Epidemiology of epilepsy in children

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MANY people equate epidemiology with studies of incidence and prevalence, that is, studies that enumerate the number of cases in a population affected by a specific condition. Such head-counting investigations are important for a variety of reasons including their relevance to health planning and research priorities. Most epidemiologists, however, are primarily interested in studies directed at understanding determinants of disease and factors which may modify the course of illness—in essence, information which may contribute to efforts at prevention. To this end, incidence and prevalence studies are useful chiefly in providing clues to hypotheses concerning etiology.

This paper focuses chiefly on the antecedents and prognosis of epilepsy and other seizure disorders in children. It will deal briefly with incidence and even more briefly with prevalence. Reports to be discussed will be drawn primarily from the work of the authors and their associates.

INCIDENCE

Incidence is the rate at which new cases of a condition occur in a population. The incidence of epilepsy for all age groups is about 40/100,000 person years.[1] The age-specific incidence of unprovoked seizures in virtually all studies is highest in the first month of life.[2–4] Seizure incidence then remains relatively high but in decline during the first year of life, and tends to decrease slightly thereafter through the second decade, after which incidence remains constant at about 30/100,000 in the adult years, only to increase again after the age of 60 (*Table 1*).

Contrary to common opinion, only about 50% of all cases of epilepsy start in childhood.[1] In most studies, about 60% to 70% of cases are of unknown cause; and, in childhood, the majority of new cases in children involve generalized seizures from onset. Most total population studies of incidence report a slight male preponderance.

The large pediatric population, followed from the first prenatal visit of the mothers in pregnancy until children born of those pregnancies were 7 years old, sampled by the Collaborative Perinatal Project (NCPP) of the National Institute of Neurological and Communicative Disorders and Stroke, provides valuable information regarding the epidemiology of epilepsy. In that population, 8.0 white children per thousand had at least one nonfebrile seizure, not considered to be symptomatic of acute neurologic illness, between the ages of 1 month and 7 years.[5] This is similar to the cumulative incidence for one or more unprovoked seizures of 1.1% by age 10 in the population of Rochester, Minnesota.[1] In black children in the NCPP study, the cumulative incidence rate was 9.0 per thousand. The difference between the racial groups was not statistically significant. Seizures occurred with similar frequency in boys and girls of the two racial groups. Minor motor seizures and neonatal seizures were not different in frequency by race or sex.

PREVALENCE

Active prevalence of epilepsy is a measure of the proportion of patients currently suffering from active epilepsy or experiencing the consequences of epilepsy

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TABLE 1
AGE-SPECIFIC INCIDENCE RATES (ROCHESTER, MINNESOTA, 1935–1979)

Age group (years)	No. patients	Rate/100,000 person-years	Proportion		Male/female (%)
			idiopathic (%)	partial (%)	
<1	41	121	54	17	120
1–4	85	63	81	28	97
5–14	129	44	84	47	123

as measured by taking anticonvulsant medication. Since one needs only to identify existing cases of the illness, prevalence studies are considerably easier to conduct than incidence studies. Prevalence studies have been performed across numerous populations varying by geographic area, race, and socioeconomic status. From an epidemiologic standpoint, prevalence is of value chiefly as it is a reflection of cumulative incidence. Since prevalence represents the complex interaction of incidence, mortality, and remission, prevalence, as a rule, is of limited value for the generation of hypotheses concerning etiology.

The estimated prevalence of epilepsy varies widely in reported studies by a factor of 20, and ranges from a low of 2/1,000 in the Marianas Islands[6] to a high of 37/1,0000 in Nigeria.[7] Unfortunately, this variation seems more related to study methodology and to definitions of epilepsy in individual studies than to true population variations. In prevalence studies based upon incidence cohorts, prevalence tends to increase with advancing age through early childhood, only to stabilize in the teenage and young adult years.

