Epidemiology of Encephalitis in Children: A 20-Year Survey

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Four hundred five children from the Helsinki area who were 1 month to 16 years old were treated for acute encephalitis at the Children's Hospital, University of Helsinki, from January 1968 through December 1987. Encephalitis occurred most commonly in children 1 to 1.9 years of age, among whom the incidence was 16.7 per 100,000 child-years. The incidence remained quite high until the age of 10 years, and then gradually declined to 1.0 per 100,000 child-years at the age of 15 years. Since 1983, when mumps, measles, and rubella vaccination eradicated the encephalitides associated with these microbes, the major associated agents have been varicella-zoster, *Mycoplasma pneumoniae,* and respiratory and enteroviruses. In infants younger than 1 year of age, the major agents were enteroviruses, herpes simplex virus, and the group of "others," whereas in older children, respiratory viruses and *Mycoplasma pneumoniae,* as well as varicella-zoster virus, dominated. In children aged 1 to 11 months, the causal agent could not be identified in one-half of all cases, whereas in children who were at least 10 years old, the etiology remained unknown in only one-fourth of cases. Male dominance was most evident in the 4- to 9-year age group. The difference in etiology between males and females was significant ($p = 0.02$); mumps and varicella were more common in boys, and adenovirus and *Mycoplasma pneumoniae* were more common in girls. The overall male-to-female ratio was 1.4:1. Characteristic seasonal variation occurred in encephalitides associated with mumps, measles, and entero- and respiratory viruses. In the whole series, some accumulation appeared in February and March. Less than one-half of this number appeared in July and August.

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Encephalitis appears to be a disease of young children [1] and is most severe among the youngest ones [2]. For certain severe types of encephalitides, specific therapy is available, but early institution is essential for a favorable outcome. In central nervous system (CNS) infections, there appears to be age-dependent and seasonal variation [3, 4]. Knowing this variability may help us to detect the patients with encephalitis and confirm the etiological diagnosis early enough for therapy to be effective. Therefore, we have analyzed the incidence and epidemiology of encephalitis in children, in the course of 20 years.

Patients and Methods

Geographic Area

Our series included children with encephalitis treated at the Children's Hospital, University of Helsinki, during a 20-year period, January 1968 through December 1987, initiated in a prospective manner by our colleagues and continued by us in 1981. Fifty-seven patients with encephalitis, transferred from other parts of Finland to the Children's Hospital in Helsinki, were excluded from all calculations. Thus, only the patients originating from the Helsinki area and covered by the University Central Hospital were included. Patients with mild encephalitis may be treated at other governmental hospitals as well, but children with severe disease are referred to the Children's Hospital from all parts of southern Finland, including from a new hospital built in the area in 1977. Thus, the incidence figures are underestimates rather than overestimates.

Clinical Diagnosis

Acute encephalitis was defined by neurological symptoms lasting for not more than 1 month before admission and not due to purulent, systemic, neoplastic, or other diseases. The most characteristic neurological symptoms were lowered consciousness (disorientation, confusion, somnolence, coma), focal or generalized seizures or both, opisthotonos, pareses, tremors, ataxia, hypotonia, mental changes (aggressiveness, staring, apathy), dizziness, impaired speech, and diplopia. Meningeal symptoms and signs or cerebrospinal fluid (CSF) alterations were not a prerequisite for diagnosis. Neonatal infections (at 0–4 weeks) were excluded because they often are generalized and are seldom restricted to the CNS.

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Microbiological Diagnosis

The microbiological diagnosis of encephalitis was regarded as confirmed if the virus or its antigen was detected from brain tissue or CSF, or the serum/CSF antibody ratio was ≤ 20 (normal, 200–300) (5 patients, 2%). The diagnosis was suggested if in the course of clinical encephalitis there appeared at least a fourfold rise in antibody titer in paired serum specimens (111 patients, 40%) or a high titer (≥ 64, occurring in ≤ 1% of all specimens) in one serum specimen (59 patients, 21%), or a positive virus culture or antigen finding in some extracranial source (41 patients, 15%). Antigens of herpes simplex virus (HSV), varicella-zoster virus (VZV), influenza A and B, parainfluenza 1 and 3, respiratory syncytial virus (RSV), and adenoviruses were detected in a biopsy or throat specimen by the immunofluorescence (IF) technique. Antibody titers were measured by the complement fixation (CF) technique to the following antigens: adenovirus, coronavirus, coxsackie virus B5, cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B, HSV, influenza A and B, polio, and reoviruses, as well as RSV, VZV, chlamydia group antigen, Mycoplasma pneumoniae, and Toxoplasma gondii antigens. If the patient had a well-defined clinical disease (e.g., mumps, measles, varicella, or rubella) within 4 weeks before or 1 week after the onset of encephalitis, the clinical disease was considered the cause (93 patients, 33%). In some of these patients, a microbiological test was done.

