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Original article

Neurodevelopmental outcomes of premature infants with bronchopulmonary dysplasia

F. Gallini, R. Arena, G. Stella, S. Frezza, L. Maggio
Neonatal Unit, Department of Paediatrics, Catholic University, Rome – Italy

Abstract. Bronchopulmonary dysplasia (BPD) is a chronic lung disorder common among very preterm infants affecting significantly not only mortality and morbidity but also neurodevelopmental outcomes. This review aims to identify the short and long-term neurodevelopmental outcomes of infants with BPD, considering that the new definition of BPD allows to relate severity of BPD with greater risk of developmental delay. (www.actabiomedica.it)

Key words: premature infants, extremely low birth weight infants, bronchopulmonary dysplasia, neurodevelopmental outcome

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disorder affecting preterm infants; it was first described in 1967 as a requirement for supplemental oxygen at 28 days of life with chest X-ray particular findings (1). Over the decades, a "new" BPD has emerged, characterized by fewer and larger alveoli and decreased pulmonary microvasculature development (2-5). This "new" BPD and the improved survival rates of infants born at extremely low gestational ages, led to a new definition of BPD allowing to quantify severity following the National Institutes of Child Health and Human Development (NICHD)/National Heart, Lung and Blood Institute Workshop criteria (2).

During hospital stay, infants with BPD were found to have increased incidence of respiratory problems and other serious complications such as intraventicular hemorrhage, infections and frequent episodes of hypoxia which may lead to brain injury (6, 7). Poorer growth and some therapies, such postnatal steroids, may also negatively affect brain development in these children.

Several studies have investigated the short and long-term follow-up of preterm infants with BPD, in order to identify the impact of this disease on neurological development (8-10). Until recently, most studies used the old dichotomous definition of BPD; the introduction of the new definition of BPD permits to determine whether the severity of BPD can predict developmental delay, beyond the negative effects of other risk factors. To date, however, only few studies examined the neurodevelopmental outcomes of infants with BPD according to the severity of the disease (7, 11-15).

This paper reviews the neurodevelopmental outcomes of preterm infants with BPD, proposing a chronological exposition of these outcomes, starting from the first months of life until school age.

Neurodevelopmental outcomes

First year of life

Only recently a severity-based definition was used to investigate neurodevelopmental outcomes in preterm infants with PBD in the 1st year of life.

In 2008 Jeng et al.(13) examined the developmental and clinical outcomes in VLBW infants with or without BPD from 36 weeks' post-menstrual age (PMA) until 12 months' corrected age (CA). Neurodevelopment was initially assessed at 36 and 39 weeks' PMA, using Neonatal Neurobehavioural Examination-Chinese Version (NNE-C), founding a significantly negative linear relation between severity of BPD and the NNE-C index scores. Neurobehavioural alterations associated with BPD become more evident as age increases from 36 to 39 weeks' PMA (13). Children were also assessed at 6 and 12 months CA using Bayley Scale of Infant Development, 2nd Edition (BSID II). Even though different grades of severity of BPD were associated with linear reduction on Mental Development Index (MDI) and Psychomotor development index (PDI) scores, at 6 months' CA the rates of cognitive and motor delay were similar across the different groups of children. At 12 months' CA only infants with severe BPD showed significant higher rates of cognitive and motor delay than those without BPD, while non statistically significant differences were noted in the other groups (13).

Using BSID II, Martins et al. founded that incidence of lower PDI at 6 months CA was significantly associated with BPD (supplemental O_2 need at 36 weeks). The authors concluded that infants with BPD showed four-fold odds of presenting altered PDI at 6 months CA as compared to infants without BPD (15).

Karagianni et al. in 2011 (7) showed that severe BPD predicts poor neuromotor outcomes at 6 months CA. Children were tested at 6 months CA with Hammersmith Infant Neurological Examination (16,17) and scores were significantly lower in infants with severe BPD, which resulted to be an independent risk factor for poor neuromotor outcome. At 12 months CA the results were quite different; only periventricular leukomalacia and days of hospital stay significantly reduced the global scores, while severe BPD did not influenced the performance. These findings indicate that severe BPD is a major cause for poor neuromotor outcome at age 6 months, but improvement can occur over time.

Some caution should be used in diagnosing a neurological condition at very early ages because part of the observed alterations my be due to transient neurological abnormalities (18); however, early assessment and diagnosis of neuromotor alterations ars very important because neuroplasticity is more prounounced in the first months of life and the impact of treatment is greater in younger infants (19,20).

Second year of life

Studies investigating the relationship between BPD and neurological outcomes in the second year of life show controversial results.

Natarajan et al. looked at the outcomes at 18-22 months CA of ELBW preterm infants with "physiologic BPD" in order to investigate its predictive validity for adverse neurodevelopmental outcomes; their results showed that moderate to severe cerebral palsy (CP), spastic diplegia and spastic quadriplegia were significantly more frequent in children with BPD. Deafness rate was higher in the BPD group even though the difference didn't reach statistical significance. Physiologic BPD was independently associated with cognitive impairment, also assessed using BSID-III. Cognitive scores < 70 were more frequent in children with BPD than in those without (21).

