

Acute viral infection of the central nervous system in children: an 8-year review

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Reliable information on acute viral infections of the central nervous system (CNS) in Canadian children has not been available. To investigate this disease in Halifax the medical records of 180 patients with presumed or definite acute viral CNS infection diagnosed at the Izaak Walton Killam Hospital for Children over an 8-year period were reviewed. The yearly incidence was estimated at 19.5/100 000 for children up to 16 years of age, and the peak incidence was in July, August and September. The cause was determined in 64 (36%) of the 180 patients; it was most commonly a known infectious disease — mumps (in 24 patients) or varicella (in 9 patients). An enterovirus was responsible in nine cases, herpes simplex virus in eight and measles virus in six. The clinical manifestations were variable and included apnea in three infants who would otherwise have been considered to have nearly suffered the sudden infant death syndrome. Localizing features were present on the electroencephalograms of nine patients, including six with herpes simplex infection. Serologic study of paired serum samples obtained during the acute phase of the illness and during convalescence was the most useful laboratory method of establishing the diagnosis. As medical therapy for specific causes of acute viral CNS infection advances, greater attention should be placed on establishing the correct diagnosis.

Il n'existe pas d'information fiable sur les infections virales du système nerveux central (SNC) chez l'enfant canadien. A Halifax, dans le but d'étudier cette affection, on a passé en revue les dossiers médicaux de 180 patients chez qui une infection virale du SNC présumée ou typique a été diagnostiquée à Izaak Walton Killam Hospital for Children au cours d'une période de 8 années. L'incidence annuelle a été évaluée à 19.5/100 000 pour les enfants jusqu'à 16 ans, et le plus grand nombre de cas sont survenus en juillet, août et septembre. La cause a été déterminée chez 64 (36%) des 180 patients; il s'agissait le plus souvent d'une infection virale connue, soit les oreillons (chez 24 patients) ou la varicelle (chez 9 patients). Un entérovirus a été responsable de neuf cas, l'herpes simplex de huit et le virus de la rougeole de six. Les manifestations cliniques étaient variables; celles-ci se traduisaient par de l'apnée chez trois enfants qui par ailleurs auraient pu paraître avoir échappé de peu au syndrome de mort soudaine du nourrisson. Des signes de localisation étaient présents sur l'électroencéphalogramme de neuf patients, dont six souffraient d'infection à herpes simplex. Les études sérologiques des

échantillons pairés de sérum prélevés durant la phase aiguë de la maladie et durant la convalescence a été l'examen de laboratoire le plus utile pour établir le diagnostic. Puisque le traitement médical des causes spécifiques de l'infection virale aiguë du SNC s'améliore, une plus grande attention devrait être accordée à l'établissement du diagnostic exact.

Acute viral infection of the central nervous system (CNS) is more common than is generally appreciated. Since the diagnosis is usually made by excluding other possibilities, it is difficult to obtain reliable estimates of incidence. In the United States 1536 cases were reported for 1977,¹ and in Canada 631 cases were reported in 1979.² Such estimates may be misleading, however, since diagnostic criteria vary and the reporting of this disease is optional. In addition, regional differences may affect the final results and mask significant trends. There are no recent comprehensive published reviews of acute viral or presumed viral CNS infection in Canada. Therefore, to obtain more reliable information on the incidence and causes of encephalitis and aseptic meningitis than is presently available, we conducted a thorough review of the case histories of all patients with acute viral CNS infection cared for at the Izaak Walton Killam Hospital for Children, Halifax, over a recent 8-year period. The population served by this hospital is relatively stable, with less immigration and emigration than in other areas of Canada. The information that we obtained may serve as a guide for other areas of Canada.

Materials and methods

The Izaak Walton Killam Hospital for Children serves as a pediatric hospital of immediate access for a surrounding population of approximately 250 000. It also serves as a secondary care referral centre for a regional population of approximately 500 000. For this report we carefully reviewed patient records and laboratory results for the period January 1972 through April 1980, as well as significant viral isolations and serologic conversions reported to our hospital over this period. We found 249 cases in which a clinical diagnosis of acute viral encephalitis, viral meningitis, viral meningoencephalitis, viral encephalomyelitis or aseptic meningitis had been made by the time of discharge. The 69 patients who had received antibiotics before admission, had incomplete medical records or were found to have other conditions were excluded from the analysis. An etiologic agent was ascribed if any of

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the following criteria were met: isolation of a virus from cerebrospinal fluid (CSF) or brain tissue; a four-fold or greater increase in antibody titre in serum obtained during convalescence, as compared with that obtained during the acute phase of the illness; and clinical documentation of preceding or coincident mumps, measles, rubella or chickenpox. CSF, throat swabs and stools for virus isolation and paired serum samples for antibody detection were evaluated by Dr. Juan Embil, of our hospital, and at the D.J. MacKenzie Laboratory and Diagnostic Centre, which is adjacent to our hospital.

