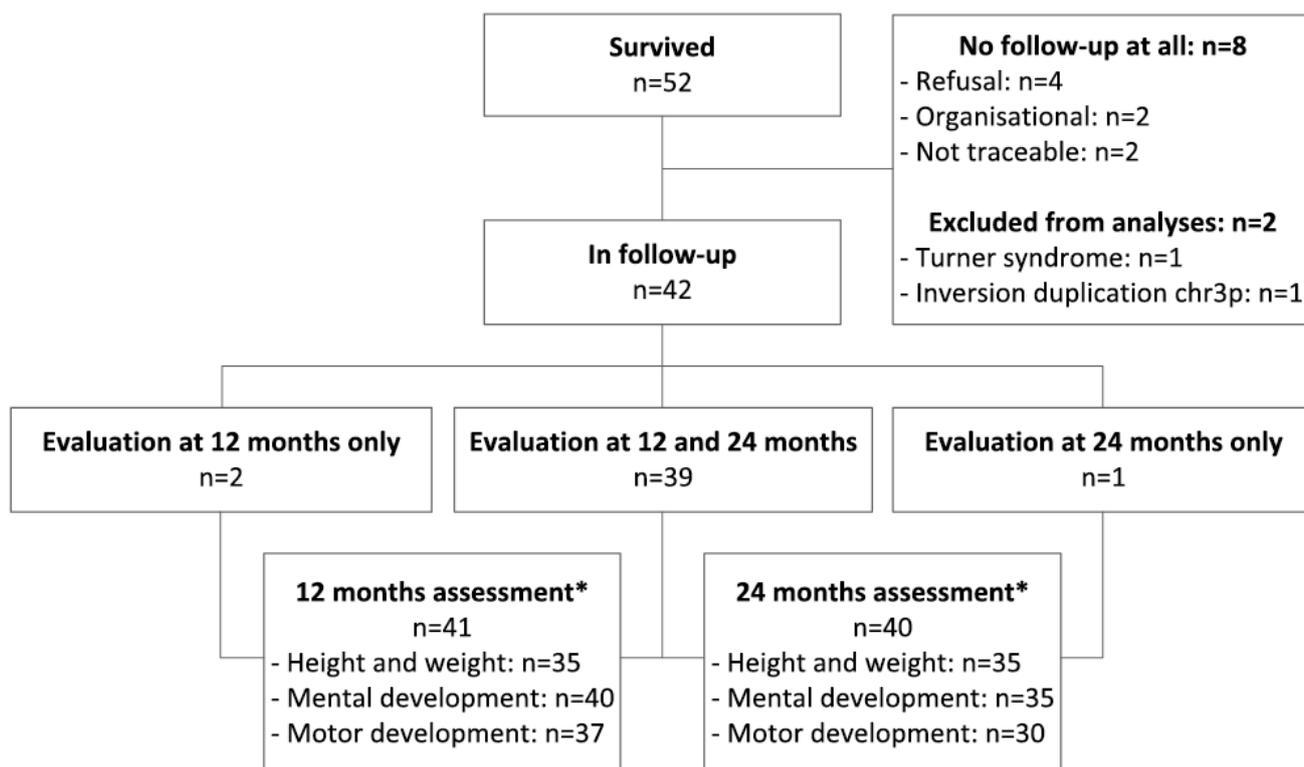


Figure 2. Flowchart of children with omphalocele included in follow-up analyses of physical growth and neurodevelopment

* Reasons for missing data on growth at 12 months: excluded because of Beckwith-Wiedemann Syndrome (n=5); organisational (n=1). At 24 months: excluded because of Beckwith-Wiedemann Syndrome (n=5).

Reasons for missing data on development at 12 months: refusal n=1 (both mental/motor); non-cooperative n=1 (motor); immobilisation of legs n=1 (motor); organisational n=1 (motor). At 24 months: refusal n=1 (both mental/motor); non-cooperative n=10 (both mental/motor n=3; mental n=1; motor n=6)

Prenatal frame of reference

Overall, 50/126 (40%) fetuses diagnosed with omphalocele were liveborn, and 35 (28%) survived ≥ 2 years.

