cases, major outbreaks of influenza in 1983, 1984, and 1985, and no change in reported varicella cases during the 6-year period.\(^2\)\(^{21}\)

Starko’s paper, and those that followed, dramatically and permanently changed the choice of antipyretics for children in North America. Every study supported the relationship between aspirin use and risk of Reye’s syndrome. Furthermore, the ORs increased rather than decreased in the more rigorously designed studies. A formal meta-analysis was not necessary to conclude that this was a real and probably causal association. Fortunately, an acceptable alternative to aspirin that was not associated with increased risk of Reye’s syndrome was readily available. Both the case–control studies and marketing data document the replacement of aspirin with acetaminophen for childhood antipyretic treatment after 1980. Today, acetaminophen products dominate the pediatric antipyretic market, largely because of the documented association of aspirin with increased risk of Reye’s syndrome. The shift from aspirin to acetaminophen in the early 1980s represents a dramatic and rapid change in consumer and physician behavior with respect to antipyretic use in response to public dissemination of information through a variety of media sources. It is worth noting that implementation of public policy on this issue lagged far behind consumer and physician behavior. Nevertheless, careful and rigorous clinical research led to changes in antipyretic use, in spite of economic and political pressures, that reduced dramatically the incidence of a devastating illness for which a specific cause or treatment has not and may never be found.

REFERENCES


COMMENTARY

Apgar Scores as Predictors of Chronic Neurologic Disability, by Karin B. Nelson, MD, and Jonas H. Ellenberg, PhD, Pediatrics, 1981;68:36–44

Comments by Gerald S. Golden, MD

ABSTRACT OF ORIGINAL ARTICLE. Apgar scores were recorded at one and five minutes for ~49,000 infants, and at 10, 15, and 20 minutes for babies who did not achieve a score of 8 or higher at five minutes. These children were followed to 7 years of age. Low Apgar scores were risk factors for cerebral palsy, but 55% of children with later cerebral palsy had Apgar scores of 7 to 10 at one minute, and 73% scored 7 to 10 at five minutes. Of 99 children who had Apgar scores of 0 to 3 at 10, 15, or 20 minutes and survived, 12 (12%) had later cerebral palsy; 11 of the 12 also were mentally retarded (in 10, IQ <50) and half had seizure disorders. Eight children who survived after having very low late Apgar scores and who did not have cerebral palsy had lesser but significant disabilities. Of the children who had Apgar scores of 0 to 3 at 10 minutes or later and survived, 80% were free of major handicap at early school age.

COMMENTARY

The relationship between perinatal asphyxia and prematurity, the condition of the infant at birth, and motor and mental disability has been of interest since 1861 when William John Little,
an orthopedic surgeon, first described cerebral palsy.\textsuperscript{1,2} His hypothesis was that \textit{asphyxia neonatorum} was frequently the cause of the subsequent disability.

Sigmund Freud, who was trained in neurology and neuropathology, made extensive contributions to the understanding of cerebral palsy, culminating with the publication of his important monograph \textit{Die Infantile Cerebellähmung (Infantile Cerebral Paralysis)} in 1897.\textsuperscript{3} He basically supported Little’s concepts, but pointed out that in approximately one third of cases of cerebral palsy, no adverse perinatal events could be documented. Freud also hypothesized that in some cases, the abnormalities found in the neonate might not be attributable to obstetric factors, but rather were the result of prenatal problems.

The relationship between the infant’s condition at birth and subsequent neurologic status could not be explored rigorously until the development of a simply administered, well standardized, reproducible method of assessment of the neonate. Apgar first published her approach in 1953, and the Apgar score became the standard for assessment of the condition of the newborn infant.\textsuperscript{4} Additional studies demonstrated that this score was most valuable in defining the subgroup of infants requiring active resuscitation. Although a correlation was demonstrated between a low Apgar score and subsequent neonatal mortality,\textsuperscript{5} very little information on late adverse outcomes was available.

The National Collaborative Perinatal Project (NCPP) began in 1959 and was designed to follow \textasciitilde 54 000 pregnant woman throughout their pregnancies and to study the children until 7 years of age.\textsuperscript{6} The data acquisition was carried out at 12 teaching hospitals and completed in 1966. The Apgar score was an important assessment tool and was obtained at 1 and 5 minutes for virtually all infants. Children whose Apgar scores were \textasciitilde 8 at 5 minutes also were evaluated at 10, 15, and 20 minutes.

The NCPP had three features that were important for subsequent data analyses. The first was the large sample size. This permitted the determination of statistically significant findings, not only for the entire group, but also for subgroups that would have been too small to be meaningful if the original study population had not been as large. The second feature was the highly standardized protocols for data capture and recording. The nurses and physicians who gathered the data were trained, and a number of quality-control measures were built into the study protocol. The third important feature of the NCPP was the long follow-up period for the children. By the time a child reached 7 years of age, most subtle or not so subtle neurologic and behavioral abnormalities, except some learning disabilities, should be evident, and many reliable assessment tools, such as the Wechsler Intelligence Scale for Children, are available.

