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# CONTRIBUTORS

**FREDERICK ANDERMANN,** M.D., FRCP(C), Professor, Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada H3A 2B4

**ILDIKO ARADI,** Ph.D., Postdoctoral Researcher, Department of Anatomy/Neurobiology, University of California at Irvine, Irvine, California 92697

**TALLIE Z. BARAM,** M.D., Ph.D., Professor, Departments of Pediatrics, Anatomy/Neurobiology and Neurology, Danette D. Shepard Professor of Neurological Sciences, University of California at Irvine, Irvine, California 92697

**T. BARTFAI,** Ph.D., Professor, The Harold L. Dorris Neurological Research Center, Department of Neuropharmacology, The Scripps Research Institute, Lajolla, California 92037

**ROLAND A. BENDER,** Ph.D., Postdoctoral Researcher, Departments of Pediatrics and Anatomy/Neurobiology University of California at Irvine, Irvine, California 92697

**ANNE T. BERG,** Ph.D., Associate Professor, Department of Biological Sciences, Northern Illinois University, DeKalb, Illinois 60115

**CAROL CAMFIELD,** M.D., FRCP(C), Professor, Department of Pediatrics, Dalhousie University and IWK Health Centre, Halifax, Nova Scotia, Canada B3J 3G9

**PETER CAMFIELD,** M.D., FRCP(C), Department of Pediatrics, Dalhousie University and IWK Health Centre, Halifax, Nova Scotia, Canada B3J 3G9

**FERNANDO CENDES,** M.D., Ph.D., Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada H3A 2B4

**KANG** CHEN, M.D., Postdoctoral Researcher, Department of Anatomy/Neurobiology, University of California at Irvine, Irvine, California 92697

**CELINE DUBE,** Ph.D., Postdoctoral Researcher, Departments of Pediatrics and Anatomy/Neurobiology University of California at Irvine, Irvine, California 92697

**ROBERT S. FISHER,** M.D., Ph.D., Maslah Saul M.D. Professor of Neurology, Neurological Sciences, and Neurosurgery, Stanford University School of Medicine, Stanford, California 94305

**S. GATTI,** Ph.D., Researcher, CNS Preclinical Research, Pharmaceutical Division Hoffmann-LaRoche, 4070 Basel, Switzerland

**ISABELLE M. GERMANO,** M.D., Assistant Professor, Department of Neurosurgery, Mt. Sinai School of Medicine, New York, New York 10024

**KEVIN GORDON,** M.D., FRCP(C), Associate Professor, Department of Pediatrics, Dalhousie University and IWK Health Centre, Halifax, Nova Scotia, Canada B3J 3G9

**DAVID A. GREENBERG,** Ph.D., Professor of Biostatistics and Psychiatry, Co-Director, Mathematical Genetics Unit, Division of Clinical-Genetic Epidemiology, New York State Psychiatric Institute, New York, New York 10032; and Director, Division of Statistical Genetics, Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York 10029

**W. ALLEN HAUSER,** M.D., Gertrude H. Sergievsky Center, Professor, Departments of Neurology and Epidemiology, Columbia University, New York, New York 10032; and Department of Neurology, New York Presbyterian Hospital, New York, New York 10032

**DALE C. HESDORFFER,** Ph.D., Gertrude H. Sergievsky Center, Assistant Professor, Department of Epidemiology, Columbia University, New York, New York 10032

**DEBORAH HIRTZ,** M.D., Program Director, Clinical Trials, National Institute of Neurological Disorders and Stroke, Neuroscience Center, National Institutes of Health, Rockville, Maryland 20892

**GREGORY L. HOLMES,** M.D., Departments of Psychiatry and Biomathematics, Mt. Sinai School of Medicine and the Columbia University Genome Center, New York, New York 10029; and Director, Clinical Neurophysiology Laboratory, Department of Neurology, Harvard Medical School, Children's Hospital, Boston, Massachusetts 02115

**FRANCES** E. **JENSEN,** M.D., Associate Professor, Department of Neurology,

Children's Hospital and Program in Neuroscience, Harvard Medical School, Boston, Massachusetts 02115

**FINN URSIN KNUDSEN,** Ph.D., Senior Neuropediatric Consultant, Lecturer, Department of Pediatrics, Glostrup University Hospital, DK-2600 Glostrup, Denmark

**DARRELL V. LEWIS,** M.D., Professor, Departments of Pediatrics (Neurology) and Neurobiology, Duke University Medical Center, Durham, North Carolina 27710

**TERESA V. MITCHELL,** Ph.D., Research Associate, Brain Imaging and Analysis Center, Department of Radiology, Duke University Medical Center, Durham, North Carolina 27710

**SOLOMON L. MOSHE,** M.D., Professor, Departments of Neurology, Neuroscience, and Pediatrics, Director of Pediatric Neurology and Clinical Neurophysiology, Martin A. and Emily L. Fisher Fellow, Albert Einstein College of Medicine, Bronx, New York 10461

