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ORIGINAL PAPER

Dysphonia at 12 months corrected age in very low-birth-weight-born children

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Abstract Preterm newborn infants may suffer laryngeal injuries after multiple intubations and long-term mechanical ventilation. Former studies have focused on acute laryngeal injuries diagnosed by endoscopy, performed within the neonatal period. This retrospective case–control study aims to investigate the prevalence and clinical risk factors for voice disorders in former very low-birth-weight (<1,500 g) infants (VLBW) at 1-year follow-up examinations. We screened former VLBW infants for presence of dysphonia at the corrected age of 1 year and compared cases with unaffected infants matched by birth weight and gestational age. Of the 843 former VLBW infants, admitted from January 1998 to May 2006, 18 subjects had persistent dysphonia. All cases had a birth weight below 1,000 g. Surgical ligation of a ductus arteriosus had been performed in ten infants. Duration of ventilation and number of intubations were not different between cases and controls, but a documented difficult intubation was a predictor of subsequent dysphonia. The rate of dysphonia at 1 year of life was 6.6% among formerly ventilated infants with birth weights <1,000 g (extremely low-birth-weight infants). Persistent dysphonia has to be added to the list of specific long-term consequences of extremely immature birth and given attention at follow-up examinations.

Keywords VLBW · Premature infant · Endotracheal intubation · Mechanical ventilation · Aphonia · PDA ligation · Vocal fold paralysis

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Introduction

Preterm infants may suffer laryngeal injuries after multiple intubations and long-term mechanical ventilation. Prospective endoscopic studies have detected acute upper airway injury in 25% to 35% of neonatal and pediatric patients at the time of elective extubation [8–10, 13, 16]. The spectrum of lesions includes local edema, erosions, ulcerations, cartilage dysfunction, vocal fold paralysis, and formation of granuloma or cysts resulting in glottic or subglottic stenosis. Little is known about the follow-up and functional recovery of patients with tubus-related trauma.

Risk factors for the development of anatomical lesions published to date are prematurity [7], duration of intubation, number of intubations [11, 13], inadequate tube diameter [5], and early infections [24]. Instigated by anecdotally encountered former preterm children who showed various degrees of persistent dysphonia at follow-up examinations, we aimed to determine the rate of dysphonia in a larger sample of very low-birth-weight (VLBW; <1,500 g)-born children and to analyze risk factors, hypothesizing that the dysphonia observed might be a result of laryngeal injury caused by intubation or ventilation.

Our present retrospective study screened 843 VLBWs for presence of vocal dysfunction. We then constituted a matched control group and analyzed clinical data of the

neonatal course in order to reveal risk factors for subsequent dysphonia.

Methods

Patients

Neonatal and follow-up data of all VLBWs who were admitted to our neonatal intensive care unit (NICU) from January 1998 to May 2006 were analyzed. This study period was chosen because of unchanged intubation protocol and material as well as relatively constant staff. Follow-up examinations for former VLBWs were performed at 6 and 12 months corrected age at our institution, including an evaluation of neurological development with the Griffiths Mental Developmental Scales at 12 months corrected age [3]. A speech therapist (AS) examined every child with a pathological voice.

To identify patients with dysphonia present at 12 months corrected age, the electronic files of our documentation system (Equinox® software, version 3.5, Empfingen, Germany) and the written documentation of the speech therapist and physicians were screened for the diagnoses "dysphonia", "aphonia", "stridor", "laryngospasm", "vocal dysfunction", and "chronical hoarseness". According to an "in house" perceptual dysphonia score (AS), patients' voice quality was classified by one single speech therapist (AS) as follows: group 1, chronic hoarseness; group 2, incomplete aphonia (weak voice); and group 3, complete aphonia at the time of 12 months corrected age follow-up examination.

As all identified cases had a history of mechanical ventilation, we then performed a retrospective case–control study to analyze possible ventilation-associated risk factors. We matched the controls according to the following criteria: (1) no documented dysphonia within the first year of life, (2) intubation and mechanical ventilation during the neonatal period, (3) birth weight ±25% compared to the matched case-patient's birth weight, and (4) gestational age ±7 days compared to the gestational age of the matched case-patient. Patients with craniofacial malformations and congenital disorders of the central nervous system were excluded. To find the matching controls, we screened the medical files of all VLBW infants born within the study period. If a VLBW infant fulfilled all abovementioned matching criteria, the infant was chosen as corresponding control. If more than one infant fulfilled the matching criteria, the infant born chronologically next to the case infant's date of birth was chosen as the matching partner.

