

## Brief communication (Original)

# Neurodevelopmental outcomes of children with gastroschisis at university hospital in northeast Thailand

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**Background:** Gastroschisis is common among congenital abdominal wall defects. The cause is unknown but it was found to be associated with young maternal age. The association between gastroschisis and delayed development is undetermined.

**Objective:** We described neurodevelopmental outcomes in patients with gastroschisis at 24±6 months corrected age (CA) and identify factors associated with delayed neurodevelopmental outcomes.

**Method:** This is a cross sectional descriptive study, in patients with gastroschisis born between July 2007 and December 2008, who were admitted to the neonatal unit at Srinagarind hospital, a university hospital in northeast Thailand. The patients underwent developmental assessment at 24±6 months CA by Bayley Scales of Infant Development III (BSID III) which assesses three domains: cognitive, language and motor development.

**Result:** Fifteen of 21 patients with gastroschisis were included in the study. The mean age at follow up was 21.8±3.9 months. Four patients (26.7%) had delayed development. One was mildly delayed in all aspects including cognitive, language, and motor development. Three patients (20%) had mild delay in language development only. No significant risk factor associated with delayed neurodevelopmental outcomes was identified. Transient hypothyroidism from iodine excess was found in three out of four patients (75%) who had undergone the silo-operation ( $p=0.01$ ).

**Conclusion:** Developmental evaluation should be performed in patients with gastroschisis because we found that 26.7% of patients with gastroschisis had delayed development. However, significant risk factors could not be identified due to limited number of subjects. If the patient underwent the silo-operation, thyroid function should be tested and closely followed-up.

**Keywords:** Complications, gastroschisis, neurodevelopmental outcomes, operation, transient hypothyroidism, risk factor

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Gastroschisis is a congenital abdominal wall defect with an incidence of 1.4-5.2 / 10,000 live births [1]. The etiology of gastroschisis is unknown but there is an association with young maternal age [2-3]. Patients with gastroschisis can be divided into two groups, simple and complex gastroschisis. Gastroschisis is considered complex when there are associated gastrointestinal anomalies such as intestinal atresia, stenosis, perforation, or volvulus [4]. The survival of patients with gastroschisis is excellent, but post-operative hospital stay is often lengthy, and complications occur frequently, especially

complications related to the gastrointestinal tract such as necrotizing enterocolitis, feeding difficulty and cholestatic jaundice [5-10]. There are few studies on the long-term neurodevelopmental outcomes of patients with gastroschisis. Three studies demonstrated delayed development in these patients [11-13], whereas another three studies did not find any neurodevelopmental delay [14-16].

Gastroschisis is a disease that is commonly found in northeastern part of Thailand. Between 2007 and 2009, 45 patients with gastroschisis were admitted to Srinagarind hospital, a referral center in northeast Thailand while 1500 sick newborn infants were admitted during the same period. There is no previous study done in Thailand to evaluate neurodevelopmental outcomes in patients with gastroschisis. The aim of this study was to describe neurodevelopmental

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outcomes in patients with gastroschisis and to identify factors associated with developmental delay in these patients.

### Materials and method

This study is a cross-sectional descriptive study performed at Srinagarind Hospital, Khon Kaen University. The population eligible for the study was patients 1) diagnosed with gastroschisis 2) born between July 2007 and December 2008 3) who were admitted to the sick neonatal unit at Srinagarind Hospital and 4) underwent developmental assessment with Bayley Scale of Infant Development III (BSID III) at  $24 \pm 6$  months corrected age (CA) with parental permission. The patients were excluded if they were diagnosed with genetic or other congenital disorders likely to affect neurodevelopment, did not have developmental assessment with BSID III at  $24 \pm 6$  months CA, or had incomplete data. Demographic characteristics, treatment, and outcomes were obtained from medical records. The BSID III measures level of development in three domains: cognitive, language and motor. This was assessed by one psychologist. Chi square test was used for categorical data and a  $p$ -value of  $<0.05$  was considered statistical significance.

The study received approval by the Ethics Committee for Human Research of Khon Kaen

University.

### Results

During July 2007 to December 2008, there were 21 neonates with gastroschisis admitted to the neonatal unit. Six patients were excluded due to lost follow-up (4 cases), arthrogryposis (1 case) and death from severe sepsis during admission (1 case). The survival of the patients in this study was 95.2%. Fifteen patients had complete neurodevelopmental assessment, six patients were born at Srinagarind Hospital and nine patients were referred from other provincial hospitals; Udon Thani (4 cases), Nong Khai (3 cases), Nongbua Lamphoo (1 case) and Khon Kaen Regional Hospital (1 case). Five patients (33.3%) were prenatally diagnosed by abdominal ultrasound and the route of delivery was caesarean section in eight patients (53.3%) including all of the five patients who were prenatally diagnosed with gastroschisis. Eleven patients were male, six patients were preterm infants, the mean gestational age was  $36.6 \pm 1.67$  weeks (range 33-39 weeks) and the mean birth weight was  $2,289 \pm 476.8$  grams (range 1,675-3,210 grams). All patients had simple gastroschisis. The mean maternal age at delivery was  $21.4 \pm 4.5$  year (range 18-30 years). The demographic data and details of management are described in **Table 1**.