**CHRISTINE O'DELL,** RN, MSN, Clinical Nurse Specialist, Comprehensive Epilepsy Management Center, Montefiore Medical Center, Bronx, New York 10467

**N. PAUL ROSMAN,** M.D., Professor of Pediatrics and Neurology, Tufts University School of Medicine; Chief, Division of Pediatric Neurology, Floating Hospital for Children; Director, Center for Children with Special Needs, New England Medical Center, Boston, Massachusetts 02111

**RUSSELL M. SANCHEZ,** M.D., Postdoctoral Researcher, Department of Neurology, Children's Hospital and Program in Neuroscience, Harvard Medical School, Boston, Massachusetts 02115

**SHLOMO SHINNAR,** M.D., Ph.D., Professor, Departments of Neurology and Pediatrics, and Director, Comprehensive Epilepsy Management Center, Martin A. and Emily L. Fisher Fellow in Neurology and Pediatrics, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York 10467

**IVAN SOLTESZ,** Ph.D., Associate Professor, Department of Anatomy/Neurobiology, University of California at Irvine, Irvine, California 92697

**ELLEN E SPERBER,** Ph.D., Associate Professor, Departments of Neurology and Neuroscience, Albert Einstein College of Medicine, Bronx, New York 10461; and Department of Psychology, Mercy College, Dobbs Ferry, New York 10522

**CARL E. STAFSTROM,** M.D., **Ph.D.,** Associate Professor, Departments of Neurology and Pediatrics, University of Wisconsin, Madison, Wisconsin 53792

NIKLAS THON, Department of Anatomy/Neurobiology, University of California at Irvine, Irvine, California 92697

A. VEZZANI, Ph.D., Chief, Laboratory of Experimental Neurology, Department of Neuroscience, Mario Negri Institute for Pharmacological Research, 20157 Milan, Italy

JIE WU, M.D., Ph.D., Senior Staff Scientist, Department of Neurology, Barrow Neurological Institute/St. Joseph's Hospital and Medical Center, Phoenix, Arizona 85013

# PREFACE

With all the new books on epilepsy, why do we need a book on febrile seizures? There are several reasons. Febrile seizures are the most common form of childhood seizures, occurring in 2 to 5% of children in Western Europe and North America. As such, these seizures are of great interest to those specializing in clinical and basic research on seizures, especially developmental seizures, as well as to all involved in the care of children. Febrile seizures have specific features that make them distinct from all other forms of seizures and epilepsy, and a controversy about their relationship to subsequent epilepsy has been ongoing for many years. The last book devoted to febrile seizures appeared 20 years ago and much has been learned since. In the clinical arena, epidemiological studies have provided a better understanding of the incidence of febrile seizures, risk factors for their occurrence, and their short- and long-term outcomes. Imaging techniques now allow us to study the possible effects of seizures in children. Advances in genetics should allow us to define the role of genetic factors in this common disorder. In the basic sciences, the availability of animal models, combined with a better understanding of mechanisms of excitation and injury that are unique to the developing brain, has resulted in major advances in our understanding of the pathophysiology of febrile seizures and their possible consequences. The bottom line in terms of treatment has also changed in the past 20 years. For all these reasons, a new book is both timely and necessary.

Fortunately, we, the editors, are not the only people who feel this way. We received a tremendous and enthusiastic response and commitment, with outstanding chapters, from a stellar group of scientists and clinicians who are leaders in their field. We were thus able to assemble a book that truly reflects the state of the art. It includes the latest clinical research findings on incidence and outcome and the most recent and exciting basic science work on mechanisms and consequences, including work published in 2001. The latest treatment rec-

ommendations, such as the recent practice parameters of the American Academy of Pediatrics, are also included.

As clinician scientists, the editors firmly believe that, whether you are a clinician taking care of patients or a basic scientist working in the laboratory, it is important to have an understanding of both the clinical problem and what is known about the basic mechanisms of the disorder. The book is therefore intended to be a comprehensive overview of the state of the art that is detailed enough for the specialist while at the same time presents the data in a manner that is accessible to the nonspecialist. For this reason we have avoided the use of most abbreviations and have included brief explanations of technical terms. In the basic science sections, clinicians will find data that are both useful and informative, while in the clinical sections, basic scientists will find the information they need to understand the phenomenon they are attempting to model. This approach should also make the book accessible to the educated layman interested in febrile seizures.

As editors, it is our hope that this book will serve at least two purposes. The first is to provide a comprehensive review of the current state of the art. We have come a long way in our understanding of the clinical phenomenon and the basic mechanisms underlying it. This book both documents and celebrates these accomplishments. The second goal is to provide a road map of where we are headed. While much has been accomplished, much work remains to be done in both the clinical and the basic science arenas. The various sections of this book address the problems that remain and suggest ways to approach them. The editors' individual perspectives on where we are and where we are headed are presented at the end of the book. We hope that this book will not only inform the reader about the current state of the art but also help the next generation of researchers get started.

