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A Multicenter Lung Ultrasound Study on Transient Tachypnea of the Neonate

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Neonate · Lung · Ultrasound · Transient tachypnea of the neonate

Abstract
Background and Aim: Discordant results that demand clarification have been published on diagnostic lung ultrasound (LUS) signs of transient tachypnea of the neonate (TTN) in previous cross-sectional, single-center studies. This work was conducted to correlate clinical and imaging data in a longitudinal and multicenter fashion. ***Methods:*** Neonates with a gestational age of 34–40 weeks and presenting with TTN underwent a first LUS scan at 60–180 min of life. LUS scans were repeated every 6–12 h if signs of respiratory distress persisted. Images were qualitatively described and a LUS aeration score was calculated. Clinical data were collected during respiratory distress. ***Results:*** We enrolled 65 TTN patients. Thirty-one (47.6%) had a sharp echogenicity increase in the lower lung fields (the "double lung point" or DLP sign). On admission, there was no significant difference between patients with and without DLP in Silverman scores (4 ± 1.5 vs. 4 ± 2.1; $p = 0.9$) or LUS scores (7.6 ± 2.6 vs. 5.6 ± 3.8; $p = 0.12$); PaO_2/FiO_2 (249 ± 93 vs. 252 ± 125; $p = 0.91$). All initial LUS scans (performed at the onset of distress) and 99.5% of all scans showed a regular pleural line with no consolidation, with only 1 neonate showing consolidation in the follow-up scans. The Silverman and LUS scores were significantly correlated (rho = 0.27; $p = 0.02$). ***Conclusion:*** A regular pleural line with no consolidation is a consistent finding in TTN. The presence of a DLP is not essential for the LUS diagnosis of TTN. A semi-quantitative LUS score correlates well with the clinical course and could be useful in monitoring changes in lung aeration during TTN.

Introduction

Transient tachypnea of the neonate (TTN) was originally described by Avery et al. [1] in 1966 as the clinical manifestation of delayed clearance of fetal lung fluid. The

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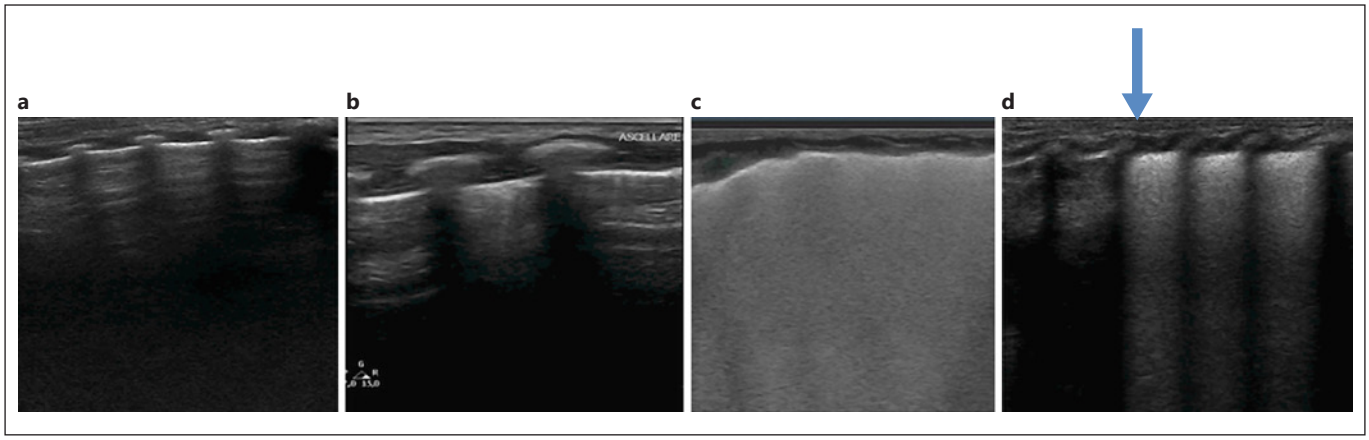

