Mechanical Ventilation Duration, Brainstem Development, and Neurodevelopment in Children Born Preterm: A Prospective Cohort Study

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Objectives To determine, in children born preterm, the association of mechanical ventilation duration with brainstem development, white matter maturation, and neurodevelopmental outcomes at preschool age.

Study design This prospective cohort study included 144 neonates born at <30 weeks of gestation (75 male, mean gestational age 27.1 weeks, SD 1.6) with regional brainstem volumes automatically segmented on magnetic resonance imaging at term-equivalent age (TEA). The white matter maturation was assessed by diffusion tensor imaging and tract-based spatial statistics. Neurodevelopmental outcomes were assessed at 4.5 years of age using the Movement Assessment Battery for Children, 2nd Edition, and the Wechsler Primary and Preschool Scale of Intelligence, 4th Edition, full-scale IQ. The association between the duration of mechanical ventilation and brainstem development was validated in an independent cohort of children born very preterm.

Results Each additional day of mechanical ventilation predicted lower motor scores (0.5-point decrease in the Movement Assessment Battery for Children, 2nd Edition, score by day of mechanical ventilation, 95% CI −0.6 to −0.3, $P < .0001$). Prolonged exposure to mechanical ventilation was associated with smaller pons and medulla volumes at TEA in 2 independent cohorts, along with widespread abnormalities in white matter maturation. Pons and medulla volumes at TEA predicted motor outcomes at 4.5 years of age.

Conclusions In neonates born very preterm, prolonged mechanical ventilation is associated with impaired brainstem development, abnormal white matter maturation, and lower motor scores at preschool age. Further research is needed to better understand the neural pathological mechanisms involved. *(J Pediatr 2020;226:87-95)*.

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Despite advances in neonatal medical care over the last decades, bronchopulmonary dysplasia (BPD) continues to be one of the most frequent complications of prematurity, affecting approximately 40% of neonates born before 28 weeks of gestational age.[1] Historically, survivors with BPD were described as having impaired development early in life, which typically evolved into global dysfunction, affecting their cognitive, motor, and behavioral abilities in childhood.[2-7] Identifying the brain changes and the associated modifiable clinical risk factors leading to poorer functioning in children with BPD is crucial for informing prognosis, potential treatments, and interventions.

BPD is a heterogeneously defined diagnosis, based on respiratory status at a specific time point, which is problematic when used as an end point for prognostication. Instead, ventilation strategies can be reliably measured, modified, and customized for individual neonates born preterm to aim for better outcome. As such, exposure to mechanical ventilation is an important

BPD	Bronchopulmonary dysplasia
M-ABC2	Movement Assessment Battery for Children, 2nd Edition
MAGeT	Multiple Automatically Generated Templates
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
PMA	Postmenstrual age
ROP	Retinopathy of prematurity
TBSS	Tract-based spatial statistics
TCV	Total cerebral volume
TEA	Term-equivalent age

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risk factor, which is potentially modifiable, in the pathway to BPD and adverse outcomes.[8-12] A retrospective study of ventilated neonates born preterm showed that prolonged mechanical ventilation was associated with poorer neurodevelopmental outcomes at 18-24 months.[13] Yet, the consequences of prolonged ventilation on development at preschool age remain to be determined.

The neuropathologic substrate leading to impairment in neonates born preterm with respiratory illness is not completely understood. Previous studies demonstrated that smaller brain volume, abnormal white matter microstructure, and delayed brain maturation were associated with adverse neurodevelopmental outcomes in neonates with lung disease.[14-17] From early preclinical studies, we recognize that prolonged exposure to mechanical ventilation and hyperoxia are associated with abnormal brainstem development.[18,19] However, in earlier brain imaging studies, the brainstem, a crucial brain structure for respiratory control, was not addressed.

The objectives of this contemporary prospective cohort study of neonates born preterm with advanced serial brain imaging were to determine the association of mechanical ventilation duration in the neonatal period with brainstem regional volumes at term and white matter development, as well as neurodevelopmental outcomes at preschool age.

Methods

Neonates born between 24 and 32 weeks of gestational age at British Columbia's Children's & Women's Hospital were recruited to a large prospective study over a 7-year period (April 2006 to September 2013).[20-25] Only those born before 30 weeks of gestational age were considered in this study, given the decreased exposure to mechanical ventilation in neonates born after 30 weeks of gestational age and the low risk of BPD in these older neonates.

Neonates were included if regional brainstem volumes on magnetic resonance imaging (MRI) at term-equivalent age (TEA) were successfully quantified. Neonates were excluded if they had congenital infection, genetic syndrome, or ultrasound evidence of large parenchymal hemorrhagic infarction (>2 cm). The Clinical Research Ethics Board at the University of British Columbia and Children's & Women's Hospital approved the study protocol. Written informed consent from the parent or legal guardian was obtained for each neonate.

