ORIGINAL ARTICLE

The causes of prolonged transient tachypnea of the newborn: A cross-sectional study in a Turkish maternity hospital

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ABSTRACT

Aim Transient tachypnea of the newborn (TTN) is one of the most important acute respiratory diseases in the newborn period, caused by delay in absorption of fetal lung liquid. The aim of this study was to describe risk factors for prolonged tachypnea in TTN.

Methods Forty-one of 3,766 infants (1%) born alive in our hospital between September 1 2009 and February 28 2011 were diagnosed with TTN. Forty healthy babies born in the same period were selected as a control group.

Results Twenty-three (56%) of our patients were males and 18 (43.9%) females. The gestational age (37.7±1.8 weeks) and Apgar score at 5 min (9.1±0.8) were significantly lower than those of controls (38.4±1 weeks and 9.5±0.7, respectively; p=0.043 and p=0.04, respectively). The durations of tachypnea in patients were less than 72 h in 34 (82.9%) cases and over 72 h in seven (17%). When compared to the newborn whose tachypnea duration was less than 72 h, male gender (100% vs. 0%, p=0.028), high respiratory rates (105.2±17.4/min vs. 79.8±15.1/min, p=0.007), and high leukocyte count (23200±16807 vs. 15319±5608/mL, p=0.034) were found risk factors for tachypnea in more than 72 h. The most important factor prolonging hospitalization was long duration of tachypnea (p=0.027).

Conclusion The most important risk factors for the development of TTN were prematurity and asphyxia. Tachypnea durations were longer in males with high respiratory rates and leukocyte counts. The duration of hospitalization was directly proportional to the duration of tachypnea.

Key words: newborn, transient tachypnea, risk factors.

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INTRODUCTION

Transient tachypnea of the newborn (TTN) was defined for the first time in eight babies in 1966 by Avery (1). Rising endogenous catecholamines levels at commencement of birthing cause fetal lung liquid to be removed to the blood and lymph via high-level absorption of sodium and water, triggering chloride secretion by fetal alveoli (2). Epithelial sodium channel (ENaC), plays an important role in lung liquid clearance (3). This process is complete in most normal newborns within several hours after birth. Tachypnea occurs when fetal lung fluid is not adequately or rapidly cleared, for various reasons (4). TTN is associated with clinical findings such as tachypnea more than 12 h in duration commencing in the first hours after birth; a septic appearance absent in the mother; laboratory failure to identify infection; increasing aeration apparent on chest x-ray; and identification of perihilar edema. TTN occurs in 1–2% of all newborns (5). The condition is generally self-limiting and benign and frequently improves within 2 d. However, TTN can cause respiratory failure in some cases (6). The identification of prognostic factors for TTN would help the prevention of this outcome. The aim of this study was to describe the risk factors for prolonged tachypnea in TTN.

MATERIALS AND METHODS

The records of babies born alive in Izzet Baysal Maternity Hospital between 1 September 2009 and 28 February 2011 were retrospectively reviewed. Abant Izzet Baysal University Ethics Committee had given approval for the study. Cases with clinical findings such as tachypnea (more than 60/min) that occurred during the first 24 h after birth, who showed increased aeration on chest x-ray, and/or who exhibited perihilar edema, and need of supplemental oxygen for at least 6 h were included in the assessment. Babies with hypoglycemia, hypocalcaemia, polycythemia, aspiration of the meconium, and congenital heart disease were excluded. Forty mature healthy babies born over the same period were selected to form a control group.

Maternal parameters (age of the mother and parity) and infant perinatal data (gestational age, gender, birth weight, mode of delivery, antenatal steroid use, Apgar score, blood gas analysis, respiratory rate, tachypnea duration, antibiotics prescribed, duration of oxygen support, complications, hospitalization time, white blood cell count, and hematocrit) were recorded. Gestational age was defined using prenatal ultrasound and by noting the time of the last menstrual period. The patients who applied antibiotic were considered as treated infants. Antibiotics were discontinued in patients who did not show blood sepsis at the end of the day 5. Patients who were infected were excluded from the study.

Continuous variables are presented as means±standard deviations. The $\chi 2$ test, Student's t-test, ANOVA and the Mann–Whitney U-test were used as appropriate for comparisons. A p value <0.05 was considered to indicate significance.