CEREBRAL PALSY, MENTAL RETARDATION, AND EPILEPSY

The relationship between mental retardation (MR), cerebral palsy (CP), and occurrence of epilepsy is well established. Conventional wisdom suggests that approximately a third of mentally retarded children will also experience unprovoked seizures. In a recent study of the frequency of epilepsy in neurologically handicapped children, 10% of children with MR alone (IQ <70) or with CP alone had also had epilepsy. (MD Benedetti, MD, unpublished data, 1986). While these risks were more than ten times those expected, the frequency was considerably less than that observed in children with both CP and MR. In this latter group, about 50% developed epilepsy. The risk for epilepsy was increased both by more severe MR as measured by lower IQ, and severity of motor handicap.

Like epilepsy, MR is a condition which has as yet to be correlated with adverse pre- and perinatal events.[8] There is little question that individuals with moderate or severe MR are at increased risk for seizures, and the likelihood of seizures is higher in those with more severe retardation.[9]

A number of investigators have observed that, although persons with epilepsy may function at a very high level, groups with epilepsy tend to have lower average scores on tests of intelligence than do nonepileptic groups. There have been several studies asking whether seizures, as opposed to a possible underlying brain abnormality, medications, or social milieu may account for this difference. Such studies have been plagued by a number of problems including selective sampling and inability to control well for important determinants of tested intelligence, such as socioeconomic status.

Using sibling-control comparisons and a comparison of IQ test results before and after onset of seizures, the observations of the NCPP study[10] led to the conclusion that occurrence of nonfebrile seizures was not associated with significant change in full-scale IQ score. An earlier investigation had observed no difference in IQ at 7 years in children with febrile seizures, as compared with their seizure-free siblings.[11]

RISK FACTORS FOR EPILEPSY

Perinatal risk factors

The NCPP study was a large prospective study designed specifically to explore the relationship of prenatal and perinatal factors with childhood neurologic disorders. Discussion of the relative advantages and disadvantages of the NCPP study for this purpose has been offered elsewhere.[12] The relationship between pre- and perinatal difficulties and childhood epilepsy has been studied extensively in the NCPP study.[5] In this population, 14% of children who had nonfebrile seizures also had CP of some degree. Conversely, 21% of children with CP had at least one nonfebrile seizure by the age of 7 years.

Antecedents of seizure disorders were examined in the NCPP study. Since some proportion of CP is attributable to birth asphyxia, it was considered desirable to examine the relationship of perinatal asphyxia with childhood epilepsy without birth factors being "carried in" by an association with motor disorders; therefore, the 14% of children with CP were excluded in this evaluation.

Low birth weight is well known to be an important risk factor for infant death and for CP. Although early death was 11 times as common in children born weighing less than 2500 g, seizure disorders in children without CP were not significantly more frequent among low-birth-weight infants. Children of low birth weight were more likely to die or to have CP than those of higher birth weight, but were not more susceptible to seizures without CP.

Fourteen obstetric factors were evaluated for their association with death, CP, or seizures. Complication of some kind in labor and delivery is common, but long-term neurologic consequences are not common. Of the more than 51,000 pregnancies studied, 62% had one or more of the complications studied. Breech delivery, abruptio placentae, and placenta previa were risk factors for death and for CP but not for seizures, nor were any of the other complications in the study significantly associated with childhood seizure disorders. Ninety-seven percent of children with nonfebrile seizures but no CP, and 98% of the total populations, had an Apgar score of 7 to 10.[13] Complications present in the small subgroup of children who had low Apgar scores in addition to the complication did show some relationship with CP but not with seizures in the absence of CP. It was concluded that of the late pregnancy and birth conditions evaluated, including conditions considered to be potentially anoxigenic and markers of fetal distress, none were important antecedents of seizure disorders in children free of motor handicap.

In fuller explorations in the NCPP study, more than 400 factors were considered in approximately 54,000 pregnancies and related to any nonfebrile unprovoked seizures after the newborn period, to minor motor seizures, neonatal seizures, and to the total seizure group excluding minor motor seizures, neonatal seizures, and CP. These factors were examined first by consideration of the characteristics one at a time, and then in staged multivariate procedures.

A history of toxemia, previous miscarriages, early pregnancy bleeding, and assisted delivery have been reported to be associated with seizure disorders in children in at least one previous study. None of these was a risk factor for postnatal seizures in the NCPP study, nor was vaginal breech delivery, other malpresentations, low birth weight, or cesarean section, whether indicated or elective. Smallness for birth date was associated with a nonsignificant increase in risk for seizure disorders.