Clinical Data Collection

Clinical data regarding prenatal, perinatal, and postnatal information were collected by systematic chart review. Based on the most commonly used definition, BPD was defined as the need for supplemental oxygen beyond 36 weeks of postmenstrual age (PMA).[26-28] Ventilation data included days of mechanical ventilation (ie, invasive ventilation involving endotracheal intubation, which includes high frequency and conventional ventilation), days on noninvasive ventilation (ie, support that provides positive end-expiratory pressure such as high-flow nasal cannula, continuous positive airway pressure, or bilevel positive airway pressure), and days on supplemental oxygen. Other clinical characteristics included histologic chorioamnionitis defined by clinical pathology assessment, Apgar score, and a Neonatal Resuscitation Score reporting on the amount of resuscitation at birth from 0 (no intervention) to 5 (endotracheal intubation with positive pressure ventilation and medication).[29] Neonatal complications included necrotizing enterocolitis (NEC) stage ≥2,[30] multiple infections, defined by ≥3 infectious episodes in accordance with our previous report,[24] and retinopathy of prematurity (ROP) stage ≥3.[31] Maternal level of education, categorized into 3 groups, completed primary/secondary school, undergraduate degree, and postgraduate degree,[25] was considered to reflect socioeconomic status.

MRI

Neonates underwent MRI of the brain early in life when clinically stable (mean 32.1 weeks PMA, SD 2.7) and again at TEA (mean 40.4 weeks PMA, SD 2.8). The MRI scans were acquired without sedation using a Siemens 1.5T Avanto scanner (Siemens, Erlangen, Germany). An experienced neuroradiologist blinded to the clinical history assessed the images for intraventricular hemorrhage grade 2 or greater[32] and cerebellar hemorrhage. White matter injury identified on early T1-weighted images were quantified in volumes and normalized as the percentage of total cerebral volume (TCV), as previously reported.[33]

Automatic Segmentation of Brainstem

Segmentation of brainstem regional volumes (midbrain, pons, and medulla) was performed with the MAGeT-Brain (Multiple Automatically Generated Templates) pipeline.[34] Requiring only a small number of manually labeled atlases, MAGeT-Brain is a well-established method that has been widely applied to robustly segment different brain structures in various populations.[33-35] Manual segmentations of brainstem regional volumes on 5 TEA T1-weighted images were acquired and used as atlases that are propagated to an intermediate template library to serve as multiple atlases to segment all images.[34,36] The anatomical landmarks for midbrain, pons, and medulla were described previously.[37] The automatically segmented brainstems (**Figure 1**; available at www.jpeds.com) were individually reviewed for quality assurance and manual corrections were applied to 14 (10%) images.

Diffusion Tensor Imaging

MRI diffusion tensor imaging and tract-based spatial statistics (TBSS) analysis were used to assess the white matter

microstructural development.[38] The white matter skeleton resolved with TBSS extended caudally to the level of the pons. Detailed methods have been previously described.[21] Fractional anisotropy is a diffusion tensor imaging parameter that increases with white matter maturation.[39,40] Four age-appropriate fractional anisotropy templates thresholded at fractional anisotropy >0.15 were created according to the PMA at scan (<30 weeks [n = 28], 30-33 weeks [n = 72], 34-36 weeks [n = 25], and 37-41 weeks [n = 84]). Voxel-wise regression analyses were performed on the 2 largest groups (30-33 weeks and 37-41 weeks) to assess the association of fractional anisotropy and mechanical ventilation duration, adjusting for gestational age at birth and PMA at scan. Family-wise error correction for multiple comparisons was performed using threshold-free cluster enhancement.[41]

Neurodevelopmental Outcomes

Neurodevelopmental outcomes were assessed at age 4.5 corrected years by experienced staff in the Neonatal Follow-up Program, blinded to the imaging findings. Cognitive outcome was assessed in 113 children with the Wechsler Primary and Preschool Scale of Intelligence, 4th Edition, which provides the Full Scale IQ (mean 100, SD 15).[42] Four children were unable to complete testing due to severe cognitive impairment and were imputed with a score of 49.

Motor function was assessed in 113 children by an experienced occupational therapist, with the Movement Assessment Battery for Children, 2nd Edition (M-ABC2).[43] The M-ABC2 evaluates 3 components of motor performance: manual dexterity, aiming and catching, and balance.

Statistical Analyses

Statistical analyses were performed using Stata, version 15.1 (StataCorp, College Station, Texas). Participant characteristics were compared using the Pearson χ^2 test for categorical variables and Student t test for continuous variables. Descriptive statistics are presented with means and SD. We categorized the neonates into 2 groups (low vs prolonged mechanical ventilation) to identify potential clinical confounders. Prolonged ventilation was defined as >28 days of mechanical ventilation. For all subsequent analysis, days of mechanical ventilation were used as a continuous variable.

