



YOU'VE COME A LONG WAY, BABY: OR HAVE YOU?

Long-Term Prognosis in Children with Neonatal Seizures: A Population-Based Study. Ronen GM, Buckley D, Penney S, Streiner DL. *Neurology* 2007;69(19):1816–1822. **OBJECTIVE:** To examine outcome and explore for prognostic markers in a cohort <10 years following neonatal seizures. **METHODS:** We prospectively diagnosed clinical neonatal seizures with high specificity for true epileptic seizures in a population-based setting of all live newborns in the province of Newfoundland, Canada, between 1990 and 1995. Children with neonatal seizures were followed by specialized provincial health services. Follow-up data were collected on epilepsy, physical and cognitive impairments, and other health issues. **RESULTS:** Data were available on 82 out of 90 subjects. We added information on six others whose outcome was clearly predictable from earlier information. Prognosis was better for term than for preterm infants ($p = 0.003$): term: 28 (45%) normal, 10 (16%) deaths, and 24 (39%) with impairments; preterm: 3 (12%) normal, 11 (42%) deaths, and 12 (46%) with impairments. Of survivors, 17 (27%) developed epilepsy, 16 (25%) had cerebral palsy, 13 (20%) had mental retardation, and 17 (27%) had learning disorders. Variables associated with poor prognosis were Sarnat stage III or equivalent severe encephalopathy, cerebral dysgenesis, complicated intraventricular hemorrhage, infections in the preterm infants, abnormal neonatal EEGs, and the need for multiple drugs to treat the neonatal seizures. Pure clonic seizures without facial involvement in term infants suggested favorable outcome, whereas generalized myoclonic seizures in preterm infants were associated with mortality. **CONCLUSIONS:** Poor prognosis for premature infants with seizures is reflected in high rates of subsequent long-term disability and mortality. The severity and timing of the pathologic process continue to be the major determinants for outcome.

Gestational Age, Birth Weight, Intrauterine Growth, and the Risk of Epilepsy. Sun Y, Vestergaard M, Pedersen CB, Christensen J, Basso O, Olsen J. *Am J Epidemiol* 2008;167(3):262–270. The authors evaluated the association between gestational age, birth weight, intrauterine growth, and epilepsy in a population-based cohort of 1.4 million singletons born in Denmark (1979–2002). A total of 14,334 inpatients (1979–2002) and outpatients (1995–2002) with epilepsy were registered in the Danish National Hospital Register. Children who were potentially growth restricted were identified through two methods: 1) sex-, birth-order-, and gestational-age-specific z score of birth weight; and 2) deviation from the expected birth weight estimated based on the birth weight of an older sibling. The incidence rates of epilepsy increased consistently with decreasing gestational age and birth weight. The incidence rate ratios of epilepsy in the first year of life were more than fivefold among children born at 22–32 weeks compared with 39–41 weeks and among children whose birth weight was <2,000 g compared with 3,000–3,999 g. The association was modified by age but remained into early adulthood. Incidence rate ratios of epilepsy were increased among children identified as growth restricted according to either of the two methods. In conclusion, short gestational age, low birth weight, and intrauterine growth restriction are associated with an increased risk of epilepsy.

COMMENTARY

When the National Collaborative Perinatal Project (NCP) published the results of their prospective follow-up of 54,000 pregnancies occurring between 1959 and 1966, important information about neonatal seizures and the outcomes experienced by these children were obtained. In that study, neonatal seizures occurred in 277 children (0.5%), with a mortality rate of 34.8% (1). At the 7-year follow-up, 70% of the survivors were normal. However, among these survivors, epilepsy was the most common neurologic sequelae: 22% of patients had one or more afebrile seizures compared with a rate

of 0.9% in the NCP population as a whole. The data clearly showed that in the neonatal seizure group, there was a significant increase in the number of babies who were born at <2,500 g in weight and <36 weeks gestation ($p < 0.001$). A companion paper examined the factors that predicted death, mental retardation, cerebral palsy, and epilepsy; it concluded that neonatal seizures (and/or their duration) may be a better indicator of the severity of intrauterine stress than the Apgar score (2).