Maternal seizures, with at least one generalized convulsion within five years of the birth, hospitalization of the mother in the past year, MR of the mother, and history of motor disability in an older sibling were the other chief risk factors identifiable before pregnancy or by the time of the first prenatal visit. These factors did not account for much of the outcome.

Major malformations, cerebral and noncerebral, were important predictors. Among factors observable in the neonatal period, delay of first cry to three minutes or longer, abnormality of tone, and neonatal seizures or meningitis were leading predictors of later seizures. When predictors from each period (prepregnancy, pregnancy, labor and delivery, neonatal period) were examined together in sequence, there was little increase in variance explained when birth characteristics were added to prepregnancy and pregnancy information. None of the characteristics of labor and delivery were important risk factors for childhood seizure disorders after the neonatal period.

Family history of epilepsy and other disorders

There is little doubt that seizures tend to aggregate in families. While a number of diseases follow Mendelian patterns of inheritance and have as part of their manifestations the occurrence of seizures, these conditions, in aggregate, will account for no more than 1% of seizures in childhood.[14] Risk for epilepsy is increased by a factor of three for individuals with a first-degree relative with epilepsy, an overall risk similar to that associated with head injury or infection of the central nervous system (CNS).[15] Similarly, risk for epilepsy is increased by a factor of three for children with a sibling who has had febrile seizures.[16] While there is a perception that generalized-onset seizures are associated with higher risk for epilepsy in relatives, this seems a result of the very high risk among siblings with epilepsy manifested by absence seizures or myoclonic seizures. If these unique but rare subgroups are excluded, risks for epilepsy among relatives of probands with epilepsy characterized by generalized-onset seizures are similar to those in relatives of probands with epilepsy manifested by partial seizures. Family history is important in

modifying risk for epilepsy even in the presence of a history of overt cerebral insult.

In the NCPP study, familial factors were also predictors of seizure disorders in children. Family history factors showing significant univariate association with seizure disorders included *maternal seizure disorders*, *maternal MR*, *paternal congenital malformations*, and seizures or motor deficits in older siblings. Paternal seizures were not observed to be predictive; however, histories were taken from the mothers, who might not always have been well acquainted with the fathers' medical histories. Except in one mother-child pair with tuberous sclerosis, specific heritable disorders were not recognized.[12]

Congenital malformations discovered in the children in the first year of life, and including both cerebral and non-neurologic anomalies, were the second category predictive of seizure disorders. An association between congenital maldevelopment and childhood epilepsies has been observed by other workers.[2,17–19] In the NCPP study, such findings were especially frequent in children with minor motor seizures and with neonatal seizures.

Postnatally acquired infection

Clinical intuition has long suggested a strong association between infections of the CNS and subsequent development of epilepsy. In the incidence studies of epilepsy in Rochester, Minnesota, prior CNS infection had occurred in over 2% of all incidence cases of epilepsy.[4]

By age 10, at least 1% of all children in the United States will suffer from a CNS infection.[20] There are few longitudinal clinical studies of the frequency of epilepsy following CNS infections, and virtually none which quantify risk in epidemiologic terms.

In a review of risk for subsequent epilepsy among 734 survivors of CNS infections identified as incident cases in Olmstead County, Minnesota, over the past half century, incidence of epilepsy among those with CNS infections was compared with that expected, based on the age-specific incidence of epilepsy in the same community.[21] Overall, risk for epilepsy was increased sevenfold over that expected in the general population. Risk was highest in the first five years after infection (10.3 times, based on population rates) but remained significantly elevated (relative risk: 4) over the next 20 years. Age at time of infection could not be shown to alter these risks.