RESULTS

Forty-one (1%) of 3,766 infants born alive in our hospital had TTN. Twenty-three (56%) patients were male and 18 (43.9%) female. Respiratory support was given to 35 (85.3%) infants via CPAP and 6 (14.6%) infants via high-flow nasal cannula. The gestational ages of TTN infants and controls were 37.7±1.8 and 38.4±1 weeks, respectively (p=0.043), and the Apgar scores at 5 min 9.1±0.8 and 9.5±0.7, respectively (p=0.04). Thus, both parameters

Table 1. Characteristics of the transient tachypnea of the newborn cases and the control group

Characteristics		Transient tachypnea of the newborn	Control	p
Gender (n, %)	Males	23 (56)	18(45)	0.32
	Females	18 (43.9)	22(55)	
Gestational age (weeks) (Mean±SD)		37.7±1.8	38.4±1	0.043
Birth weight (g) (Mean±SD)		2966±554	3154±431	0.09
Mode of delivery (n, %)	Vaginal	20 (48.7)	23(57.5)	0.43
	Caesarian	21 (51.2)	17(42.5)	
Age of mother (years) (Mean±SD)		28.2±5.5	26.1±4.9	0.08
Parity (Mean±SD)		2±1.1	2.1±1.1	0.84
Apgar scores (Mean±SD)	1st minute	8.4±1.1	8.1±0.6	0.21
	5th minute	9.1±0.8	9.5±0.7	0.04

Table 2. Respiration speed and tachypnea periods according to the characteristics of the cases

Characteristics (Mean±SD)		Respiration rate (/min)	p	Duration of tachypnea (/h)	p
Birth weight (g)	≤2500 (n=9)	74±12.5	0.054	20.5±19.3	0.32
	>2500 (n=32)	87±18.5		36±44.9	
Gender	Males (n=23)	87.5±20.1	0.18	45.6±51.2	0.02
	Females (n=18)	79.9±14.4		16±5.5	
Gestational age	<37(n=14)	89.7±18.4	0.005	39.1±49.2	0.069
	≥37 (n=27)	73.5±11.8		20±16.1	
Mode of delivery	Vaginaly (n=20)	78.7±13.2	0.058	17.1±13.1	0.016
	Caesarian(n=21)	89.4±20.7		47.3±52.2	
Age of mother (years)	≤20	81.3±6.1	0.5	23.3±11	0.84
	20-35	85.9±19.6		34.6 ±44.8	
	≥35	76.6±10.9		26.5±28.2	
Parity	Primiparity (n=15)	75.8±10.3	0.023	15.9±6.4	0.046
	Multiparity (n=26)	89±19.9		42.2±49	
1st min Apgar scores	≤7 (n=7)	83.4±8.7	0.9	24.4±26.2	0.56
	>7 (n=34)	84.3±19.5		34.3±43.5	
5th min Apgar scores	≤7 (n=2)	80.5±7.7	0.77	49±49.4	0.55
	>7 (n=39)	84.4±18.5		31.7±41.1	
Acidosis	(+) (n=9)	97.1±20.6	0.11	65.4±59.6	0.16
	(-) (n=14)	83.1±18.9		35±42	
Hospitalization time	<3 (n=17)	82.8±14.4	0.68	16±6.7	0.27
	≥3 (n=24)	85.2±20.5		44.4±50.4	
Additional diagnosis	(+) (n=19)	83.7±19.3	0.87	42.5±50	0.15
	(-) (n=22)	84.6±17.3		24±29.8	
Antibiotic treatment	(+) (n=21)	90.8 ±19.8	0.014	41.7±45.3	0.14
	(-) (n=20)	77.2±13.2		23.1±34.5	

were significantly lower in tests compared to controls. No other significant association was noted (Table 1).

The respiratory count was significantly higher in premature infants (89.7±18.4/min) compared to term infants (73.5±11.8/min) (p=0.005), in infants of multiparous mothers (89±19.9/min) than in infants of primiparous

Table 3. Distribution of cases' characteristics according to the tachypnea duration

Characteristics		Tachypnea duration		p
		<72 h (n=34)	≥72 h (n=7)	
Gestational age (weeks) (Mean±SD)		37.6±1.8	38±1.9	0.67
Birth weight (g) (Mean±SD)		2963±559	2981±576	0.93
Gender (No, %)	Males	16 (47)	7 (100)	0.028
	Females	18 (52.9)	0	
Mode of delivery (No, %)	Vaginal	19 (55.8)	1 (14.2)	0.08
	Caesarian	15 (44.1)	6 (85.7)	
Age of mother (years) (Mean±SD)		28.2±5.7	28.4±4.9	0.92
Parity (Mean±SD)		2±1.1	2.4±0.7	0.4
Apgar scores (Mean±SD)	1st min	8.4±1	8.4±1.5	0.97
	5th min	9.1±0.7	9±1.4	0.69
Acidosis (No, %)	(+)	4 (25)	5 (71.4)	0.08
	(-)	12 (75)	2 (28.5)	
Respiration rate (/min) (Mean±SD)		79.8±15.1	105.2±17.4	0.007
Duration of respiratory support (/h) (Mean±SD)		13.6±26.6	55.2±37	0.001
Blood leucocyte count (/ml) (Mean±SD)		15319±5608	23200±16807	0.034
Hematocrite (Mean±SD)		50.2±6.5	49.7±5	0.83
Additional diagnosis (n, %)	(+)	14 (41.1)	5 (71.4)	0.22
	(-)	20 (58.8)	2 (28.5)	
Antibiotic treatment (No, %)	(+)	15 (44.1)	6 (85.7)	0.08
	(-)	19 (55.8)	1 (14.2)	