Results

The 180 patients included 108 boys (60%) and 72 girls (40%); 106 came to the hospital from the metropolitan Halifax area, 65 from other parts of Nova Scotia, 7 from other provinces and 2 from other countries. The annual incidence of acute viral CNS infection was estimated as 19.5/100 000 and the peak incidence was in children aged 6 months or less (Fig. 1).

The annual and monthly distribution of cases over the 8-year period is shown in Figs. 2 and 3. The largest proportion of cases occurred during July, August and September (47%); however, the cause was established in only nine of these cases.

Cause of the infection

The cause of the acute viral CNS infection was determined in 64 cases; serologic study of paired serum samples was the most useful laboratory tool in establishing the diagnosis (Table I). Not included in Table I

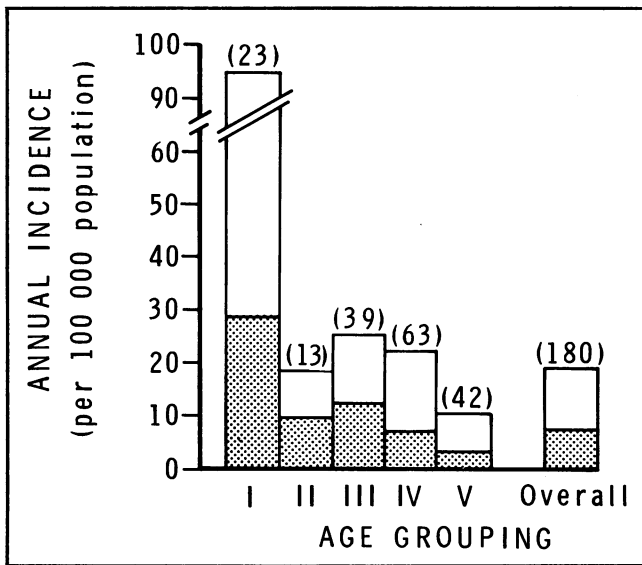


FIG. 1—Estimated annual incidence of acute viral infection of the central nervous system per 100 000 population in 1972–80 in metropolitan Halifax in various age groups: I, 0 to 6 months; II, 7 to 23 months; III, 2 to 5 years; IV, 6 to 10 years; V, 11 to 16 years. Based on estimated population base of 500 000 and age distribution data from Statistics Canada for 1979.³ Numbers in parentheses are actual numbers of patients in each age group. Stippled areas indicate cases in which cause was identified, blank areas those in which it was not.

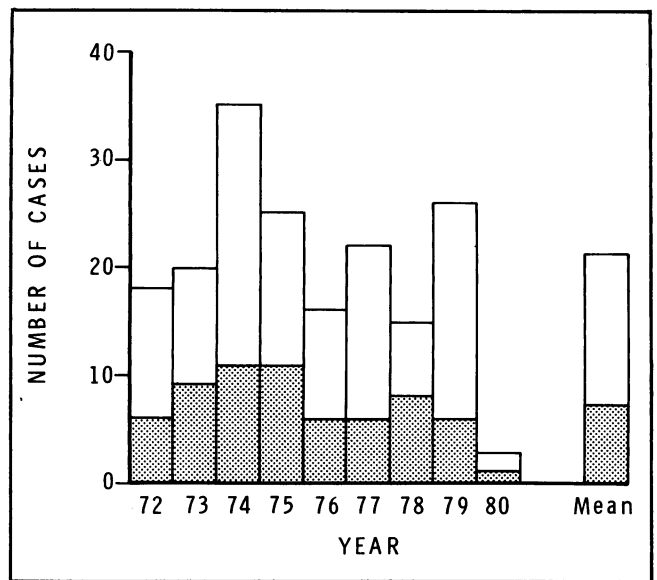


FIG. 2—Total number of cases and number in which cause was identified (stippled areas) in each of years 1972 to 1979 and in first 4 months of 1980.