The association between days of mechanical ventilation and neurodevelopmental outcomes was tested with univariable and multivariable linear regression accounting for gestational age at birth, white matter injury volume, and cerebellar hemorrhage. In clinical studies and experimental models, preterm white matter injury is strongly associated with ischemia and infections[24,44]; as such, the volume of white matter injury was used as the mediating variable for these vary pathways. The linearity assumption was confirmed by the normal distribution of residuals, the absence of cut-off point using locally weighted scatterplot smoothing, and the homogeneous variances of residuals.

We used univariable and multivariable linear regression models to examine the association between the number of days of mechanical ventilation and brainstem regional volumes, accounting for gestational age at birth, PMA at scan, TCV, and white matter injury volume. Subsequently, the relationships between brainstem regional volumes and neurodevelopmental outcomes were assessed with linear regression models accounting for TCV and white matter injury volume. A significance threshold of $P < .05$ was used for all statistical analysis.

Independent Cohort Validation

We validated our hypothesis regarding the relationship between days of mechanical ventilation and brainstem regional volumes at TEA by combining the data from the original cohort with an independent cohort of 48 neonates born <30 weeks of gestational age (both exposed and not exposed to mechanical ventilation) and admitted to the neonatal intensive care unit of the University Hospital in Lausanne (Switzerland) between February 2011 and May 2013 (cohort previously described[35,45,46]). As shown in **Table I** (available at www.jpeds.com), gestational age at birth, birth weight, and use of antenatal corticosteroids were similar in neonates from the validation cohort (Lausanne) and neonates from the primary cohort (Vancouver). However, neonates in the validation cohort differed from the primary cohort by their shorter duration of mechanical ventilation (mean 4.7 days of mechanical ventilation [SD 7.6] vs 22.1 days [SD 25.1] in the primary cohort, $P < .0001$), their longer duration of noninvasive ventilation (mean 45.9 days [SD 18.2] in the validation cohort vs 27.2 days [SD 17.4] in the primary cohort, $P < .0001$), and their lower incidence of BPD (15% in the validation cohort vs 32% in the primary cohort, $P = .02$). The brainstem regional volumes of the validation cohort were automatically segmented on their brain images at TEA (mean PMA at scan 40.9 weeks, SD 1.7) using the same technique (MAGeT-Brain) used for the primary cohort.

Results

Of the 234 neonates born very preterm (112 male [48%], mean gestational age at birth 27.9 weeks [SD 2.2]) included in the original cohort, 187 (80%) were born before 30 weeks of gestational age. As shown in **Figure 2** (available at www.jpeds.com), among the 187 neonates <30 weeks, 150 (80%) had ventilation data available and MRI performed at TEA. Brainstem segmentation was not performed on 6 scans due to motion artifact. A total of 144 neonates (75 males [52%], mean gestational age at birth 27.1 weeks [SD 1.6]) were included in the analysis, 46 (32%) were diagnosed with BPD, and 117 (82% of survivors) were followed up to 4.5 years' corrected age. There were no significant

Table II. Demographics and clinical characteristics of neonates 24-30 weeks of gestational age for low vs prolonged mechanical ventilation exposure

Characteristics	No. available for analysis	Low ventilation (≤28 d) (n = 96)	Prolonged ventilation (>28 d) (n = 48)	*P* value
Prenatal				
Male	144	48 (50)	27 (56.3)	.48
Antenatal corticosteroids	143	90 (93.8)	38 (80.9)	.02
Antenatal $MgSO_4$	144	25 (26)	6 (12.5)	.06
Histologic chorioamnionitis	139	39 (41.5)	18 (40.0)	.87
Maternal level of education	128			
Primary/secondary school		13 (15.5)	7 (15.9)	.90
Undergraduate degree		57 (67.9)	31 (70.5)	
Postgraduate degree		14 (16.7)	6 (13.6)	
Postnatal				
Gestational age at birth, wk	144	27.8 (1.4)	25.6 (1.1)	<.001
Birth weight, g	144	1055 (234)	782 (206)	<.001
Apgar score at 5 min	142	7 (2)	6 (2)	<.001
Resuscitation score	143	3.2 (1.2)	3.8 (1.0)	.005
CPAP, d	144	20.1 (14.4)	16.1 (11.4)	.09
Mechanical ventilation				
High-frequency ventilation, d	144	0.9 (3.8)	10 (12.0)	<.001
Conventional ventilation, d	144	5.8 (6.9)	42.8 (18.1)	<.001
NEC stage ≥2	144	1 (1)	7 (14.6)	.001
ROP stage ≥3	144	7 (7.3)	21 (43.8)	<.001
Multiple infections	144	17 (17.7)	32 (66.7)	<.001
Dexamethasone, no. exposed	144	4 (4.2)	34 (70.8)	<.001
Caffeine, no. exposed	144	95 (99.0)	47 (97.9)	.62
Brain imaging				
Age at early MRI	136	31.2 (2.2)	34.2 (2.6)	<.001
Age at TEA MRI	144	40.6 (2.7)	40.1 (2.9)	.36
IVH grade 2-4 (early MRI)	136	30 (31.3)	19 (39.6)	.16
Cerebellar hemorrhage (early MRI)	136	13 (14)	17 (39.5)	.001
White matter injury volume, mm^3, % TCV (early MRI)	131	0.08 (0.3)	0.02 (0.05)	.26
TCV, cm^3, (TEA MRI)	144	351.2 (6.2)	312.4 (6.0)	<.001
Brainstem volume, mm^3, (TEA MRI)	144			
Midbrain volume		2292 (344)	2124 (285)	.004
Pons volume		2849 (553)	2469 (475)	<.001
Medulla volume		1379 (201)	1239 (185)	<.001