Intubation protocol

In all cases, nasotracheal intubations were performed using non-cuffed, single-lumen plastic tubes designed to be used for long-term ventilation (Vygon GmbH & Co. KG, Aachen, Germany). We aimed to position the tube at midtrachea (vertebra Th1–Th2) and checked the correct position by X-ray. Nonemergent intubations were performed after premedication with 0.1 mg/kg morphine as a slow intravenous bolus. If the drug effect was considered to be insufficient, repetitive doses of morphine up to a maximum dose of 0.25 mg/kg were provided. Intubations, as analyzed by a retrospective chart review, were considered as complicated when more than two attempts were required or when bleeding during or after intubation or narrow laryngeal anatomy or swollen vocal cords were reported, or if the procedure was characterized as difficult. We used a Babylog 8000 plus ventilator (Draeger, Lübeck, Germany) for synchronized intermittent ventilation. No sedatives were used for ventilation.

Data collection

We reviewed the medical reports of all identified cases and controls. Analyzed risk factors in the context of intubation and ventilation were (1) duration of mechanical ventilation, (2) number of intubations per infant, (3) number of complicated intubations and (4) size of the endotracheal tube.

In addition, clinical data as sex, age at the time of discharge, surgical closure of patent ductus arteriosus (PDA) and other neonatal operations, intraventricular hemorrhage (IVH) >2°, periventricular leucomalacia (PVL), retinopathy of prematurity (ROP) >2°, necrotizing enterocolitis (NEC) requiring laparotomy and the results of the Griffiths Mental Developmental Scales at the age of 12 months corrected age were analyzed.

Statistical analysis

Patients' baseline characteristics are described as proportions (%) or median (range), respectively. Comparisons were done by chi-square for proportions and by Mann–Whitney *U* test for continuous variables. A p of <0.05 was considered as significant. Calculations were made using SPSS software, version 12.02G (SPSS, Chicago, IL).

Ethics

The local institutional review board (Ethikkommission der Charité Universitätsmedizin Berlin) approved our retrospective study and waived the need to obtain informed parental consent.

Results

Figure 1 shows the population profile. According to our inclusion criteria we identified 18 patients with dysphonia.

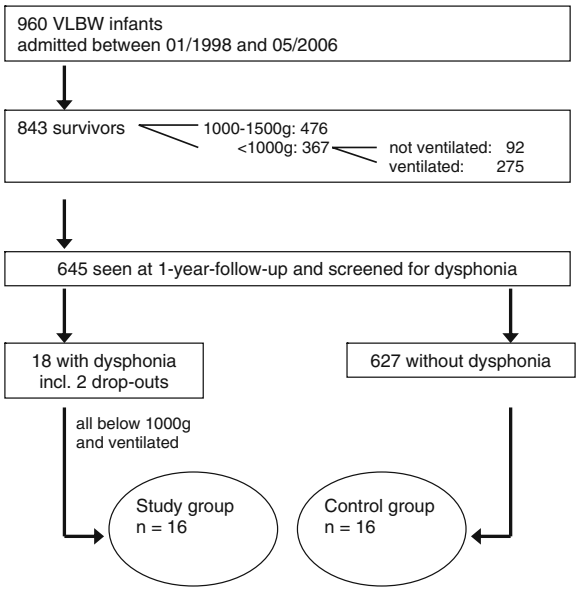

Fig. 1 Population profile. The control group consisted of ventilated infants, who were matched for gestational age and birth weight

Two of these had to be excluded from further analysis because of incomplete data. No case had to be excluded because of congenital disorders. We classified the severity of vocal dysfunction in the remaining 16 cases as shown in Table 1.

All details about clinical data of cases and controls are presented in Table 2. There were no significant differences between cases and matched controls regarding sex, incidence of IVH >2°, PVL, NEC, ROP >2°, surgical closure of PDA, age at the time of discharge, and the Griffiths total developmental quotient and the Griffiths hearing and language subquotient at the corrected age of 12 months. Within the subgroup of ventilated survivors below 1,000-g birth weight, the calculated prevalence of dysphonia was 6.6% (18/275).

A total number of 126 intubations in cases (73) and controls (53) were analyzed. The median number of intubations per patient was four (range 2–11) and three (1–6) in cases and controls, respectively (p=0.12) (Fig. 2a). Patients with dysphonia experienced significantly more complicated intubations than their controls (Fig. 2b). No complicated intubation was documented in 12/16 controls vs. 5/16 cases (p=0.013). The duration of ventilation in both groups showed no significant difference (p=0.522; Fig. 2c). The inner tube diameter at the first [cases (n): 9× 2.0 mm, 7×2.5 mm; controls (n): 10×2.0 mm, 6×2.5 mm] and second intubation [cases (n): 2×2.0 mm, 13×2.5 mm, 1×3.0 mm; controls (n): 1×2.0 mm, 12×2.5 mm, 0×3.0 mm] was not different between cases and controls.

