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Congenital heart defects in newborns with apparently isolated single gastrointestinal malformation: A retrospective study

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ABSTRACT

Background: Congenital gastrointestinal system malformations/abdominal wall defects (GISM) may appear as isolated defects (single or complex), or in association with multiple malformations. The high incidence of association of GISM and congenital heart defects (CHD) in patients with syndromes and malformative sequences is known, but less expected is the association of apparently isolated single GISM and CHD. The aim of this study was to investigate the frequency of CHD in newborns with isolated GISM, and the possibility to modify the diagnostic-therapeutic approach just before the onset of cardiac symptoms or complications.
Methods: Anamnestic, clinical, and imaging data of newborns requiring abdominal surgery for GISM, between 2009 and 2014, were compared with a control group of healthy newborns. Distribution of GISM and cardiovascular abnormalities were analyzed, and risk factors for adverse outcomes were identified.
Results: Seventy-one newborns with isolated GISM were included in this study. More frequent GISM were intestinal rotation and fixation disorders. CHD were observed in 15.5% of patients, augmenting their risk for morbidity. Risk factors for morbidity related to sepsis were identified in central venous catheter, intestinal stoma, and H2-inhibitor-drugs. Moreover, 28.2% of newborns presented only functional cardiac disorders but an unexpectedly higher mortality.
Conclusions: The high incidence of congenital heart disease in infants with apparently isolated GISM confirms the need to perform an echocardiographic study before surgery to improve perioperative management and prevent complications such as sepsis and endocarditis.

1. Background

Congenital gastrointestinal system malformations/abdominal wall defects (GISM) may be found in 1.8 per 1000 live births [1,2]. In the gastrointestinal tract we can observe a variety of congenital defects because of the interference of genetic/environmental factors on splanchnic mesoderm differentiation during blastogenesis or successive phases of the development of primitive gut tube, including elongation, herniation outside the abdominal cavity, rotation, fixation, and neuronal migration [3]. GISM can occur as an isolated defect (single or complex defect confined to the gastrointestinal system), e.g. anorectal malformation (ARM) combined with oesophageal atresia (EA) [4], or in association with multiple malformations in other organ systems (cardiovascular, genitourinary, or skeletal system) [5].

High association rate of congenital heart defects (CHD) and GISM is well recognized in newborns with chromosomal abnormalities, malformative sequences, or syndromes: trisomies, pentalogy of Cantrell, VACTERL association, Feingold syndrome, DiGeorge syndrome, CHARGE syndrome, cat eye syndrome, Pallister-Hall syndrome and McKusick-Kaufman syndrome, Silver-Russell syndrome, Meckel-Gruber syndrome, Fryns-Syndrome, heterotaxy syndrome, Beckwith-Wiedemann syndrome, Brachmann-de Lange syndrome, Goldenhar syndrome, Smith-Lemli-Opitz syndrome, RASopathies, and other even rarer syndromes [6–18]. Instead, few studies analyzed the incidence of heart diseases in apparently isolated GISM [19,20]. However, the partially common embryological origin of the two systems from the splanchnic mesoderm [21] could hypothesize developmental defects simultaneously in both the systems. In newborns, GISM mainly result in symptoms of intestinal obstruction and often require surgical and

Abbreviations: ARM, anorectal malformation; AVD, aortic valve disease; ASD, atrial septal defect; GISM, congenital gastrointestinal system malformations/abdominal wall defects; CHD, congenital heart defects; ECG, electrocardiogram; Fgf10, fibroblast growth factor 10; ICD-10, International Classification of Diseases; NICU, Neonatal Intensive Care Unit; NN50, number of adjacent NN intervals differing by >50 ms; EA, oesophageal atresia; PDA, patent ductus arteriosus; PS, pulmonary stenosis; pNN50, rate of NN50; RAA, right aortic arch; SDNN, standard deviation of NN intervals; VSD, ventricular septal defect.

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intensive care interventions in the early days of life. The concomitant presence of associated CHD may complicate the perioperative management of these newborns and may change prognosis. For this reason, it has long been debated whether an echocardiogram should be performed in all newborns, even in those with apparently isolated GISM and with seemingly normal physical examination, electrocardiogram, and chest X-ray [22].

The aim of the present study was therefore to investigate the frequency of CHD in newborns with apparently isolated GISM, and to review the diagnostic-therapeutic approach to these patients in relation to increased risk of morbidity and mortality.

2. Materials and methods

A retrospective chart review in a Neonatal Intensive Care Unit (NICU) with reference Centre for genetics and paediatric surgery was performed. All newborns who required surgery for GISM between 2009 and 2014 were recruited. GISM were divided based on International Classification of Diseases (ICD-10) into EA, pyloric atresia, duodenal atresia/stenosis, jejunal-ileal atresia/stenosis, colon atresia/stenosis, disorders of intestinal rotation and fixation, intestinal duplication, ARM, abdominal wall defects, and neuronal migration disorders [23]. Anamnestic, clinical and imaging examinations of 108 newborn were collected. All newborns were routinely screened by ultrasound at admission for associated anomalies. Newborns with multiple congenital anomalies, associated skeletal anomalies detected by X-ray investigation, or failed transient-evoked otoacoustic emissions (37/108 newborns) were excluded from the subsequent analyses.

Infants with isolated GISM (group A; n = 71) were further divided in group A1 (n = 11; 15.5%), with associated structural CHD, group A2 (n = 20; 28.2%), with only functional cardiopathy, and group A3 (n = 40; 56.3%), without any cardiovascular abnormality. Group A was compared with a control group (group B) of 71 healthy newborns with the same mean gestational age who did not have any prenatally diagnosed known risk factors, and were born between 2013 and 2014. A written consent was obtained. Echocardiography (according to last updated guidelines of American Echocardiography Society [24]) and 5′-ECG, usually before gastrointestinal surgery, were performed to investigate cardiovascular abnormalities. The ECG was further analyzed for heart rate variability (RR- or NN-interval), standard deviation of NN intervals (SDNN), number of adjacent NN intervals differing by >50 ms (NN50) and rate of NN50 (pNN50) [25,26]).