CPAP, continuous positive airway pressure; *IVH*, intraventricular hemorrhage; *$MgSO_4$*, magnesium sulfate.
Values are shown as n (%) or mean (SD).

differences among the clinical characteristics of the neonates with and without TEA MRI, nor with children lost to follow-up.

Mechanical Ventilation Duration: Clinical Characteristics and Association with Adverse Preschool Age Motor Scores

As summarized in Table II, neonates with prolonged mechanical ventilation were born earlier compared with neonates with low ventilation exposure (mean gestational age at birth 25.6 weeks vs 27.8 weeks, $P < .001$), had lower Apgar score (mean Apgar score at 5 minutes 6 vs 7, $P < .001$), and needed slightly more extensive resuscitation at birth (mean Neonatal Resuscitation Score 3.8 vs 3.2, $P = .005$). Neonates exposed to prolonged ventilation were also sicker during the neonatal period (NEC in 14.6% vs 1%, $P = .001$, severe ROP in 43.8% vs 7.3%, $P < .001$, and multiple infection in 66.7% vs 17.7%, $P < .001$), and more likely to develop cerebellar hemorrhage (39.5% vs 14%, $P = .001$). Of the 47 neonates with white matter injury, 4 had cystic periventricular leukomalacia concurrent with the largest white matter injury volumes (Table II).

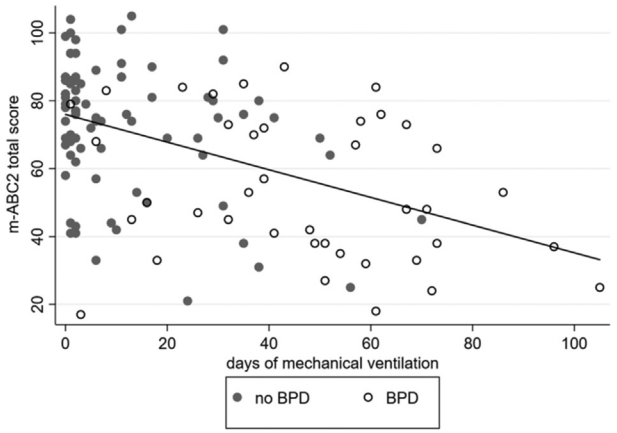

Figure 3. Relationship of days of mechanical ventilation in the neonatal period and motor scores at 4.5 years of age in children with and without BPD.

The number of days of mechanical ventilation in the neonatal period was associated linearly with preschool age motor outcomes (Figure 3). In the univariable regression analysis, each 10-day period of mechanical ventilation was associated with a decrease of 4.6 points in the M-ABC2 score at 4.5 years of age (95% CI −6.1 to −3.3, $P < .0001$). This association was unchanged when accounting for gestational age at birth, white matter injury volume, and cerebellar hemorrhage (−5.0 points in the M-ABC2 score per 10 days-period of mechanical ventilation, 95% CI −6.9 to −3.2, $P < .0001$). Including dexamethasone cumulative dose (mg/kg) and sex in the model did not affect the relationship between days of mechanical ventilation and motor scores (−4.6 points in the M-ABC2 score per 10 days-period of mechanical ventilation, 95% CI −6.9 to −2.3, $P < .0001$). However, the number of days on noninvasive ventilation was not associated with motor outcomes. In univariable and multivariable analysis, both days of mechanical ventilation and days on noninvasive ventilation were not associated with

Table III. Association between days of mechanical ventilation and brainstem regional volumes at TEA

Brainstem regional volumes at TEA	Unadjusted			Adjusted*		
	Days of mechanical ventilation β coefficient	95% CI	*P* value	Days of mechanical ventilation β coefficient	95% CI	*P* value
Midbrain, TEA volume, mm^3	−2.9	−5.0, −0.7	.009	−1.2	−2.8, 0.3	.13
Pons, TEA volume, mm^3	−7.3	−10.8, −3.8	<.001	−5.8	−8.3, −3.4	<.001
Medulla, TEA volume, mm^3	−2.7	−3.9, −1.4	<.001	−1.6	−2.5, −0.6	.002

*Models adjusting for gestational age at birth, PMA at scan, total cerebral volume, and white matter injury volume.

cognitive outcomes. The impact of very brief exposure to mechanical ventilation was not explored as only a small number of neonates were exposed to mechanical ventilation for a day or less (n = 15) or not at all (n = 13).