One of the real pleasures of editing this book was that we the editors, even though we have both worked in this field for many years, learned new data and novel approaches and perspectives. This is almost inevitable in a productive collaboration, especially when so many of the leaders in the field agree to contribute and two editors with different perspectives but a shared passion for finding solutions to the problem are involved. We hope that you the reader share our excitement and pleasure.

*Tallie Z. Baram*
*Shlomo Shinnar*

CHAPTER 1

# The Incidence and Prevalence of Febrile Seizures

CARL E. STAFSTROM

*Departments of Neurology and Pediatrics, University of* Wisconsin, *Madison*, Wisconsin 53792

Epidemiological studies have made substantial contributions to our understanding of the frequency, natural history, and prognosis of febrile seizures. Using a wide variety of methodologies, epidemiological studies have consistently estimated that febrile seizures occur in 2-5% of children under 5 years of age. In certain populations (e.g., Japan, Guam), febrile seizures may be even more common (8-14%). The reason for this geographical discrepancy remains unexplained, but may be related to genetic predisposition, environmental factors, or both. This chapter critically reviews the studies that have led to the widely accepted febrile seizure occurrence rates (incidence, prevalence) and examines the assumptions and methods underlying those studies, e 2002 Academic Press.

## I. INTRODUCTION

Nearly every article or text written about febrile seizures contains a statement relating that "febrile seizures are the most common type of seizure in childhood, occurring in 2-5% of children." How is this percentage derived, and from what population(s)? Is there geographical, seasonal, or sexual variation in febrile seizure rates? Has the occurrence of febrile seizures changed over time, as different management approaches have evolved? Does the incidence differ according to febrile seizure type (e.g., simple vs. complex)? How can such data help us understand the pathogenesis of febrile seizures and arrive at a consensus for managing them? These are some of the questions considered in this chapter, as a prelude to more detailed discussions of febrile seizure natural history, prognosis, and pathophysiology in subsequent chapters. First, febrile seizure definitions, past and present, are discussed. Next, epidemiological con-

*Febrile Seizures*

cepts and methods for measuring febrile seizure incidence and prevalence are reviewed. Finally, some pivotal epidemiological studies that have contributed to our current understanding of febrile seizure frequency are considered.

## II. WHAT IS A FEBRILE SEIZURE?

### A. HISTORICAL PERSPECTIVE

Before embarking on an analysis of epidemiological studies of febrile seizures, the fundamental question must be considered: What is a febrile seizure? Over the past several decades there has been an evolution in what the term "febrile seizure" connotes. Some series, especially prior to about 1980, did not exclude seizures precipitated by fever that may have been accompanied by an underlying neurologic disturbance such as meningitis, encephalitis, or toxic encephalopathy (van den Berg and Yerushalmy, 1969; Millichap, 1981). The prognosis of febrile seizures in the early literature was fairly pessimistic, due to the inclusion of symptomatic causes of seizure other than fever and to patient selection bias (Wallace, 1980). In addition, early studies were predominantly performed at tertiary care facilities and selected the more severe cases (Ellenberg and Nelson, 1980). The modern viewpoint is that the vast majority of febrile seizures have a benign outcome, with no lasting neurologic sequelae.

The consensus that febrile seizures do not constitute a form of epilepsy is an important conceptual advance with relevance to the consideration of febrile seizure incidence and prevalence. The distinction between febrile seizures and epilepsy has been fairly recent; it was formerly thought that febrile seizures represented "epilepsy unmasked by fever" and that they were a frequent harbinger of afebrile seizures (epilepsy) (Lennox, 1953, 1960; Livingston, 1958). Peterman stated emphatically that a febrile convulsion "does not occur in a normal child" (Peterman, 1952). E. M. Bridge (quoted in Millichap, 1968, p. 3) stated, in 1949, "There is no good reason for considering febrile convulsions as a clinical entity distinct from epilepsy. In reality, both belong in a single group, best described with the name of convulsive disorders. The differences are not of a fundamental nature but only of type and degree" (Bridge, 1949). The current definition of epilepsy as unprovoked, recurrent seizures excludes febrile seizures, which are always provoked by fever. Of course, some children experience a febrile seizure as the first manifestation of what will subsequently emerge as epilepsy, but it is not possible to predict with certainty which child will develop afebrile seizures (Berg and Shinnar, 1994).

