ASSOCIATION BETWEEN TRANSIENT TACHYPNEA OF THE NEWBORN AND WHEEZING SYMPTOMS IN INFANCY

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ABSTRACT

Background: *Transient tachypnea of the newborn (TTN) has rare complications during the acute period and has a good prognosis. In addition it is generally believed that TTN does not lead to any long-term sequelae. However, in limited studies, the frequency of wheezing attacks and asthma was found to be increased in patient who had TTN diagnosis in the neonatal period in comparison to patients who had no respiratory problem in neonatal period.*

Objectives*: The aim of this study was to determine the association between TTN and the development of wheezing in early life.*

Patients and Methods: *This was a prospective study. It included 115 full term infants. It carried out in the NICU of Bab Alsharyia University Hospital. Follow up of all cases after parental consent from February 2017 to July 2018 for 18 month. Where 100 cases complete the follow up with regular assessment in the outpatient clinic for any symptoms of respiratory distress and clinical examination and attacks of wheeze or need for hospital admission, 15 cases missed the study period.*

Results: *Our study revealed that 63 (63%) out of 100 studied cases developed wheezy chest during the follow up period. The studied cases were male gender 35(55.6%) and smoking history especially the father 56 (88.9%) were risk factors for the development of wheeze in the studied cases with statistical significance ($p<0.05$). There was no statistical significant correlation between wheezy and non-wheezy groups regarding maternal history (bronchial asthma, hypertensive and DM). There was a positive correlation regarding hospital admission 63(100%) after neonatal period in studied cases with statistical significance difference in the wheezy group (P-value of 0.001).*

Conclusion: *The risk factors to developed wheezing symptoms in diagnosed term infant with TTN include male gander, smoking history of father. There is no correlation between maternal bronchial asthma of diagnosed term infant of TTN and development of wheezing symptoms.*

Keywords: *TTN, risk factors, wheeze.*

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. Although it is common, the pathophysiology of TTN has not been fully explained **(Kasap et al., 2008)**.

This transition is thought to be facilitated by changes in the maternal-fetal hormonal milieu, including a surge in glucocorticoids and catecholamine's, associated with physiologic events near the end of the pregnancy and during spontaneous labour. Amiloride-sensitive sodium channels play an important role in lung fluid clearance. Adrenergic stimulation and other changes near birth lead to passive transport of sodium through the epithelial sodium channels, followed by transport into the intersitium via basolateral Na+/K+ ATPase and passive movement of chloride and water through paracellular and intracellular pathways **(Kirsten, 2012)**.

TTN is associated with caesarean section delivery and it has been traditionally defined as a self-limited disease with no risk of recurrence or residual deficit of pulmonary function. In contrast, more recent epidemiological studies have shown an association of TTN and the subsequent development of asthma in young children, suggesting that TTN may not be a self-limited condition, but that it is instead a marker and or risk factor for future asthma **(David et al., 2006)**.

Recent studies have revealed that TTN is associated with the development of wheezing syndromes (bronchiolitis, bronchitis, and bronchial asthma, or prescription of asthma medications) in early childhood and subsequent diagnosis of asthma. The risk of TTN is increased in babies born to mothers with asthma **(Gomella et al., 2013)**.

However, in a limited number of studies, TTN has been shown to lead to long-term respiratory morbidity, such as childhood asthma. The allergic march is a postulated progression of atopic disease in infants with eczema to subsequently develop asthma, followed by allergic rhino-conjunctivitis **(Esengül et al., 2015)**.

AIM OF THE WORK

The aim of this study was to determine the association between TTN and the development of wheezing in early life.

PATIENTS AND METHODS

A cross-sectional study was conducted to assess the knowledge, attitude and practice of house officers toward diarrhea and its management in children under five years.

Inclusion criteria:

- Full term newborns (≥37 weeks) diagnosed as TTN after exclusion of other conditions.

Exclusion criteria:

- Any preterm babies.
- Any full term with other cause of respiratory distress (e.g. Sepsis, meconium aspiration or hypoxia).

Ethical consideration:

- Approval of research ethics committee of Al-Azhar University was obtained before conducting the study with informed written consent was obtained from parents.
- The steps of the study and the aims, was discussed with the parents.
- Confidentiality of all data was ensured.
- The author declined that there was no conflict of interest regarding the study and publication
- No financial discharge and fending for the research and publication.
- The patient had the right to withdraw at any time.