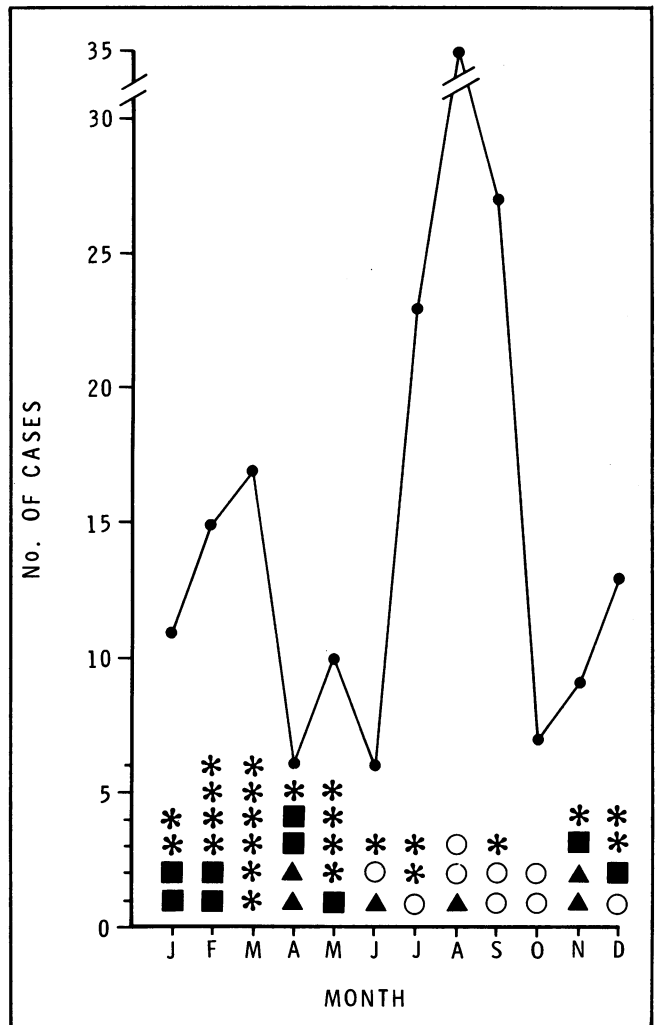


FIG. 3—Number of cases each month. Symbols represent cases in which cause was identified; asterisks indicate mumps (24 cases), squares varicella (9 cases), circles enterovirus infection (9 cases) and triangles measles (6 cases).

are stool and throat isolates from several patients (from stool, two echoviruses, two adenoviruses, one echovirus 9 and one unclassified picornavirus; from throat swabs, adenovirus 7, echovirus 3 and *Mycoplasma pneumoniae*).

Clinical and laboratory features consistent with a diagnosis of aseptic meningitis or meningoencephalitis were documented in 102 cases, in 33 of which the cause was determined. Of the 24 patients with mumps meningoencephalitis 21 had parotitis, 2 submandibular adenopathy and 1 orchitis beforehand or concurrently; in all the cases in which paired serum samples were examined an increase in the titre of antibody to mumps virus was detected. A clinical diagnosis of encephalitis was made in 76 cases; common causes were varicella (in 9 cases), herpes simplex (in 8 cases) and measles (in 6 cases). A fourfold or greater increase in antibody titre was detected in all of the patients with measles and varicella encephalitis from whom paired serum samples were obtained.

Clinical and laboratory manifestations

Fever, vomiting, drowsiness and irritability were common, each occurring in at least 72% of patients. Headache was noted by children older than 2 years. Nuchal rigidity was noted in 97 of the 102 patients who had aseptic meningitis or meningoencephalitis and in 24 of the 76 who had encephalitis, but was not observed in the 2 patients with encephalomyelitis.

Convulsions and coma were common among the patients with features of encephalitis, occurring in 26 and 11 patients respectively. Paralysis was present in 10 patients, including 5 with herpes simplex encephalitis (3 had limb paralysis and 2 had quadriplegia) and 2 with varicella encephalitis (1 had hemiplegia and the other had palsy of the oculomotor nerve). Five other patients had transient cerebellar ataxia, and one was thought to have the Guillain-Barré syndrome. Apneic spells were the sole clinical manifestation in three infants aged 20 days, 5 weeks and 8 weeks; an enterovirus, echovirus 3, was isolated from the CSF of one of these infants.