Risk for subsequent epilepsy varied by type of infection. Risk was highest in those with a diagnosis of brain abscess; for these, the crude percentage who subsequently developed epilepsy was 28%. This was more than a fortyfold increase over that expected in the general population. Risk for subsequent epilepsy was also high for those with a diagnosis of encephalitis, a group in which approximately 16% had developed epilepsy by 20 years following infection. This is a rate approximately 20 times that expected in the general population. Without early seizures, risk is increased about twentyfold in the first year following infection and is associated with a five- to tenfold increase thereafter. Risk for epilepsy was more modest in those with bacterial meningitis. Only 4% developed subsequent epilepsy, a rate about six times that expected. Risk for unprovoked seizure is highest in the first 14 years after infection, and falls thereafter. For those with bacterial meningitis without early seizures, risk is increased about fiftyfold in the first year after infection, is increased tenfold in the subsequent four years, and is little different from baseline population rates thereafter. Risk for epilepsy was only slightly (and not significantly) elevated in those with a diagnosis of aseptic meningitis.

A major risk factor for development of subsequent epilepsy following CNS infection was occurrence of early seizures. Risk was more than doubled for those with encephalitis who had early seizures. Over 20% of those with encephalitis and early seizures can be expected to have epilepsy by 20 years following infection compared with 13% of those without. In those with encephalitis and early seizures, more than 7% will have unprovoked seizures in the first year following infection, and the rate is almost 1% per year for the following nine years. Risk of epilepsy between 10 and 20 years following infection is still elevated by a factor of 10 over that expected in the general population.

In patients with bacterial meningitis, risk for later epilepsy was increased more than fivefold among those with early seizures when compared to those without. For those with bacterial meningitis and early seizures, risk is elevated by a factor of 35 through the first five years following infection, and by a factor of seven or eight through the next 15 years. (By definition, no patients with aseptic meningitis had early seizures.)

This study confirms the clinical impression that CNS infections are powerful risk factors for epilepsy, and that this risk remains elevated through at least 20 years following the infection. It also suggests that those with mass lesions (abscess) and those with early seizures will have a much greater risk of developing subsequent epilepsy.

Head injury

Head injury has long been recognized as a risk factor for unprovoked seizures. Annually, between two and three of every 1,000 persons in this country will require medical care for a head injury, and a considerably higher number will experience minor head trauma which will lead to brief emergency room evaluation.[22] Age-specific incidence of head trauma demonstrates a trimodal distribution with a peak in the first years of life, a peak in the late teenage years and in young adults, and a third peak in the elderly. Falls account for a great proportion of cases in both the very young and in the elderly.

It is clear from longitudinal studies that persons with a history of head injury have an increased risk of developing epilepsy, but again there are few epidemiologic studies in civilian populations which allow quantification of level of risk.

In general, persons with a history of head injury have a three- to fourfold increase in risk for subsequent unprovoked seizures over baseline population rates.[23] This risk varies, depending on age at the time of injury, severity of injury, and whether early seizures have occurred. Much of the data regarding the risk of epilepsy after head trauma is derived from studies of head injuries in battlefield situations. In many of these military studies, comprising almost exclusively cases with dural penetration, frequency of late epilepsy approaches 50%.[24] The proportion of cases developing epilepsy following head injury is considerably lower in civilian series, even for those with "severe" injuries. Thus, extrapolation of results from military to civilian populations must be approached with caution. Since risks for epilepsy following civilian head injuries appear to differ in pediatric populations when compared with adults, there may be few factors from military studies which can be applicable to pediatric populations.

The majority of patients with severe head injury (defined as injuries involving penetration of the dura, large intracerebral hematoma, or injuries associated with loss of consciousness of more than 24 hours) die of this injury.[22] In military series, less than 5% of patients survive such injuries. Data from civilian series are little better: only 25% to 45% will survive, although young age at time of injury is a major predictor of survival. In children who survive injuries of this severity, upwards of 20% can be expected to develop unprovoked seizures, and that risk extends for many years following the injury.

Moderate head injury (defined as an injury associated with loss of consciousness for more than 30 minutes, but less than 24 hours, and without dural penetration) is associated with a threefold increase in risk for epilepsy through the first five years following injury. Without early seizures, the risk is elevated in the first two years after injury by a factor of 15 to 20.[23] After two years, but before five years, risk is only slightly elevated above baseline population rates. Risks seem not to be elevated significantly beyond this five-year interval.

