

ORIGINAL ARTICLE

Down's Syndrome - An Independent Risk Factor of Outcomes in Isolated Congenital Duodenal Atresia

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ABSTRACT

Introduction: There is no consensus in the available literature whether the coexistence of Down's syndrome has adverse effect on the outcomes of neonates born with congenital duodenal atresia. **Materials and Methods:** A total of 29 neonates with congenital duodenal atresia were retrospectively studied for demographic details, sepsis parameters at admission, management, morbidity, and mortality. The neonates who were premature (<37 weeks of gestation), those having associated cardiac/gastrointestinal malformations and/or those who were hemodynamically unstable at initial presentation were excluded from the study. The subjects were divided into two groups - one without associated Down's syndrome (Group A) and those with Down's syndrome (Group B), and subsequently compared. After collection of data, statistical analysis was done and relative/attributable risks were studied. **Results:** The sepsis parameters such as total leukocyte counts, erythrocyte sedimentation rate, serum procalcitonin levels, and serum C-reactive protein levels were significantly increased, and the platelets were significantly decreased at admission in Group B subjects, as compared to Group A subjects. There were no complications noted in Group A, while Group B had significant morbidity. The neonates with congenital duodenal atresia with Down's syndrome had 3.27 times more relative risk of mortality than those without Down's syndrome. Down's syndrome appears to be an independent risk factor for mortality in isolated congenital duodenal atresia with attributable risk of 37.8%. **Conclusion:** The presence of Down's syndrome is a significant independent adverse risk factor of outcomes in isolated congenital duodenal atresia.

Key words: Down's syndrome; C-reactive protein; duodenal atresia; immunological dysfunction; procalcitonin; sepsis

INTRODUCTION

Congenital duodenal atresia is the most common cause of neonatal intestinal obstruction with a reported incidence of 1:2500–1:10000 [1]. Congenital duodenal atresia could be either because of extrinsic or intrinsic causes. Complete failure of recanalization results in duodenal atresia which presents in the immediate neonatal period, whereas incomplete recanalization results in duodenal stenosis, or duodenal web that can have a variable and delayed presentation [2].

Advancements in surgical operative techniques, post-operative intensive care, and early nutritional rehabilitation have improved the survival outcome of duodenal atresia. The most important medical causes of post-operative mortality are due to complex

cardiac anomalies, prematurity, sepsis, and pneumonia and the most common surgical complications seen are anastomotic leak and gastroduodenal paresis [3]. Associated congenital anomalies have been identified as an independent risk factor for mortality in duodenal atresia, with prematurity and low birth weight increasing the mortality risk [4,5]. Literature suggests that Down's syndrome *per se* does not affect the survival of duodenal atresia postoperatively; however, the association of multiple anomalies, especially major cardiac anomalies, can affect the outcome [3,6].

Down's syndrome is the most common genetic disorder associated with mental retardation and is also associated with a high incidence of congenital heart diseases and gastrointestinal malformations.

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The children with Down's syndrome have an increased susceptibility to infections due to various inherent abnormalities in the immune system and anatomical comorbidities. The clinical relevance of this predisposition to sepsis has not been well defined in neonates and in the relevance to post-operative outcomes [7,8].

This study was conducted to determine whether an underlying immunological dysfunction predisposes neonates with Down's syndrome to an increased risk of sepsis, as against commonly held opinion that Down's syndrome does not affect the surgical outcome. Early identification of sepsis can lead to early initiation of treatment, which can help in improving the outcomes of neonates diagnosed with duodenal atresia. Hence, this study was conducted to study the role of sepsis markers such as C-reactive protein (CRP) and procalcitonin (PCT) as prognostic indicators of outcome in neonates with duodenal atresia.

MATERIALS AND METHODS

This study was a retrospective cohort study conducted in three tertiary care hospitals in Hyderabad, India. The data were collected over a period of 12 years, from 2000 to 2012. The data were collected from patients' hospital records (case records, intensive care unit (ICU) registers, ward registers, and theater records) after obtaining consent from the parents.

All the 29 neonates diagnosed having congenital duodenal atresia who satisfied inclusion criteria were included in the studies. We divided these subjects into two main groups - control group comprised neonates with congenital duodenal atresia but not associated with Down's syndrome (Group A) ($n = 18$) and neonates with congenital duodenal atresia with a confirmed diagnosis of Down's syndrome (Group B) ($n = 11$). Down's syndrome was diagnosed antenatally on karyotyping after amniocentesis in three neonates, whereas eight neonates were diagnosed postnatally with fluorescence *in situ* hybridization (FISH) for trisomy 21. All 18 neonates in the control group were tested negative on FISH for trisomy 21.

To negate the effect of associated congenital anomalies and prematurity, we excluded neonates with major cardiac and gastrointestinal malformations, preterm neonates (<37 weeks of gestation), neonates with severe sepsis, and hemodynamically unstable neonates from the present study.