Fig. 1. a The normal LUS scan shows a regular, hyperechoic pleural image and its horizontal reverberations, also known as A-lines. **b** At increasing fluid/air ratios, A-lines are progressively substituted by vertical hyperechoic artifacts also known as B-lines. **c** The presence of numerous and compact B-lines generates a "white lung" image. **d** There is a sharp increase in echogenicity between the upper and lower lung fields (vertical arrow), known as the "double lung point" (DLP) sign.

common clinical picture consists of mild to moderate respiratory distress in late preterm or term neonates. Symptoms are generally transient, with infants usually improving within 24–48 h but the respiratory disorder may occasionally be more severe. From the clinical standpoint, TTN is mainly a diagnosis of exclusion. Chest radiographs typically demonstrate hilar streaking that may be due to perivascular lymphatic and interstitial edema [1]. The use of lung ultrasound (LUS) in the diagnosis of neonatal respiratory conditions is rapidly increasing [2, 3]. In contrast to other organs, the ultrasound examination of the lung combines the interpretation of images from real anatomic structures and that of artifacts generated by the ultrasonic beam at the air/fluid interface. A normal lung scan shows a smooth and regular pleural surface that moves synchronously with the patient's respiration, and horizontal repetition artifacts of the pleural surface, also known as A-lines (Fig. 1a). With decreasing air/fluid ratio, vertical, dynamic, hyperechoic artifacts, also known as B-lines, appear and may erase the A-lines (Fig. 1b). The presence of numerous and compact B-lines may finally generate a "white lung" image (Fig. 1c). In the first single-center study on LUS and TTN, Copetti et al. [4] described a hyperechoic, thin pleural line, and compact B-lines in the lower pulmonary fields compared to normal or almost-normal upper lung areas. They proposed the term "double lung point" (DLP) sign (Fig. 1d) to describe the sharp limit between these 2 areas of different echogenicity. The diagnostic accuracy of the DLP for TTN varies in studies published to date (sensitivity range 100–45.6% and specificity range 100–94.6%) [4, 5]. Moreover, TTN presentation at ultrasound is also variable, ranging from a "white lung" image to a benign pattern with a prevalence of A-lines [6, 7]. These different LUS findings might be quite confusing for the physician wishing to include LUS in the diagnostic process. In order to clarify this issue, we conducted a prospective multicenter study on the ultrasound features of TTN.

Methods

Patients

This was a prospective, multicenter, descriptive, case series study conducted in 6 level III NICUs in 3 European countries from January to December 2017. We enrolled neonates with a gestational age between 34^{+0} and $-39^{+6/7}$ weeks affected by TTN. TTN was clinically defined as the presence of tachypnea (respiratory rate >60/min) and dyspnea (Silverman score >1) appearing within the first 24 h of life, needing only oxygen supplementation and/or nasal continuous airway pressure (CPAP). Exclusion criteria were: (1) major malformations or chromosomal abnormalities; (2) early-onset sepsis or pneumonia (defined by the presence of clinical, radiological, and microbiological criteria as detailed elsewhere [8]) and increased inflammatory markers as per local NICU protocols, or the diagnosis of clinical chorioamnionitis (defined elsewhere [9]); (3) lack of parental consent; (4) a diagnosis of neonatal acute respiratory distress syndrome according to the Montreux definition [10]; (5) a diagnosis of classical hyaline membrane disease, i.e., respiratory distress syndrome (RDS) (as previously described [10]). Basically, RDS was defined as the presence of typical chest X-rays (a diffuse ground-glass appearance) and the need for surfactant replacement. The latter was defined as CPAP ≥6 cm H_2O and FiO_2 ≥0.4 or invasive ventilation to maintain an adequate gas exchange (described in current European guidelines [11]).

Table 1. Main data of the study population

	Total (n = 65)	With DLP (n = 31)	Without DLP (n = 34)	p value[a]
Birth weight, g	2,794±676	2,855±590	2,732±759	0.47
Gestational age, weeks	36.4±1.8	36.6±1.5	36±2	0.39
Age at onset of respiratory distress, h	1.7±0.79	1.6±0.78	1.8±0.79	0.84
Duration of respiratory distress, h	25.2±30	32±38.6	18±15.4	0.06
Silverman score at onset	4.0±1.8	4.0±1.5	4±2.1	0.9
LUS score at onset	6.7±3.4	7.6±2.6	5.6±3.8	0.12
PaO_2/FiO_2 at onset	250±108	249±93	252±125	0.91
Need for CPAP	48/65 (73%)	24/32 (75%)	24/32 (75%)	0.724

Data are expressed as mean ± standard deviation, unless otherwise indicated. CPAP, continuous positive airway pressure; DLP, double lung point; LUS, lung ultrasound.