Additional structural or chromosomal anomalies were found in 71/126 (56%) fetuses. Most of these

anomalies were lethal (42/71 (59%); Figure 1). Two fetuses classified as having a lethal prognosis were

liveborn but died shortly after birth. Thirteen fetuses had a very poor prognosis; 6/13 (46%) couples

continued the pregnancy, which resulted in four livebirths of whom one child survived. Sixteen fetuses had

an uncertain prognosis; 8/16 (50%) couples decided to continue the pregnancy; two fetuses died in utero and 5/6 liveborn neonates survived.

Isolated omphalocele was diagnosed in 55/126 (44%) fetuses. Thirty of them (55%) had OC/AC <0.82 and 26/30 (87%) were liveborn, compared to 12/25 (48%) fetuses with OC/AC ≥0.82 (p=0.003). With TOPs excluded, 93% versus 71% of continuing pregnancies resulted in livebirth, respectively (p=0.086). Of 38 liveborn neonates with an isolated omphalocele, 29 (76%) survived.

Postnatal frame of reference

Including the nineteen (13%) neonates diagnosed after birth, 69 neonates were liveborn. Eight died within one week after birth, nine during infancy. Fifty-two (75%) children survived at least two years, and 42 children participated in our follow-up (Figure 2). One child with minor omphalocele died at three years due to volvulus. All children with minor omphalocele underwent primary closure (Table 1).

Table 1. Prenatal, perinatal and postnatal characteristics of children in follow-up (n=42).

	Minor omphalocele n = 31	Giant omphalocele n = 11	P - value
Maternal age (years) ^A	31 (28-35)	31 (29-33)	0.890
Male sex	15 (48%)	4 (36%)	0.726
Multiple pregnancy	3 (10%)	0 (0%)	0.554
Socio-economic status score at birth	0.08 (-0.53-0.88)	0.06 (-0.95-0.53)	0.463
- Low status score (<-1)	8 (26%)	2 (18%)	1.000
Prenatal characteristics			
Prenatal diagnosis	18 (58%)	10 (91%)	0.067
- Gestational age (weeks) at diagnosis	22.9 (19.5-30.4)	21.2 (15.6-33.4)	0.654
- OC/AC ≥0.82 at diagnosis	0 (0%) ^B	8 (73%)	<0.001
- Liver protruding at diagnosis	4 (22%)	9 (90%)	0.001
Perinatal characteristics			
Caesarean section	8 (26%)	6 (55%)	0.136
Gestational age at birth (weeks)	38.9 (38.0-39.9)	38.4 (37.0-38.9)	0.163
Preterm birth	3 (10%)	2 (18%)	0.593
Birth weight (grams)	3180 (2500-3640)	2750 (2140-3430)	0.124
Small for gestational age	6 (19%)	3 (27%)	0.676
Apgar score at 5 min ^A	10 (9-10)	9 (8-9)	0.043
- Apgar score <7 at 5 min ^A	0 (0%)	1 (9%)	0.282
Postnatal characteristics			
Ruptured omphalocele	5 (16%)	3 (27%)	0.412
Content of omphalocele ^C			
- Liver	5 (16%)	11 (100%)	<0.001
- Stomach	0 (0%)	3 (27%)	0.014
- Bladder	0 (0%)	1 (9%)	0.262

Multiple congenital anomalies ^D	11 (35%)	3 (27%)	0.723
Primary closure	31 (100%)	1 (9%) ^E	<0.001
Number of procedures under general anaesthesia ^F	1 (1-2)	3 (2-5)	0.003
Duration of initial mechanical ventilation	0 (0-1)	3 (0-119)	0.062
Chronic lung disease	0 (0%)	6 (55%)	<0.001
Time to full enteral feeding (days)	6 (3-9)	20 (13-49)	<0.001
- Intestinal failure ^G	2 (6%)	3 (27%)	0.103
Length of initial hospital stay (days)	7 (5-13)	50 (23-108)	<0.001
Paediatric physiotherapy			
- At 12 months of age	4 (13%) ^H	6 (55%)	0.013
- At 24 months of age	2 (7%) ^I	2 (18%)	0.300