Mild head injury (defined as injuries with no dural penetration, no evidence of intracranial mass lesions, and loss of consciousness less than 30 minutes) is associated with little identifiable increase in risk for unprovoked seizures at any point following the injury.

Role of early seizures after head trauma

Early seizures occur in approximately 5% of patients in most series of head trauma. Early seizures seem, in general, to be a measure of severity of injury. They occur more frequently in those with longer duration of unconsciousness and in persons with evidence of intracranial hematoma. Early seizures are considerably more frequent in children than in adults. There may also be a bias to admitting children with seizures to hospitals in the absence of other indications of cerebral pathology. Nonetheless, the proportion of children experiencing seizures is higher than that reported in adults, regardless of severity.

In general, early seizures are predictive of later epilepsy. Risk for subsequent epilepsy is substantially higher in subjects with early seizures, possibly increased as much as fortyfold over the first five years following injury; but again has not been shown to be elevated significantly after that time. This increased risk for late epilepsy following early seizures is much higher in adults than in children.

It is generally felt that "impact seizures" (seizures occurring immediately at time of injury) alter risk for later epilepsy. Only one study has evaluated the risk of late epilepsy following seizures within 30 minutes of the impact, and has reported an increased risk for late epilepsy.[25]

Shunts are a form of head trauma occurring in presumably controlled (operative) conditions. Incidence of unprovoked seizures following shunting procedures is exceedingly high—in the neighborhood of 20%.[26,27] This may be related to a high level of epileptogenicity of the anatomic areas in which shunts are placed; but, in general, children who undergo shunting procedures have other pathology which may also be associated with increased propensity for sei-

zures.

Brain tumors are clearly a risk factor for epilepsy at all ages. Incidence of brain tumors is very low in children, and tumors account for a low proportion of cases of seizures in childhood. Most brain tumors in children are below the tentorium in areas less likely to be the site of epileptogenic foci.

Cerebrovascular insults are a major risk factor for epilepsy, but are rare in childhood following the postnatal period, and frequently occur in association with other conditions. Thus, seizures and later epilepsy related to cerebrovascular insults are frequent complications in children with sickle cell disease or with congenital heart disease either in relation to a primary heart lesion with presumed embolism or in relation to complications of surgery. Seizures at the time of surgery for cardiac malformations may not be associated with increased risk for later epilepsy.[28] Such events account for an exceedingly small proportion of cases of childhood-onset epilepsy.

FACTORS NOT PREDICTIVE OF SEIZURE DISORDERS

A very long list could be offered of factors *not* associated with increased risk of seizure disorders in children in the NCPP study. Socioeconomic factors, important predictors of MR and learning disorders, and inversely related to risk of febrile seizures in white children, were not predictors of postneonatal nonfebrile seizures (KB Nelson and JH Ellenberg, unpublished data, 1988). Neither were maternal age, parity, smoking history (number of cigarettes per day or number of years smoked), most maternal illnesses including diabetes and hypertension or hypotension, height, weight or weight gain in pregnancy, induction of labor, prolapse of umbilical cord, cesarean section, breech delivery, infarcts of placenta, anesthetic agents, most drugs in labor and delivery, number of prenatal visits, and many other characteristics of the mother, the pregnancy, and the birth. Use of forceps for delivery was *negatively* associated with childhood seizure disorders.

PROGNOSIS

Seizure recurrence following a single seizure

Approximately 20,000 children in the United States are seen annually for a first unprovoked seizure. These children represent potential patients with epilepsy. From a diagnostic standpoint, they should be evaluated in a manner similar to that used for the child with recurrent seizures; but the therapeutic approach to the child (or adult) with a single unprovoked seizure remains controversial. This, in part, relates to the paucity of information regarding the ultimate prognosis of such patients in terms of risk for further seizures, and a lack of knowledge as to whether early and aggressive anticonvulsant treatment can modify the natural history of the disorder. While the approach to such patients must be individualized, it is helpful to the clinician as well as the patient to have the following: 1) data regarding risks for further seizures and factors which may modify these risks; 2) data on risks for immediate or long-term complications from any therapeutic intervention; and 3) knowledge of whether early treatment will provide any benefits beyond immediate seizure prevention.