Large epidemiological studies in the 1970s were pivotal in differentiating febrile seizures from epilepsy (van den Berg and Yerushalmy, 1969; Nelson and Ellenberg, 1976, 1978; Annegers *et al,* 1979). The natural history of febrile

seizures is quite different from that of epilepsy, as supported by several observations (Berg, 1992): (1) The risk of developing epilepsy after febrile seizures is small, on the order of 2-4%. (2) There are different risk factors for developing febrile seizures vs. epilepsy. About one-third of children with febrile seizures will experience another febrile seizure in a subsequent febrile illness, whereas 2-4% will later develop afebrile seizures (epilepsy) (van den Berg and Yerushalmy, 1969; Hauser and Kurland, 1975; Nelson and Ellenberg, 1978; Verity *et al,* 1985; Annegers *et al,* 1987; Berg *et al,* 1990; Hackett *et al,* 1997). The major predictors of recurrent febrile seizures are (1) occurrence before 1 year of age, (2) a positive family history of febrile seizures (not a family history of epilepsy), and (3) a low degree of fever (Berg *et al,* 1997). These risk factors are *not* predictive of later epilepsy. Rather, the risk factors for epilepsy in children with febrile seizures are (1) complex febrile seizures, (2) a family history of epilepsy, and (3) neurologic impairment prior to the febrile seizure (Berg *et al,* 1990). [One study did find that a complex initial febrile seizure increased the risk for febrile seizure recurrence (Al-Eissa, 1995).] Notably, prevention of recurrent febrile seizures does not appear to alter the risk of developing afebrile seizures (see Chapters 3, 7, and 19, this volume). Several randomized studies of febrile seizure prevention showed that although febrile seizure recurrence could be reduced, the development of later afebrile seizures was not altered by treatment (Knudsen, 1985; Wolf and Forsythe, 1989; Rosman *et al,* 1993; Berg andShinnar, 1994).

The controversy as to whether febrile seizures initiate a pathophysiological cascade that ultimately results in mesial temporal sclerosis and hence temporal lobe epilepsy (TLE) has been unresolved for decades (Liu *et al,* 1995). A disproportionate number of patients (up to 20%) with TLE had febrile seizures (especially prolonged ones) as young children (Falconer *et al,* 1964; Cendes *et al,* 1993). However, prospective series cite only a minority of children with febrile seizures going on to develop epilepsy (2-4%) (Nelson and Ellenberg, 1976, 1978; Camfield *et al,* 1994; Hamati-Haddad and Abou-Khalil, 1998). This controversy is discussed in detail elsewhere in this volume (Chapters 5-8, 21, 22).

## B. MODERN DEFINITIONS

### 1. National Institutes of Health and International League Against Epilepsy Definitions

According to the International League Against Epilepsy classification of the epilepsies, febrile seizures are an acute, symptomatic type, i.e., a "special," situation-related seizure (Commission, 1989). Because they are always evoked by a specific precipitant (fever), febrile seizures cannot be considered a true form

of epilepsy. Nevertheless, febrile seizures do constitute a "syndrome" because they fulfill several characteristics that are similar among affected children:

1. Febrile seizures generally occur within a restricted age range.
2. The majority of febrile seizures occur in children who are neurologically normal and continue to develop normally after the febrile seizures.
3. Febrile seizures are not associated with a structural or maldevelopmental anomaly of brain, though the existence of such pathology may enhance the susceptibility to febrile seizures (Germano *et al,* 1996).

Two operational definitions of febrile seizures have been published, one from a National Institutes of Health (NIH) Consensus Conference (National Institutes of Health, 1980; Nelson and Ellenberg, 1981), and the other from the International League Against Epilepsy (ILAE) (Commission, 1993). These definitions are compared in Table 1. In light of the huge disparities in epidemiological studies of febrile seizures, especially prior to 1980, the NIH conference represented a major advance, forming a coherent definition that has been used subsequently in many epidemiological and therapeutic investigations (e.g., Verity *et al,* 1985; Offringa *et al,* 1991; Okan *et al,* 1995). The ILAE proposed guidelines for epidemiological studies of epilepsy in general, as an attempt to standardize methods of case ascertainment, diagnostic accuracy, and seizure classification, and these recommendations are relevant to studies of febrile seizures as well.

Although the NIH and ILAE definitions are similar, their differences are worth noting. The lower age limit for febrile seizures is 1 month in the ILAE definition and 3 months in the NIH definition, although the NIH guideline is made purposefully flexible by use of the phrase "usually occurs." Each of these lower age limits have been employed in epidemiological studies of febrile

**TABLE 1 Definitions of Febrile Seizures**

| National Institutes of Health Consensus Conference (1980) | International League Against Epilepsy Commission on Epidemiology and Prognosis (1993) |
|---|---|
| **Febrile seizure:** A febrile seizure is an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who have suffered a previous nonfebrile seizure are excluded | **Febrile seizure:** A seizure occurring in childhood after age 1 month, associated with a febrile illness not caused by an infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures<br>**Febrile seizure with neonatal seizure:** One or more neonatal seizures in a child who has also experienced one or more febrile seizures as heiein defined |