Data presented as n (%) or median (interquartile range). OC/AC: omphalocele circumference / abdominal circumference. ^A Unknown in n=3 minor omphalocele; ^B unknown in n=4 prenatally diagnosed minor omphalocele; ^C Percentages do not necessarily add up to 100, as multiple organs can be herniated; ^D Minor omphalocele: cryptorchidism (n=1); cryptorchidism + ren arcuatus (n=1); Beckwith-Wiedemann Syndrome (n=4); enlarged monokidney (n=1); intestinal atresia (n=2); intestinal atresia + microcolon (n=1); ileal cyst (n=1); Giant omphalocele: Beckwith-Wiedemann Syndrome (n=1); aortic stenosis (n=1); cryptorchidism + epiglottic dysfunction (n=1); ^E ruptured omphalocele; ^F unknown in n=1 minor omphalocele. ^G Time to full enteral feeding: 49->730 days. Minor omphalocele: intestinal atresia (n=1); intestinal atresia + microcolon (n=1); Giant omphalocele: respiratory insufficiency due to sepsis, therefore nil per os (n=1); intestinal passage problems (n=2). ^H unknown in n=1 (no follow-up at 12 months); ^I unknown in n=2 (no follow-up at 24 months).

Of eleven children with giant omphalocele, one underwent primary closure and ten had definitive closure at a median age of 19 months (range: 13-95). Children with giant omphalocele needed three times as many procedures under general anaesthesia as those with minor omphalocele. While more than half of the children with giant omphalocele developed chronic lung disease, none of those with minor omphalocele did. Three children with giant omphalocele needed mechanical ventilation for over 100 days; all got a tracheostomy cannula. The others breathed spontaneously within one week. Median TFEF was less than one week in neonates with minor omphalocele. TFEF was three times longer in those with giant omphalocele; almost one third developed intestinal failure. Children with giant omphalocele stayed seven times longer in hospital than those with minor omphalocele (Table 1).

Physical growth and neurodevelopment

Height and weight SDS are shown in Figure 3. The general linear model analysis showed no significant differences over time. At 12 months, the estimated marginal mean height SDS was significantly below 0 in children with giant omphalocele (-1.24 [95% CI: -2.01, -0.46]); weight SDS fell significantly below 0 both in children with minor (-0.61 [-1.04, -0.18]) and in those with giant omphalocele (-1.49 [-2.20, -0.78]). At 24 months, height and weight SDS were significantly below 0 in both children with minor

omphalocele (height: -0.57 [-1.05, -0.09]; weight: -0.86 [-1.35, -0.37]) and in those with giant omphalocele (height: -1.32 [-2.10, -0.54]; weight: -1.58 [-2.37, -0.79]).

Head circumference SDS was measured in 23 children with minor omphalocele (median [IQR]: -0.56 [-0.89, 0.42]), and in six with giant omphalocele (-0.22 [-1.18, -0.05]), with no statistically significant difference between those groups ($p=0.854$).