In our unit, tracheotomy is being performed in a highly restrictive fashion. During a postnatal course with multiple complications Patient 5 was ventilated for 52 days and was discharged with 65% supplemental oxygen at 2 months corrected age. A few days later he was readmitted at another hospital because of respiratory insufficiency and received a tracheostoma for suspected subglottic stenosis. Patient 7 required prompt reintubation four times because of respiratory failure associated with inspiratory stridor. The laryngotracheoscopy showed only mild subglottic stenosis, but almost complete airway collapse at the epilaryngeal level. We transferred the infant to a specialized unit for long-term-ventilation at 1 month corrected age, where a tracheotomy was performed a few weeks later. Patient 9 was weaned from ventilation and supplemental oxygen at days of life 26 and 35, respectively, and was discharged with moderate intermittent stridor. Two months later he was readmitted at another hospital because of respiratory distress with stridor caused by a subglottic stenosis with a residual lumen of 10%. After failure of surgery by knife and laser, a tracheostoma was put in place at a corrected age of 4 months.

Discussion

This single-center retrospective analysis found vocal dysfunction at the age of 1 year to be a substantial problem in immature infants with a birth weight below 1,000 g. We had not expected the group of cases to be as homogeneous as we found them in respect to birth weight, gestational age, and history of ventilation. In this cohort of patients, a birth weight below 1,000 g and a history of endotracheal intubation were prerequisites for later dysphonia. This study shows that dysphonia must be added to the undesired sequelae in extremely low-birth-weight (ELBW) infants.

As no standardized cry or voice analysis has been performed in the patients reported here, we applied a clinical "'in house" dysphonia score aimed to classify the patients to one of three groups describing the predominant perceptual voice characteristics. Shah et al. [22] presented a more differentiated description of voice characteristics in children with unilateral vocal fold paralysis; however, this was not useful for our population of 1-year-old infants. The assumption that the clinical finding of dysphonia might result from a laryngeal trauma is supported by the fact that

Table 1 Clinical classification of dysphonia

Group 1	Chronic hoarseness	Six patients[a]
Group 2	Incomplete aphonia	Two patients
Group 3	Complete aphonia	Eight patients (including three patients with tracheostoma)

[a] Two without stridor, four with stridor

Table 2 Clinical characteristics of study patients

Case No.	Sex	Birth weight (g)	GA (weeks)	Severity of dysphonia	Intubations: total/ complicated (*n*)	Duration of ventilation (h)	PDA ligation	Griffiths score at 12 month	Hearing and language subquotient
Cases									
1	F	534	24 2/7	2	4/4	943	Yes	92	85
2	M	690	24 5/7	1	3/1	293	No	105	96
3	M	764	24 0/7	1	7/2	664	No	92	87
4	F	590	24 4/7	1	6/3	422	No	Not tested	62
5	M	735	27 3/7	3[a]	4/3	1,247	No	51	27
6	F	560	24 1/7	1	3/0	660	No	Not tested	73
7	F	705	27 0/7	3[a]	11/6	2,355	Yes	Not tested	Not tested
8	M	780	24 3/7	2	2/1	396	Yes	73	71
9	M	704	24 4/7	3[a]	6/0	421	No	74	84
10	M	770	24 6/7	1	3/0	363	Yes	93	91
11	F	570	24 6/7	3	5/1	1,383	Yes	89	104
12	M	705	24 6/7	3	4/1	1,013	Yes	80	96
13	F	750	25 3/7	3	2/0	364	Yes	99	100
14	F	465	24 3/7	3	6/1	637	Yes	80	95
15	M	880	25 4/7	3	3/0	215	Yes	85	81
16	M	630	24 1/7	1	4/2	538	No	105	92
Median		705	24 4/7		4/1	588		89	87
Controls									
1	M	614	25 2/7	0	3/0	338	Yes	87	92
2	M	860	25 0/7	0	4/1	763	No	88	83
3	M	763	24 2/7	0	3/0	493	Yes	81	76
4	F	624	24 1/7	0	3/0	742	No	102	97
5	F	870	27 3/7	0	1/0	10	No	98	Missing
6	F	540	24 0/7	0	2/0	741	No	98	89
7	M	720	27 1/7	0	1/0	6	No	97	97
8	F	590	24 3/7	0	5/0	514	Yes	86	96
9	M	704	24 0/7	0	5/1	463	Yes	Not tested	64
10	M	640	24 6/7	0	1/0	555	Yes	90	91
11	M	579	24 0/7	0	6/0	615	Yes	95	89
12	M	705	25 1/7	0	2/2	932	No	44	38
13	F	795	25 0/7	0	2/0	69	Yes	96	85
14	F	397	26 0/7	0	4/2	406	No	97	88
15	F	790	26 1/7	0	6/0	622	No	90	77
16	F	675	24 4/7	0	5/0	1,724	Yes	Not tested	Not tested
Median		690	24 6/7		3/0	535		93	89