[a] Comparisons between neonates with and without DLP.

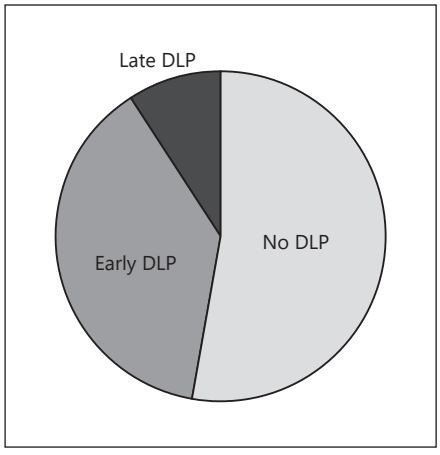

Fig. 2. Pie chart of DLP presence in our series. The majority of TTN patients did not present with DLP during the disease course. Black, hatched, and gray areas, respectively, represent the percentages of neonates without DLP, and those with an early (before 24 h of life) or late (beyond 24 h of life) appearance of DLP.

Respiratory Support Protocol

TTN babies were supported in servo-controlled incubators with oxygen supplementation and/or variable flow CPAP, according to the attending clinicians' evaluation. Appropriately sized nasal prongs or masks were used together with pacifiers of adequate size with drops of 30% glucose solution to reduce leaks and provide sedation. CPAP was set at 4 cm H_2O and increased to 6 cm H_2O if needed, according to the severity of respiratory distress; supplemental oxygen was added to keep the peripheral oxygen saturation between 90 and 95%, when CPAP was not sufficient to achieve this [12]. Initial fluid intake was ≤60 mL/kg/day.

Measurements

Every 4–6 h, a neonatologist, well-trained in LUS, examined the infant for signs of respiratory distress, recorded the Silverman score, and performed the LUS scans. LUS scans were acquired with a linear, high-frequency probe set at 10–15 MHz along standardized vertical plans of the anterior, lateral, and posterior chest walls of both lungs in the supine position, while the baby was in a quiet state. LUS scans were assessed by means of a previously validated semi-quantitative LUS score illustrated in the supplemental online material (see www.karger.com/doi/10.1159/000495911 for all online suppl. material). In detail, this LUS score is calculated based on 3 chest areas for each side (anterior, lateral, and posterior fields). A score of 0–3 points is given for each area according to basic LUS semiology; the total score ranges from 0 to 18 and is inversely correlated with lung aeration [13]. All LUS images were digitally recorded, anonymized and then centralized to the coordinating center, where they were reviewed by a senior independent ultrasonographer experienced in LUS (G.V.) for interobserver variability. At this time, a careful review of patients' files was also performed. The first LUS scan was performed at 60–180 min of life and repeated every 6–12 h if signs of respiratory distress persisted. Blood gas values were obtained by arterialized capillary blood gas analysis or by using transcutaneous devices appropriately calibrated according to current guidelines [14].

Statistics

Data distribution was tested with Kolmogorov-Smirnov test and all continuous variables were expressed as mean ± standard deviation. Based on data from the coordinating center in the 6 months preceding the study, the prevalence of TTN among infants fulfilling the inclusion criteria was estimated at 75%. Considering $\alpha = 0.05$, $\beta = 0.80$, and 75% sensitivity for DLP to diagnose TTN, a sample size of 62 neonates was needed. We chose a 75% sensitivity since this was an intermediate value between the 100% reported by Copetti et al. [4] and the 45.6% found by Liu et al. [6]. Interobserver agreement was calculated with Cohen's κ coefficient. Continuous data were contrasted with Student's t test and dichotomous variables were compared with the χ^2 or Fisher's exact test, as appropriate. Patients were also stratified into 3 subgroups based on the severity of respiratory distress at onset (group 1, Silverman score >7; group 2, Silverman score ≤7 and >4; group 3, Silverman score ≤4).

