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罹患慢性肺疾病之早產兒的神經發展與影響因素研究(2/3)

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執行單位：國立臺灣大學醫學院物理治療學系暨研究所

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罹患慢性肺疾病之早產兒的神經發展與影響因素研究

計畫類別：■個別型計畫　　□整合型計畫

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行政院國家科學委員會專題研究計畫進度報告

罹患慢性肺疾病之早產兒的神經發展與影響因素研究

Neural Development and Its Influencing Factors in Premature Infants with Chronic Lung Disease

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一、摘要

There were three purposes of this study: (1) to use the Neonatal Neurobehavioral Examination- Chinese version (NNE-C) to evaluate the neurobehavioral development in premature infants with chronic lung disease (CLD) and premature infants without CLD during neonatal period, (2) to use the clinical and roentgenographic scoring systems to assess the severity of respiratory disease in these infants, and to examine the relation between the severity of respiratory disease and the neurobehavioral performance, and (3) to use the cranial ultrasonography to assess the neural integrity of these infants, and to examine the relation between neural lesions and the neurobehavioral development. This study included 57 premature infants with CLD and 53 premature infants without CLD. The infants were administered the clinical and roentgenographic scoring systems, cranial ultrasonography and magnetic resonance imaging, and the NNE-C during neonatal period. The results showed that the infants with CLD manifested comparable NNE-C scores at PCA 36 weeks (p=0.09) but lower NNE-C scores at PCA 39 weeks (p<0.0001) than those without. The infants with CLD showed higher clinical and roentgenographic scores of respiratory disease on day 14 and 28 compared with those without (p<0.001). The cranial ultrasonographic examinations revealed that the infants with CLD had similar incidences of neural lesions (i.e., intraventricular hemorrhage, periventricular leukomalacia, prolonged periventricular echogenicity and ventriculomegaly) than those without. Regression analysis showed that when adjusted for CLD, the severity of respiratory disease (R^2 = 0.20-0.30, p< 0.01) and neural lesions each had significant relations with the NNE-C scores during neonatal period (R^2 = 0.04-0.06, p< 0.05). Our results suggest that respiratory insufficiency and neural lesions may contribute to the neurodevelopmental outcome during neonatal period in infants with CLD.

關鍵詞：早產兒、慢性肺疾病、神經發展、影響因子

二、緣由與目的

The advent of mechanical ventilation and oxygen therapy for management of neonatal respiratory problems has been a major factor in improved survival of smaller and less mature infants. However, this has been offset by an increased risk for chronic lung disease (CLD), which is defined by the requirement of oxygen supplementation at 28 days of life and continuing at 36 weeks post-conceptional age in a severe form. The estimated prevalence of CLD among very low birth weight (VLBW) infants who survive the neonatal period is between 25-40%. Developmental studies showed that premature infants resolving from CLD are associated with poor neurodevelopmental outcomes, 11-18% developing cerebral palsy and 20-40% sustaining neurological impairment. Furthermore, children with a history of CLD tend to exhibit poorer cognitive performance at school age than those without. Considering the magnitude of this respiratory problem and its implications for medical and educational systems, attention should be focused on investigating the course and causes of abnormal neurodevelopment in premature infants with CLD.

Current approaches to management of premature infants at risk for neurodevelopmental disabilities have emphasized early assessment and intervention within the first year of life. However, the information concerning the early neurodevelopment of infants with CLD is limited. Perlman and Volpe first documented a movement disorder in premature infants with severe respiratory disease during the first months of life. The movement disorder generally developed in the third postnatal month and involved limbs and axial structures. The movements of limbs were most prominent distally, especially in hands and feet, and consisted of rapid, random and jerky movements. Katz-Salamon et al. applied the Movement Assessment of Infant Scale to evaluate the neuromotor performance in infants with CLD and infants without CLD in the first year of life. They noted no differences at 5 months of age, but a deviance in volitional movements in the former at 10 months of age. Because the accuracy of the assessment tools was not described in these studies, the natural history of early neuromotor impairment in CLD and its relation to developmental outcome remain to be determined.

The Neonatal Neurobehavioral Examination – Chinese Version (NNE-C) is a valuable tool for assessment of early neuromotor development in premature infants. The NNE-C was aimed to evaluate the neurological and behavioral performance of premature babies from post-conceptional age 30 to 42 weeks. The scale provides important information to assist clinicians in determining the neuromaturation status of an infant and to help the parents understand the behavioral characteristics of their child that is beneficial for the parent-child relationship. Acceptable levels of internal consistency, reliability and responsiveness have been found for its application on premature infants. Furthermore, the assessment is discriminative of the neurobehavioral performance of VLBW infants from that of normal full-term infants at term age. The first purpose of this study was therefore to use the NNE-C to evaluate the neurobehavioral

development in premature infants with CLD and premature infants without CLD during neonatal period.

Although the unfavorable effects of CLD on neurodevelopmental outcome are well recognized, the pathways that explain the relationship between CLD and subsequent developmental disabilities remain unclear. Several potential pathways, i.e. respiratory insufficiency, neural lesions and other influencing factors (such as medication and environment) have been proposed as contributors to the poor neurodevelopment in CLD. Respiratory insufficiency may cause adverse impacts on the neurodevelopment of premature infants with CLD. Infants affected by CLD have increased respiratory morbidity compared with a similar neonatal course in whom CLD does not develop. They require an extended duration of ventilation and oxygen therapy during newborn period and manifest abnormal pulmonary function, e.g., increased airway resistance and reactivity, decreased lung compliance, high arterial carbon dioxide tension and low arterial oxygen tension, during the first year of life. As survival beyond that age, children with resolving respiratory disease are able to function at normal capacity even though abnormalities on pulmonary function may still persist. Studies that examined the relation between respiratory insufficiency and neurodevelopmental outcome in premature infants revealed inconclusive results. The incongruence might be due in part to differences in the assessment of severity of respiratory disease.

