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Cognitive Development One Year After Infantile Critical Pertussis

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Pertussis is an important cause of infant death around the world, and continues to be a public health problem even in high income countries. The diagnosis is usually made by culture or polymerase chain reaction testing in children with paroxysms of cough with an inspiratory whoop and post-tussive vomiting lasting more than 2 weeks(1). Pertussis can cause serious and sometimes fatal complications in babies and young children, especially those who have not received the recommended pertussis vaccines. About half of babies younger than 1 year old who get pertussis need care in the hospital and many are cared for in the intensive care unit (2). More than 60% have apnea or hypoventilation, which may require mechanical ventilation, and more than 20% have pneumonia (2). Fatal cases often have lower birth weight, younger gestational age, younger age at time of cough onset and higher peak neutrophil and lymphocyte counts in blood than those who survive(2, 3). Encephalopathy and seizures occur in about 3% of babies with pertussis. However, little is known about the neurodevelopmental outcomes of these children after they graduate from the PICU. Several small studies reported neurodevelopmental problems including reduced intelligence and poor school performance, but others have not found cognitive impairment in children with acute neurological complications (4).

A prospective study of cognitive development in a cohort of children with critical pertussis in PICUs in the United States carried out by Berger, et al in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN) was published in this issue of *Pediatric Critical Care Medicine* (5). The Mullen Scales of Early Learning (MSEL) were administered to 57% of 196 eligible patients with confirmed pertussis who were less than 12 months on admission to a PICU in the network and were followed up at one year. The cohort included infants with laboratory confirmed pertussis from 2008 to 2013. The MSEL measures development in infants and preschoolers in the domains of gross motor functions, visual reception, motor skills, receptive language, and expressive language. The four cognitive scales (visual, fine motor, receptive language, and expressive language) are combined to yield an Early Learning Composite that is presented as a measure of overall cognitive functioning (6). The study found that the mean scores for visual reception, receptive language and expressive language domains in the pertussis group were

significantly lower than the age appropriate norms ($p<0.001$) but fine and gross motor domains were within the normal range. 37% of patients had abnormal scores in at least one domain and 9% had an Early Learning Composite score of 2 or more standard deviations below population norms for one year after discharge. Older age and Hispanic ethnicity were associated with lower mean Early Learning composite scores, but the presenting symptoms and PICU course were not.

The study also assessed functional status at discharge and at one year in the domains of feeding, arousal, communication and motor assessments. There were no statistically significant differences in PICU discharge assessments in those with and without the one year follow-up. For the group assessed with the MSEL, 35% of patients were receiving some feeds with a nasogastric, nasojejunal or gastrostomy tube at PICU discharge, but at one year 98% were feeding without a device. There was a small increase in children with communication problems at one year compared to discharge but no significant reduction in hearing.

These findings indicate that neurodevelopmental disorders are common in this group of children with critical pertussis, and they should receive neurodevelopmental follow-up and intervention if needed. It is noteworthy that the pertussis group had greater deficits in receptive and expressive language and visual function than in motor function so that deficits may be missed on follow-up on routine examinations unless specifically tested for. Possible mechanisms proposed for neurobehavioral deficits in infants with pertussis include inflammation, hypoxic injury associated with breathing difficulties, coughing, and apnea and hemorrhages due to increased intracranial pressure from coughing(7). In this study, clinical factors such as pulmonary hypertension, shock, and high peripheral white blood cell counts were not associated with worse scores on the MSLE(5). However it is possible that the lack of association with clinical features such as pulmonary hypertension may have been due to inadequate power.

Neuropathological evidence of inflammation and demyelination have been reported in the brains of children dying with pertussis (7). Inflammation may be associated with seizures, which occur in some children with acute encephalopathy secondary to pertussis (8). There appears to be considerable crossover of signaling cascades in the immature brain between hypoxic-ischemic injury and neuroinflammation with each type of injury being able to trigger similar molecular and histologic changes. Seizures can trigger these cascades and seizures are also facilitated by them (9–11).

In Denmark, the cumulative risk of seizures over 10 years after being hospitalized for pertussis is higher than in the general population who did not have pertussis based on a study of population-based medical registries.(12) Interestingly, numerous children with seizures and encephalopathy attributed to pertussis vaccine in the United States have been shown to have genetic mutations in voltage-dependent sodium channels associated with Dravet syndrome, a genetic epileptic encephalopathy(13).

Overall this is an outstanding study that is unique in providing outcome data on the neurobehavioral effects of critical pertussis in children hospitalized in the PICU, and a

model of teamwork from the NIH-NICHD Pediatric Critical Care Network. As pointed out by the authors, the data are limited by several factors, including the loss to follow-up of a substantial portion of patients in the PICU, lack of data on potential confounding influences such as exposure to sedative drugs in the PICU or parental socioeconomic status, and difficulty in separating the effects of pertussis from general critical illness.

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