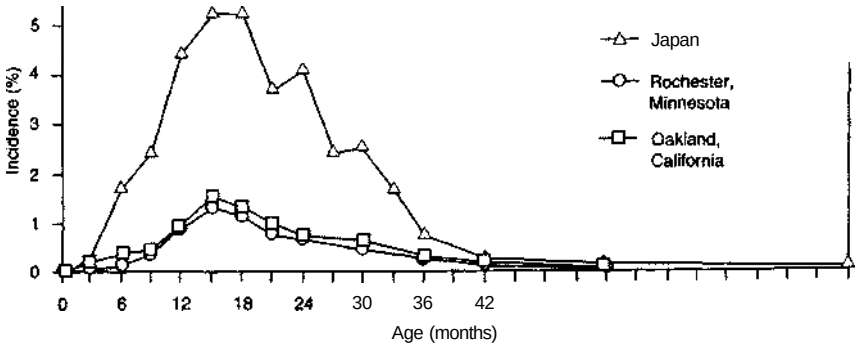


**FIGURE 1** Age-specific incidence of febrile seizures among children in Japan; Rochester, Minnesota; and Oakland, California. From Hauser (1994). The prevalence and incidence of convulsive disorders in children. *Epilepsia* 35 (Suppl. 2), S1-S6. Reprinted by permission of Blackwell Science, Inc.

seizures [1 month (Nelson and Ellenberg, 1976, 1978; Berg *et al,* 1997); 3 months (Verity *et al,* 1985; Al-Eissa, 1995)]. Other studies do not state a lower age limit (Hauser and Kurland, 1975) or use another definition [e.g., 6 months (Hackett *et al,* 1997)]. Both of the NIH and ILAE definitions exclude children with prior afebrile seizures and those with seizures due to an intracranial infection or other specific cause, but neither definition excludes children with prior neurologic impairment. However, the ILAE definition subdivides febrile seizures into those with and without prior neonatal seizures. Seizures with fever occurring during the second and third months of life, included in the ILAE definition, might not be included under the NIH definition. Practically speaking, children in this young age range probably account for a very small proportion of cases (Figure 1) (Hauser, 1994). The specific age during the first few months of life when the maturing brain first expresses an increased susceptibility to fever-induced seizures is not known precisely and may vary somewhat between children; this variability theoretically could impact epidemiological data.

Another notable difference is the lack of an upper age limit in the ILAE definition. The majority of febrile seizures occur between 6 months and 3 years of age, with the peak incidence at about 18 months (Figure 1) (Friderichsen and Melchior, 1954; van den Berg and Yerushalmy, 1969; Hauser and Kurland, 1975; Nelson and Ellenberg, 1976; Tsuboi, 1986; Annegers *et al,* 1987; Offringa *et al,* 1991). The observation that these data comprise a bell-shaped curve, regardless of the population studied, attests to the unique age specificity of the brain's sensitivity to fever. Only about 6-15% of first febrile seizures occur after 4 years of age (Hauser and Kurland, 1975; Aicardi, 1994) and onset after 6 or 7 years of age is unusual.

Neither definition includes a specific criterion as to what temperature defines "fever." A temperature of at least 38.4°C (101°F) would probably be accepted by most authorities and has been utilized in many epidemiological studies. Some researchers have accepted lower values (38°C) (Tsuboi, 1984; Al-Eissa, 1995). The route of temperature determination is not always mentioned (Tsuboi, 1984). Other rigorous studies have differentiated axillary (37.8°C) from rectal (38.3°C) temperatures, and have required that these be documented by emergency room personnel (Berg *et al,* 1997). Despite the common belief that the rate of temperature rise is more important than the ultimate temperature achieved, there are no data supporting that view (Michon and Wallace, 1984; Berg, 1993). Many febrile seizures (at least half) occur early in the course of a febrile illness, especially within the first 24 hours, and can even be the presenting sign of the febrile illness (Wolf *et al,* 1977; Berg *et al,* 1992, 1997). In clinical practice, it is difficult to establish the exact temperature just prior to or at the onset of a febrile seizure. Such a determination would ordinarily be in the hands of the parent or other caretaker. In most cases, a temperature is not recorded by the parent at the time of the seizure, and by the time the child's temperature is recorded at the physician's office or emergency room, the seizure is likely to be over and the information may be of limited relevance. Despite the lack of a uniform temperature criterion, several studies have shown that the height of the fever is related to febrile seizure recurrence (El-Radhi *et al,* 1986; Berg, 1993; Berg *et al,* 1997).

The definition of "seizure" is not specified in either the NIH or the ILAE definition. Some authorities emphasize the presence of convulsive activity (Millichap, 1981; Camfield and Camfield, 1995); indeed, febrile seizures are also known as "febrile convulsions." But is convulsive activity necessary? The lack of tonic-clonic rhythmic motor activity certainly makes the diagnosis of febrile seizure less secure, but clinicians routinely diagnose febrile seizures in children who present with limpness, altered consciousness, apnea, or nonconvulsive activity suggestive of partial complex symptomatology. In fact, the NIH definition uses the vague term "event" rather than seizure, perhaps to emphasize that some febrile seizures may not involve convulsive activity. Other clinical phenomena in the differential diagnosis of febrile seizures are mentioned in Section III,C. Inclusion of nonconvulsive activity under the febrile seizure umbrella could alter epidemiological results.

