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High mortality among children with gastroschisis after the neonatal period: A long-term follow-up study

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ABSTRACT

Background: During the last decades neonatal outcomes for children born with gastroschisis have improved significantly. Survival rates >90% have been reported. Early prenatal diagnosis and increased survival enforce the need for valid data for long-term outcome in the pre- and postnatal counseling of parents with a child with gastroschisis.
Methods: Long-term follow-up on all newborns with gastroschisis at Odense University Hospital (OUH) from January 1 1997–December 31 2009. Follow-up included neonatal chart review for neonatal background factors, including whether a GORE®DUALMESH was used for staged closure, electronic questionnaires, interview and laboratory investigations. Cases were divided into complex and simple cases according to the definition by Molik et al. (2001). Survival status was determined by the national personal identification number registry. Because of the consistency of the registration, survival status was obtained from all children participating in the study.
Results: A total of 71 infants (7 complex and 64 simple) were included. Overall seven out of the 71 children (9.9%, median age: 52 days (25–75% percentile 0–978 days) had died at the time of follow-up. Three died during the neonatal period and four died after the neonatal period. Parenteral nutrition (PN) induced liver failure and suspected adhesive small bowel obstruction were the causes of deaths after the neonatal period. Overall mortality was high in the "complex" group compared to the simple group (3/7 (42.9%) vs 4/64 (6.3%), $p = 0.04$).
Forty (62.5%) of the surviving children consented to participate in the follow-up. A total of 12 children had had suspected adhesive small bowel obstruction. Prevalence of small bowel obstruction was not related to the number of operations needed for neonatal closure of the defect. Staged closure was done in 5/12 (41.7%) who developed small bowel obstruction vs 11/35 (31.43%) without small bowel obstruction, $p = 0.518$. A GORE®DUALMESH was used in 16 children (22.5%). Of these 2 were complex and 14 were simple cases. Prevalence of recurrent abdominal pain was 22.5% (9/40) among children with gastroschisis compared to 12% in a study on Danish school children, $p = 0.068$. Gastrointestinal symptoms had led to hospital admission after primary discharge in significantly more children with gastroschisis 16 (40.0%) than children younger than 16 years old in the general Danish population 129.419/1.081.542 (12.0%), $p = 0.000$. Fecal calprotectin level was above the reference level (>50 mg/kg) in 6/16 (37.5%) children >8 years old with gastroschisis compared to 1/7 (14.3%) healthy children. (Fisher's exact = 0.366). Only 8/38 (21.1%) children with gastroschisis reported to have an umbilicus.
Conclusion: Mortality among children with gastroschisis is still significant with the highest risk among complicated cases. The majority of the deaths is potentially preventable as PN-related causes and suspected adhesive small bowel obstruction counted for five of seven deaths. Neither categorization upon method of abdominal wall closure nor categorization into simple and complex cases can predict the risk of adhesive small bowel obstruction. With improved administration of PN and timely information and attention to the risk of the small bowel obstruction there is good possibility that the associated mortality could decrease. Type of study and level of evidence: Prognosis study, level II.

Gastroschisis is a congenital malformation in which intraabdominal organs herniate through a defect in the abdominal wall. There are no covering membranes to protect the herniated organs which are thus exposed to the amniotic fluid throughout pregnancy. Prevalence data from the EUROCAT registries from 2008 to 2012 show a prevalence of live born infants with gastroschisis of 2.78:10.000 births [1]. The malformation is often recognized early in pregnancy by routine prenatal screening programs [2].

The evaluation of potential prognostic predictors of the prenatally diagnosed fetus with congenital abdominal wall defect has been the focus of several studies [3–5]. Likewise the immediate neonatal outcome of being

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born with gastroschisis is well described [6–9]. During the last decades neonatal outcomes improved significantly. Survival rates >90% and few long-term sequelae have been reported. However these reports are based on short-term outcome or incomplete long-term follow up.

With increasing numbers of survivors there is an enforced need of insight into long-term outcome as well as to identify those cases being in highest risk of complications.

Earlier long-term studies have reported good physical outcome for gastroschisis with the main problems being concerns about the scar and functional gastrointestinal problems [10–13].

However, long-term follow up is often complicated by difficulties in identifying all patients, thus leaving the possibility of selection bias. Because of the Danish national personal number registry we have the possibility of a high identification rate.

Early intrauterine diagnostics produces an increased demand of knowledge on long-term outcome in order to advice the parents. We therefore conducted the present follow-up study with the intention to describe the children's long-term outcomes regarding survival and gastrointestinal morbidity.

