Research Roundtable Summary 10

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Early Cortisol Deficiency and Bronchopulmonary Dysplasia

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About This Series

The Research Roundtable Series, sponsored by the Maternal and Child Health Bureau (MCHB), disseminates the results of MCHB-funded research to policymakers, researchers, and practitioners in the public and private sectors. The results of these projects influence future service, research, and policy development. The Research Roundtable sessions provide an opportunity for researchers to discuss their findings with policymakers, MCH program directors, service providers, and other health professionals.

The Maternal and Child Health Research Program is directed by Dr. Gontran Lamberty and administered through the Division of Systems, Education and Analysis, Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA). HRSA is a component of the Public Health Service (PHS), part of the U.S. Department of Health and Human Services (DHHS). The purpose of the research program is to support applied research relating to maternal and child health services that shows promise of making a substantial contribution to the advancement of those services.

Introduction

Dr. Kristi Watterberg is an associate professor in the Department of Pediatrics at the Milton S. Hershey Medical Center, Pennsylvania State University. She serves as a reviewer for several journals, including *Pediatrics* and *The Journal of Pediatrics.* Dr. Charlotte Catz is the chief of the Pregnancy and Perinatology Branch at the Center for Research for Mothers and Children, National Institute of Child Health and Human Development at the National Institutes of Health. She is active on a number of advisory panels on pediatrics, including the Maternal and Child Health Research Grants Review Committee for the Maternal and Child Health Bureau.

Presentation

Introduction

Bronchopulmonary dysplasia (BPD), or chronic lung disease following acute neonatal lung injury, has been defined and redefined over the years and is now referred to as an oxygen dependence at 28 days postnatal life. As doctors have dealt with increasingly younger infants, some have suggested redefining it as an oxygen requirement at 36 weeks postconception. Thus, the number of infants identified as having the disease has changed depending on how the disease has been defined.

BPD is a major cause of morbidity and mortality in low birthweight infants, and it has not

been significantly decreased by the introduction of exogenous surfactant. Smaller infants have an increased incidence of BPD. In a study that defined BPD as oxygen dependence at 28 days, BPD occurred in one-third of premature infants over 1,000 grams, 71 percent of infants 750–1,000 grams, and 91 percent of infants less than 750 grams. Even when BPD is redefined as an oxygen requirement at 36 weeks postconception, the same increase in incidence with decreasing birthweight is observed.

Even tiny infants who initially do not have respiratory distress syndrome will eventually have chronic lung disease. In one study, birthweights below 1,000 grams were associated with chronic lung disease, and 70 percent of the infants weighing less than 800 grams had a significant oxygen requirement for a long period of time.

A study done before the use of exogenous surfactant examined infants who had respiratory distress syndrome and had recovered and infants who got BPD. Infants in both groups seemed to get better over the first few days, and then on days 6 and 7 their condition worsened. Another group of intubated infants showed the same pattern.

Many scientists have studied possible etiologies for BPD, and the more they have learned, the more they have realized that the causes of BPD are complex. In addition to the classic etiologic agents of oxygen toxicity and barotrauma, other factors influencing BPD include ductus arteriosus, excess fluid administration, infection, and intubation. Studies of exogenous surfactants to treat respiratory distress syndrome in premature infants showed that, while mortality was decreased, the incidence of BPD was not decreased among survivors.

Thus attention has gradually shifted away from external causes of BPD and toward the infants themselves. Studies performed in the early 1980s reported that infants with BPD had elevated markers of inflammation in their airways. While there has been controversy over which markers and reference values to use, researchers have continued to find elevated levels of inflammatory cells and inflammatory cell mediators, particularly at the end of the first week of life in those infants who get BPD. Researchers began to wonder whether infants who are prone to BPD lack the ability to dampen the inflammation that comes from oxygen exposure, barotrauma, intubation, etc.

Cortisol is a central agent in inflammatory response, as well as an important hormone associated with birth and early postnatal life. A study of adult rats that were adrenalectomized revealed that an absence of cortisol led to a marked increase in the inflammatory response to injury. In newborn animals, the literature describes a period of stress nonresponsiveness in the first few days of life. An early study reported that full-term infants have a transiently decreased response to adrenocorticotropic hormone (ACTH) at around day 4, and then it comes back to expected levels after the first week of life.

Cortisol has been shown to relieve hypotension in preterm infants who were unresponsive to fluid management or dopamine. A lack of cortisol leads to an excess of antidiuretic hormone and impairs excretion of free water. Many premature infants retain fluid during the first week of life, which may reflect this phenomenon.

