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High incidence of acute lung injury in children with Down syndrome

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Abstract *Objective:* Acute respiratory tract infection is a common reason for hospitalization in children with Down syndrome (CDS) and is characterized by a high morbidity. The severe course of disease in CDS may be related to a higher incidence of acute lung injury (ALI). This study evaluated the incidence of ALI and acute respiratory distress syndrome (ARDS) in mechanically ventilated CDS. *Design and setting:* Retrospective cohort study in a pediatric ICU. *Patients and participants:* Cases were all mechanically ventilated CDS admitted to our unit between January 1998 and July 2005. All mechanically ventilated patients without Down syndrome from January 1998 to January 2001 served as controls. Postoperative patients (cases and controls) and those with a cardiac left to right shunt were excluded. *Measurements and results:* The main outcome measure was the incidence of ALI and ARDS. The criteria for ALI were met in 14 of 24 CDS (58.3%) in 41 of 317 of controls (12.9%; OR 9.4, 95% CI 3.9–22.6). The criteria for ARDS were met in 11 of 24 CDS (46%) and in 21 of 317 of controls (7%; OR 11.9, 95% CI 4.8–29.8). None of the CDS with ALI died; in the control group ten patients with ALI died. *Conclusions:* CDS had a significantly higher incidence of ALI and ARDS than children without Down syndrome. The explanation for this remains to be elucidated; further study is necessary before clinical implications become clear.

Keywords Acute respiratory distress syndrome · Down syndrome · Epidemiology · Cohort studies · Mechanical ventilation · Child

Introduction

Down syndrome (DS) is the most common chromosomal abnormality and occurs in 1 of 800 live births [1]. Although survival beyond the first year of life has increased considerably in recent decades, children with DS (CDS) still have a shorter life expectancy than those without DS [2]. Acute respiratory tract infection is a common reason for hospitalization in CDS and is characterized by high morbidity [3]. In children with DS it has been suggested to be related to pharyngeal incoordination predisposing to aspiration in combination with concomitant immunodeficiencies [4, 5]. High morbidity in CDS with respiratory disease may also be related to a higher incidence of acute lung injury (ALI). The aim of this study was to evaluate the incidence of ALI and acute respiratory distress syndrome (ARDS) in children with DS who were admitted to the pediatric intensive care unit (PICU) and needed mechanical ventilation. Preliminary data from this study were presented at the 35th Congress of the Society of Critical Care Medicine [6].

Methods

This study compared the occurrence of ALI/ARDS in two groups of patients requiring mechanical ventilation because of respiratory insufficiency. The first group

Table 1 Baseline patient characteristics and cause for respiratory failure

	Down syndrome (n = 24)	Control group (n = 317)	p
Median age (months; range)	15.2 (0–127.2)	6.1 (0–217.7)	0.39 [c]
Males	14 (58.3%)	199 (62.8%)	0.67 [d]
Median PRISM II score (range)	13.5 (0–40)	9.0 (0–47)	0.19 [c]
Sepsis	3 (12.5%)	52 (16.4%)	0.78 [e]
Lower respiratory tract infection	18 (75%)	130 (41%)	0.001 [d]
Upper respiratory tract infection	1 (4.2%)	23 (7.3%)	0.96 [e]
Congenital heart disease	1 (4.2%)	22 (6.9%)	0.99 [e]
CNS disorders [a]	0	53 (16.7%)	0.04 [e]
Other [b]	1 (4.2%)	37 (11.7%)	0.50 [e]

[a] *CNS disorders*: convulsions, infections, asphyxia, contusion, cerebral hemorrhage; [b] *Others*, e. g., trauma, cardiomyopathies, electrolyte disturbances, metabolic disease; [c] Mann–Whitney test; [d] Pearson's χ^2 test; [e] Fisher's exact test

consisted of all 24 consecutive children with genetically confirmed DS admitted to our PICU for mechanical ventilation between January 1998 and July 2005. The second group consisted of all 317 mechanically ventilated children without DS admitted to our PICU between January 1998 and January 2001. Baseline characteristics for CDS and the control group are shown in Table 1. The PICU at Emma Children's Hospital is a 16-bed, tertiary, multidisciplinary unit serving the greater Amsterdam area. Data on the incidence rate of ALI/ARDS in the second group have been published previously [7]. In both groups patients who were admitted for postoperative care directly following a surgical procedure, and those with a cardiac left to right shunt were excluded. Patients were retrospectively evaluated for ALI/ARDS during the second 24 h after admission according to the American–European Consensus Conference criteria [8]. Gas exchange criteria for ALI and ARDS were considered to be met if the PaO_2/FIO_2 ratio was less than 40.0 kPa for ALI and less than 26.7 kPa for ARDS in at least two consecutive measurements (> 8 h apart). A radiologist blinded to clinical information reviewed the chest radiographs for the presence of bilateral infiltrates. The presence of left heart failure was assessed based on echocardiographic results and/or clinical information. Disease severity on admission was expressed by the Pediatric Risk of Mortality (PRISM) II score, which depends on diagnosis and clinical parameters in the first 24 h of admission [9]. Sepsis was defined as systemic inflammatory response syndrome in the presence of clinical evidence for infection. Lower respiratory tract infection was defined as clinical infection with radiological evidence of alveolar consolidation. Upper respiratory tract infection was defined as infection of the oral and nasal airways, larynx, trachea, and/or bronchi without signs of lower respiratory tract infection.