Patients

There were 405 patients, 239 males (59%) and 166 females (41%). Their ages ranged from 1 month to 16 years, with a mean of 6.0 ± 3.9 years. The patients were divided into the following four groups, according to age: 1 to 11 months (33 patients), 1 to 4 years (139 patients), 5 to 9 years (159 patients), and 10 to 16 years (74 patients). The etiology was confirmed or suggested in 279 patients (69%) and remained unknown in 126 patients (31%).

Parameters Analyzed

The following variables were analyzed: age and sex, microbiological diagnosis, month of onset of the disease, and year of the disease. Different age groups and microbiological entities were analyzed both separately and together. The χ^2 test was used to assess the significance of the difference in the etiology of encephalitis between males and females.

Results

Age

The occurrence of encephalitis was highest in the age groups of children younger than 2 years (85 patients, 21.0% of all), whereas the number was very low in the oldest children, 14 to 16 years of age (8 patients, 2.0% of all). The incidence was 16.7 per 100,000 child-years at the age of 1.0 to 1.9 years, then declined, but was still quite high to the age of 10 and even 12 years. At the age of 15 years, the incidence was 1.0 per 100,000 child-years.

The proportion of children with encephalitis of unknown etiology was consistently at the highest level in the youngest children, among whom one-half of all causes remained unknown, whereas in children at least 10 years of age, the proportion was only one-fourth (Figs 1 and 2; Table). The known or suggested etiology varied considerably with age. In the 1- to 11-month age group, the major role was played by enteroviruses and HSV, followed by the group of "others" (this group includes CMV, EBV, rotavirus and reovirus, multiple etiologies, and bacterial and vaccination-associated encephalitides) (see Fig 2). The agents of the measles-parotitis-rubella (MPR) group did not occur in children younger than 1 year of age. Mumps and measles viruses were previously the major associated agents in preschool and school-aged children, but since their eradication by MPR vaccination, respiratory viruses have dominated in the age group of 1 to 4 years, and VZV in the age group of 5 to 9 years. Additionally, adenovirus and *M. pneumoniae* appeared important agents at these ages. *M. pneumoniae* was quite evenly distributed over the age scale beginning at 1 year of age (see Fig 1), and 10 years of age, but from the age of 10 years on, it was a dominating agent besides VZV.

Sex

Males outnumbered females in encephalitides associated with mumps (3.4:1) and VZV (2.5:1), and females more frequently had encephalitides associated with adenovirus (1.3:1) and *M. pneumoniae* (1.2:1) (see Fig 1). The difference was statistically significant (p = 0.02). In the series as a whole, males outnumbered females (1.4:1).

Seasonal Distribution

Encephalitis occurred in children throughout the year, although an increase was seen in winter and early spring. The incidence was 14.5 per 100,000 child-years in February (Fig 3). The lowest numbers appeared in July and August, 6.4 and 5.9 per 100,000 child-years, respectively. Mumps and measles, characteristically, were the most frequent agents in the winter and spring months. Respiratory viruses were seen most frequently in February, whereas enteroviruses occurred chiefly during the summer and autumn, especially in August. The occurrence of HSV, VZV, *M. pneumoniae,* and the group of others was quite even throughout the year. VZV remained at the level of about 1 per 100,000 child-years. February, September, and December were the primary months for the occurrence of encephalitis with unknown etiologies (see Fig 3).

The high level of unknown causes in the youngest children aged 1 to 11 months (see Table) may reflect underdiagnosis of respiratory virus infections (see Fig 3). In children aged 1 to 4 years and 5 to 9 years, the proportion of unknown causes is at its highest in autumn, suggesting that enteroviruses and *M. pneumoniae* may escape diagnosis.