### 2. **Simple and Complex Febrile** Seizures

Febrile seizures are typically divided into two types, simple and complex. A *complex febrile seizure* has one or more of the following features (Commission 1993): (1) partial onset or focal features during the seizure, (2) prolonged duration [>10 minutes (Annegers *et al,* 1987; Berg *et al,* 1997) or >15 minutes

(Berg and Shinnar, 1996; Nelson and Ellenberg, 1978)], or (3) recurrent febrile seizures within 24 hours of the first episode (Nelson and Ellenberg, 1976; Annegers *et al,* 1987). Some authors use a phrase such as "within the same febrile illness" instead of "within 24 hours" (Camfield and Camfield, 1995; Shinnar, 1999). A *simple febrile seizure* consists of less than 10 or 15 minutes of generalized tonic-clonic activity, resolving spontaneously, in the context of a febrile illness, without focal features or recurrence during the subsequent 24 hours. Approximately 20-30% of febrile seizures are complex (Nelson and Ellenberg, 1976; Verity *et al,* 1985; Annegers *et al,* 1990; Berg and Shinnar, 1996; Offringa *et al,* 1991; Al-Eissa, 1995). Early studies that showed a much higher percentage of complex febrile seizures [e.g., 62% in Wallace (1974)], but these series comprised hospitalized patients, representing the more severe end of the spectrum. In the large National Collaborative Perinatal Project (NCPP), a cohort of 54,000 children was followed from before birth until 7 years of age. In this study, 1706 children with febrile seizures were identified. Focal features were present in 4%, prolonged durations (>15 minutes) in 8%, and recurrent febrile seizures within 24 hours of the first one in 15-20% (Nelson and Ellenberg, 1976). Complex febrile seizures are associated with a higher risk of afebrile seizures but not of febrile seizure recurrence (Verity *et al,* 1985; Berg, 1992). Because complex febrile seizures are associated with a higher risk of subsequent epilepsy, it is important to establish whether complex features are present when evaluating a child with a febrile seizure. Of the complex features, recurrence within 24 hours is perhaps the easiest to document. The presence of focal features can often be overlooked by the observer. Finally, as discussed in Section III,C, seizure duration is likely to be quite inaccurate. As discussed in depth in other chapters, the two subtypes of febrile seizures may form biologically distinct conditions with different risks for future seizures and neurologic deficits.

In summary, epidemiological studies vary in their operational definitions of febrile seizures, age limits employed, methods for determining whether they are simple vs. complex, seizure duration, and other factors. Such variations should be considered when comparing studies.

## III. DETERMINING FEBRILE SEIZURE INCIDENCE AND PREVALENCE

### A. DEFINITIONS OF EPIDEMIOLOGICAL TERMS

Much of our understanding of the risk factors, natural history, and prognosis of febrile seizures comes from epidemiological studies. However, epidemiological conclusions are only as reliable as the initial data obtained. To analyze the literature on febrile seizure frequency, certain epidemiological terms must be de-

TABLE 2 Epidemiological Terminology

| Term | Definition |
|---|---|
| Incidence (or incidence rate) | The number of new cases in a defined population over a specified time period; expressed as individuals at risk per standard population per unit time |
| Age-specific incidence | Incidence adjusted for age |
| Cumulative incidence | The expected risk of developing the disorder by a specific age, i.e., the summation of age-specific incidence |
| Prevalence | The proportion of individuals in a population with the disorder at a specific time point; a function of incidence and average duration of illness |
| Lifetime prevalence | The proportion of the population with a history of the disorder, active or not |

fined (Table 2) (Sander and Shorvon, 1987; Hauser and Hersdorffer, 1990; Berg, 1995). Unfortunately, incidence and prevalence are not always used correctly in the literature, and the terms are sometimes used interchangeably.

*Incidence* (or incidence rate) is the number of new cases occurring in a defined population over a specified period of time. For example, febrile seizure incidence is often denoted as the number of new cases per 1000 persons in a population, per year. Incidence can only be determined from longitudinal studies. *Prevalence* is the proportion of individuals in a population that has ever had the disorder, determined at a specific time point. Prevalence can be obtained from cross-sectional surveys. For example, prevalence is often specified as the number of children with a history of febrile seizures on a given date that a population survey is performed. Prevalence is dependent on both the incidence of the disorder and its average duration. Because the number of cases accumulate over time, prevalence can be high even if incidence is low, and knowledge of prevalence does not always lead to accurate incidence statistics. Although both incidence and prevalence can be adjusted for age, prevalence is not as useful in an age-specific syndrome such as febrile seizures. Febrile seizure incidence should decrease with age and become zero after about 7 years of age (Figure 1).