Estimates of risk for further seizures in patients seen at the time of a first seizure have varied widely in studies of children as well as adults. The estimated recurrence ranges from as low as 20% over a three-year period following the first seizure to as high as 75%. This wide variation in recurrence rates seems more related to study design than to the natural history of the condition. In general, highest recurrence rates have been reported from retrospectively ascertained cohorts identified from specialty clinics, and lowest rates from prospectively followed cohorts identified through emergency room or primary case contacts.

A prospective study identified and recruited 237 persons of all ages (but predominantly teenagers and adults) within 24 hours of their first unprovoked seizure, and followed them from that time, in an effort to estimate overall risk for seizure recurrence.[29] Median follow-up time was 48 months. Overall, recurrence was estimated to be 14%, 28%, and 36% at one, three, and five years respectively, following the first convulsive episode. While the patient population in this study was predominantly over age 10, age could not be shown to influence recurrence risks. Using similar recruitment strategies, a second prospective study of children (median age 7), for the most part untreated, has found similar recurrence risks through three years following the first convulsive episode.[30]

In both studies, a history of a presumed "organic" insult to the CNS has been an important predictor of seizure recurrence with risk of further seizures being more than doubled in such cases. For example, in the study of older patients, estimated recurrence risk for patients with idiopathic seizures was 10%, 25%, and

30% at one, three, and five years, compared to 24%, 42% and 51% at these same respective time points among patients with remote symptomatic epilepsy.

There was considerable variation in recurrence risks based upon clinical and historical features. In five years following the first seizure, recurrences were found in only 25% of patients with idiopathic disease and a normal electroencephalogram (EEG), and no family history of epilepsy. This risk increased to 40% if there was a generalized spike-and-wave pattern on the EEG, or if a sibling also had epilepsy. Among those with a remote symptomatic seizure and either a Todd's paresis or prior acute seizures, 80% had a recurrence. In the study dealing with younger children, a history of previous febrile seizures was also predictive of recurrence: of those who had a second seizure, most had additional seizures.

The course of treated seizure disorders in children was often not smooth in the Camfield experience.[31] In the first six months, 41% of treated children had a recurrent seizure despite serum levels of anticonvulsant drugs in the therapeutic range. Side effects, clinical or laboratory-observed, were present with substantial frequency. In the Camfield study, the NCPP study, and in the study by Hauser[32] in a predominantly adult population, administration of antiepileptic agents, although followed by good patient compliance in the Camfield study, did not significantly alter the rate of recurrence. All of these studies were observational. A randomized clinical trial will be needed to appropriately address the question of benefit from anticonvulsant medications following a first seizure.

Remission

At the time of diagnosis of epilepsy, most parents wish to know if they can expect total seizure control, and if the diagnosis represents a lifelong commitment to anticonvulsant therapy. For the most part, answers are favorable on both counts.

Longitudinal population studies suggest that approximately 70% of patients who receive a diagnosis of epilepsy will ultimately become seizure-free, and that the majority can expect to discontinue anticonvulsant medication.[33–35] In general, a higher likelihood of remission has been reported in children than in adults, although children with epilepsy in association with MR or CP have very low rates of remission.

At the time of diagnosis of epilepsy and in the absence of neurologic deficit from birth, only two factors significantly predict poor prognosis (defined as failure to achieve a five-year remission): 1) a generalized spike-and-wave EEG pattern, and 2) a generalized major motor seizure.[35] This latter category includes patients with either primary generalized or secondary generalized major motor seizures according to the International Seizure Classification. While statistically significant, neither factor is associated with a reduction in remission of sufficient magnitude to influence clinical decision making. Patients with both factors still have better than a 50% likelihood of remission.