**Table 1.** Demographic characteristics and management of 15 patients with gastroschisis (n=number of patient)

Demographics	n (%)
Male	11 (73.3%)
Vaginal delivery	7 (46.7%)
Caesarean section	8 (53.3%)
Gestational age: weeks (mean $\pm$ SD)	$36.6 \pm 1.7$
Birth weight: grams (mean $\pm$ SD)	$2,289 \pm 476.8$
Small for gestational age	6 (40%)
Preterm	6 (40%)
Prenatal diagnosis of gastroschisis	5 (33.3%)
Simple gastroschisis	15 (100%)
<b>Management</b>	
Primary closure of defect	11 (73.3%)
Duration of ventilatory support: days-median (range)	3 (1, 20)
Time from birth to initiation of enteral feeding: days-median (range)	12 (6, 45)
Time from birth to full enteral feeding: days-median (range)	21 (14, 112)
Length of hospitalization: days-median (range)	30 (15, 117)

The operative management included primary fascial closure in 11 patients and the silo-operation in four patients. For patients who underwent the silo-operation, topical povidone iodine dressing was applied to promote tissue granulation and prevent infection. The two most common complications were infection (including sepsis, septicemia, and pneumonia) and cholestatic jaundice (**Table 2**).

Three out of four patients in the silo-operation group who were exposed to povidone iodine dressing since birth were found to have very high serum thyroid-stimulating hormone (TSH) levels from routine newborn screening tests. After confirmation by thyroid function test, thyroid scans in all patients showed organification defects and transient hypothyroidism was diagnosed. The age at newborn screening test and repeated thyroid function test in each patient are described in **Table 3**. After thyroid scan was done, all of the patients were treated with levotyroxine and dressing with povidone iodine was discontinued. All

patients had normal thyroid function after treatment for 2-13 months and treatment was discontinued before the time of neurodevelopmental assessment.

Developmental assessments were performed at the mean age of  $21.8 \pm 3.9$  months (range 18-30 months). Four patients (26.7%) had delay in development; one patient was delayed in all domains including cognitive, language and motor development, whereas three were delayed only in language development, one of which was the patient with transient hypothyroidism (**Table 4**). Characteristics of patients with normal and delayed developmental outcomes are described in **Table 5**. There was no significant difference in duration of maternal education, gestational age, route of delivery, small for gestational age, prematurity, sex, type of procedure, complications including hypothyroidism and length of hospital stay between the two groups due to the small number of patients.

**Table 2.** Complications after surgical management among patients with primary fascial closure and those who underwent silo operation (n=number of patient)

Complications	Total (%) (n=15)	Primary closure (%) (n=11)	Silo-operation (%) (n=4)	p-value
Wound evisceration	1 (6.7)	0 (0)	1 (25)	0.26
Wound infection	3 (20)	0 (0)	3 (75)	0.01*
Hypothyroidism	3 (20)	0 (0)	3 (75)	0.01*
Necrotizing enterocolitis	4 (26.7)	2 (18.1)	2 (50)	0.51
Pneumonia	4 (26.7)	3 (27.2)	1 (25)	>0.99
Septicemia	5 (33.3)	4 (36.3)	1 (25)	>0.99
Clinical sepsis	5 (33.3)	3 (27.2)	2 (50)	0.56
Cholestatic jaundice	7 (46.7)	4 (36.3)	3 (75)	0.28

\*statistical significance

**Table 3.** Transient hypothyroidism in patients who underwent silo-operation

Patients	Age (days) NBSC	Age (days) at diagnosis and start treatment	TFT		TFT		Duration of treatment (month)
			Before treatment		After treatment		
			TSH m (U/L)	FT4 ng/dl	TSH m (U/L)	FT4 ng/dl	
1	11	22	>100	0.36	1.31	3.72	3
2	7	32	>100	0.23	2.74	1.37	13
3	8	24	>100	0.41	3	1.80	2

NBSC: newborn screening, TFT: thyroid function test, TSH: thyroid-stimulating hormone, FT4: free thyroxine (tetraiodothyronine)

**Table 4.** Neurodevelopmental outcomes of patients with gastroschisis at 24±6 months corrected age assessed by BSID III (n= number of patient)

Bayley score	Cognitive domain n (%)	Language domain n (%)	Motor domain n (%)
≤69 (significantly delayed performance)	0	0	0
70-84 (mildly delayed performance)	1 (6.7)	4* (26.7)	1 (6.7)
85-114 (normal limits)	14 (93.3)	11 (73.3)	14 (93.3)
≥115 (accelerated performance)	0	0	0