*Cumulative incidence* is the summation of age-specific incidence rates, i.e., expected risk of developing febrile seizures by a specific age. Therefore, this term is probably the most appropriate one to compare febrile seizure occurrence between populations, because all cases are expected to occur by about 5 years of age. Cumulative incidence should approach the *lifetime prevalence,* that is,

the proportion of the population that has ever had a febrile seizure. This point is illustrated well in van den Berg and Yerushalmy (1969), which showed that cumulative incidence reaches a plateau by about 4 years of age. *Annual incidence* refers to the incidence only within the year studied; this value should be summated over the years of febrile seizure susceptibility to arrive at a rate approximating the cumulative incidence. Finally, the *first attendance rate* (Forsgren *et al,* 1990) is defined as the number of new cases in the population at risk per year, including both new cases during the study period and those who had their first febrile seizure prior to the study period but were diagnosed during the study period.

## B. STUDY DESIGNS TO DETERMINE INCIDENCE AND PREVALENCE

The wide variety of study designs may strongly impact incidence and prevalence figures. To determine those rates, a number of techniques have been used. The goal of any method is to determine the number of cases (numerator) and the total population from which the cases are drawn (denominator). The two main types of study designs are clinic based and population based. Clinic-based studies are often performed in a specialized clinic, hospital setting, or other tertiary care facility. They have the advantage of providing a ready-made set of patients with detailed clinical information available. However, the type of patient that seeks care or has access to such a facility may skew the results. In general, these would be the most severely affected patients, with poorest outcomes (Ellenberg and Nelson, 1980). Clinic-based studies of febrile seizure occurrence are rarely performed anymore; older studies are reviewed by Rose *et al.* (1973).

Many studies have used larger populations to investigate febrile seizure incidence and prevalence, using case-finding methods such as medical record reviews, mailed questionnaires, telephone interviews, and door-to-door surveys (Table 3). Although these techniques are useful to investigate a much larger population base and thus better reflect the spectrum of disease severity and frequency, they are also subject to methodological biases. Such large-scale surveys are ordinarily carried out by personnel with limited medical training. Home visits are expensive and time consuming. Medical records are subject to some of the same biases discussed above, with documentation dependent on the training, time, and interest of the personnel collecting the data.

Population-based data are more difficult to obtain but have the advantage of surveying a large number of people. Population-based studies are of two basic types: cohort/cumulative incidence studies (Nelson and Ellenberg, 1976; Verity *et al,* 1985) and prevalence surveys (Tsuboi, 1984; Forsgren *et al,* 1990; Offringa *et al,* 1991). A cohort may be followed from birth, allowing a prospec-

**TABLE 3 Selected Studies of Febrile Seizure Incidence and Prevalence**

| Author | Location | Study type | Case ascertainment | Population size | Febrile seizures |
|---|---|---|---|---|---|
| Lessell *et al* (1962) | Guam | Population based | First phase, survey of all 5- to 13-year old school registrants, followed by home visits; second phase, total community survey | 1350 | 14% (age-specific prevalence in children 0-14 years old) |
| Schuman and Miller (1966) | Tecumseh, Michigan | Population based | Retrospective survey | 3953 | 3.6% (prevalence) |
| Mathai *et al* (1968) | Guam | Population based | Door-to-door total community survey, followed by screening examination by physician | 6967 | 8.9% (age-specific incidence in children 0-4 years old) |
| van den Berg and Yerushalmy (1969) | Oakland, California | Cohort | Hospital and clinical records of children born 1960-1967 (Kaiser Foundation) | 18,500 | 2% (cumulative incidence by 5 years old) |
| Stanhope et al. (1972) | Guam | Cohort and Population based | Retrospective; follow up of two birth cohorts in four villages—mailed questionnaires, interviews, and medical record review | 419 | 11% (prevalence by 5 years old) |
| Rose et al. (1973) | Washington County, Maryland | Population based | Mailed questionnaire to families of all third graders; follow-up examinations in random subset | 1866 | 4.8% (prevalence at 8-9 years old) |
| Hauser and Kurland (1975) | Rochester, Minnesota | Population based | Retrospective review of records (patient registry); children born 1935-1967 | 472 (city population, -55,000) | 0.4% (mean annual incidence in children <5 years old) |
| Rossiter et *al.* (1977) | Geelong, Australia | Cohort | Prospective study of consecutive births | 580 | 34.0% (cumulative incidence, 0-3 years old) |