Sepsis parameters studied at admission included CRP, total leukocyte counts (TLCs), platelet counts, serum PCT, and micro erythrocyte sedimentation rate (ESR) levels. Outcome studied was mortality before discharge from the hospital.

10 patients (8 in non-Down's syndrome group and 2 in Down's syndrome group) had barium studies in addition to the upright abdominal X-rays that were done in all the 29 neonates.

The inclusion or exclusion from the study did not alter the course of clinical management for the baby in the hospital, and the study was approved by the institute's ethical committee.

Statistical analysis was done using open EPI statistical software. The comparison was done using two-tailed *t*-test. $P < 0.05$ was taken as statistically significant. For proportions, Chi-square test and relative and attributable risks were calculated.

RESULTS

The demographic data of the patients in two groups are given in Table 1 and were comparable. Most of the babies underwent surgery within 24 h of diagnosis. All the neonates underwent diamond-shaped duodenoduodenostomy. The type of duodenal atresia diagnosed in each of the two groups is mentioned in Table 2. The post-operative management after surgical correction of duodenal atresia is depicted in Table 3. The post-operative complications were compared between both the groups and are shown in Table 4; none of the 29 patients had anastomotic leak.

The laboratory sepsis parameters at the time of admission were compared between the two groups and are shown in Table 5. However, despite the differences in the laboratory parameters, the infants in both the groups were clinically stable at the time of surgery. It was found that TLC, ESR, and PCT were significantly higher in Down's group compared to non-Down's group ($P < 0.05$). Platelets were significantly reduced in the Down's group compared to non-Down's group ($P < 0.05$).

Table 1: Baseline variables

Variable	Non-Down's ($n=18$)	Down's ($n=11$)
Birth weight (Mean)	2400 g	2800 g
Age at admission (Mean)	8 days	7 days
Sex (Males)	10	7
Sex (Females)	8	4
Time from diagnosis to surgical intervention (Mean)	8 h	8 h

This study showed that infants with Down's syndrome had a significantly higher mortality rate compared to infants in the non-Down's group ($P = 0.04220$; $RR = 3.27$; $AR = 37.8\%$) [Table 6].

DISCUSSION

Congenital duodenal atresia is a common cause of neonatal intestinal obstruction, with a reported incidence of 1:2500–1:10000. Males are more commonly affected than females [1].

Down's syndrome is commonly associated with several developmental abnormalities of the gastrointestinal tract such as trachea-esophageal fistula, duodenal atresia, annular pancreas, imperforate anus, and Hirschsprung's disease [3]. 5% of all patients with Down's syndrome have duodenal atresia, and 25–40% of cases of congenital duodenal atresia are associated with Down's syndrome [4].

Table 2: Type of duodenal atresia

Type of duodenal atresia	Non-Down's (n=18)	Down's (n=11)
Type 1	10	8
Type 2	5	2
Type 3	3	1

Table 3: Post-operative management

Variable	Non-Down's	Down's
Time of initiation of feeds	POD 1	POD 1
Time to full feeds (Mean)	7 days	9 days
Duration of NICU stay (Mean)	22 days	29 days
NICU: Neonatal intensive care unit		

Table 4: Post-operative complications

Variable	Non-Down's	Down's
Anastomotic leaks	0	0
Gastroduodenal paresis	0	1
Pneumonia	0	2
Duration of ventilation	0	2
Culture-positive sepsis	7/18	3/11

Several studies have shown that Down's syndrome *per se* does not affect the survival outcome of congenital duodenal atresia, but the association of major congenital anomalies, especially cardiovascular anomalies significantly, affects the outcome [3-6].

Advances in immunology and molecular biology have shown that infants with Down's syndrome have an underlying immune dysfunction. The immune dysfunction in Down's syndrome is due to decreased expression of critical genes due to trisomic imbalance resulting in global thymic hypofunction [9-11]. The thymus in patients with Down's syndrome has been reported to be smaller and hypocellular, with a reduced proportion of phenotypically mature T-cell receptor (TCR)- $\alpha\beta^+$ thymocytes [12]. The number of TCR excision circles and the subset of T-cell subpopulations (CD4+, CD8+, and CD4 + CD45 + RA cells) in the peripheral blood in patients with Down's syndrome has been reported as reduced at various age groups [13]. Not only this, innate immune dysfunction such as defective neutrophil chemotaxis [14], low humoral immune responses [15], zinc deficiency, and accelerated immunosenescence^[16] has been reported in patients in Down's syndrome, which along with common anatomical defects associated with Down's syndrome, causes this cohort of patients to higher predisposition to sepsis. Although these immunological defects have not been studied in detail in the early neonatal period, several of the above studies suggest that these defects manifest from the neonatal period onward.