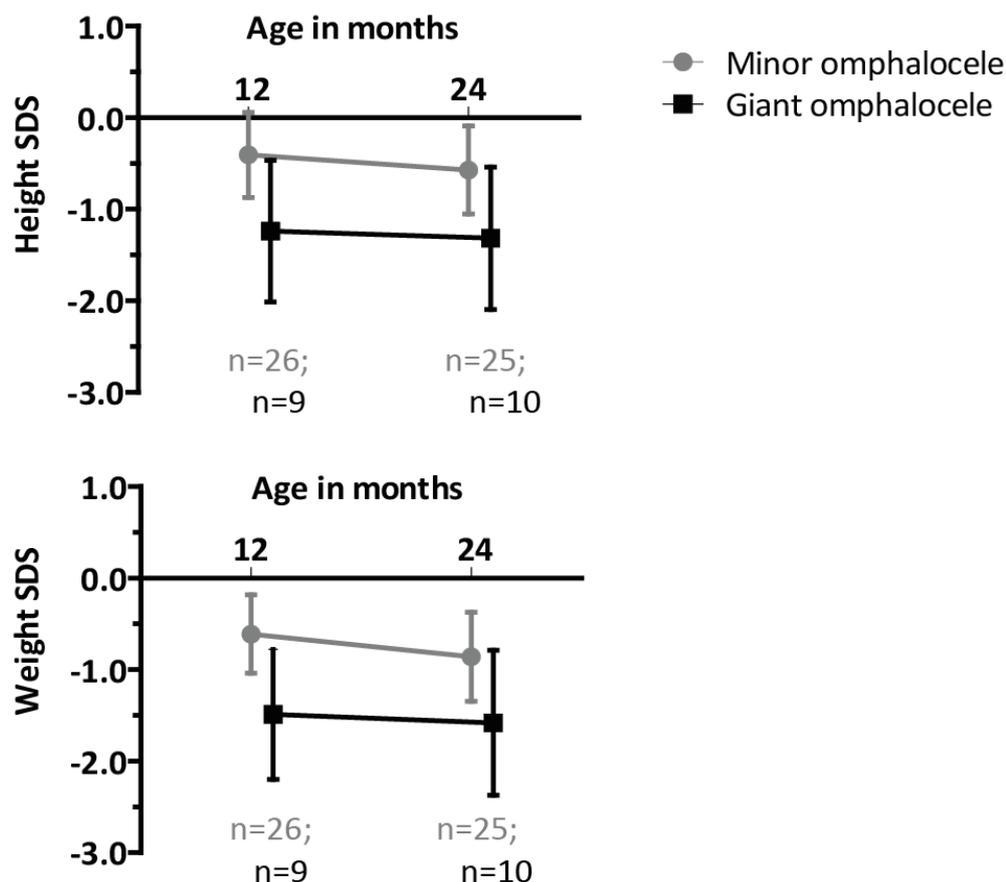


Figure 3. Height and weight standard deviation scores (SDS) of children with minor or giant omphalocele.

Symbols represent estimated marginal means with 95% confidence intervals, based on a general linear model that includes age, type of omphalocele, and their interaction term as explanatory variables.

At 12 months, height SDS was <-2 in 1/26 (4%) children with minor and in 2/9 (22%) children with giant omphalocele.

Weight SDS was <-2 in 3/26 (12%) children with minor and in 4/9 (44%) children with giant omphalocele.

At 24 months, height SDS was <-2 in 2/25 (8%) children with minor and in 3/10 (30%) children with giant omphalocele.

Weight SDS was <-2 in 4/25 (16%) children with minor and in 4/10 (40%) children with giant omphalocele.

The estimated marginal mean MDI was comparable to reference norms at both time points in children with minor omphalocele (12 months: 106 [100, 112]; 24 months: 100 [93, 108]) and in those with giant omphalocele (12 months: 97 [87, 107]; 24 months: 98 [86, 110]), and did not differ between these groups. The mean PDI in children with minor omphalocele was significantly below 100 but within the normal range of 85-115, both at 12 months (89 [82, 95]) and 24 months (93 [87, 99]). PDI in those with giant omphalocele was significantly below normal at both time points (12 months: 75 [65, 86]; 24 months: 77 [69, 86]); overall, children with giant omphalocele scored 15 [5, 26] points less than those with minor omphalocele. At 24 months, motor developmental delay occurred significantly more often in children with giant omphalocele (82%) than in those with minor omphalocele (21%, $p=0.002$); Figure 4.