Table 4. Distribution of cases' characteristics according to the duration of hospitalization

Parameter		Duration of hospitalization		p
		<3 days (n=17)	≥3 days (n=24)	
Gestational age (weeks) (Mean±SD)		38.4±1.5	37.2±1.8	0.025
Birth weight (g) (Mean±SD)		3176±513	2817±544	0.04
Gender (n, %)	Males	8 (47)	15 (62.5)	0.33
	Females	9 (52.9)	9 (37.5)	
Mode of delivery (No, %)	Vaginal	11 (64.7)	9 (37.5)	0.09
	Caesarian	6 (35.2)	15 (62.5)	
Age of mother (years) (Mean±SD)		26.9±4.9	29.1±5.9	0.21
Parity (Mean±SD)		2±1.4	2.1±0.8	0.85
Apgar scores (Mean±SD)	1st min	8.4±0.9	8.4±1.2	0.98
	5th min	9.1±0.8	9±0.9	0.74
Acidosis (No, %)	(+)	1 (16.6)	8 (47)	0.2
	(-)	5 (83.3)	9 (52.9)	
Respiration rate (/min) (Mean±SD)		82.8±14.4	85.2±20.5	0.68
Duration of tachypnea (/h) (Mean±SD)		16±6.7	44.4±50.4	0.027
Duration of respiratory support (/h) (Mean±SD)		9.1±7.8	29±40	0.026
Blood leucocyte count (/ml) (Mean±SD)		15326±6859	17713±10186	0.43
Hematocrite (Mean±SD)		50.2±8.6	50.1±4.2	0.99
Additional diagnosis (No, %)	(+)	3 (17.6)	16 (66.6)	0.002
	(-)	14 (82.3)	8 (33.3)	
Antibiotic treatment (No, %)	(+)	6 (35.2)	15 (62.5)	0.09
	(-)	11 (64.7)	9 (37.5)	

mothers (75.8±10.3/min) (p=0.023), and in untreated infants (90.8±19.8/min) compared to treated infants (77.2±13.2/min) (p=0.014). No other significant association was noted (Table 2).

The duration of tachypnea was significantly greater in males (45.6±51.2 vs. 16±5.5 / min, p=0.02), in infants born via C-section (47.3±52.2 vs. 17.1±13.1 /min in normally delivered infants, p=0.016) and in infants of multiparous mothers (42.2±49 vs. 15.9±6.4 /min in infants of primiparous mothers, p=0.046). No other significant association was noted (Table 2).

The duration of tachypnea was shorter than 72 h in 34 (82.9%) cases and longer than 72 h in seven (17%). The tachypnea longer than 72 h was found more frequently in males (100%) compared to females (0%) (p=0.028), infants had higher respiratory rate (105.2±17.4 /min) compared to lower respiratory rate (79.8±15.1/ min) (p=0.007), infants were given longer duration of respiratory support (55.2±37 h) compared to lower duration of respiratory support (13.6±26.6 h) (p=0.001), and infants had higher leukocyte count (23200±16807 /mL) compared to lower leukocyte count (15319±5608 /ml) (p=0.034). No other significant association was noted (Table 3).

The duration of hospitalization was shorter than 72 h in 17 (41.4%) cases and more than 72 h in 24 (58.5%). When these two groups were compared, longer hospitalization was found associated with lower gestational age (37.2±1.8 weeks vs. 38.4±1.5 weeks, p=0.025), lower birth weight (2,817±544 g vs. 3,176±513 g, p=0.04), longer duration of tachypnea (44.4±50.4 h vs. 16±6.7 h, p=0.027), longer duration of respiratory support (29±40 h vs. 9.1±7.8 h, p=0.026), and presence of an additional complication (66.6% vs.17.6%, p=0.002). No other significant association was noted. Further, the duration of hospitalization of patients with complications was significantly higher than that of others (6±4 days vs. 3±2.9 days, p=0.008) (Table 4).