Upper panel, study group; lower panel, control group

Severity of dysphonia: (1) chronic hoarseness, (2) incomplete aphonia (weak voice), (3) complete aphonia

GA, gestational age; *PDA*, persistent ductus arteriosus; *F*, female, *M*, male

[a] Complete aphonia and tracheostoma

dysphonia exclusively was present in formerly ventilated infants. However, laryngotracheoscopy has not been performed as a standard procedure in our patients. So we do not know whether the clinical classification correlates with any type or localization of upper airway injury and our score remains to be validated.

There is no data about vocal dysfunction at the age of 1 year in preterm infants, and acute laryngeal injury has not been systematically studied in VLBW infants. Therefore we discuss our results in comparison with the literature about acute laryngeal injury following intubation and ventilation in neonates and infants. Gomes Cordeiro et al. [13] reported

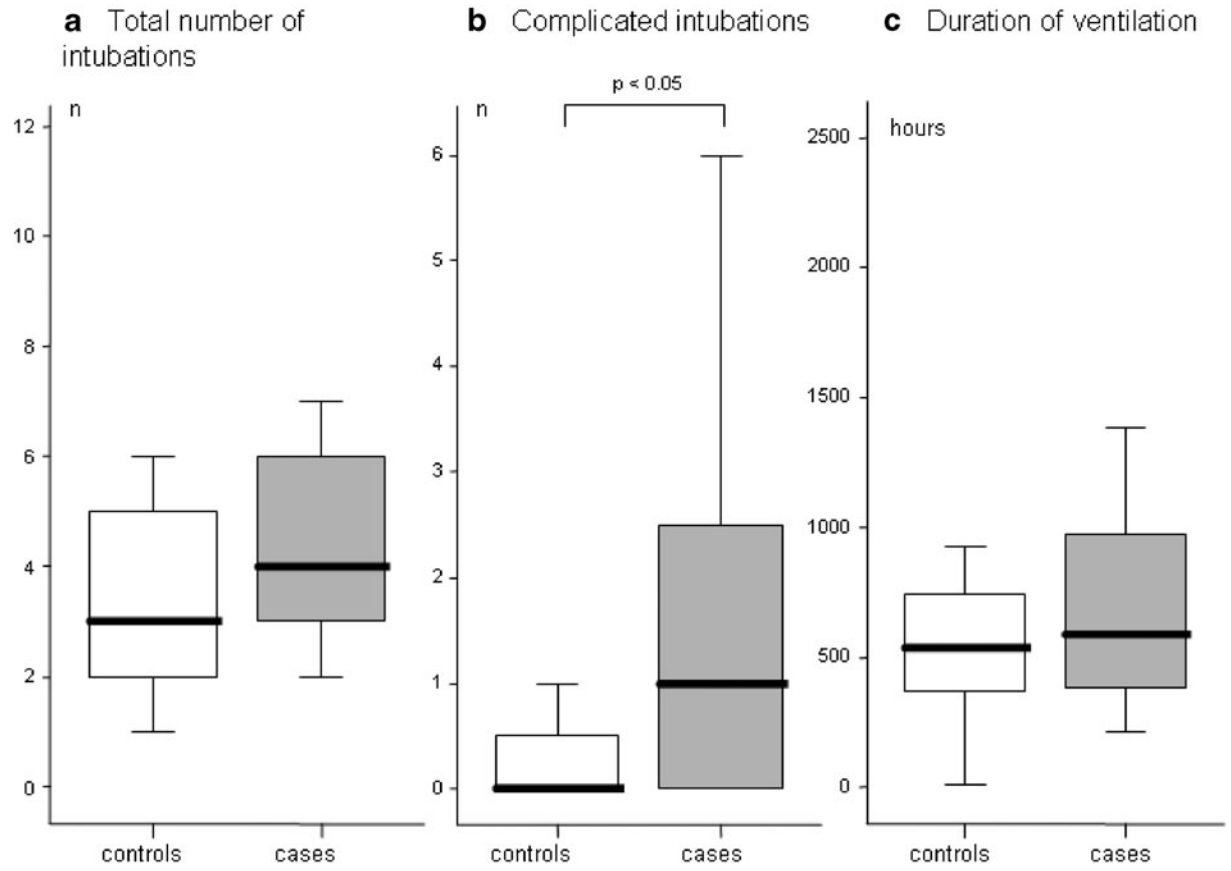

Fig. 2 **a** Total number of intubations per infant, **b** number of complicated intubations per infant, **c** total duration of ventilation (h). Cases in *gray columns*; controls in *white columns*; *boxes*, median and 25/75 centiles; *whiskers*, 2.5/97.5 centiles

an incidence of acute upper airway injuries following intubation of 35% in their cohort of 215 newborns (>1,250-g birth weight) and children. By contrast, we could not identify any patient with a birth weight >1,000 g with persisting vocal dysfunction at the age of 1 year. This may indicate that a high proportion of acute lesions heal without clinical sequelae. However we cannot exclude an underestimation bias as our follow-up rate of less than 77% is low, but nonetheless comparable with other studies.

Within the high-risk population of ventilated infants <1,000 g, the only predictor of vocal dysfunction was the finding of at least one complicated intubation. As no standardized documentation of the intubation procedure was used, this categorization remains subjective and may underestimate the real number of complicated intubations.

It is a matter of controversial debate what kind of premedication should be used to achieve a successful intubation in neonates with as little distress, pain, and harm as possible. A number of recent randomized controlled trials have shown that effective premedication with mivacurium [21], sevoflurane [14], propofol [12], or remifentanil [19] results in less traumatic intubation with fewer attempts and therefore might prevent laryngeal injury associated with complicated intubations.

Some studies [5, 6, 18, 23] have suggested a relationship between the size of tube and laryngeal lesions in the pediatric patient. In our population, we have no indication of an influence of the diameter of endotracheal tubes on prolonged vocal dysfunction or upper airway obstruction.