Considering that the recruitment was conducted over a 7-year period, the timing of recruitment was examined in the analyses by comparing 2 epochs (neonates recruited before 2009 [n = 80] vs after 2009 [n = 64]). Although the duration of mechanical ventilation did not differ between the 2 epochs (mean of 24 days in neonates recruited before 2009, vs 20 days in neonates recruited after 2009, $P = .32$), the duration of noninvasive ventilation was longer in neonates born after 2009 (mean of 27 days of noninvasive ventilation in neonates recruited before 2009, vs 38 days in neonates recruited after 2009, $P < .001$). Importantly, there was no interaction between timing of recruitment and outcomes for neurodevelopmental outcomes and brainstem regional volumes ($P > .1$).

Association of Mechanical Ventilation Duration with Brainstem Regional Volumes

The number of days of mechanical ventilation was significantly associated with smaller pons and medulla volumes at TEA (Table III). The relationship was attenuated when adjusted for gestational age at birth, PMA at scan, TCV, and white matter injury volume in multivariable regression analysis. The association was not modified by including cerebellar hemorrhage in the model. No signal changes in the brainstem were apparent on diagnostic brain imaging, even in cases of very restricted brainstem growth.

Similarly, in the validation cohort of neonates born preterm from Lausanne who were exposed to significantly less mechanical ventilation, there was a comparable association between the number of days of mechanical ventilation and smaller pons and medulla at TEA (in adjusted models, for pons volume: $\beta = -4.6$ mm^3 per day of mechanical ventilation, $P < .001$, for medulla volume: $\beta = -1.3$ mm^3 per day of

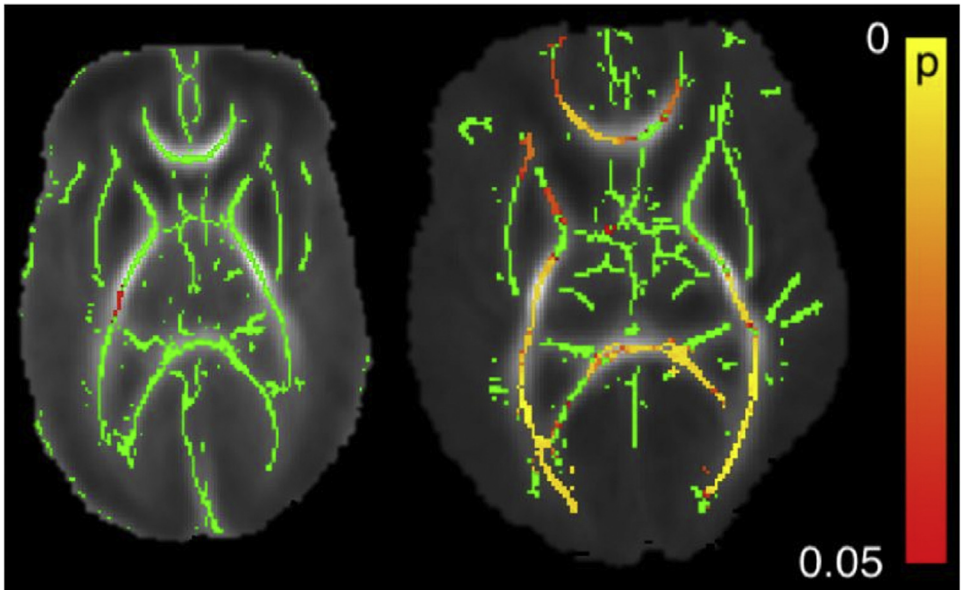

Figure 4. TBSS analysis of preterm MRI (30-33 weeks of gestational age) and term MRI (37-42 weeks) showing the association of days of mechanical ventilation with minimal fractional anisotropy changes early in life and widespread fractional anisotropy changes at term. Voxel-wise regression analyses adjusting for gestational age at birth and PMA at scan.

mechanical ventilation, $P = .03$). As shown in Table I, TEA MRI were obtained at the same gestational age period in both cohorts (mean of 40.9 weeks [SD 1.7] in the validation cohort vs 40.4 weeks [SD 2.8] in the primary cohort, $P = .32$). Notably, brainstem regional volumes were similar in both cohorts (Table I).

Mechanical Ventilation Duration Predicted Impaired White Matter Development

As shown in Figure 4, the TBSS analysis of the preterm MRI completed at 30-33 weeks of gestational age showed minimal diffusion anisotropy changes in association with mechanical ventilation duration. In contrast, in scans performed at 37-41 weeks of gestational age, the number of days of mechanical ventilation was negatively associated with widespread fractional anisotropy changes in the white matter tracts, including the midbrain and pons.