Methods;

1. The cases were collected by simple random method which included any term infant admitted in the NICU of Bab Alsharyia University Hospital and diagnosed as TTN.
2. There were 115 cases included in the study in which 100 cases complete the follow up and the other 15 cases not included in the study they did not completed the follow up period. The period of the study was from 1/2/2017 to 1/8/2018. The cases collected in 6 month and follow up every three month in pediatric out clinic of Bab Alsharyia University Hospital for one year.
3. all the studied cases were subjected to;

   A- complete history including:

   - Demographic characteristics: sex, gestational weeks, birth-weight, method of delivery.

- Maternal characteristics: Mother's age, number of pregnancies, maternal illness and drug use.

B- Post natal evaluation: Apgar scores at 1 and 5 min, duration of tachypnea, need for respiratory support and method of oxygen supply, need for phototherapy, antibiotic use, hospitalization period. With exclude the presence of postnatal complications e.g. perinatal asphyxia, hemorrhage, sepsis, infection, malformations, and congenital heart diseases.

D- Laboratory evaluation: laboratory values and chest X-ray findings.

4. Follow up of all cases for 12 months with regular assessment in the outpatient clinic for any symptoms, attacks of wheeze or need for hospital admission.
5. The collected data were subjected to statistical analysis.

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data with parametric distribution were presented as mean, standard deviations and ranges while with non-parametric distribution were presented as median with inter-quartile range (IQR). Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using Chi-square test. The comparison between two groups regarding quantitative data with parametric distribution was done by using Independent t-test. The comparison between two groups regarding quantitative data with non-parametric distribution was done by using Mann-Whitney test.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

$P > 0.05$: Non significant (NS)

$P < 0.05$: Significant (S)

$P < 0.01$: Highly significant (HS)

RESULTS

Table (1): Characteristic data of the studied cases

Variables		Number (no) = 100%
Sex	Male	72 (72%)
	Female	28 (28%)
.Gestational age (wks.)	Mean ± SD	38.61 ± 1.09
	Range	37 – 40
Weight (gm)	Weight <2.5	18 (18%)
	Weight 2.5:3.5	72 (72%)
	Weight >3.5	10 (10%)
Mode of delivery	CS	76 (76%)
	NVD	24 (24%)
Parity	Primipara	42 (42%)
	Multipara	58 (58%)
Smoking history	Smoking father	78 (78%)
	Mother	3 (3%)
	Both	7 (7%)
	Non	12 (12%)

This table shows that the Most of the studied cases were male and delivered by CS with mean G.A 38.61 ± 1.09 wks. & birth weight ranging 2.5 kg to 3.5 kg.

Table (2): Risk factors for development of wheeze in the studied cases (No. =100)

Risk factor		Diagnosis: Non wheezy group	Diagnosis: wheezy group	Test value	P-value	Sig.
		No. = 37	No. = 63			
Sex	Male	37 (100.0%)	35 (55.6%)	22.840*	0.000	HS
	Female	0 (0.0%)	28 (44.4%)			
GA (Wks.)	Mean ± SD	38.78 ± 1.29	38.51 ± 0.95	1.224•	0.224	NS
	Range	37 – 41	37 – 41			
Weight (kg)	Weight <2.5	7 (18.9%)	11 (17.5%)	2.712*	0.258	NS
	Weight 2.5:3.5	24 (64.9%)	48 (76.2%)			
	Weight >3.5	6 (16.2%)	4 (6.3%)			
Mode of delivery	CS	30 (81.1%)	46 (73.0%)	0.831*	0.362	NS
	NVD	7 (18.9%)	17 (27.0%)			
Parity	Primipara	16 (43.2%)	26 (41.3%)	0.037*	0.847	NS
	Multipara	21 (56.8%)	37 (58.7%)			
Smoking history	Father	22 (59.5%)	56 (88.9%)	23.251*	0.000	HS
	Mother	1 (2.7%)	2 (3.2%)			
	Both	2 (5.4%)	5 (7.9%)			
	Non	12 (32.4%)	0 (0.0%)			

NS: Non-significant (P > 0.05) S: Significant (P < 0.05) HS: Highly significant (P < 0.01)

Table (2) showed that sex male and smoking father were risk factors for the development of wheeze in the studied cases with statistical highly significance.