This background provides a basis for a reexamination of the situation among babies born almost 30 years later. The NCP data provided a perspective that informed many of the ensuing attempts to understand and characterize neonatal seizures more fully, in the hope that better interventions would lead to better outcomes. The Ronen et al. study reviewed here suggests that these hopes have not been realized. Although neonatal seizures

were less frequent (0.26%) than in the initial (NCP) study, the finding may simply reflect more rigid “entry” criteria and fewer hypocalcemic seizures, as these seizures are currently prevented and managed far better. Death has been somewhat averted; however, there does not appear to be an increase in normal outcomes, with epilepsy occurring in 34% of all births and 48% of premature infants. Epilepsy that follows neonatal seizures may be particularly problematic, as the risk of infantile spasms in this group is 100 times the normal population. A question that always arises with studies from different eras is whether the comparison is actually among apples and oranges. The populations differed significantly, and certainly more premature babies are kept alive today than were 40 years ago.

Of note in the Ronen et al. paper is that the number of seizures did not correlate with outcome, but the type of seizures did. Premature babies with myoclonic seizures had a particularly high mortality. Continuing controversy exists with respect to whether particular seizure types correlate with poorer outcome, and if so, why? Is it because, as Lombroso suggests (3), that these infants have experienced more severe CNS insults—reflected by the inability to detect EEG changes embedded in very abnormal background activity? The severity of the underlying disorder (e.g., encephalopathy) as well as the period of development in which it occurs influences outcome. Brunquell et al. similarly reported that clinical semiology was predictive of outcome and asserted that unique pathophysiologic processes underlie the different seizure types (4). The authors speculated that understanding these relationships might well lead to improved interventions.

In the past few decades, neuroscience has continued to probe the unique aspects of neonatal seizures. Recognizing the unique role of GABA_A receptors in neonates, Dzhala and colleagues (reviewed in the Basic Science section of this issue) have demonstrated enhanced phenobarbital efficacy with the use of bumetanide that blocks the NKCC1 transporter and alters Cl⁻ flux (5). Similarly, Sankar and Rho emphasize the detrimental effects of prolonged seizures on brain plasticity on the developing brain (6). Finally, Lombroso questions whether neonatal seizures “plant the roots for epileptogenesis and cause long-term deficits” (7). Lombroso concludes that there is no convincing evidence that the seizures themselves produce epileptogenesis, but rather that they are the marker of the underlying problem. This assertion does not mean that the outcome of the underlying etiology (often hypoxia-ischemia) is immutable.

Although the paper by Sun and colleagues, reviewed here, does not deal with neonatal seizures, it provides further information about the vulnerability of the newborn and examines some of the factors associated with developing epilepsy. In this

population-based study in which children were followed for up to 24 years, a crude incidence rate of epilepsy of 92.6 in 100,000 is provided. The incidence rate of epilepsy was associated with decreasing gestational age and intrauterine growth restriction. Thus, it may be of value to examine again the reasons for premature delivery—reassessing the causal roles of the intrauterine environment and fetal health in the development of neonatal seizures. The immature brain of a premature child is disadvantaged and susceptible to further insults, making it more difficult to successfully achieve developmental processes critical to normal outcome. A somewhat similar, recent population-based study from Nova Scotia again found neonatal seizures to be a most important risk factor for development of epilepsy and went so far as to suggest that: “if no infants were born small for gestational age, then 7.4% of epilepsy would be prevented (assuming causality)” (8). There is always a caveat!

Researchers and clinicians have come a long way in helping vulnerable newborns survive; however, many challenges lay ahead. The possibilities of strategies (e.g., hypothermia, novel anticonvulsants, or neuroprotective agents) to treat neonates with seizures are alluring (9), but we have a long way to go.

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