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Research Article

Transient Tachypnea of the Newborn May Be the First Presentation of Atopic March

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Abstract. *Methods*: This study was conducted to determine whether the beginning of atopic march is related to transient tachypnea of the newborn (TTN). Seventy-eight term infants were treated in the newborn Intensive Care Unit due to TTN. A case-matched control group of 78 term newborns without any health problem was selected. *Results*: There were no statistically significant differences between groups in terms of demographic and clinical characteristics. The rate of childhood asthma and atopic dermatitis among patients with a diagnosis of TTN was found to be higher than the controls (odds ratio [OR]=5.87, 95% confidence interval [CI]=2.88–11.98, $P<0.01$; OR=2.87, 95% CI=1.30–6.37, $P<0.05$, respectively). *Conclusion*: This study showed that TTN may be the first presentation of atopic march and large-scale studies should be performed to elucidate this possible relation.

Keywords: Transient tachypnea of the newborn, atopic march, childhood asthma

1. Introduction

Transient tachypnea of the newborn (TTN) is the most common cause of respiratory distress in newborns. It is defined as respiratory distress that is thought to arise from a delay in fetal lung fluid absorption. It appears within the first 6 hours after delivery and resolves spontaneously with supportive therapy within a couple of days [1, 2]. Although it is common, the pathophysiology of TTN has not been fully explained. Potential factors include failure to evacuate fetal lung fluid due to insufficient pressure in the thorax related to cesarean section delivery. Other possible causes include lack of exposure to the increased effect of catecholamines and other hormones in the delivery, which are initiated before labor begins, and insufficient activity of amiloride-sensitive epithelial sodium channels EnaC [3]. In the literature, TTN has been reported to have an excellent prognosis, although it can occasionally cause complications in the acute period [4]. However, in a limited number of studies, TTN has been shown to lead to long-term respiratory morbidity, such as childhood asthma [5]. The allergic march is a postulated progression of atopic disease in infants with eczema to subsequently develop asthma, followed by allergic rhino-conjunctivitis. Atopic dermatitis (AD) is often the first

manifestation of allergic diseases [6]. This study focuses on the relationship between TTN, AD, and respiratory allergic diseases.

2. Patients and Methods

The present study was retrospectively performed to determine whether the beginning of atopic march is related to TTN. We examined a total of 156 cases aged between 4 to 6 years, born and followed up at the Fatih University Hospital between January 2006 and December 2009. The TTN group was consisted of 78 term infants with a diagnosis of TTN who were treated in the newborn intensive care unit (NICU), and followed up in the pediatrics department. The control group included patients (n=78) who were case-matched and retrospectively selected according to age, gender, birth weight, and mode of delivery. The diagnosis of TTN was determined according to the Rawlings and Smith's criteria based on radiological and laboratory findings [7]. Chest X-ray, acute phase reactants, complete blood count, blood glucose, and calcium levels were determined in all cases. Patients with hypoglycemia, hypocalcemia, polycythemia, meconium aspiration, congenital heart disease, sepsis, and respiratory problems were excluded from the study. Diagnosis of asthma was based on the GINA guidelines [8]. Diagnosis of atopic dermatitis was based on Hanifin and Rajka's guidelines [9]. Among the patients' demographic features, use of antibiotics during the first 6 months of life, maternal age, and number of pregnancies, parental history of asthma, passive smoke exposure, and in vitro fertilization were evaluated.

Informed consent was obtained from parents, and the study was approved by the local ethics committee.

3. Statistical Analysis

Software programs used for the statistical analysis were the Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA). For categorical variables, the χ^2 test was employed. For group comparisons, the Student t test was used for normal distribution, while the Mann-Whitney U test was used in case of abnormal distribution. A P level of <0.05 was accepted as statistically significant.