DISCUSSION

Transient tachypnea of the newborn, one of the most prevalent respiratory problems during infancy, occurs at a frequency of 1–2%

(7). In our present study, the rate was 1%.

It is accepted that TTN is caused by immaturity of the lung surfactant system. Phosphatidylglycerol and phosphatidylcholine levels may be low in TTN patients (8,9). Surfactant deficiency is often identified in premature infants. Thus, prematurity is a risk factor for the development of TTN (9-11). Pulmonary lymphatic flow is slower in premature infants (12). These features pave the way for the development of TTN. Prematurity is closely associated with low Apgar scores (13). In asphyxia, the protein content of the fetal lung fluid is increased as is pulmonary capillary permeability, which renders fluid absorption difficult (14). In the present study, we found that TTN was identified more frequently in premature infants and in those with low Apgar scores at 5 min. In the literature 1-minute Apgar score less than 7 was closely associated with low Apgar scores (9).

Cesarean delivery significantly increases the complexity of respiratory problems (15). In recent years, the frequencies of elective C-sections have increased, associated with a rise in the numbers of iatrogenic respiratory problems of prematurity (16). Upon Cesarean delivery, infant lungs are inadequately pressurized and clearance of fetal lung fluid is difficult (17). Additionally, catecholamine levels, important in terms of lung maturation, are low (18). The respiratory counts of our infants born via C-section were higher than normal, with borderline statistical significance. Also, the tachypnea duration was significantly greater in such infants.

Male (compared to female) gender is important in increasing the complexity of respiratory problems (19). Male fetuses develop lower catecholamine responses when subjected to asphyxia (20). Additionally, male fetuses have lower numbers of cuboidal cells that change into Type II alveolar cells (21). Dihydrotestosterone synthesized by males delays surfactant production (22) and the levels of mRNA encoding ENaC (responsible for apical transepithelial Na transport by Type II alveolar cells) are lower in males (23). As a consequence, males become distressed more easily when encountering hypoxia. In our present study, the respiratory count of TTN males was somewhat higher than controls, but this difference did not attain statistical significance. However, the duration of tachypnea was indeed significantly higher.

Multiparity increases the complexity of respiratory problems (24), for reasons that remain unclear. We found that both the respiratory counts of TTN cases delivered by multiparous mothers and tachypnea durations in such cases were significantly greater than those of singly born TTN infants.

The symptoms of TTN are generally nonspecific and are similar to those of sepsis or pneumonia, both of which are common life-threatening conditions in newborns. Thus, the early symptoms are respiratory in nature. For this reason, antibiotic treatment of such cases is usually commenced early (25). As 51.2% of our cases were not differentially diagnosed with sepsis or pneumonia, antibiotic treatment was given. The respiratory counts of these cases were significantly higher than those of cases not commenced on antibiotics.

Tarcan et al. (26) identified male gender and high respiration rate as risk factors for extension of tachypnea beyond 3 d. Chang et al. (27) also found that high respiration rate extended the duration of tachypnea. Tudehupe et al. (28) found that male gender and C-section birth were risk factors prolonging tachypnea. Tachypnea lasted for longer than 3 min in males with higher respiratory counts (29). The results of our study were in line with those in the literature. We also found that tachypnea duration was longer in cases with high leukocyte counts. This might be associated with excessive bone marrow stimulation caused by prolonged stress. The extent of antibiotic use in such cases was also prominently higher than normal. However, such antibiotic use did not differ significantly from that in cases in which the duration of tachypnea did not exceed 3 d. The duration of oxygen support for cases with severe tachypnea was also significantly higher than normal.

Prematurity and low birth weight are important factors prolonging hospitalization of infants (30,31). The present study showed that infants who were premature or who were of

low birth weight, in addition to having TTN, were hospitalized for longer than 3 d. Prolonged tachypnea and diagnosis of other complications also prolonged hospitalization. The duration of respiratory support in such infants was also rather prolonged.

In conclusion, the most important risk factors for the development of TTN were prematurity and asphyxia. Respiratory counts were significantly higher in premature infants, infants of multiparous mothers, and treated infants. The duration of tachypnea was greater in males, infants delivered via C-section, and infants of multiparous mothers. The duration of tachypnea in such patients was greater than 3 d in males, high respiratory rates and elevated leukocyte counts. The duration of hospitalization reflected the duration of tachypnea.

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TRANSPARENCY DECLARATIONS

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