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Early unexplained deaths of Norwich Terrier puppies are associated with abnormal lung development and pulmonary vascular disease

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Background: Childhood interstitial lung diseases include several rare disorders that are characterized by developmental abnormalities of alveolar and vascular growth and are commonly fatal. Insights into basic mechanisms that contribute to developmental lung disorders are necessary to understand underlying pathomechanisms, improve the identification of at risk newborns and to design future interventions. However, spontaneous mammalian animal models to study human neonatal lung disease are lacking. Recently, we have identified abnormal lung development in several breeds of domestic dogs, which may be an under-recognized cause of neonatal mortality in puppies. Sudden unexplained death in Norwich Terrier (NT) puppies has been recognized, however, the underlying cause is unknown. Based on these findings, we hypothesized that abnormalities of lung development contribute to high mortality of NT puppies; further this may provide a unique model to study mechanisms of developmental lung disease in humans.

Methods: Lung tissue from NT puppies with spontaneous demise < 1 month of age were collected. Complete autopsies were performed and the lungs were inflation-fixed with 10% neutral buffered formalin. Sections of right and left cranial and caudal lung lobes were routinely processed and HE stained sections were evaluated. One age matched control with no known respiratory pathology was also included.

Results: Five female and four male puppies were identified with the average age of 10.5 days (range: 1 day – 25 days). Reported clinical signs consisted of poor weight gain, failure to thrive and tachypnea. Lungs were mottled, but otherwise lacked gross structural abnormalities. There were no congenital cardiac anomalies and the main pulmonary vessels appeared grossly normal. All lung sections of each of the NT puppies showed marked histologic signs of abnormal distal lung structure. The acinus appeared underdeveloped with decreased septation of distal airspaces and marked thickening and hypercellularity of alveolar septa. Small pulmonary arteries were markedly remodeled, with smooth muscle thickening. Double capillary layers as well as dysplastic capillaries within the interstitium were often present. Aberrant bronchopulmonary anastomotic vessels were occasionally noted.

Conclusion: We report that early deaths in NT puppies are associated with striking signs of developmental lung vascular and airspace disease, including evidence of decreased alveolarization, interstitial thickening, pulmonary vascular remodeling, and prominent capillary growth. We speculate that genetic and molecular studies of lung development in NT puppies may provide novel insights into human developmental lung disease.