In an other study, Hintz et al. found that supplemental oxygen at 36 weeks or at discharge was one of the-significant risk factors for CP, neurodevelopmental impairment and PDI < 70 at 18-22 months CA (22). Similar results were obtained by two older studies (23, 24).

In contrast, in 2013 Trittmann et al. reported that there was no significant difference in BSID III scores at 18 months' CA between those patients with no/mild BPD and moderate/severe BPD (25). However, 96% of infants in the study had BPD, with 89% having a moderate/severe BPD; it cannot be excluded that the low incidence of infants with no/mild BPD could have significantly influenced the difference in outcomes between the two groups.

In a recent analysis from the ELGAN study, the association between BPD and developmental delay at 2 years of age was examined: BPD, even when adjusted for severity, was not associated with an increased risk of delayed development at 24 months CA. However since the cut off score of MDI and PDI was very low

(-3 SD from the mean), data from this study should be carefully interpreted (25).

Pre-school age

Only few studies investigated the long-term impact of BPD on neurodevelopmental outcomes in preschool age infants.

Short et al. reported that children with BPD, at 3 years of age, performed at the lower end of the average range of cognitive and psychomotor tests. Moreover, children with mild BPD had significantly better outcomes on all langauge measures than did those with severe BPD (14).

Lodha et al. showed that, at 3 years of age, cognitive impairment was significantly more frequent in children with BPD and in those with BPD and home oxygen dependency than those without BPD. The incidence of mild and severe CP was significantly greater in children with BPD with or without need for supplemental oxygen at discharge, reafferming that BPD is an independent factor leading to increased neurodevelopmental disablity. However, this study did not demonstrated that chronic oxygen dependency is associated with significantly increased rates of neurodevelopmental disability at 36 months CA (26).

School age

Is well known that, as preterm infants grow up to school age, they can display some specific neuropsychological impairments, such as attention problems, memory and learning deficits and executive dysfunction. Therefore, it is very important to understand the effect of BPD on neuropsychological outcome of preterm infants at school-age, in order to set up a more careful and effective follow-up and the appropriate interventions.

The study of Short et al. showed that, at 8 years of age, the children with severe BPD scored significantly worse on Performance IQ and Perceptual Organization and langauge assessment. Furthermore, these children required more educational interventions, occupational or physical therapy than did children with mild BPD (14). Since authors assessed the same population also at 3 years of age showing similar results, they concluded that neurocognitive impairment increases as a fuction of severity of BPD and persisted in both the pre-school and school-age periods.

In an older study, Gray et al. also found that children with BPD, when assessed at 8 years, had lower scores and differences with preterm infants without BPD were statistically significant for the Verbal, Performance and Full Scale IQ (27).

Attention impairments seem to be more frequent and severe in children with BPD, as described by Farel et al. (28). Consistent with these findings, the rate of ADHD in 8 years old VLBW children with BPD was reported to be two-fold the rate of non-BPD children (14) and BPD was now recognized as a strong predictor for ADHD symptoms (14, 28-31).

Receptive language impairments is more frequent and severe in VLBW children with BPD, and the number of children with BPD enrolled in speech-language therapy is twice over the number of children without BPD (28, 29, 31). However, since long-term outcomes studies are not available, it is not yet established whether these deficits persist into adolescence and adulthood.

Although few studies have specifically assessed memory and learning in children with BPD, there is some indication that these children exhibit greater memory difficulties than preterm children without BPo. Immediate auditory and working memory have shown to be the most compromised in children with BPD (28). However, these results have to be further investigated.

Conclusions

It has been clearly demonstrated that BPD is an additional risk factor for long-term cognitive, educational and behavioral impairments in very preterm children. However, it is difficult to establish the real impact of BPD on neurodevepmental outcomes firstly because BPD often occurs with other serious medical complications and it's not easy to identify the independent role of BPD. Moreover, follow-up studies are often too heterogeneuos in terms of inclusion criteria, scales of assessment used and duration of follow-up. The introduction of a new definition for BPD allowed

to describe more accurately different degrees of disease severity and also to outline different populations of children with own characheristics.

In conclusion, BPD is associated to a global cognitive impairment; more research and longer follow-up studies are needed to determine the exact nature and timing of the problems faced by chidren with BPD, and its independent role on specific neuropsychological impairments. Follow-up programs with comprehensive evaluation and monitoring of children with BPD are essential to establish individual and preventive intervention in order to achieve a more effective and productive educational approach and to minimize the adverse effects of BPD on neurocognitive outcomes.

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Correspondence:
Francesca Gallini, MD
Department of Pediatrics, Neonatal Unit
Catholic University
Largo F. Vito 1, 00136 Rome – Italy
Tel. 06/30154357
E-mail: francesca.gallini@fastwebnet.it