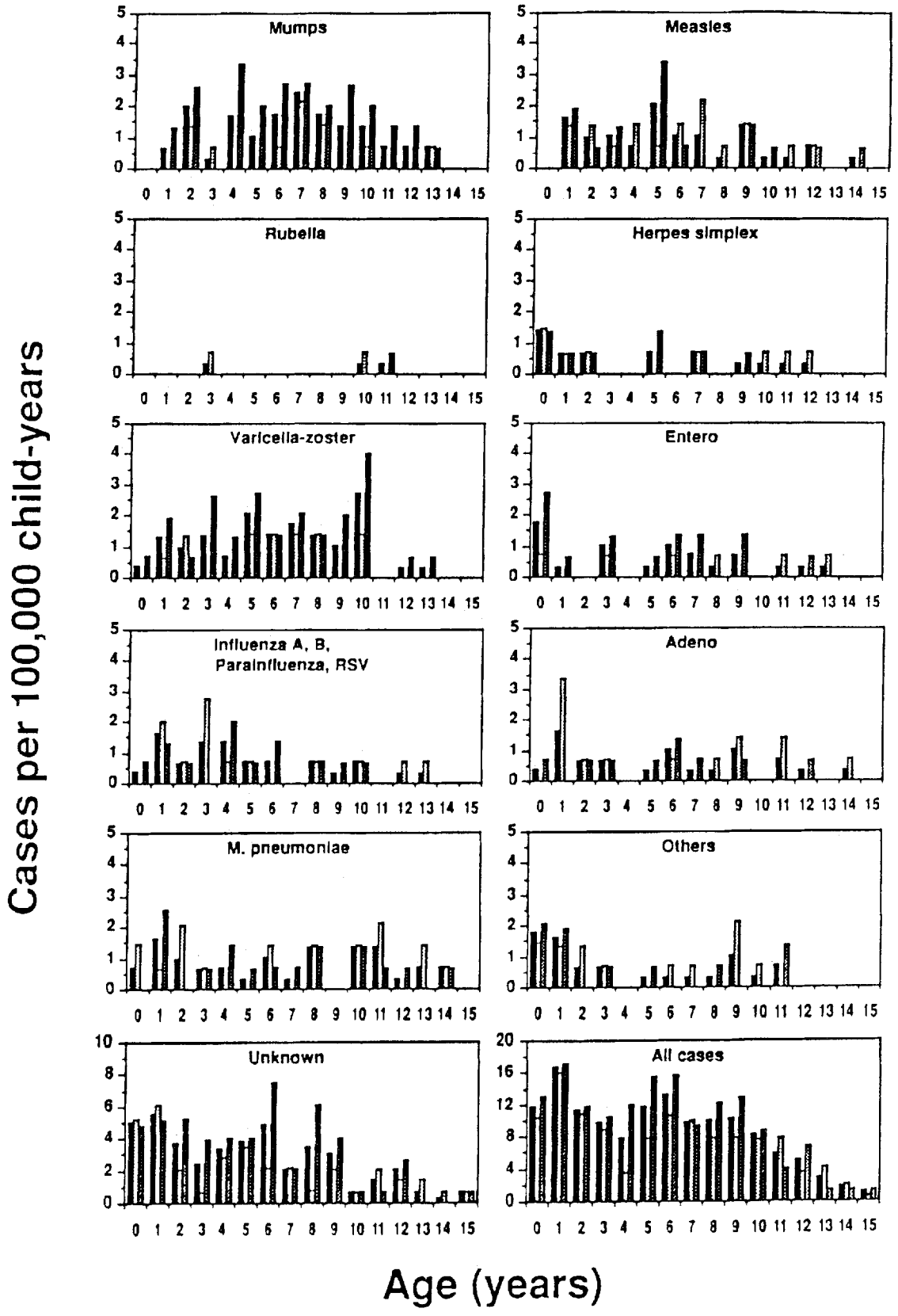

Fig 1. Etiology of acute encephalitis in successive age groups of children during the 20-year period, 1968–1987. Dark bars denote all patients, lined bars females, and crossed bars males. The "others" include cytomegalovirus, Epstein-Barr virus, rotaviruses and reoviruses, multiple etiologies, and bacterial and vaccination-associated encephalitides.