4. Results

A total of 3,960 live births occurred at our hospital between 2006 and 2009. Of these, 579 (14.6%) had to be hospitalized in the NICU, and 78 (13.5%) of these were diagnosed with TTN. There were no statistically significant differences between the TTN and control groups according to parity, maternal age, and parental history of asthma, in vitro fertilization, passive smoke exposure, Apgar score, or the use of antibiotics during the first 6 months of life. The rate of atopic dermatitis among patients with TTN was found to be higher than that of the controls (odds ratio [OR]=2.87, 95% confidence interval [CI]=1.30–6.37). Forty-seven (60.3%) cases in the TTN group and 16 (20.5%) cases in the control group were diagnosed with childhood asthma according to the GINA guidelines. The rate of childhood asthma was found to be higher in the TTN group compared to the control group (P<0.01, OR=5.87, 95% CI=2.88–11.98; Table 1). In the TTN group, the maternal age of the patients developing asthma during the follow-up was higher. Relative risk of asthma risk was 2.72 times higher for newborns born from mothers aged >29 (OR=2.72, 95% CI=1.42–5.23). Demographic findings of asthmatic children for both the TTN and control groups are shown in Table 2.

Patients whose oxygen saturations were below 90% according to the pulse oximeter, despite 60% or more oxygen administration through the hood, those with a $PaCO_2$ of 60 mmHg or above, and those who were severely apneic underwent continuous positive airway pressure (CPAP) therapy. In the TTN group, 4 (5%) patients were administered CPAP therapy and 67 (95%) patients O_2 therapy with a hood. Three patients (75%) who received CPAP therapy and 44 (59.5%) patients who were administered O_2 therapy with a hood developed asthma. No statistically significant difference was found between the groups in terms of the oxygen administration technique and childhood asthma development (P<1.00; see Table 3).

5. Discussion

This study supports the idea that TTN may be an early sign of allergic march. Allergic march is a postulated progression of atopic disease in infants. The march was identified by many clinical observations during the 20th century; yet, the first meta-analysis of this subject was only carried out in 1999 [10]. The allergic march can occur at any age, and does not always follow the classic sequence of illness. In most cases, atopic dermatitis is the first manifestation of atopic diseases and the first step in the atopic march. On the other hand, TTN has been reported to have excellent prognosis and occasionally cause complications in the acute period. In past studies TTN has been shown to lead to long-term respiratory morbidity, such as childhood asthma.

First, in 1989, Shohat et al. [11] followed 58 newborns with TTN and 58 controls up to the age of 5 years. They found that children with TTN had a significantly higher incidence of recurrent episodes of wheezy breathlessness, symptoms consistent with asthma, and signs consistent with atopy (hay fever and atopic dermatitis). Schaubel et al. [12] studied 16,588 children born in the province of Manitoba from 1984 to 1985 and identified an OR of 1.38 (95% CI=1.00–1.92) for the development of physician-diagnosed preschool asthma (up to 4 years of age). The OR increased to

Table 1: Demographic and clinical data according to TTN (+) and TTN (–) groups.

		TTN (n = 78)	Control (n = 61)	P
Parity	*Min–Max*	1–3	1–3	*0.051*
	Mean ± SD	1.59 ± 0.65	1.38 ± 0.55	
	Median	1.50	1.00	
Apgar 1	*Min–Max*	5–8	8–8	*0.001***
	Mean ± SD	7.94 ± 0.41	8.10 ± 0.00	
	Median	8.00	8.10	
Apgar 5	*Min–Max*	7–10	10–10	*0.209*
	Mean ± SD	9.94 ± 0.41	10.00 ± 0.00	
	Median	10.00	10.00	
[a]Birth weight (gr)	*Min–Max*	1,880–4,700	2,550–4,000	*9.110*
	Mean ± SD	3,418.46 ± 502.56	3,409.67 ± 393.36	
	Median	3,400	3,300	
[a]Mother's Age(years)	*Min–Max*	20–38	21–38	*0.082*
	Mean ± SD	29.90 ± 3.56	28.70 ± 4.47	
	Median	30.00	28.00	
		n (%)	*n* (%)	
[b]Sex	Male	62 (79.5%)	42 (68.9%)	*0.216*
	Female	16 (20.5%)	19 (31.1%)	
[a]Mother's Age(years)	= 28	26 (33.3%)	37 (60.6%)	*0.001***
	>29	52 (66.7%)	24 (39.3%)	
[c]Method of Delivery	C/S	59 (75.6%)	44 (72.1%)	*0.639*
	Vaginal	19 (24.4%)	17 (27.9%)	
[d]Mother's History of Asthma		3 (3.8%)	0 (0%)	*0,256*
[c]Birthweight (gr)	<3,000 gr	14 (17.9%)	6 (9.8%)	*0,332*
	3,000–3,999	52 (66.7%)	47 (77.0%)	
	>4,000 gr	12 (15.4%)	8 (13.1%)	
[b]Tobocco consumption inside house	–	61 (78.2%)	47 (77.0%)	*1,000*
	+	17 (21.8%)	14 (23.0%)	
The use of antibiotics	—	9 (11.5%)	2 (3.3%)	0.112
Father's Historyof Asthma	—	4 (5.1%)	4 (6.6%)	0.730
Current Asthma	—	47(60.3%)	16(20.5%)	0.01
Atopic Dermatitis	—	25 (32.1%)	8 (13.1%)	0.00