| | | | | | |
|---|---|---|---|---|---|
| Nelson and Ellenberg (1976, 1978) | United States | Cohort | Prospective study of children born 1959-1966 at 12 urban teaching hospitals (National Collaborative Perinatal Project) | -54,000 | 3.5% (prevalence by age 7 years) |
| Bauman *et al.* (1978) | Rural Kentucky | Population based | Questionnaire, interview with neurologist | 4023 | 1.7% (prevalence in children 6-16 years old) |
| Chiofalo *et al.* (1979) | Chile | Population based | Interview, examination by neurologist in positive cases; children born in 1966 | 2085 | 5.2% (prevalence at age 9 years) |
| Ross et *al.* (1980) | United Kingdom | Cohort | Questionnaire to all children born during one week of March 1958 (National Child Development Study) | 15,496 | 2.4% (prevalence at age 11 years) |
| Heijbel *et al.* (1980) | Northern Sweden | Population based | Prospective | 15,284 | 0.7% (annual incidence in children 0-5 years old) |
| Tsuboi (1984) | Fuchu, Tokyo Miyake, Tokyo | Population based | Retrospective. All 3-year-old children presenting to physicians for regular health examinations; urban and rural populations | 17,587 | 8.3% (prevalence) |
| Verity et al. (1985) | United Kingdom | Cohort | Prospective study of children born during one week in April 1970; interviews by local health visitors at age 5 years | 13,135 | 2.3% (cumulative incidence by age 5 years) |
| Zhao et *al.* (1987, 1991) | China—six cities | Population based | Door-to-door survey by neurologist; case-control study | 63,195 (9198 under age 12; calculated from data in paper) | 1.7% (prevalence in children <4 years old); 2.1% (prevalence through age 12 years); 0.6% (incidence in children <4 years old) |

*(continues)*

TABLE 3 (continued)

| Author | Location | Study type | Case ascertainment | Population size | Febrile seizures |
|---|---|---|---|---|---|
| Forsgren *et al.* (1990) | Northern Sweden | Population based | Prospective | 15,420 | 4.1% (cumulative incidence by age 5 years); 0.46% (annual first attendance rate) |
| Offringa *et al.* (1991) | Rotterdam suburbs | Population based | Cross sectional prevalence survey | 3570 | 3.9% (cumulative incidence by age 6 years) |
| Monetti *et al.* (1995) | Northeastern Italy | Population based | Questionnaire, interview by M.D.; compare with clinic files | 165 controls without epilepsy | 1.8% (cumulative incidence) |
| Okanetal. (1995) | Turkey | Population based | Retrospective survey; interviews by medical students, examinations by pediatricians | 5002 | 4.5% (prevalence, 0-5 years) |
| Hackett *et al.* (1997) | Southern India | Population based | Home interview of 8- to 12-year-olds in a defined district, by psychologist or psychiatrist | 4340 | 10.1% (lifetime incidence) |
| Pal (1999) | West Bengal, India | Population based | Structured questionnaire, home visit; unmatched case-control study | 59 controls | 5.1% (prevalence among controls) |
| Huang *et al.* (1999)<br>Chang *et al.* (2000) | Taiwan | Population based | Prospective survey, case-control study: telephone interview, home visit | 10,460 | 2.4% (prevalence among children 3 years old) |

tive evaluation of febrile seizure occurrence. A potential disadvantage is that a cohort born on the same day may reach the age of peak incidence for febrile seizures during a month or season that is not the peak for the disorder (see Section IV,C).

The major differences between outcomes of clinic-based and population-based studies of febrile seizures are illustrated in a metaanalysis of twenty-six studies (Ellenberg and Nelson, 1980). Clinic-based studies reported the development of epilepsy in a much higher proportion of children with febrile seizures (median 17%) than was found in population-based studies (median 3%). These results support the notion that clinic-based studies are skewed toward disproportionately severe cases (Berg and Shinnar, 1994).

## C. CASE ASCERTAINMENT: WAS IT A FEBRILE SEIZURE?

In studying the frequency of febrile seizures, the initial and most obvious task is to figure out if a clinical event was actually a febrile seizure. This determination can be challenging, as most pediatricians and pediatric neurologists will attest. To determine whether an event was a seizure, we must usually rely on the history given by a witness, usually a parent. The historical details are often colored by vague recollections of the child's abnormal behavior at a time of extreme stress. Important variables such as height (or even presence) of the preceding fever, seizure onset characteristics (focal versus generalized), and duration of the event are rarely recalled clearly. It is unlikely that the seizure duration will be accurately estimated by the caretaker, especially for shorter events, which are often overestimated. For longer febrile seizures, i.e., those still ongoing on arrival of emergency medical personnel or at the emergency room, durations may be easier to estimate. In addition, there is uncertainty inherent in parental reporting of febrile seizures. Based on their personal perceptions, cultural background, and medical sophistication, parents may underplay the episode (e.g., if they fear the stigma of an epilepsy diagnosis) or exaggerate its severity or duration [many parents feel their child is dying during a febrile seizures (Baumer *et al,* 1981)]. In an interesting study, approximately 25% of patients with known epilepsy (from medical records) denied having epilepsy on a questionnaire (Beran *et al,* 1985).

Even physicians have a variable degree of comfort evaluating spells such as febrile seizures. Other episodic conditions that may occur during a febrile illness must be differentiated from a *bona fide* febrile seizure (Baumann, 1981). The most frequent mimic of febrile seizures is a shaking rigor (shiver) (Rosman, 2000). Other conditions include febrile syncope (Stephenson, 1990), breath-holding spells, febrile "toxic delirium," and even temper tantrums. Like a