Table (3): Correlation between maternal risk factors & wheeze in the studied cases:

Maternal history \ Groups		Diagnosis: Non Wheezy Group		Diagnosis: Wheezy Group		Test value*	P-value	Sig.
		No.	%	No.	%			
Bronchial asthma	Yes	7	18.9%	21	33.3%	2.402	0.121	NS
	No	30	81.1%	42	66.7%			
Disease (hypertensive-DM)	Yes	19	29.7%	25	25.4%	0.222	0.637	NS
	No	17	70.3%	39	74.6%			
Maternal history of atopy	Yes	6	16.2%	12	19.0%	0.127	0.722	NS
	No	31	83.8%	51	81.0%			

NS: Non significant (P > 0.05) S: Significant (P < 0.05) HS: Highly significant (P < 0.01)

There was no statistical significant correlation between wheezy and non-wheezy groups regarding maternal risk factors.

Table (4): Frequency of respiratory & allergic symptoms in studied cases

Groups / Chest and allergic symptoms		Diagnosis: Non Wheezy Group No.	Non Wheezy Group %	Wheezy Group No.	Wheezy Group %	Test value	P-value	Sig.
Runny nose	Yes	17	45.9%	41	65.1%	3.503	0.061	NS
	No	20	54.1%	22	34.9%			
Cough	Yes	0	0.0%	63	100.0%	100.000	0.000	HS
	No	37	100.0%	0	0.0%			
Wheezy	Yes	0	0.0%	63	100.0%	100.000	0.000	HS
	No	37	100.0%	0	0.0%			
Milk allergy	Yes	0	0.0%	6	9.5%	3.749	0.052	NS
	No	37	100.0%	57	90.5%			
Napkin dermatitis	Yes	4	10.8%	17	27.0%	3.675	0.055	NS
	No	33	89.2%	46	73.0%			

NS: Non significant (P > 0.05) S: Significant (P < 0.05) HS: Highly significant (P < 0.01)

This Table (4) shows that there highly significant correlation between wheezy and non-wheezy groups regarding cough and wheezy chest.

Table (5): number of hospital admission in studied cases after neonatal period

Infant illness / Groups		Diagnosis: Non wheezy group No. = 37 No.	Non wheezy group No. = 37 %	Wheezy group No. = 63 No.	Wheezy group No. = 63 %	Test value	P-value	Sig.
Number of admission	0	22	59.45%	0	0.00%	57.345	0.000	HS
	1	15	40.54%	58	92.06%			
	2	0	0.00%	5	7.93%			
Diagnosis	Bronchiolitis	0	0.00%	45	71.42%	48.627	0.000	HS
	Pneumonia	0	0.00%	17	26.98%			
	Gastroenteritis	15	32.43%	6	9.52%			

NS: Non significant (P > 0.05) S: Significant (P < 0.05) HS: Highly significant (P < 0.01)

Table (5) there was a positive correlation regarding hospital admission after neonatal period in studied cases between wheezy and non-wheezy group.

Table (6) follows up results of studied cases

Time		At 3 month		At 6 month		At 9 month		At 12 month	
groups / Variable		Non Wheezy Group	Wheezy Group	Non Wheezy Group	Wheezy Group	Non Wheezy Group	Wheezy Group	Non Wheezy Group	Wheezy Group
Diagnosis	Bronchiolitis	0	5	0	12	0	15	0	14
	Pneumonia	0	23	0	17	0	15	0	8
	Gastroenteritis	2	8	8	9	12	8	10	15
Hospital admission		2	23	2	17	5	15	4	8
History of Bronchodilator		0	23	0	17	0	15	0	8

This Table (6) shows the follow up results of the studied cases regarding time of wheezing, hospital admission and history of bronchodilator administration.

DISCUSSION

These present prospective study included 100 full term infants diagnosed as TTN after exclusion of other cause of RD (meconium aspiration, hypoxia , sepsis & congenital heart disease….) aiming to detect association between TTN and the development of wheezing in infancy for one year (1ST year of life).

In our study we have two groups the 1st that develop wheezing symptoms one or more time 63 infant (63%) and the 2nd who didn't develop wheezing symptoms 37 infant (37%) during one year of life. Indicating that there was relation between TTN and developed of wheezing symptoms. And this agree with **(Mohammad et al., 2016)** in cohort study in infant result on the rate of wheezing attacks in newborns with TTN was more than patients with no TTN diagnosis.