Mann Whitney U test [a]Student t test [b]Yates test [c]Chi-kare test [d]Fisher's exact test **P<0,0

2.08 (95% CI=1.12–3.86) for hospital admissions for asthma. Birnkrant et al. [13] conducted a large scale study between 1996 and 2000 with 18,379 term newborns. In this study, TTN was independently and significantly associated with the subsequent diagnosis of childhood asthma, especially among male infants.

All of these studies investigated the development of respiratory morbidity. These neonates tend to have asthma later in childhood, and TTN may be the first manifestation of this disorder [14].The critical link may be the association of the β-adrenergic response and activation of sodium transport in the fetal alveolar epithelium to help clear neonatal

Table 2: Demographic findings of asthmatic children for TTN group and control groups are shown in.

	(–) *n*=93	(+) *n*=63	*P*
Male	67 (72.0%)	52 (81.54%)	*0.187
Multiparity	39 (38.8%)	29 (46.0%)	[c]*0.613*
IVF	1 (1.1%)	2 (3.2%)	[d]*0.566*
C/S	67 (72.0%)	50 (79.4%)	[b]*0.397*
Mother's history of asthma	5 (5.4%)	6 (9.5%)	[d]*0.353*
Mother' s age >29	43 (46.2%)	42 (66.7%)	[b]*0.019**
Atopic dermatitis	19 (20.4%)	17 (27.0%)	[b]*0.447*
Use of antibiotics	7 (7.5%)	7 (11.1%)	[d]*0.629*
Tobacco consumption inside house	23 (24.7%)	11 (17.5%)	[b]*0.378*
Birth weight (g)			
<3,000	15 (16.1%)	8 (12.7%)	[b]*0.717*
3,000–4,000	67 (72.0%)	46 (73%)	*1.000*
>4,000	11 (11.8%)	9 (14 .3%)	[b]*0.836*

[b]*Yates test* [c]*Pearson chi-square* [d]*Fisher's exact test* **P<0,05*

Table 3: Assessment of asthma risk according to oxygen demand and type of delivery in the TTN group.

	CPAP (*n*=4)	HOOD (*n*=74)	*P*-value
Childhood Asthma	3 (75%)	44 (59.5%)	1.00

Fisher's exact test

lung fluid. Stimulation of β-adrenergic receptors with β-2 adrenergic agonists (β2AA) up-regulates alveolar epithelial Na+ transport by increasing the activity of ENaC and Na+ - K+ - ATPase and protein abundance in the plasma membrane [15, 16].

Impairment of the β-adrenergic system, if persistent, would predispose such children to have subsequent diffulty with asthma [17]. This is consistent with a recent prospective study suggesting that diminished lung function is a predisposing factor for the development of wheezing [18]. Based on this information, Didem et al. [19] concluded that inhaled salbutamol treatment was effective with respect to both clinical and laboratory findings of TTN without adverse events.

In our study, the asthma incidence was found to be significantly higher in the TTN group compared to the control group (P<0.01, OR=5.87, 95% CI=2.88–11.98). Moreover, the diagnosis of TTN alone is a risk factor for childhood asthma regardless of its severity. In the first 2 years, the rate of AD among patients with the TTN group was found to be higher than that of the control group (P<0.05, OR=2.87, 95% CI=1.30–6.37).

In our study, we compared two groups according to additional causes that may affect atopic march, such as antibiotics use in the first 6 months of life, passive smoke exposure, and paternal asthma, and no significant difference was found.

6. Conclusion

Through this study, we wanted to focus pediatricians' attention on the relationship between TTN, AD, and childhood asthma. Understanding of a possible relation between TTN and atopic diseases may be the first step in awareness of the allergic march and prevention of atopic diseases. Of course, as this is a preliminary study, larger studies should be planned.

Conflict of interest

The authors confirm that there is no conflict of interest in relation to this paper.

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