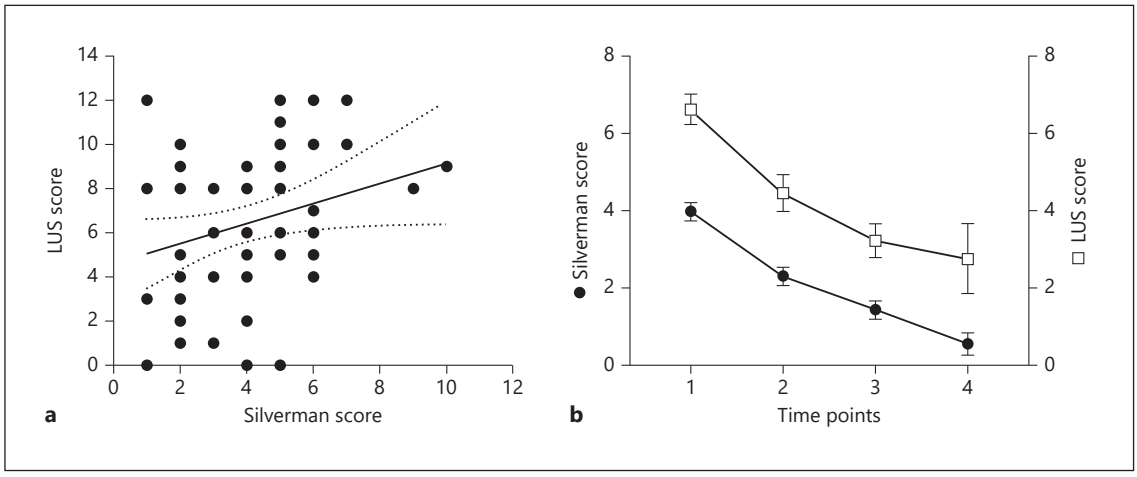

Fig. 3. a Semi-quantification of TTN respiratory distress. A significant correlation can be demonstrated between Silverman and LUS scores at disease onset (Spearman's ρ = 0.27; $p = 0.02$). **b** There is a parallel decline of both scores over pre-fixed time intervals.

Finally, correlation analysis between LUS and Silverman scores was performed calculating Spearman's correlation coefficient. $p < 0.05$ was considered statistically significant. Statistical analysis was carried out using SPSS v20.0 (SPSS Inc., Chicago, IL, USA).

Results

Eighty-three patients were eligible to participate in the study. Upon review of the patients' files, 10 were excluded due to sepsis, 6 due to RDS requiring surfactant replacement, and 2 due to the lack of a definite respiratory diagnosis. We enrolled 65 patients whose main characteristics are shown in Table 1. A total of 193 scans (with a database of 1,544 images) were collected, and the interobserver agreement was high (κ = 0.92). Table 1 shows that neonates with or without DLP had a similar oxygenation impairment, need for CPAP, and clinical severity, although the longer duration of respiratory distress in patients with DLP bordered on being statistically significant. The DLP appeared in 25/65 (38.4%) patients within the first 24 h, whilst a late (>24 h) DLP appearance was seen in 6 neonates. Thus, DLP was present in 31/65 (47.6%) patients (Fig. 2). In 19/62 (30.6%) patients, the DLP progressively disappeared, despite the persistence of respiratory distress.

There was no consolidation with a diameter >0.5 cm in any of the initial LUS scans and also in 99.5% of all scans (1 neonate showed a consolidation). All infants showing a score of 1–2 points per lung area on the first scan eventually progressed to an A-lines pattern.

We found a significant correlation between LUS and Silverman score (rho = 0.27; $p = 0.02$) (Fig. 3a); both scores decreased progressively over time as shown in Figure 3b. When patients were stratified by disease severity, a parallel decline for both Silverman and LUS scores was demonstrated (online suppl. files).

Discussion

This multicenter study reports a series of late preterm and term neonates with clinically diagnosed TTN. The main findings of this study are: (1) almost all scans showed a regular pleural line with no significant "subpleural" consolidations, (2) <50% of the patients presented with DLP, and (3) LUS score correlated with the severity of respiratory distress signs during the TTN course.