\* including one patient with transient hypothyroidism

**Table 5.** Characteristics of patients with normal and delayed development (n= number of patient)

Characteristics	Total n=15	Normal n=11	Delayed n=4
Maternal education beyond high school	5 (33.3)	4 (36.4)	1 (25)
Gestational age: weeks (mean±SD)	36.6±1.67	36.2±1.2	36.8±2.7
Small for gestational age	6 (40)	4 (36.3)	2 (50)
Preterm	6 (40)	4 (36.3)	2 (50)
Vaginal delivery	7 (46.7)	6 (54.5)	1 (25)
Caesarean section	8 (53.3)	5 (45.5)	3 (75)
Male	11 (73.3)	8 (72.7)	3 (75)
Primary closure of defect	11 (73.3)	9 (81.8)	2 (50)
Complications	14 (93.3)	10 (90.9)	4 (100)
Transient hypothyroidism	3 (20)	2 (18)	1 (25)
Length of hospitalization: days- median (range)	30 (15, 117)	32 (15, 117)	32 (18, 111)

## Discussion

Gastroschisis is a disease that is commonly found in the northeastern part of Thailand. However, the incidence of gastroschisis in Thailand is unknown. From our study, the survival of the patients was 95.2%, which is similar to studies from other developed countries [17-18]. The average maternal age was 21.4 years, which is as young as previous studies [2-3]. All of the five patients who were prenatally diagnosed by abdominal ultrasound were delivered by caesarean section. Except for the route of delivery, there were no differences in the outcomes between patients with prenatal diagnosis and patients who were diagnosed post-natally as shown in previous studies [7, 19-20].

Primary fascial closure was the preferred procedure over silo-operation; however, marked bowel swelling was the major reason for silo-operation. Complications associated with gastroschisis treatment included wound evisceration, wound infection, necrotizing enterocolitis, pneumonia, septicemia, clinical sepsis, and cholestatic jaundice which have

been described in many studies [4, 21]. In one study, hypothyroidism was diagnosed in a patient with gastroschisis but the author did not describe the cause of hypothyroidism [22]. We found that three out of four patients who underwent the silo-operation developed transient hypothyroidism ( $p=0.01$ ). The long-term exposure to povidone iodine may be the cause of hypothyroidism due to good permeability of neonatal tissue and good iodine uptake of the thyroid gland with low clearance rate, which is known as Wolff-Chaikoff effects [23-25]. All patients who had hypothyroidism had normal thyroid function test after receiving thyroid hormone replacement therapy. It is unclear whether transient hypothyroidism affected the neurodevelopmental outcomes of these infants. Some studies had demonstrated the association between transient hypothyroidism and delayed development [26]. However, all of the patients in our study had normal thyroid function at the time of BSID III assessment and only one had delay in speech development.

Henrich et al. reported that 32% of 40 gastroschisis patients had delay sitting, walking during the first to second years of life assessed by questionnaire [11]. Lodha et al. performed developmental assessment in 25 patients at a mean age of 15.3 months with BSID, 14% of their patients had minor motor delay and 5% had minor cognitive delay [12]. Berseth et al. studied growth and late morbidity of 22 survivors of gastroschisis patients at three years of age, one-third of the patients had intellectual impairment by intelligence quotient test (IQ test) [13]. In three studies, patients with gastroschisis had normal neurodevelopmental outcomes. South et al. performed developmental assessment at 16-24 months of age by BSID [14]. Unfortunately, the other two studies did not report the age at follow up and tools for developmental assessment [15, 16]. The patient's age at developmental assessment in these studies were similar to our study. The age at assessment is not too early and has less effect from the environment on neurodevelopmental outcomes. We found that 26.7% of our patients had delayed development by using the BSID III. All of these patients had delayed language and one of them was delayed in all domains. In comparison between normal and delayed developmental patients, there was no difference in the duration of maternal education, gestational age, route of delivery, small for gestational age, prematurity, sex, type of procedure, complications including hypothyroidism and length of hospital stay. Although two of four patients who underwent the silo-operation had delayed development, this factor had no statistical significance. The patient who had delayed development in all domains was in the silo-operation group. However, this patient had no history of transient hypothyroidism while another patient who had mild delayed language development had a history of transient hypothyroidism.

## Conclusion

Delayed developmental outcome was demonstrated in 26.7% of gastroschisis patients but the significant risk factors could not be identified due to the small number of the patients. In patients who underwent silo-operation followed by povidone iodine dressing, transient hypothyroidism may occur. We suggest that developmental evaluation should be performed in patients with gastroschisis and the thyroid function should be tested and closely monitored in those patients who underwent silo-operation.

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