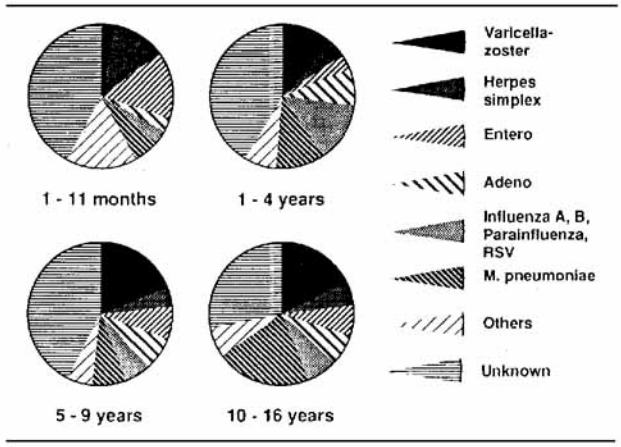

Fig 2. Etiology of encephalitis in successive age groups over the 20-year period. The measles-parotitis-rubella group has been omitted because no patient has been seen since 1983.

Seasonal Occurrence of Unknown Etiologies at Different Ages

Age group	Mar–May	Jun–Aug	Sep–Nov	Dec–Feb
1–11 mo	67	25	38	71
1–4 yr	24	37	48	33
5–9 yr	29	24	45	34
≥ 10 yr	18	29	0	25

Values are percentages.

Discussion

Encephalitides are diseases of young children and young adults [1, 3]. The multiplicity of causative and associated agents is much greater in children than in adults, and the agents are more heterogeneous [4–6]. In children, HSV is merely one of a wide array of agents, whereas in adults it is the leading cause [7]. The incidence of childhood encephalitis in the present series reached the proportions reported by Wang and Bortolussi [1]. The excess of encephalitis among the youngest children is more evident in our series than in most others, but similar to that of Wang and Bortolussi [1]. In our series, male dominance was seen most clearly in mumps and VZV, whereas female dominance is seen in adenovirus and *M. pneumoniae*–associated encephalitides.

Many agents can be eradicated by vaccination. In the early 1960s, polio vanished; and in the early 1980s, it appears that MPR vaccination has eliminated the encephalitides associated with these agents [4, 8, 9]. Thus, the spectrum of CNS infections evidently is a changing one [4], and the total number of encephalitides may have declined. In children younger than 1 year old, however, the number of encephalitides may even be increasing [9, 10]. Furthermore, encephalitis does the most damage in infants [2, 11]. Thus, encephalitis in young children needs more attention.

The leading causes among childhood encephalitides are now VZV and *M. pneumoniae.* Against both of them specific therapy is available, and it is especially important in *M. pneumoniae* infections because they are severe [12]. In *M. pneumoniae*–associated CNS infections, however, we cannot be sure of the most effective therapy. VZV causes a severe disease in children younger than 1 year old [13]; our series included only one such patient, and the child made a good recovery. HSV-associated encephalitis, fortunately, is relatively rare in childhood except in infants younger than 1 year old, and the drug of choice is currently acycloguanosine [14, 15]. Besides HSV, enteroviruses play a major role in this age group. For these viruses, no specific therapy is available as yet. Diagnosis is important, however, because enteroviruses are common in young infants [12, 16], have a high affinity for the CNS, and may damage insidiously without evident clinical symptoms [17].

A characteristic seasonal distribution of several microbes was seen, such as mumps in the spring months and enteroviruses in August. Meyer and colleagues [4] obtained similar results, however, few authors report on this aspect of encephalitides, presumably because of small series. Compared with the previous Finnish reports on mainly adult patients, the present series showed a greater heterogeneity of etiologies [6, 7]. We had no patient with arbovirus encephalitis although we screened for arboviruses until the early 1980s, whereas at the Mayo Clinic these patients formed the majority [18]. Thus, the incidence of encephalitis needs both regional and periodic evaluation.

The proportion of unknown etiologies in different series varies from 27 to 74%, and vigorous efforts are always needed to determine the causative or associated microbe [9, 14]. In young children, encephalitis often escapes clinical, let alone etiological, diagnosis, which is often only established at autopsy [10]. Additionally, we have seen many patients with convulsions of unknown origin [19] as well as ill-defined encephalopathies [20, 21]. These diseases may be caused by viruses and so, basically, be encephalitides. The number of unknown causes in the winter months suggests failure to identify respiratory viruses and adenovirus, and in autumn, underdiagnosis of enteroviruses. Despite this, our series reached one of the highest levels in microbiological identification. We admit that the association is not always firm [22] and is sometimes coincidental rather than causative, but in CNS diseases, direct evidence for causality is difficult to obtain.