There are inconsistent findings about how the number of intubations and the duration of ventilation influence the risk for acute laryngeal trauma [1, 11, 13]. Our data showed no significant difference of these conditions regarding to the presence of dysphonia. The very best measure to prevent tubus-associated laryngeal pathology is to avoid endotracheal intubation. Combining early nasal CPAP with the administration of surfactant via a thin endotracheal catheter reduced the need for mechanical ventilation during the first 4 days of life in ELBW infants from 63% to 27% in a single-center experience and therefore bears the potential to prevent tubus-associated trauma [17].

Recurrent laryngeal nerve injury is a known complication after cardiac surgery. Surgical ligation of a patent ductus arteriosus was reported to be complicated by left-sided vocal

cord paralysis in 11% to 67% of ELBW infants [2, 4, 15, 20, 26]. Most symptomatic patients with left-sided vocal cord paralysis present with weak cry or voice, stridor, and hoarseness, but failure to extubate, aspiration and feeding problems also occur [2, 25]. As in our NICU, an endoscopic laryngeal assessment was not performed after surgical ligation we cannot exclude that an injury of the left recurrent laryngeal nerve may have contributed to persistent dysphonia in our patients. However, the frequency of PDA ligation in cases (10/16) and controls (8/16) was not different.

Because of the retrospective nature of our study and a follow-up-rate of less than 77%, we cannot exclude an underestimation bias and our findings may represent a conservative approximation of the true incidence of dysphonia in VLBW infants. In addition, the small sample size of the study does not allow us to draw conclusions regarding other risk factors for dysphonia. We acknowledge that defining primary outcomes by use of a clinical score is imperfect and subject to clinician bias.

This exploratory study did not investigate upper airway pathology and only allows us to develop hypotheses. A prospective longitudinal study with a standardized protocol regarding documentation of relevant intubation and ventilation variables, longitudinal assessment of voice disorders and inclusion of laryngotracheoscopy for assessment of the underlying anatomical injury is needed to continue exploring these avenues.

In conclusion, dysphonia has to be kept in mind when counseling parents of ELBW-born infants. Follow-up examinations of former ventilated preterm infants, especially of those with a birth weight <1,000 g, have to consider persisting dysphonia. In individual patients, prospective endoscopic laryngeal assessments are necessary to further characterize the damage done. Efforts are needed to avoid traumatic intubations.

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Conflict of interest The authors declare no conflict of interest.

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