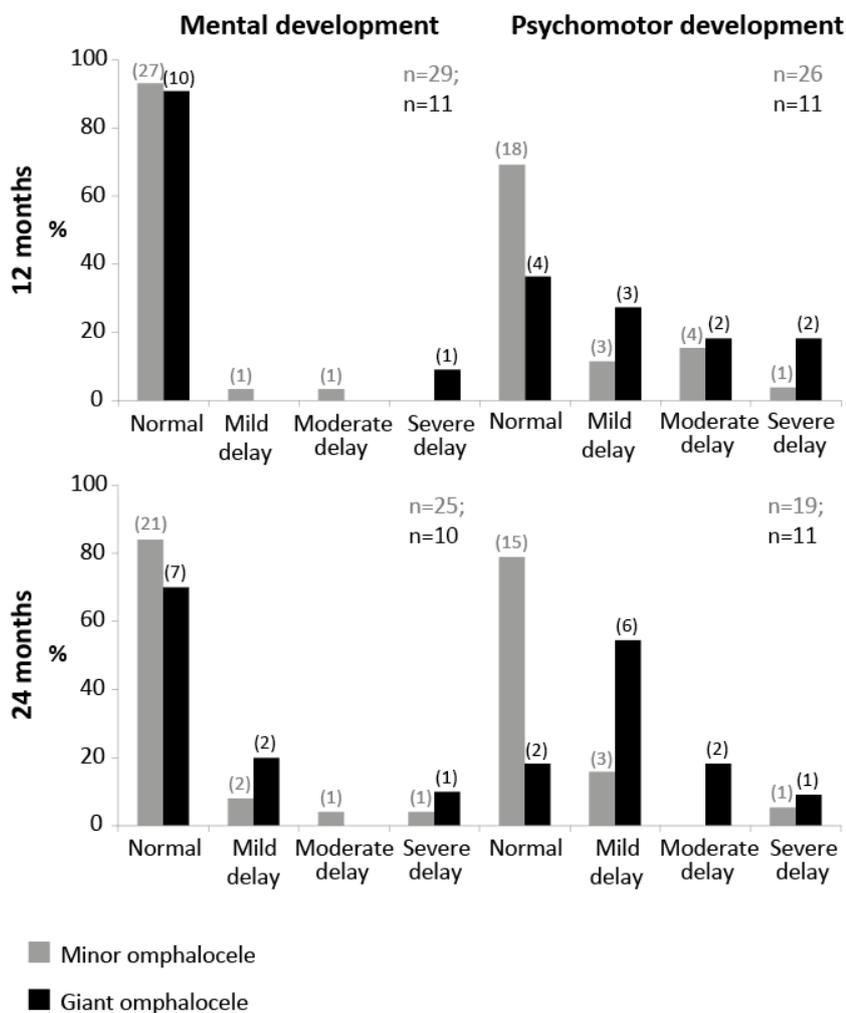


Figure 4. Proportions of children with minor or giant omphalocele with normal or delayed mental (left panel) and motor (right panel) at 12 and 24 months of follow-up.

Mild delay: developmental index 70-84; moderate delay: 55-69; severe delay: <55. Numbers of children are shown between brackets.

At 12 months, four (13%) children with minor and six (55%) with giant omphalocele received physiotherapy at home. This was continued up to at least 24 months in two (7%) children with minor and two (18%) with giant omphalocele.

DISCUSSION

We evaluated the course of omphalocele from diagnosis to growth and development at two years of age. As we hypothesized, the prenatal frame of reference was considerably worse than that after birth; additional structural or chromosomal anomalies—mainly lethal—were found in more than half of the fetuses. Physical growth at two years mainly fell within normal range. Mental development was generally normal. Motor development was delayed in over 80% of children with giant omphalocele.

The two-year survival rate in liveborn neonates was 75%, which is in concordance with previous literature.(4, 20) The two-year survival rate in prenatally diagnosed omphalocele was almost three times as low, causing a considerable difference between prenatal and postnatal frame of reference of this anomaly. The low survival rate in prenatally diagnosed omphalocele was mainly determined by the high prevalence of additional anomalies, and concomitantly high rate of TOP. In addition, IUD and neonatal death occurred frequently in this group, which confirms previous literature.(21-23)

The OC/AC-ratio is intended to provide individualised counselling by predicting type of closure.(12) In our study, many parents of fetuses with an isolated omphalocele and $OC/AC \geq 0.82$ opted for TOP. In the continuing pregnancies, IUD occurred in 29%. In fetuses with $OC/AC < 0.82$, the rates of TOP and IUD were much lower. Earlier studies on omphalocele ratios only included liveborn neonates (12, 24-26) or were unable to distinguish between isolated and non-isolated omphalocele due to small sample sizes.(27) Our finding that the OC/AC-ratio may predict survival requires further research.

This study emphasizes the importance of a multidisciplinary approach in parental counselling; paediatric surgeons and paediatricians may be more optimistic about survival rates than obstetricians and prenatal specialists. Moreover, inclusion criteria in studies on survival rates in omphalocele should be considered accurately: those including only prenatally diagnosed children are more likely to report lower survival rates than those including all children with omphalocele.