We need a keener interest in childhood acute encephalopathies, in general. By knowing the age, sex, and season, we may anticipate the exact diagnosis and confirm it by rapid methods. Presently, we have antigen tests for respiratory viruses (influenza A and B, RSV, and parainfluenza 1, 2, and 3), adenoviruses, and herpes viruses (HSV, VZV, and CMV) as well as for

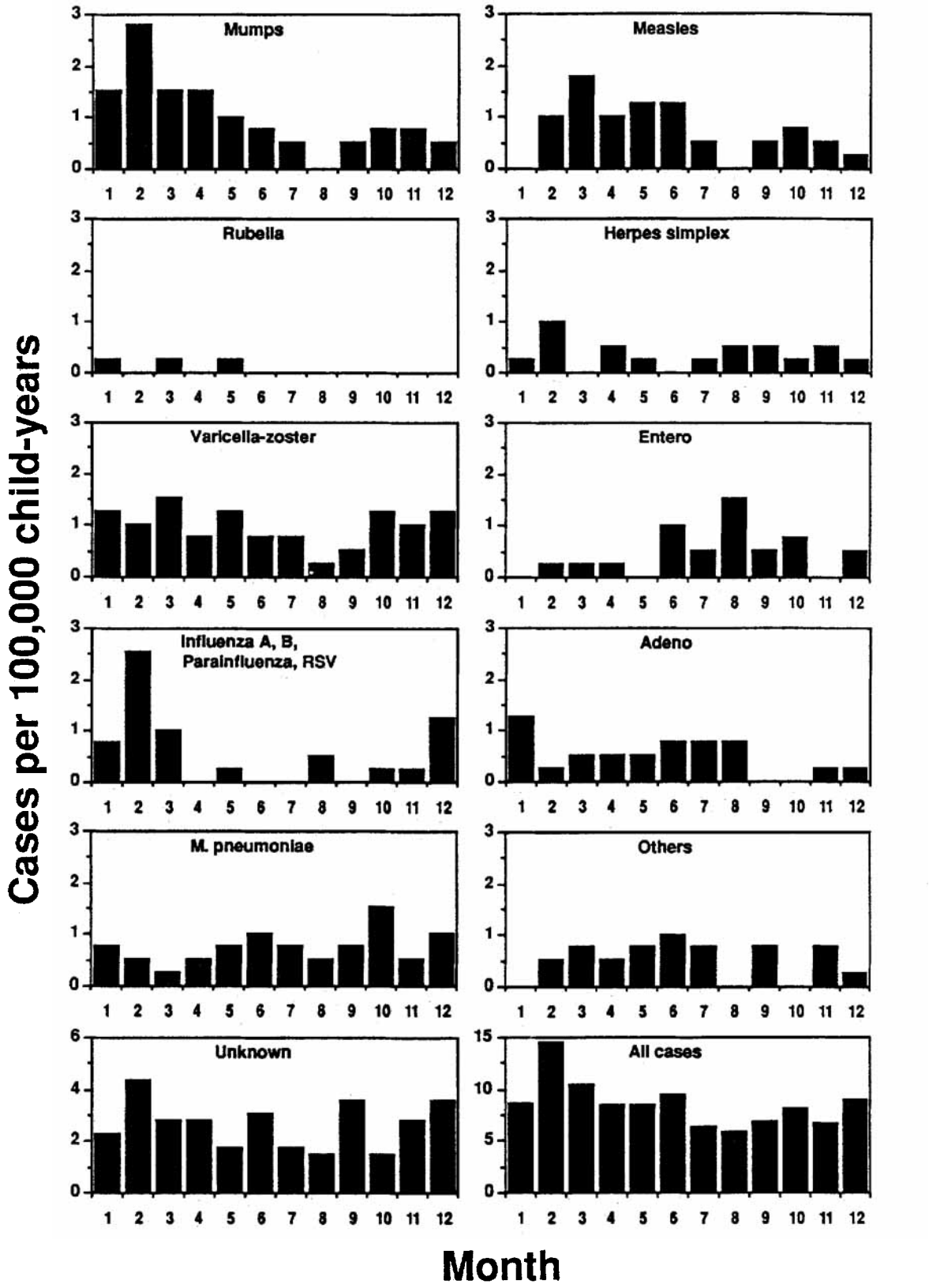

Fig 3. Seasonal distribution of the different etiologies associated with acute encephalitis in children during the 20-year period.

M. pneumoniae. By these tests, the diagnosis is obtained within 1 day, sometimes within 3 hours. In addition to these IF techniques, tests based on DNA techniques are forthcoming [23] and may be helpful, especially in CSF diagnostics.

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