Several studies have reported increases in cortisol precursors but no actual increase in cortisol concentration in some premature infants. This suggests that these infants may have difficulty with enzymes and suppression of enzymes, which leads to an inability to produce the amount of cortisol required. Dr. Watterberg compiled some preliminary data on a small group of premature infants on days 2, 4, and 6 after birth. The data revealed that the sickest infants had no increase in cortisol, and in fact cortisol levels declined despite their illness.

From these data, Dr. Watterberg developed a hypothesis about how cortisol may be involved in the pathogenesis of BPD. Barotrauma and diseases such as pneumonia do their damage through the release of inflammatory mediators. Intubation has also been associated with inflammation. From

this, Dr. Watterberg theorized that an adequate anti-inflammatory capacity would lead to lung repair and resolution, but a lack of cortisol or an overwhelming lung disease such as pneumonia would lead to chronic injury.

Study Design

The following three hypotheses were developed:

1. All very low birthweight infants develop a nadir in cortisol concentrations at the end of the first week of life;

2. A transient cortisol deficiency develops in a subset of these infants, resulting in an inflammatory response; and

3. Abnormally low cortisol concentrations in the first week result in development of BPD. Abnormal in this sense refers to the need versus the supply (i.e., in a well infant a low cortisol level would be normal, but in a sick infant it would be abnormal).

In the study, basal and stimulated cortisol concentrations were correlated with acute respiratory illness, clinical cortisol effects, biochemical effects (such as epidermal growth factor), markers of lung inflammation, and respiratory outcome. The researchers studied very low birthweight infants (defined as less than 1,500 grams) at appropriate weight for gestational age. The population was drawn from neonatal intensive care units at Pennsylvania State University Children's Hospital and the University of New Mexico Children's Hospital. Infants with congenital sepsis or major congenital anomalies were excluded, as were infants who underwent major surgery within the first week of life.

The study plan focused on days 0–14, and then days 21 and 28. Days 2, 4, and 6 were chosen to avoid the initial cortisol surge around delivery. The ACTH stimulation test was arranged for day 6; a baseline cortisol was drawn, ACTH analog was administered, and 30 minutes later another cortisol was drawn. Urinary epidermal growth factor (EGF) was analyzed daily for the first 2 weeks, and tracheal lavage was performed on days 0, 2, and 6. Clinical data were collected on these infants over time.

Population and Sampling Plan

The two centers enrolled 161 infants, ranging in weight from 523 to 1,500 grams. They were 23–33 weeks' gestation, and about two-thirds of them received surfactant. The researchers were going to divide them into nonintubated control versus intubated infants, but decided to divide them according to whether or not surfactant was given. The infants were relatively evenly divided between boys and girls. Prenatal steroids were administered to only 33 of the infants; this study would be difficult to replicate, because now 70–80 percent of these infants would receive steroids. Relatively few infants died before discharge. A few babies were withdrawn from the study, and data on 145 infants, 83 of whom had BPD, were the basis of the analysis for this project.

Findings

The pattern of oxygen dependence in the intubated infants who developed BPD versus those who resolved the lung disease was similar to the pattern seen in previous studies. An initial decrease in supplemental oxygen was followed by an increase at the end of the first week.

Basal cortisol levels were studied on days 2, 4, and 6 in three groups of infants divided by gestational age (24–27 weeks, 28–31 weeks, and 32–35 weeks). Surfactant-treated infants had lower cortisol on day 2, which makes sense in that higher cortisol means more cortisol effect, and therefore an infant would not be as likely to have respiratory distress syndrome and therefore would not require surfactant. In the two older groups, cortisol levels started out lower in the surfactant-treated infants,

but by the end of the first week they had increased to the same levels as in the nontreated infants. The tiniest infants with or without surfactant continued to trend downward toward the end of the first week. Therefore, the pattern of cortisol concentration was inversely correlated with gestational age.

As noted, cortisol is intimately associated with antidiuretic hormones, and the correlation between cortisol and weight loss was very good. Infants with higher cortisol had greater weight loss in the first week of life. The study found that infants with higher cortisol at any gestational age were more likely to tolerate enteral feedings at the end of the first week of life. A positive correlation between cortisol and EGF concentrations was found.

In studying markers of lung inflammation, the researchers discovered that infants who had BPD developed increased concentrations of interleukin 6 and 8 and decreased concentrations of prostaglandin E2, an anti-inflammatory agent. However, the study was not able to statistically correlate this with any cortisol results at the time of this presentation. Cortisol concentration and inflammation in the airways may be unrelated, or they may be so distantly related that they cannot be directly linked. (Using a multiple regression analysis that included “day of life” as a factor, Dr. Watterberg has since found that cortisol does correlate with interleukin 6 concentrations and with protein concentrations.)