Brainstem Regional Volumes Predicted Preschool-Age Motor Scores

Pons and medulla volumes at TEA positively predicted motor function at 4.5 years of age (Table IV; available at www.jpeds.com). After we adjusted for TCV at TEA and white matter injury volume, an increase of 0.1 cm^3 in the volume of the pons was associated with an increase of 2 points in the M-ABC2 total score, whereas an increase of 0.1 cm^3 in the medulla volume corresponded to a 5-point M-ABC2 total score increase.

Discussion

Mechanical Ventilation Duration and Neurodevelopmental Outcomes

In this prospective contemporary cohort of neonates born very preterm, every additional day of mechanical ventilation predicted lower motor scores at preschool age. Our data are consistent with other contemporary reports demonstrating the increased risk for adverse motor outcomes in neonates born preterm exposed to prolonged mechanical ventilation.[10,13] Similarly, a subset of the ELGAN (Extremely Low Gestational Age Newborns) study including 915 neonates born extremely preterm showed a strong association between the severity of respiratory disease in the neonatal period and motor performance at 2 years.[9] Moreover, the duration of noninvasive ventilation was not associated with adverse outcomes, which suggests that limiting the use of mechanical ventilation in favor to noninvasive ventilation strategies can potentially improve outcomes in neonates born very preterm.

Mechanical Ventilation Duration and Brain Changes

In this prospective cohort study of neonates born very preterm, we observed that the brainstem is implicated in the relationship between exposure to mechanical ventilation and impaired motor development at preschool age. This association was observed in 2 independent cohorts from different countries: one with high exposure to mechanical ventilation (Vancouver, Canada) and the other with more restricted use of mechanical ventilation (Lausanne, Switzerland). The brainstem, critical for respiratory control and motor function, undergoes rapid development during the third trimester and may be more vulnerable to injury during this time period.[47] Although several clinical studies have shown the negative impact of respiratory illness on total brain growth at term,[14,15,35] there is a paucity of research regarding brainstem volume in the neonates born preterm. Consistent with the findings from 2 other groups,[48,49] we demonstrated that the duration of mechanical ventilation was strongly associated with the brainstem size at term age. Importantly, smaller pons or medulla at term age correlated with lower motor scores at preschool age.

Smaller Brainstem and Underlying Mechanisms

We considered 3 possible pathogenic mechanisms leading to smaller pons and medulla at term in neonates born preterm receiving mechanical ventilation. First, smaller brainstem volumes may result from abnormal brain myelination. From preclinical studies, we recognize that prolonged exposure to mechanical ventilation leads to increased brain damage, particularly involving a decrease in oligodendroglia, white matter and, subsequently, volume loss.[50] As such, the reduced volumes of the pons and the medulla, 2 structures with abundant white matter, may be related to the disrupted maturation of white matter progenitor cells, which in turn leads to subsequent myelination failure, thus explaining the disrupted growth. This hypothesis is in keeping with our findings showing concurrent adverse changes in white matter development on TBSS analysis and impaired brainstem growth at TEA in neonates exposed to prolonged mechanical ventilation. Importantly, the white matter microstructural changes were not observed on preterm MRI, which suggests an evolving process over time and a possible window of opportunity for interventions promoting white matter development. Such interventions could include improving nutrition in the first 2 weeks of life, which was recently shown to attenuate the negative association of mechanical ventilation with brain growth.[35]

Second, the brainstem hypoplasia may be secondary to the degeneration of the white matter tracts associated with supratentorial white matter injury. Similarly to the strong association reported between cerebellar growth failure and cerebral white matter injury, pontine hypoplasia has been linked to supratentorial lesions, particularly periventricular leukomalacia.[48,51,52] The corticospinal tract, the main descending motor tract in the ventral brainstem, may be more susceptible to cerebral injury due to its anatomical pathway.[51] Thus, a degeneration process affecting principally the corticospinal

fibers would contribute to the motor impairment associated with abnormal brainstem development. Yet, neonates exposed to prolonged mechanical ventilation did not exhibit more supratentorial white matter injury compared with their counterparts with low ventilation exposure. In our study, because of their critical illness, the early scan for neonates born preterm with prolonged mechanical ventilation was acquired at significantly later gestational age. However, punctate white matter injury is better identified in the first weeks of life,[33,53] which could have contributed to underestimate the severity of white matter injury in the prolonged ventilation group.

Third, the impaired brainstem development might be secondary to focal necrotic changes due to hypoxia–ischemia, hyperoxia, and hypocarbia during a crucial period for brain development. These conditions are recognized as important contributors in the pathogenesis of pontosubicular necrosis, a distinct type of selective neuronal injury affecting, among others, the neurons of the base of the pons.[18,54,55] This neuropathology finding has not been correlated previously with diagnostic imaging changes.