Previous studies on physical growth in children with AWD—not distinguishing between gastroschisis and omphalocele—reported suboptimal growth in infancy(10, 11), and normal(28) or suboptimal(9) growth in childhood. Henrich and coworkers reported weight <p3 in 3/15 (20%) children with omphalocele aged 1-10 years, and height <p3 in two (13%) children.(29) These proportions are similar to our results in two-year olds, and higher than those in the reference population (i.e. 2.3%, based on a standard normal distribution). Although their height and weight fell within the normal range at both time points, children with omphalocele seem to be at greater risk of failure to thrive. Our data did not allow for conclusions regarding determinants of poor growth. We assume that several aspects play a role, including neonatal surgery, work of breathing, prolonged hospitalisation, and impaired mother-child interaction. We recommend close monitoring of growth, and early nutritional intervention if necessary.

Neurodevelopment has previously been studied in cohorts combining different types of non-cardiac anatomical anomalies(8, 30, 31) or AWD,(9-11) and in cohorts limited to giant omphalocele.(5-7) Similar to our results, Burnett and coworkers reported motor function delay in two-year old children with omphalocele.(32) Studies that did not differentiate between non-cardiac anatomical anomalies reported high prevalences of neurodevelopmental problems.(8, 30, 31) In contrast, studies that evaluated children with AWD showed normal neurodevelopment in infancy,(10, 11) and normal motor development in childhood.(9) Note, however, that gastroschisis and omphalocele are two different entities; the prenatal and postnatal outcomes of children with omphalocele included in the present study differ much from those in children with gastroschisis in our previous study.(33)

Parental counselling should stress the importance of the difference between giant and minor omphalocele, as we found that giant omphalocele carried a greater risk of motor developmental delay. A previous study reported both mental and motor developmental delay in more than half of 31 children with giant omphalocele aged 6-35 months.(6) We suspect the higher proportion of mental developmental delay could be explained by the inclusion of children with major MCA and rare syndromes in that study.(6)

We assume that in many children with giant omphalocele, the ventral hernia and altered trunk stability—due to abnormal development of the anterior abdominal muscles—contribute to impaired motor development in infancy, with a catch-up effect in childhood. A previous study reported normal motor

function in children with giant omphalocele aged 3.5-12 years.(5) Nevertheless, monitoring of motor development in children with giant omphalocele with timely interventions if needed may be helpful. Moreover, parents should be encouraged to stimulate physical activity and should be counselled on leisure and sport participation of their children.

Strengths of our study are the data collection from a longitudinal prospective follow-up programme of mostly prenatally diagnosed children; the high proportion (81%) of children that entered this programme; the relatively large sample size for such a rare disease; and the use of standardized assessments both prenatally and during follow-up. Several limitations need to be addressed. First, the sample size was too small to study determinants of neurodevelopmental delay. Second, we compared height SDS to reference norms rather than to target height SDS, as parental height was often missing.

In conclusion, the prenatal frame of reference of omphalocele differs considerably from the frame of reference after birth, and a multidisciplinary approach in parental counselling is recommended. As two-year old children with giant omphalocele often had delayed motor development, we recommend timely referral to a paediatric physical therapist and prolonged follow-up, at least until these children have reached school age.

Acknowledgements

Ko Hagoort provided editorial advice. Joost van Rosmalen provided statistical advice.

Competing interests

None to declare.

Funding

None to declare.

Contributorship Statement

Each author has contributed to the article. Each author listed has seen and approved the final version of the manuscript and takes full responsibility for the manuscript.

What is already known on this topic

1. Fetuses and neonates with an isolated omphalocele usually have a good prognosis.
2. Longitudinal data on growth and neurodevelopment in children with minor and giant omphalocele are scarce.

What this study adds

1. The prenatal and postnatal frame of reference of omphalocele differ considerably; a multidisciplinary approach in parental counselling is recommended.
2. Two-year old children with minor and giant omphalocele have similar growth and mental development; those with giant omphalocele are more likely to have motor delay.

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