The most extensive study about this subject was done by **(Çakan et al., 2011)** who found that TTN is a risk factor for wheezing symptoms.

(Liem et al., 2007) conducted a study with TTN patients and they found that infants with TTN

at birth were at a significantly increased risk of a wheezing disorder in childhood.

In other study by **(Jason et al., 2004)** and **(Birnkrant et al., 2006)** babies had TTN diagnosis among newborns. All of the patients were followed up. Increased frequency of asthma and wheezing attack in patients with TTN was observed.

Regarding the characteristic & demographic data of the studied cases (table 1), most of the studied cases were male and delivered by CS and this in agreement with most of textbooks & lectures as CS and male were a risk factor for TTN **(Bak et al.,2012)**.

The mean gestational ages of studied cases were 38.51 ± 0.95wks. & weight was 2.5kg to 3.5kg and the multipara more than the primipara in the studied cases and most of parent was smoking father. There was maternal history of disease e.g. bronchial asthma (28 cases) & urinary tract infection (27 cases) &diabetic (10 cases) & hypertension (7 cases) and family history of bronchial and allergic disease (18 cases).

Regarding the risk factor to develop wheeze in the studied cases (table 2), the male infants were a risk factor by (P-value: 0.000) in agreement with **(David et al., 2006)** study by (P-value: 0.150) and **(Liem et al., 2007)** study.

In our study the infants with smoking father had high risk to developed wheeze rather than the cases with non-smoking father with (P-value: 0.000) in agreement with **(Esengül et al., 2015)**.

In our study the mode of delivery, gestational age, parity and birth weight had no role in develop of wheezing symptoms as in **(David et al., 2006)** with (P-value: 0.000) said that there was an independent and insignificant association of TTN and the subsequent diagnosis of wheeze but in **(Mohammed et al., 2016)** and **(Liem et al., 2007)** study have caesarian section a risk factor because of the absence of a surge in catecholamine's, which are normally released in a vaginal delivery. This surge results in a b-adrenoceptor- mediated response and subsequent Na pump absorption of the fluid in the distal airways. TTN one potential mechanism for the association between TTN and asthma has been the possible genetic predisposition for b-adrenergic hypo responsiveness

in these infants. The critical link may be the association of b-adrenergic response and activation of Na transport in fetal alveolar epithelium, which is required to help clear the neonatal lung fluid. Thus, TTN may be the first manifestation of asthma in these children.

The difference may be due to the number of cases and regional variation or environmental factor or the cause of cesarean section.

Regarding maternal history of the studied cases (table 3), the maternal disease (bronchial asthma – diabetic – hypertension-atopy) has no role in develop wheeze but in **(Liem et al., 2007)** study found that maternal asthma is a risk factor for TTN. Although genetics may play a role in the development of TTN, and in subsequent wheeze, environmental forces could also be a contributing factor.

Regarding the Frequency of respiratory & allergic symptoms with the studied cases (table 4), there was non-significant between runny nose & milk allergy & napkin dermatitis and developed of wheeze. Environmental forces could also be a contributing factor. The chest symptoms (cough – wheeze) in studied cases were highly significant to developed wheeze (p value < 0.00).

Regarding frequency, etiology and number of hospital admission in studied cases after neonatal period (table 5) there was relation to developed wheezing symptoms, as in **(David et al., 2006)**.

Regarding the follow up of the studied cases (table 6) the wheezing attack in first 3 month more than in 6,9,12 months after the neonatal period, agreement with **(Kindlund et al., 2012)** due to the growth in the first 3 months of life might adversely affect lung growth, including a change in alveolar numbers, lung weight, and the developing immune system.

CONCLUSION

From the previous results we concluded that:

- The risk factor to developed wheezing symptoms in diagnosed term infant with TTN include Male, Smoking history of father.

- There is no correlation between maternal bronchial asthma of diagnosed term infant of TTN and develop of wheezing symptom.

- There is no correlation between develop of napkin dermatitis and diagnosed milk allergy of diagnosed term infant of TTN and develop of wheezing symptom.

LIMITATION OF THE STUDY

- Number and Period of follow up of studied cases.

- Missed cases follow up in out clinic patient.