Respiratory outcome was the primary outcome examined in this study. In looking at basal serum cortisol concentrations on days 2, 4, and 6, the researchers found that infants who went on to have BPD had low basal serum cortisol concentrations, particularly at the end of the first week of life. Changing the definition of BPD to the more current 36 weeks postconception oxygen requirement, it was still apparent that most infants who developed BPD had lower basal cortisol concentrations.

Regarding the response to ACTH among a small subset of infants (n=59), there initially was no apparent difference in basal cortisol concentration between those who developed BPD and those who didn't, which points to the high variability in basal cortisol concentrations; it takes large statistical groups to see a difference. However, the differences in stimulated cortisol concentrations on day 6 were significant, as was the change from basal to stimulated.

Using logistic regression analysis, the researchers found that those infants with BPD had a lower response to ACTH. Studying a larger group of infants (n=90 at day 6) in the first week of life, the researchers found that infants who developed BPD had a decrease in their response to ACTH, whereas infants who did not develop BPD showed an increase. Evaluating chronic lung disease instead of BPD, they found the same pattern.

Studying the response by gestational age group, the researchers found that the more immature infants show a significantly decreased response to ACTH at the end of the first week than the more mature infants. Interestingly, when the outcome variable, chronic lung disease, was added to the analysis of gestation and its relationship to this finding, it took away the significance of gestation. So this study defined what may be termed a normal response to ACTH versus an abnormal response; the reason that younger premature infants are more likely to get BPD is simply that they do not have a normal response.

In summary, basal cortisol levels may be correlated with respiratory illness, clinical effects, and biochemical markers (markers of inflammation were found, but could not be related to the cortisol). Clearly, both basal and stimulated cortisol concentrations are related to respiratory outcome in this group of infants. However, Dr. Watterberg emphasized that this study established only associations and correlations, not causation or effectiveness of intervention.

Other Studies

There have been very few studies of the effect of steroids on decreasing chronic lung disease in premature infants. However, in pediatric research done this spring, a study found that there was a

distinct benefit to starting steroids on day 1.

A 5-year longitudinal study of the change in lung function among adults found that those who have lower basal cortisol concentrations within normal limits have a greater loss of respiratory function over that period of time. In another study, systemic inflammatory response syndrome was associated with increased mortality in adults with adrenal cortical dysfunction.

Those studies, together with this one, strongly support the need to conduct a randomized trial of hydrocortisone supplementation in the first week of life to evaluate its effect on both acute illness and the development of chronic lung disease. Thus far, steroids given to infants have been very high dose over prolonged periods of time, and these have been linked to serious side effects. Thus, a trial of low-dose hydrocortisone replacement therapy is needed.

Reaction

Dr. Catz complimented Dr. Watterberg on the data gathering and the systematic approach of the study. The cause and effects examined here were highly complex because of the evolving nature of the infants being studied. Dr. Watterberg acquired the data, analyzed the results, and began examining ways in which the data from this study can be used in the clinical setting. Many researchers may not complete this last step, so Dr. Catz congratulated Dr. Watterberg for focusing on applying her findings to the neonatal clinical setting, which is undergoing enormous technological changes.

Dr. Watterberg also looked at the evolving process, not just one point in time. Evolving processes are more complex and involve a series of physiological systems that are changing rapidly in the first days of life.

While not a criticism of the research, Dr. Catz pointed out that there may be additional facets to the research questions beyond the absence or presence of steroids. Dr. Catz posed many questions for consideration in additional research and analysis. How can researchers distinguish between the cortisol secretion process versus the release mechanism versus levels of cortisol reserves? How are these aspects of research influenced by antenatal steroids? How long does this effect last?

Dr. Catz suggested that Dr. Watterberg may want to look at the cortisol levels in babies who died, but Dr. Catz recognized the small data set this would provide. Dr. Catz asked whether there was any evidence of the steroids acting differentially by gestational age. Dr. Watterberg responded that some babies' levels fall substantially and they don't get respiratory distress syndrome, while other babies experience no change in levels. Some of these effects are being analyzed in other settings, so Dr. Catz suggested that Dr. Watterberg look at resistance to steroids and the effects of repeated steroid use on the babies. It appears that the administration of prenatal steroids suppresses basic levels of response in the first days of life. By the end of the first week of life, there appears to be no difference in the response between the babies who received steroids and those who didn't receive steroids. This is not controlled by gestational age because of the small data set that would result in such an analysis.

Discussion questions focused on lower basal and stimulated cortisol levels among the smallest infants and lower response to ACTH, variability of the interventions given to sick infants, the relationship of severity of BPD and cortisol levels, adult respiratory distress syndrome, lack of respiratory drive among newborns, response receptors at the cellular level, and the difficulty of measuring inflammatory markers.

Publications

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