Medication withdrawal

Few would contend that the unnecessary use of anticonvulsant medication on a chronic basis is desirable, but agreement as to what is "necessary" is not general. The decision to alter drug therapy in a patient whose disease is well controlled is frequently related to personal perception of potential consequences of a seizure rather than to likelihood of successful withdrawal. Studies of planned withdrawal of medication after a specific period of seizure freedom have provided widely varying estimates of the frequency of relapse (6% to 85%), and there seems to be little agreement on potential predictors of successful medication withdrawal.[36]

Children may demonstrate different predictors for successful withdrawal than adults. In prospective studies of the ability of children whose medication is withdrawn to achieve a two-year interval of freedom from seizures, about 75% remain seizure-free.[37] Factors associated with significantly lower relapse rates include normal EEG at time of withdrawal, improvement in EEG patterns over time, early age at onset of seizures, and partial complex seizures. Conversely, spikes on EEG and worsening or no change of EEG were associated with high risk of relapse. Children with MR or CP tended to have higher relapse rates.

Relapse rates have generally been reported to be higher in adults than in children.[34] In a recent prospective study of anticonvulsant discontinuation among 62 adults, in which multivariate analysis was used, young age at last seizure, few drugs at time of discontinuation, and control with relatively low levels of anticonvulsants were associated with successful discontinuation. The EEG has not been consistent as a predictor of relapse in adults.[36]

Late relapse after remission

Even after patients have undergone apparently successful withdrawal from anticonvulsant medication, they remain at an increased risk for further seizures. Relapse rate after a five-year seizure-free interval is still

between 0.5% and 1.0% per year, a rate 10 to 20 times the incidence of new seizures in the general population.[34]

OTHER SEIZURE TYPES

Febrile seizures

Febrile seizures are the most frequent seizure class of convulsive disorder occurring in childhood. In the United States, from 2% to 5% of children are so affected before their fifth birthday, and the rate is substantially higher in some oriental and Pacific island populations.[32] Febrile seizures are associated with an increased risk for subsequent epilepsy. This risk is increased about six times, and the increase persists at least through the third decade.

In the NCPP study, magnitude of risk is in the neighborhood of 3% to 7% by age 7. Conversely, approximately 13% of children with nonfebrile seizures by the age of 7 years had a febrile seizure as their initial attack.

Clinical characteristics of febrile seizures are predictors for types of subsequent epilepsy. Focal seizures, prolonged seizures, and multiple seizures at the time of a single illness are predictors for subsequent partial epilepsy. These are quite distinct from predictors of subsequent generalized-onset epilepsy (family history of epilepsy in a first-degree relative, recurrent febrile seizures).[38]

It appears that febrile seizures are probably not causally related to the subsequent occurrence of epilepsy, but rather are an independent outcome of a common underlying substrate—either genetically determined or antecedent localized abnormalities. Longitudinal prospective studies from the NCPP study have not identified other adverse outcomes such as MR or motor deficit as sequelae of febrile convulsions.[39]

Immunization procedures may provoke fever and thereby predispose to febrile seizures.[40–42] A number of studies indicate that immunization with pertussis vaccine is not causally related to infantile spasms,[43–45] although the usual age at onset of infantile spasms and timing of common administration of the antigen can produce temporal linkages that, without study, could lead to a different impression. It is less clear whether pertussis immunization can provoke a chronic epilepsy; recent studies by Walker and colleagues[46] and by Shields and coworkers[42] suggest that this is unlikely. There may be seizure disorders such as severe myoclonic epilepsy of infancy that have as part of their natural history an age at onset within the period in which primary immunizations are commonly administered, and a tendency to progress from seizures with fever to an implacable spontaneous epilepsy often accompanied by unfavorable intellectual status. Such findings have been noted by Dravet et al[47] and by Hurst.[48] It would be easy, on the basis of occasional temporal association, to blame this seizure disorder on immunization, as has in the past been done with infantile spasms. Only careful study can establish whether any increase in risk does link immunization with severe myoclonic epilepsy of infancy, but it is clear that the seizure disorder can arise without prior immunization.

Neonatal seizures

Neonatal seizures occur in about 5/1,000 live births. As with febrile seizures, the subsequent epilepsy is probably not causally related to the neonatal seizures per se; but both are outcomes of common antecedents.