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العلاقة بين سرعة التنفس العابرة لحديثى الولادة وحدوث أعراض الصفير فى مرحلة الطفولة

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تعد سرعة التنفس العابرة للوليد هو السبب الأكثر شيوعًا لحدوث صعوبة في التنفس عند الأطفال حديثي الولادة. يعتقد أنها تنشأ من تأخير في امتصاص السائل الرئوى الجنيني. يظهر خلال أول 6 ساعات بعد الولادة ويستجيب تلقائيًا مع العلاج. على الرغم من أنه شائع ، فإن الفيزيولوجيا المرضية له لم يتم شرحها بشكل كامل.

وقد كشفت الدراسات الحديثة أن سرعة التنفس العابرة يرتبط مع حدوث أعراض الصفير (التهاب القصيبات والتهاب القصبات والربو القصبي) في مرحلة الطفولة المبكرة .

لذا كان الهدف من هذه الدراسة تحديد عوامل الخطورة لسرعة التنفس العابرة عند حديثي الولادة ووكذلك تحديد العلاقة بين سرعة التنفس العابرة وحدوث أعراض الصفير.

تم إجراء هذه الدراسة في وحدة العناية المركزة لحديثى الولادة في مستشفى باب الشعرية الجامعي التابع لجامعة الازهر لمدة 18 شهراً وتمت متابعة المرضى لمدة 12 شهرا بعد موافقة الوالدين على هذه الدراسة المستقبلية التى إشتملت على مائة(100) طفل من حديثى الولادة مكتملى النمو.

- تم إخضاع جميع الحالات لما يلي:

1. تم تسجيل جمع الحالات لأى طفل مكتمل النمو تم حجزه في وحدة العناية المركزة حديثى الولادة وتم تشخيصه على أنه سرعة التنفس العابرة.
2. تم جمع 115 حالة كانت هناك 100 حالة اشتملت داخل الدراسة و15 حالة أخرى غير مدرجة في الدراسة لانها لم تكمل المتابعة في الدراسة.
3. الفحص الاكلينيكى التفصيلي لاستبعاد وجود مضاعفات ما بعد الولادة على سبيل المثال. نقص الأكسجين في الفترة المحيطة بالولادة ، النزيف ، العدوى وأمراض القلب.
4. متابعة جميع الحالات لمدة 12 شهرا مع تقييم منتظم في العيادة الخارجية لأية أعراض لضيق التنفس ، او حدوث الصفير أو الحاجة إلى دخول المستشفى.

5. تم شرح الهدف من الدراسة للآباء والأمهات وقد تم الحصول على إذن كتابى.

- تم عمل تحليل إحصائى للمرضى وتم استنتاج أن لدينا مجموعتين الأولى التي اظهرت أعراض الصفير مرة واحد أو أكثر من مرة وعددهم 63 والمجموعة الثانية التي لم تظهر اعراض الصفير وعددهم 37 خلال سنة واحدة من العمر. وجدنا أن سرعة التنفس العابرة مرتبطة بأمراض الجهاز التنفسي اللاحق وقد يكون مظهرا مبكرا لأعراض الصفير. نفترض أن سرعة التنفس العابرة يمكن أيضًا أن يُنظر إليه على أنه مظهر من مظاهر للتفاعلات الجينية والبيئية التي تكون بداية لظهور اعراض الصفير المستقبلية.
- أوضحت النتائج وجود عوامل خطورة لمرض سرعة التنفس العابرة شملت جنس الذكور والولادة القيصرية والولادة لحمل متكرر والتاريخ العائلي الإيجابي للتدخين. كذلك تبين أن عوامل الخطورة لأعراض الصفير عند تشخيص سرعة التنفس العابرة يشمل جنس الذكور والتاريخ العائلي الإيجابي للتدخين في المقام الأول الأب.
- أوصت الدراسة بمتابعة مرضى سرعة التنفس العابرة لمدة سنة بعد الولادة لإحتمال الاصابة بأعراض الصفير وبعمل مزيد من الدراسات المستقبلية بعدد أكبر ومدة أطول لتحديد العوامل بين سرعة التنفس العابرة وحدوث اعراض الصفير للإرتباط بينهما مع العوامل البيئية الأخرى وخصوصاً فى المرحلة المبكرة من عمر الطفل والتى تنعكس مع إمكانية العلاج والتدخل المبكر.