Studies have showed an increased risk of morbidity and prolonged post-operative stay in post-operative patients with Down's syndrome. In a retrospective cohort study by conducted on 45,579 patients with congenital heart diseases undergoing surgery by Fudge *et al.*, the authors found that Down's syndrome did not confer a significant mortality risk for common cardiac conditions, but the Down's group was associated with a higher post-operative respiratory and infectious complications [17]. In a prospective cohort study conducted over 24 months by Gupta and Rettiganti on infants admitted to ICUs, the authors found that even though the mortality was similar in both Down's and non-Down's group after propensity matching, the mortality rate among Down's syndrome increased with increasing length of hospital stay [18].

Several studies have failed to show a significant difference in the incidence of sepsis in the post-operative outcomes of infants with Down's and without Down's syndrome. Tóth *et al.* conducted a propensity-matched analysis to study the post-operative complications of pediatric cardiac surgery and found that Down's syndrome was not associated with increased mortality or complication rate following pediatric cardiac surgery compared to non-Down's group [19]. In a retrospective study by Lange *et al.*, the authors stud-

ied 476 patients undergoing atrioventricular septal defect repair and compared post-operative outcomes between Down's and non-Down's groups and found that Down's syndrome was not a risk factor for surgical repair [20].

The present study was conducted to determine whether infants with Down's syndrome with congenital duodenal atresia had inherently a higher predisposition to sepsis in view of the above discussed immunological dysfunction and, hence, higher morbidity and mortality in comparison to control infants without Down's syndrome. As several previous studies attributed to the increased mortality in Down's syndrome to associated congenital malformations, babies with congenital cardiac and other gastrointestinal malformations to remove the confounding factors associated with adverse outcome were excluded from the study.

The study compared the sepsis parameters at admission in both the cases and controls and assessed the outcome postoperatively. This study showed that infants with Down's syndrome, even though clinically and hemodynamically stable, had significantly elevated positive markers for sepsis than infants without Down's syndrome. Infants with Down's syndrome had

higher TLCs, higher levels of acute phase reactants such as CRP and PCT, elevated micro ESR, and lower platelet counts compared to infants without Down's syndrome, all the values of which reached statistical significance. Postoperatively, infants with Down's syndrome had a significantly higher mortality compared to infants without Down's syndrome (3/18 in non-Down's vs. 6/11 in Down's, $P = 0.0422$, $RR = 3.27$; $AR = 37.8\%$).

The sample size of this study was small (29 babies), even though the data were collected for 12 years, which was possibly because many babies had to be excluded due to associated congenital cardiac and gastrointestinal malformations.

In this study, even though the sepsis parameters preoperatively were not elevated significantly to warrant deferring the surgical correction, they being significantly abnormal compared to the control population, and also having a significantly increased mortality postoperatively reinforces the hypothesis that immunological dysfunction sets in at a very early stage in Down's syndrome, and these infants have to be judiciously screened and treated aggressively for sepsis from a very early stage, as the

Table 5: The comparison of sepsis parameters at admission

Parameters	Non-Down's groups $n=18$ Mean \pm SD	Down's groups $n=11$ Mean \pm SD	t value	P value	Interpretation
TLC	13600 \pm 187	16100 \pm 214	33.0871	<0.0001	Significant
Platelets	110000 \pm 1350	80000 \pm 876	65.5129	<0.0001	Significant
ESR (mm/h)	6 \pm 1.2	8.5 \pm 2.1	4.0988	0.0003	Significant
PCT (pg/dl)	0.07 \pm 0.02	0.15 \pm 0.09	3.6657	0.0011	Significant
CRP	12 \pm 2.1	24 \pm 3.4	11.8024	<0.0001	Significant
TLC: Total leukocyte counts, SD: Standard deviation, ESR: Erythrocyte sedimentation rate, PCT: Procalcitonin, CRP: C-reactive protein					

Table 6: The comparison of outcomes (dead/alive) between the two groups

Outcome	Non-Down's groups (%)	Down's groups (%)	Total (%)	Yates corrected Chi square	P value	Relative risk	Interpretation
Died	3 (33.3)	6 (66.7)	9 (31.03)	2.978	0.04220	3.27	Significant
Alive	15 (75)	5 (25)	20 (68.97)				
Total	18 (62.06)	11 (37.94)	29 (100)				

timeline from early signs to fulminant stage is very narrow. This concept of immunological dysfunction from early neonatal period has to be studied in detail, and further research needed to determine this predisposition to sepsis, as early intervention can improve outcomes in congenital duodenal atresia, which is a commonly associated malformation in Down's syndrome.

CONCLUSION

The neonates with congenital duodenal atresia with Down's syndrome have 3.27 times more risk of mortality than those without Down's syndrome. Down's syndrome appears to be an independent risk factor for mortality in isolated congenital duodenal atresia with attributable risk of 37.8%.

Author's contribution

All authors contributed equally in concept, design, literature review, drafting the manuscript, and approval of the final manuscript.

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