Neonatal seizures are a marker of high risk for death, for chronic motor disability (CP), and for subsequent seizure disorders. Of the infants who survive after neonatal seizures, 20% to 25% develop subsequent seizures in early childhood.[5,49–51] Of those who had one postneonatal nonfebrile seizure, 75% went on to further recurrences. This progression from neonatal to subsequent seizures accounted for 10% of nonfebrile seizure disorders of early childhood. When postneonatal seizures developed, this commonly occurred at an early age: within the first six months of life in nearly two thirds of patients, and in three quarters before the first birthday.[3]

Congenital malformations, identified in the first year of life, were present in more than a third of children with neonatal seizures and in more than half the children with minor motor seizures.[52]

Neonatal seizures are clearly a marker of risk for later epilepsy. Whether occurrence of neonatal seizures in itself increases the risk of later seizures—or signals the presence of a seizure-prone nervous system—is unknown. Almost half the children who progressed from neonatal to later seizures also had a family history of seizures or a major congenital malformation. That observation does not induce optimism concerning the preventability of childhood epilepsy through intervention in neonatal seizures. A proper test of the question would require a controlled trial of the treatment of neonatal seizures, with lengthy follow-up, and no such study is available.

A recent report[53] notes that while neonatal seizures are indicators of serious risk of death or CP, the clinical

situation in which neonatal seizures occur is strongly related to outcome: in term babies, neonatal seizures preceded by low Apgar scores and other signs of neonatal encephalopathy were 420 times more often followed by CP as compared with neonatal seizures in infants not having these other characteristics. The group with neither low Apgar scores nor other neurologic abnormalities was as large as that with both those other characteristics, but outcomes were very different.

As to predictors of *occurrence* of neonatal seizures, several risk factors did not prove to be risk factors for other seizure disorders. These were maternal age over 35 years, primiparity, low birth weight, and low five-minute Apgar score. Meconium staining of the amniotic fluid was a significant predictor of neonatal seizures even after consideration was given to earlier predictive factors, which was not the case for postneonatal seizures. The proportion of neonatal seizures predictable by means of perinatal characteristics substantially exceeded that for postneonatal seizures, suggesting that neonatal seizures are more often related to birth events than is later epilepsy.

Perinatal events are significant predictors for neonatal seizures, and neonatal seizures are predictors for childhood epilepsy, but perinatal events are *not* important predictors of later epilepsy. This set of observations may seem anomalous. A somewhat similar situation arises with respect to the relationship between smoking, low birth weight, and CP; smoking is associated with low birth weight, and indeed a substantial proportion of low birth weight appears to be accounted for by smoking of cigarettes. Low birth weight is, in turn, an important risk factor for later CP. Yet cigarette smoking is not a predictor of CP. There may be several subvarieties of low birth weight, and the subcategory of low birth weight that is associated with cigarette smoking is not the variety of low birth weight which produces a risk for CP. These issues are of more than academic interest, since they relate to the success, or lack of it, that might be predicted from interventions. If it were possible to intervene, by education or other means, to prevent cigarette smoking by women of child-bearing age, the data cited suggest that the rate of low birth weight might be expected to decline, but there would be no predicted change in the rate of CP. Similarly, these observations suggest that interventions in the process of birth might decrease the frequency of neonatal seizures but not change the prevalence of childhood epilepsy. Information available to date from the Dublin trial of electronic fetal monitoring in labor[54] is compatible with the impression that the neonatal seizure rate does not parallel the CP rate, but no information is available on possible differences in the rate of subsequent epilepsy associated with interventions in management of birth.

One possible candidate for "explaining" some of the association between birth factors and neonatal seizures may be the use of oxytocin for augmentation in prolonged labors.[54,55] In the NCPP study, an association between these factors and minor motor seizures—a subgroup of intractable childhood epilepsies too small to be substantially reflected in the total—is of much intrinsic interest because of its severity and the mystery of its etiology. This association is worthy of further investigation. Major questions have been raised regarding clinical recognition of neonatal seizures in recent studies; and some reassessment of the meaning of neonatal seizures may require longitudinal studies of children evaluated both clinically and with EEG monitoring.

Through epidemiologic studies we are beginning to understand antecedents and prognosis in patients with epilepsy. Nonetheless, we do not understand the cause of more than 50% of epilepsy in children. It is only with further knowledge of antecedents that the ultimate objective of epidemiologic studies—primary prevention—can be achieved.

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