The clinical and roentgenographic scoring systems developed by Toce et al. are clinically feasible methods to assess the severity of respiratory insufficiency of premature infants at early stage. The systems are scored on a number of clinical, physiologic and radiologic measures that are routinely assessed in clinical care and can be easily abstracted. The clinical and roentgenographic scoring systems have been found to have constructive validity. The combined use of the two methods provides a more systematic approach to assess the clinical severity of respiratory disease than the judgment made by pathologic changes of chest x-ray alone. The roentgenographic scoring has been found to predict the duration of oxygen therapy of VLBW infants with CLD. Furthermore, the systems have been found predictive of pulmonary function in premature infants with CLD at 6 months of corrected age. The second purpose of this study was, therefore, to use the clinical and roentgenographic scoring systems to assess the respiratory function in premature infants with CLD and those without during neonatal period, and to examine the relation between respiratory function and neurobehavioral performance in these infants.

Besides the influence of respiratory disease itself, lesions of the central nervous system may also contribute to the neurodevelopmental abnormalities associated with CLD in premature infants. Buckingham and Sommers postulated the relation between respiratory distress syndrome and central hypoxia, and indicated that this might cause unfavorable impacts on later neurodevelopment. Northway et al. were the first to observe intense cerebral congestion and severe gliosis in autopsied premature infants with severe respiratory illness. With the innovation of cranial ultrasonography in

1980s that provides images of neonatal neural integrity, several follow-up studies have examined the link of impaired development of premature infants with CLD to intracranial complications. A number of studies showed that the infants with CLD who had poor developmental outcome more often had major neural lesions such as grade III-IV intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (PVL) than those who had good developmental outcome. To control for the effects of major neural lesions, some studies have contrasted the neurodevelopment among premature infants with CLD and those without, all infants being free of major intracranial complications. The cognitive and motor developmental of premature infants with CLD were found to associate with poorer outcomes. These results suggest that investigation of the neural pathway for the abnormal neurodevelopment in CLD may need to focus on the potential minor neural lesions. Therefore, the third purpose of this study was to use the cranial ultrasonography to assess the neural integrity of premature infants with CLD and those without, and to examine the relationship between neural lesions and neurobehavioral function.

三、結果與討論

This study included 57 infants with CLD and 53 infants without CLD at National Taiwan University Hospital and Mackay Memorial Hospital during the period from Jan 2003 to Oct 2004. The infants were administered the clinical and roentgenographic scoring systems, cranial ultrasonography and magnetic resonance imaging, and the NNE-C during neonatal period. The results showed that the infants with CLD manifested comparable NNE-C scores at PCA 36 weeks but lower NNE-C scores at PCA 39 weeks (p<0.0001) than those without. The infants with CLD showed higher clinical and roentgenographic scores of respiratory disease on day 14 and 28 compared with those without (p<0.001). The cranial ultrasonographic examinations revealed that the infants with CLD had similar incidences of neural lesions (i.e., intraventricular hemorrhage, periventricular leukomalacia, prolonged periventricular echogenicity and ventriculomegaly) than those without. Regression analysis showed that when adjusted for CLD, the severity of respiratory disease (R^2 = 0.20-0.30, p< 0.01) and neural lesions each had significant relations with the NNE-C scores during neonatal period (R^2 = 0.04-0.06, p< 0.05). Our results suggest that respiratory insufficiency and neural lesions may contribute to the neonatal neurodevelopmental outcome in premature infants with CLD.

四、計畫成果自評

We have continued follow-up of CLD infants and non-CLD infants in the third year.

Part of the collected data in the first and second year has been published prepared or in the following papers:

1. Chen PS, Wu YT, Wang LY, and Jeng SF. Chronic lung disease in premature infants: Respiratory assessment and physical therapy intervention. Formosan Journal of Physical Therapy. 2003;28:258-268.
2. Chen PS, Jeng SF, Hsieh WS, Peng SF,

Lee WT and Wang LY. Early neurobehavioral development and its influencing factors in preterm infants with chronic lung disease: A preliminary study. The Academic Conference of the Physical Therapy Association of the ROC (Taiwan), Sep, 2003.
3. Chen PS, Hsieh WS, Tsao PN, Chou HC, Wang LY, Jeng SF. Predictability of the Toce's clinical scoring system on the susceptibility of chronic lung disease in premature infants. The Academic Conference of the Physical Therapy Association of the ROC (Taiwan), Sep, 2004.
4. Lin TS, Luo HJ, Jeng SF. Early assessment and intervention of severe brain lesions in premature infants. (Submitted to Formosan Journal of Physical Therapy)
5. Chen PS, Hsieh WS, Hsu CS, Jeng SF. Predictability of the Toce's clinical scoring system on the susceptibility of chronic lung disease in premature infants. (In Preparation)
6. Jeng SF, Hsu CS, Tsao PN, Chou HJ, Kao SA, Horng HY, Chang RS, Chiou NC, Hsieh WS. Neonatal neurobehavioral development and its influencing factors in preterm infants with chronic lung disease. (In Preparation)