CHD were classified according to ICD-10 [23]. PDA was included in full term newborns in which the defect persisted over the first few weeks of life and was not secondary to persistent pulmonary hypertension. Patent foramen ovale is not a CHD, but was considered as functional heart disease if it was persistently haemodynamically significant. Heart defects were classified as major when they were potentially lethal or required medical and/or surgical intervention. The frequencies of cardiac anomalies in the specific categories of isolated GISM were reported. Genetic counselling, karyotype, and additional molecular and cytogenetic analyses were performed in all newborns with associated GISM and CHD, in order to identify patients with genetic and/or epigenetic alterations, despite incomplete phenotype.

A weekly surveillance protocol, with nasal and rectal swabs, has been routinely performed in all newborns to monitor the prevalence of bacterial and mycotic colonization. Data concerning cases of sepsis (clinical suspicion or culture-proven) were also recorded. Mortality and days of hospitalization were annotated.

Statistical analysis was performed by open source statistical R Commander “Palermo software package” [27].

3. Results

Isolated GISM was found in 65.8% (71/108) of evaluated newborns (group A). Male newborns resulted more affected by GISM than females (49 vs 22). Mean Apgar scores were 7 and 9 at 1 and 5 min, respectively. The mean gestational age was 37^{+1} weeks (range from 25^{+2} to 41^{+3} weeks), and mean birth weight was 2660 g (range from 700 to 4130 g). Eighteen newborns in group A versus two in group B were small for gestational age (25.4 vs 2.8%; p = 0.0001) (details in Table 1). Genetic counselling and karyotype were all normal. The average of hospital stay was 43 days in group A (not significant difference in the three subgroups), and 5.9 days in group B (p = 6.9e-8). Mortality was 0% in group A1 vs 20% in group A2 (p = 0.2) and 7.5% in group A3; in contrast, the mortality in the 37 newborns with multiple anomalies excluded from this study was as high as 32.5%.

Most frequent isolated GISM were disorders of intestinal rotation and fixation (24%), followed by EA (15.5%), ARM (15.5%), jejunal/ileal atresia/stenosis (14.1%), duodenal atresia/stenosis (11.3%), abdominal wall defects (7%), intestinal duplication (5.6%), neuronal migration disorders (4.2%), colic stenosis (1.4%), and pyloric atresia (1.4%).

CHD were detected in 15.5% (M:F = 8:3) of newborns in group A (odds ratio 6.3), in 2.8% (M:F = 1:1) of newborns in group B, and in 73% (M:F = 15:12) of newborns with multiple anomalies excluded from this study. Furthermore, three of the eleven newborns with CHD in group A1 were small for gestational age.

More detailed, the prevalence of CHD in ARM was 36.3%, in EA 27.3%, in intestinal duplication 25%, in disorders of rotation and fixation 11.7%, and in jejunal/ileal atresia/stenosis 10%. CHD were not found in pyloric, duodenal and colic atresia/stenosis, abdominal wall defects or neuronal migration disorders. Simple CHD observed in group A1 were: ventricular septal defects (VSD), atrial septal defect (ASD), aortic valve disease (AVD), PDA, and right aortic arch (RAA). In group B muscular VSD was detected.

Moreover, twenty-three newborns (32.4%) of group A presented functional cardiac disorders, especially hypertrophic cardiomyopathies; twenty of them showed only functional cardiac disease without associated structural CHD. One newborn of group B presented transitory cardiac dysfunctions. Three newborns with CHD and two with functional cardiac disorders required cardiac specific therapy (diuretic or inotropic drugs). Distribution of detailed GISM and cardiac disorders in our patients are summarized in Table 2.

Infants of group A had higher heart rates than infants of group B (131.5 vs 119.5 bpm; p = 0.004). The analysis of heart rate variability showed significant lower SDNN and NN50 in group A (17.3 vs 25.8, p = 0.0004; and 0 vs 0, p = 0.0054 respectively), and not significant lower pNN50.

Data regarding the presence of comorbidities and mortality in group A and B (prolonged fasting/total parenteral nutrition, microbial colonization, clinical or culture-proven sepsis) are listed in detail in Table 3. As can be seen in the Table 3, newborns with only functional cardiac disorders (28.2%) had the highest mortality rate (20%).

Almost all (91.5%) newborns of group A were assisted with parenteral nutrition through central venous catheter, mostly replaced several times. The average assistance with parenteral nutrition was 31 days (76 days in subgroup A1, less than half the days in subgroups A2 and A3, without a statistically significant difference). In group B only three preterm newborns required parenteral nutrition. About 41% of newborns assisted with parenteral nutrition developed a late-onset infection with a shift from commensally intestinal microbiota to nosocomial germs (Klebsiella, E. coli, Pseudomonas, and especially Candida spp.).

Data with regard to infective surveillance showed that nasal or rectal swabs became positive in 28.2% of newborns in group A (9% in group A1 vs 45% in A2 vs 25% in A3; p = 0.08), and none in group B (A vs B p < 2.2e-16). Consequently, clinically suspected sepsis (41 vs 8.8%; p < 2.7e-05) and culture-proven sepsis (18 vs 1.47%; p = 0.001) were more frequent in group A than in the control group. Particularly, culture-proven sepsis was equal in the subgroups: 18% in group A1, 20% in A2, 17.5% in A3.