Alternatively, abnormal brain development in neonates exposed to prolonged mechanical ventilation may start as early as in the delivery room, as reflected by the need for more intensive resuscitation in this group. Although antenatal insult might also be considered as a potential mechanism in the pathway to impaired brainstem development, the brainstem is relatively preserved in existing experimental models of hypoxic–ischemic brain injury and in human imaging studies.[52,56] The design of the study did not allow us to determine the antenatal predictors.

Mechanical ventilation duration is closely linked to multiple other risk factors with possible impact both on brain development and neurodevelopmental outcomes. In our cohort, neonates exposed to prolonged mechanical ventilation were more likely to have other comorbidities such as NEC, multiple infections, and ROP. Therefore, several pathways of brain injury likely coexist and might not have properly been considered. In addition, data related to intermittent hypoxic episodes, nutrition, compromised respiratory function after NICU discharge, and rehospitalization later in life, which may be important modifiers of preschool outcomes, were not available. Nonetheless, with the strong association demonstrated between mechanical ventilation duration, adverse brain development, and impaired motor function, minimizing exposure to mechanical ventilation should be part of the strategies to optimize preterm care.

Neonates born preterm exposed to prolonged mechanical ventilation are at high risk of developing adverse motor outcome at preschool age. Prolonged mechanical ventilation is associated with impaired white matter maturation and abnormal brainstem development at term age, which predicts adverse motor outcomes at preschool age. Future studies are needed to better determine the neural pathologic mechanisms involved and longer-term outcomes of the vulnerable preterm population exposed to prolonged mechanical ventilation. ■

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50 Years Ago in *The Journal of Pediatrics*

Wolf-Hirschorn Versus Cri-du-Chat Syndrome

Miller OJ, Breg WR, Warburton D, Miller DA, DeCapoa A, Allerdice PW, et al. Partial Deletion of the Short Arm of Chromosome No 4(4p-): Clinical Studies in Five unrelated Patients. J Pediatr 1970;77:792-801.

The Wolf-Hirschorn syndrome was described in 1961 and 1965 as the first human chromosome deletion syndrome, with a deletion of the short arm of chromosome number 4 (4p) and recently discussed by us.[1,2] The Cri du Chat syndrome was described in 1963, with a deletion of the short arm of chromosome 5.

There are overlapping characteristics between the two syndromes, thus in *The Journal* 50 years ago Miller et al present 5 genetically confirmed cases of Wolf-Hirschorn syndrome, listing the features that distinguish this from Cri du Chat syndrome. Although they refrain from using the term Wolf-Hirschorn syndrome in their article, they are describing the clinical and genetic findings typical for this syndrome. Wolf-Hirschorn syndrome presents with characteristic facies, lower birthweight than Cri du Chat syndrome, more severe psychomotor retardation, more frequent genital anomalies, preauricular and sacral dimples, hypoplastic dermal ridges on the palms and the feet, and the lack of the characteristic cry heard in patients with Cri du Chat syndrome. Shared features are hypotonia, microcephaly, hypertelorism, epicanthus, low-set ears, micrognathia, high-arched palate, heart defects, foot deformities, and simian crease. Cri du Chat syndrome is slightly more common than Wolf-Hirschorn syndrome, but both syndromes are very rare (1:15 000-50 000 vs 1:50 000). The exact site for the genetic lesion has been mapped to 4p16.3 in Wolf-Hirschorn syndrome, and in Cri du Chat syndrome the lesion can vary from just 5p15.2 to the entire short arm (OMIM).

This report was important at the time of publication due to the differentiation of the 2 syndromes, which cannot always be easily done clinically. Today the situation is very different; an extensive genetic testing when suspecting a syndrome gives quick and accurate results. Miller et al highlight the differences between Wolf-Hirschorn syndrome and Cri du Chat syndrome, and the extensive progress that has been made in genetic testing in the last 50 years.

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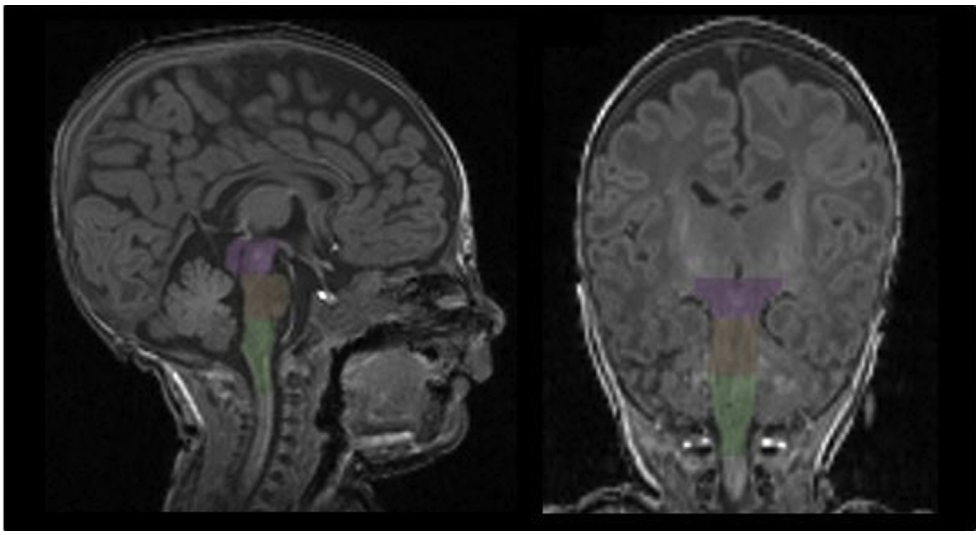