The Study

Nelson, a pediatric neurologist, and Ellenberg, an epidemiologist and biometrician, are the preeminent analysts and interpreters of the NCPP data. Their paper, \textit{Apgar Scores as Predictors of Chronic Neurologic Disability}, is one of the most important. The study group was a cohort of \textasciitilde 49 000 singleton liveborn children who had Apgar scores recorded at 1 minute and 5 minutes. Major analyses focused on the initial Apgar scores in children with and without cerebral palsy at 7 years of age, the predictive value of Apgar scores for death or cerebral palsy, the duration of very low Apgar scores, and the outcomes for infants with very low late Apgar scores who survived. They also analyzed the differential outcomes for groups of children with birth weights \textasciitilde 2500 g and \textasciitilde 2501 g. There were 37 000 children whose status was known at 7 years of age.

The authors confirmed the general concept that low Apgar scores at 1 and 5 minutes were associated with an increased risk of death or cerebral palsy, and that persistently low Apgar scores at 10, 15, and 20 minutes also were predictive of these adverse outcomes. There was, however, no one-to-one correlation. In the group of children without cerebral palsy, 5% had 1-minute Apgar scores of 0 to 3 and 14% had Apgar scores of 4 to 6. At 5 minutes, 1% had Apgar scores of 0 to 3 and 3% had Apgar scores of 4 to 6. The conclusion drawn is that a very low Apgar score, even at 5 minutes, is not an absolute predictor of cerebral palsy.

Investigating the 120 children with cerebral palsy at 7 years of age, they found that 55% had Apgar scores of 7 to 10 at 1 minute and 73% had Apgar scores of 7 to 10 at 5 minutes. One-minute scores of 0 to 3 were present in 26% of these children, and 19% had scores of 4 to 6 at 1 minute. At 5 minutes, 15% of the group with cerebral palsy had scores of 0 to 3 at 1 minute, and 19% had scores of 4 to 6 at 5 minutes. Here again, there was no absolute link between low Apgar scores and cerebral palsy. In fact, most children with cerebral palsy had high early Apgar scores.

Analyses of those children who had very low (0 to 3) Apgar scores at 10, 15, and 20 minutes also were carried out. There were 390 children with very low scores at 20 minutes, and only 31% survived until 7 years of age. The mortality rate was extraordinarily high (95.7%) in low birth weight infants in this group and substantial (55%) in full-term infants. An important and surprising finding, however, was that 87 of the 99 children in the very low Apgar score group did not have disabling cerebral palsy. In fact, only 8 of these children had any handicaps (vision, hearing, articulation), and an additional 2 had minor problems with coordination. The authors noted that many of these survivors without disabilities had bradycardia during the second stage of labor, although none had complete loss of fetal heart tones.

The children with very low late Apgar scores and cerebral palsy were severely disabled. Eleven of the 12 had birth weights >2500 g, and all had spastic quadripareisis, 6 with atethosis. All of the children in this group also had mental retardation. Six of these children had seizures that occurred beyond the neonatal period. The remaining child in this group had a birth weight of 1673 g. She had spastic diplegia with
normal intelligence, the most common type of cerebral palsy found in premature infants with periventricular leukomalacia.

**Significance**

Analysis of a large, carefully acquired dataset is of fundamental importance in testing our previous hypotheses and assumptions. During the 120 years between Little’s publication and that of Nelson and Ellenberg, a correlation between asphyxia neonatorum and cerebral palsy was taken as a matter of faith. There were some hints that this link was not as firm as thought previously, but an accurate definition of the specific risk factors and determination of the level of risk could not be quantitated until a study of the magnitude of the NCPP was implemented.

This study did confirm that the Apgar score was a useful tool for defining those children at risk of death or significant disability, but it also demonstrated that the correlation was far from absolute. The most surprising finding, and perhaps the most significant, was that 80% of children who had very low Apgar scores at 20 minutes and survived did not have significant disabilities. Those who were disabled, however, had severe multiple handicaps. There were no children in this group who had an isolated motor defect or only seizures or mental retardation without cerebral palsy. Children with very low late Apgar scores, if they survive, are either quite functional or are severely disabled.

It is nearly impossible to read a medical journal without coming across the phrase “evidence-based medicine.” Although the concept is certainly not as new as its prevalence in the literature would suggest, results of studies such as that of Nelson and Ellenberg are often ignored in another profession; one rarely sees the phrase “evidence-based law” in the context of malpractice or product liability suits. “Bad baby” lawsuits still are a real threat for the practicing obstetrician and pediatrician who attend neonates. In many of these lawsuits, expert witnesses can be found who are willing to ascribe all neurologic problems, such as isolated mental retardation or epilepsy, to asphyxia neonatorum in any child with a low Apgar score. A careful reading of this paper should demonstrate the overuse and misuse of this construct. In fact, the reader should note the entire body of research derived from the NCPP, much of it done by Nelson and Ellenberg as exemplified by some of their other publications in these areas.\(^7\)\(^9\)

A second area of significance of this study is in setting a baseline for expected outcomes in the care of the sick neonate. Although the study now is 17 years old, there is no other data source this large and well studied. In addition, the 7-year follow-up of the subjects was an important feature for minimizing both false-negative and false-positive findings. Mild neurologic, language, and sensory problems may be difficult to detect before school age. The authors also have found, in subsequent analyses, that cerebral palsy diagnosed in 1-year-old children may have disappeared by age 7 years.\(^10\) New interventions need to be put to the test of carefully controlled studies, but also need to pass the test of improving on outcomes documented in the past. This paper will remain a landmark that can be used to measure our progress in neonatal care for a long time.

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