The comparability of patient characteristics for both groups was tested by means of a chi-square test or Fisher exact test for dichotomous data and a Mann–Whitney U test for continuous data that were not normally distributed. The association between DS and ALI/ARDS was expressed as an odds ratio (OR) with 95% Confidence Interval (CI). Other well known cause for ALI/ARDS and thus possible confounders for the incidence of ALI/ARDS among CDS were identified [8, 10] and evaluated with bivariate logistic regression analysis. Statistical significance was set at 5%.

Results

The criteria for ALI were met in 14 of 24 CDS (58.3%) and in 41 of 317 controls (12.9%; odds ratio 9.4, 95% confidence interval 3.9–22.6). The criteria for ARDS were met in 11 of 24 CDS (46%) and in 21 of 317 controls (7%; odds ratio 11.9, 95% confidence interval 4.8–29.8). There were no deaths in the CDS. In the control group ten patients with ALI died during admission to the PICU. The results of the logistic regression analyses are presented in Table 2. The odds for the incidence of ALI in CDS were hardly altered by adjusting disease severity (PRISM II score), lower respiratory tract infection, or sepsis.

We excluded patients who died in the first 24 h after admission. This might have caused a selection bias. Therefore PICU deaths during the first 24 h of admission were analyzed for ALI/ARDS: 36 in the control group, none of whom met the ALI/ARDS criteria. No CDS died in the first 24 h after admission. Thus the odds of developing ALI in CDS are about 9 times those in controls, and this cannot be attributed to the presence of confounders.

Table 2 Estimated odds ratio (*OR*) for ALI (Down/control) after adjustment for possible confounders (*CI*, confidence interval)

Possible confounder	OR	95% CI
None	9.4	3.9–22.6
PRISM II score	9.6	3.9–23.6
Sepsis	12.2	4.9–30.6
Lower respiratory tract infection	10.8	4.3–26.9

Discussion

This study found a very high incidence of 58% of ALI and 46% of ARDS in mechanically ventilated children with DS. This is significantly higher than the incidence of 13% of ALI and 7% of ARDS in the general pediatric population on mechanical ventilation in our unit. Likewise, Randolph et al. [11] reported an incidence of ARDS of almost 8% in a mechanically ventilated pediatric population.

The results of this study need to be interpreted with caution due to the retrospective design and the relatively low number of CDS. The results need to be confirmed in a prospective multicenter study in a larger cohort. Due to the small number of CDS admitted annually to our unit we included CDS for a longer period of time (1998–2005) than the control group (1998–2001). This may interfere with the comparability of the study groups. However, medical care on our unit did not change substantially during this extended period. In both study periods respiratory care was based on the same clinical protocols with a low tidal volume ventilation strategy. Identical ventilators were used. In addition, the disease severity (expressed as mean PRISM II scores) did not differ between 2001–2005 and 1998–2001. Therefore we have no reason to assume that the incidence of ALI in mechanically ventilated patients changed substantially during the 2001–2005 period.

Despite the high incidence of ALI/ARDS we found no mortality in our population of CDS. Others have reported a mortality rate of almost 5% in children with ARDS [11, 12]. Although this remains speculative, it is possible that CDS are more susceptible to progression to ALI/ARDS despite less severe underlying conditions, without concomitant mortality. In addition, there were only three patients with sepsis and none with trauma as underlying cause of ALI/ARDS in the CDS group, conditions associated with a high mortality rate. However, ALI/ARDS is associated with high morbidity in CDS. The need for ventilatory support was 21 ± 21 days in CDS with ALI vs. 8 ± 5 days in CDS without ALI ($p = 0.03$). Long-term effects of ALI on morbidity in CDS are unknown and remain to be defined

by lung function measurements. The high mortality rate among patients with ALI in the control group might be explained by the relatively high number of patients ($n = 4$) with severe cerebral damage. This has been shown to be a strong predictor for mortality in ALI [13].

The mechanism leading to the high incidence of ALI in CDS remains uncertain. Initial ventilator settings have recently been shown to be a risk factor for the development of ARDS [14]. In this single-center study the ventilatory strategies for CDS did not differ from those in other patients and were based on the same low tidal volume protocol. Recently it has been shown that apoptosis or programmed cell death plays a pivotal role in the pathogenesis of injurious states of the pulmonary system such as of ALI/ARDS [15, 16]. The higher incidence of ALI/ARDS may be caused by an elevated rate of apoptosis in CDS. An enhanced level of apoptosis in DS has been shown in several cells including neurons [17, 18], thymocytes [19], and granulocytes [20]. It has been suggested that increased apoptosis in DS cells is related to an inability to deal with oxidative stress, leading to accumulation of reactive oxygen radicals [21]. One could speculate whether this is related to an imbalance in the antioxidant/oxidant status in patients with DS due to increased levels of superoxide dismutase 1, an important enzyme in the antioxidant pathway that is encoded for on chromosome 21 [22, 23]. To what extent this is associated with an increased susceptibility to develop ALI/ARDS deserves further investigation. From this point of view our findings are not only of scientific interest but may also be of clinical relevance. For example, ventilatory strategies or oxygen therapy might need to be reevaluated and adjusted for CDS.

In conclusion, we found an unexpected high incidence of ALI and ARDS in CDS. The explanation for these findings remains to be elucidated.

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