Figure 1. MAGeT-Brain segmentation of the brainstem. The colors represent the regional brainstem segmentation: *purple* = midbrain, *brown* = pons, *green* = medulla.

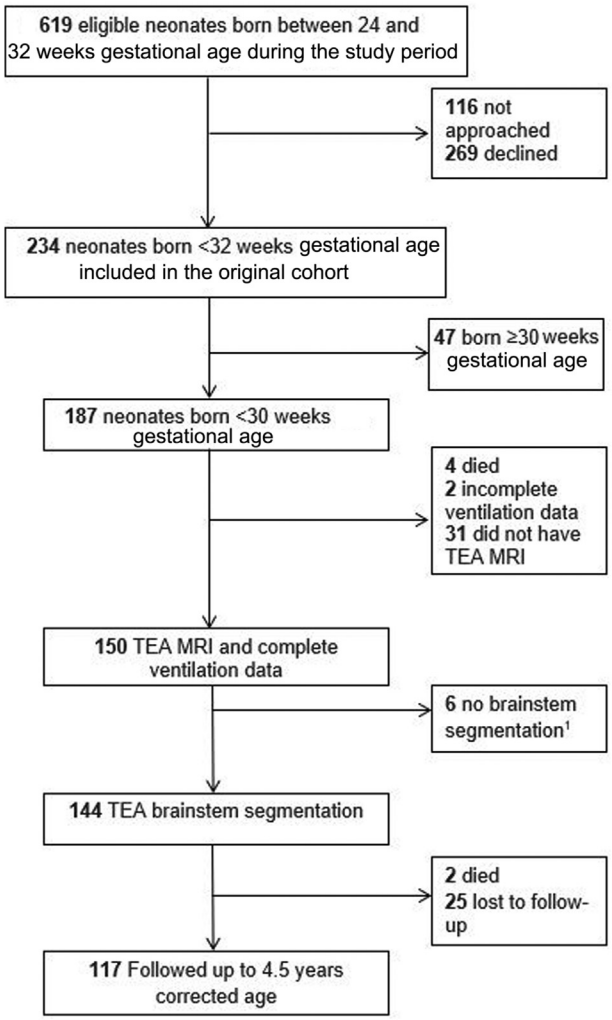

Figure 2. Participant flowchart. [1]Segmentation could not be robustly completed in 6 scans due to motion artifact.

Table I. Demographics and clinical characteristics of neonates 24-30 weeks of gestational age by cohort

Characteristics	Vancouver cohort (n = 144)	Lausanne cohort (n = 48)	*P* value
Male	75 (52.1)	21 (43.8)	.32
Antenatal corticosteroids	128 (89.5)	42 (87.5)	.70
Gestational age at birth, wk	27.1 (1.6)	27.4 (1.3)	.18
Birth weight, g	964 (259)	914 (229)	.23
Noninvasive ventilation, d	31.0 (18.2)	45.9 (18.2)	<.0001
Mechanical ventilation, d	22.1 (25.1)	4.7 (7.6)	<.0001
Dexamethasone, no. exposed	38 (26.4)	7 (14.6)	.09
BPD	46 (31.9)	7 (14.6)	.02
Brain imaging			
Age at TEA MRI	40.4 (2.8)	40.9 (1.7)	.32
Midbrain volume at TEA, mm^3	2236 (334)	2236 (342)	.99
Pons volume at TEA, mm^3	2723 (556)	2767 (436)	.63
Medulla volume at TEA, mm^3	1332 (206)	1321 (252)	.77

Values are shown as n (%) or mean (SD).

Table IV. TEA pons and medulla volumes in relation to motor outcomes at 4.5 years of age in the primary cohort

Motor score at 4.5 years of age	Predictor variable	Unadjusted			Adjusted*		
		β coefficient	95% CI	*P* value	β coefficient	95% CI	*P* value
M-ABC2 total score	Pons volume, mm^3	0.009	0.001, 0.02	.02	0.02	0.001, 0.04	.04
	Medulla volume mm^3	0.025	0.005, 0.05	.01	0.05	0.006, 0.09	.02

*Models adjusting for total cerebral volume at TEA and white matter injury volume.