1. Methods and study material

1.1. Study population

All newborns registered with a diagnostic code and/or a surgical code of gastroschisis (DQ79.3, JAG10) at Odense University Hospital (OUH) from January 1 1997–December 31 2009 were identified from the electronic hospital patient registration system. To insure complete inclusion pediatric as well as surgical electronic chart databases were evaluated. OUH is a tertiary center for pediatric gastrointestinal surgery covering an area of around 34.000 km^2 with a population of approximately 3.6 million inhabitants. All children with a diagnosis of gastroschisis within the up-take area undergo surgery and have their immediate neonatal admission at OUH.

1.1.1. Neonatal chart review

Neonatal charts were reviewed to obtain data on type of abdominal wall defect, sex, gestational age, birth weight, additional congenital anomalies, method of abdominal closure including whether a GORE®DUALMESH was used for staged closure, days at intensive care unit, number of days on total or supplemental parenteral nutrition, age when on full enteral nutrition and duration of hospital stay. The data were entered into an access database. The chart review was performed by two research nurses and one of the authors (KR).

According to the definition by Molik et al. [9] cases were divided into complex defects (intestinal atresias, perforations, necrotic segments and volvulus) and simple defects (no intestinal defects).

1.2. Survival

Survival status was determined by the national personal number registry. Because of the consistency of the registration, survival status was obtained from all study children.

1.3. Structured follow-up program

The follow-up took place from June 2013–April 2014. All children alive with an available address and without a "research-protection-mark" in the national personal number registry were invited to the follow-up-program. A brief information letter was sent to all families and those responding to the letter subsequently received thorough oral and written information about the follow-up program. Because of ethical considerations no reminders were sent.

From 1995 to 2014 it was possible to register a mark of "generally decline to research participation" regarding participation in research based on data or address–information obtained from the national personal number registry [14]. On January 1, 2008 12.6% of the Danish population had a "research-protection-mark" in the national personal number registry [15].

The structured follow-up program consisted of questionnaires sent as e-mail for self-completion followed by an invitation for a visit to the clinic for an interview and laboratory investigations.

1.3.1. Questionnaires and interview

1.3.1.1. Questionnaires. The two questionnaires, one for the child and one for the parents were designed to be answered by marking off one of 3–8 possible answers – all with the option "Do not know" or "Other" included and the option of further description in words. The child's questionnaire contained 50 questions regarding the child's knowledge about the previous surgery and present gastrointestinal complaints. The parents' questionnaire contained 35 questions concerning health issues of the child after the primary discharge from hospital.

1.3.1.2. Interview. At the follow-up visit the answers of the electronic questionnaires were reviewed and extended together with the parents by a structured interview.

1.3.2. Laboratory investigations

Blood tests were analyzed to screen for nutritional deficiencies. Blood tests included assessment of liver and kidney function, hematology (Vitamin B-12, Folate, Iron) Vitamin D profile (25-OH-Vitamin D, Ionized Calcium, alkaline phosphatase, parathyroid hormone), coagulation profile, tracers and vitamins (Copper, Zinc, Vitamin A, Beta-Carotene) Immunoglobulin E and coeliac antibodies (Endomysium antibodies (IgA), Tissue Transglutaminase antibodies (IgA), Deamidated Gliadin Antibodies (IgG) and Immunoglobulin A). A fecal sample was analyzed for fecal calprotectin as a standard analysis at the hospital laboratory, to evaluate whether a prolonged state of intestinal inflammation could be demonstrated in children born with gastroschisis.

With the attempt to include as many participants as possible in the follow up, we allowed for optional participation in separate components of the follow-up (Fig. 2):

1. "Clinical follow-up"
   Participation by answering questionnaires and attending clinical visit with interview, clinical examination and laboratory investigations (However laboratory investigations was optional based on an experienced pattern of older and younger children refusing to participate if fecal-testing or blood-tests, respectively, were mandatory).
2. "Questionnaires only"
   Participation by answering questionnaires only.
3. "Mail responses"
   Participants who sent a descriptive e-mail with a statement of the child's actual health status and gastrointestinal complications and hospitalization since primary discharge from the hospital. These participants did not answer the questionnaires or participate in the clinical visit.
   In an earlier study we have reported the use of GORE®DUALMESH in staged closure of congenital abdominal wall defect of which 23 children are included in the present study. Of these 11 consented to attend long term follow-up [16].

1.4. Ethical considerations

The study was approved by the Regional committee of Biomedical Ethics of Southern Denmark (Project-ID: S-20,120,215).

1.5. Statistical analysis

Continuous variables are expressed as means and standard deviations (SD), and non-normally distributed data are presented as medians and 25–75% percentiles.