First, the presence of a regular pleural line in TTN may be useful for ruling out other causes of respiratory distress in this group of patients. Moreover, the absence of any consolidation seems to be a consistent finding for TTN patients. This fits well with the pathophysiology of TTN, since TTN is mainly an ab extrinsico edema that should not cause alveolar collapse unless there is an associated relative surfactant deficiency [15]. These findings deserve further investigations in appropriately designed, diagnostic accuracy studies to determine their reliability.

Previous studies have reported several LUS features of TTN, with or without DLP, and a variable sensitivity of DLP [4, 6, 7, 16, 17]. Surprisingly, the incidence of DLP

was low in our population. This leads us to conclude that, although a DLP is a sign of TTN, it is not essential to the diagnosis. This is consistent with data showing that babies with or without DLP had similar oxygenation, need for CPAP, and duration and severity of respiratory distress.

Interestingly, we also documented for the first time that the DLP can be detected late in the course of TTN (beyond 24 h) and can disappear while signs of distress are still present. The differences between our results and those of previous studies may have methodological explanations. Some of the studies used a single scan per patient performed by a single ultrasonographer at an unspecified time during the disease course [6, 7, 16, 17]. Indeed, in some studies, the clinical criteria for TTN were not clearly defined [6]. In the study by Rachuri et al. [18], relevant clinical information was collected but not shown. However, a combination of clinical and ultrasound results is essential for evaluating the clinical value of LUS [19]. This multicenter study partially overcame these limitations, as our group agreed upon a standardized disease definition and focused the investigation on the population with the highest TTN incidence. Moreover, rather than a variable ultrasound appearance as described in an earlier cross-sectional study [6], we have been able to show a transition from white lung images to an A-line pattern in the same patients.

We underline the remarkable diagnostic value of the pleura, a real anatomic structure that can be reliably studied with high-frequency probes due to its superficial position in neonates. An irregular pleural-line image with significant "subpleural" consolidations is a typical sign of RDS, pneumonia, and meconium aspiration syndrome [20–23]. Consistent with previous studies, our TTN neonates showed a regular ultrasound appearance of the pleura. However, an overlapping zone between TTN and RDS can exist in some infants with particularly severe or long-lasting TTN, when coupled with a relative surfactant deficiency [15, 24]. This might have been the case with the only infant in our population who showed an irregular pleural line and "subpleural" consolidations. In the future, emerging computer-assisted techniques might improve the evaluation of pleural-line abnormalities, thus distinguishing TTN from other etiologies of respiratory distress [25].

We used a previously validated LUS score [13], adapted to our purpose, to monitor changes in the lung air/fluid ratio throughout the disease course. We performed follow-up LUS scans at set time intervals during the TTN course and were able to demonstrate that LUS and Silverman scores follow similar trends. This is consistent with previous data showing significant correlations between LUS and both the amount and quality of surfactant, as measured with a count of lamellar bodies and an adsorption test, respectively [24]. Thus, repeated LUS scans might be useful to follow up patients and reduce radiation exposure [26].

In conclusion, a regular pleural line with no consolidation is a consistent finding in TTN and may be a reliable sign to exclude other lung disorders. Future studies are needed to determine the diagnostic accuracy of these signs. The presence of a DLP does not seem to be essential for the LUS diagnosis of TTN and may appear late in the disease course. A semi-quantitative LUS aeration score correlates well with the Silverman score and could be useful to monitor changes in lung aeration throughout the disease course.

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Statement of Ethics

The study was approved by the institutional review board of the coordinating center (Comitato Etico Università "Federico II"; No. 15/17) and by local review boards, where needed. Parental consent was obtained upon patient admission.

Disclosure Statement

There were no conflicts of interest.

Funding Sources

No funds were secured for this study.

Author Contributions

Drs. Raimondi, De Luca, Rodriguez Fanjul, and Yousef conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Drs. Migliaro, Di Guardo, Corsini, Shankar-Aguilera, Sodano, and Lama designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Dr. Vallone revised the image database to calculate the interobserver agreement with the individual center investigators. Drs. Mosca, Dani, and Capasso coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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