High serum levels of glutamic oxaloacetic and pyruvic transaminase (SGOT and SGPT) were noted in five patients (two with herpes simplex encephalitis and one each with rubella encephalitis, varicella encephalitis and an acute CNS infection of undetermined cause). The highest SGOT level, 940 IU/l, was in a patient with herpes simplex encephalitis, and the highest SGPT level, 332 IU/l, was in a patient with varicella encephalitis. All the patients' transaminase levels returned to normal within 2 weeks.

CSF was available for microscopic examination in 173 cases; the leukocyte counts are shown in Table II. In five patients 80% to 90% of the cells were neutrophils; a repeat lumbar puncture in four of these patients after 12 to 24 hours showed a decrease in the proportion of neutrophils. Concentrations of glucose and protein were determined in 156 samples. The glucose concentrations were within the normal limits in all but two samples, in which the concentration was 0.32 g/l (1.8 mmol/l). The protein concentrations varied from normal to 1.85 g/l (Table III). All four patients whose CSF protein level was above 1 g/l had mumps meningoencephalitis.

Results of special investigations

Computerized tomography (CT) was done in nine patients and demonstrated focal increased density or

Table II—Leukocyte count in the CSF of 173 of the patients

Count ($\times 10^7/l$)	No. (and %) of patients		
	Cause of infection		
	Undetermined	Determined	Total
0-5.0	46 (40)	21 (36)	67 (39)
5.1-10.0	19 (17)	8 (14)	27 (16)
10.1-20.0	15 (13)	6 (10)	21 (12)
20.1-50.0	18 (16)	14 (24)	32 (18)
50.1-100.0	12 (10)	8 (14)	20 (12)
100.1-200.0	5 (4)	1 (2)	6 (3)
Total	115	58	173

Table I—Causes of 180 acute viral infections of the central nervous system

Cause	No. of patients			Total
	Diagnostic criterion			
	Fourfold increase in serum antibody titre	Isolation of virus from cerebrospinal fluid (CSF)	Preceding or coincidental documented infection	
Mumps	5	0	19	24
Varicella	2	0	7	9
Herpes simplex	7	1	0	8
Enterovirus infection				
Coxsackievirus	4	1	0	5
Echovirus	0	2	0	2
Picornavirus	0	2	0	2
Measles	4	0	2	6
Others*	4	1	3	8
Total	26	7	31	64

*Including two encephalitides occurring after vaccination (against measles and against diphtheria, pertussis, tetanus and polio) and one each of rubella, infectious mononucleosis, paramyxovirus infection, poliomyelitis, Powassan virus infection and cat-scratch disease.

localized edema with midline shift in four. The abnormal CT findings were helpful in establishing the diagnosis of encephalitis in two patients who had convulsions and coma but normal CSF.

Electroencephalograms (EEGs) were obtained in 38 patients and showed diffuse or localized wave changes in 29. Of the seven patients with herpes simplex encephalitis for whom EEGs were made, six were found to have focal changes either solely in the temporal region or at various sites in the cerebral hemispheres; none had periodic lateralized discharges of electrical activity. Three other patients (one with Powassan virus infection, one with varicella encephalitis and one with infection of undetermined cause) had localizing features on their EEG. Similar EEG abnormalities were found in eight patients whose CSF was normal but in whom the clinical diagnosis was encephalitis. Improvement was noted in a second EEG in nine patients and correlated well with the clinical course.

Patients with severe disease and localizing features revealed by CT scan or EEG were given adenine arabinoside for 5 days. If after 5 days other diagnoses were not apparent the course of therapy was extended to 10 days. Adenine arabinoside was given to seven patients in our series, including two with varicella encephalitis and five with suspected herpes simplex encephalitis, one of whom was shown serologically to have Powassan virus encephalitis. None of the seven patients had an adverse reaction to the drug, and five showed definite improvement. One of the patients with herpes simplex encephalitis, a 3½-year-old girl, was admitted to our hospital on the fifth day of illness because of repeated convulsions and coma, and died 9 days later.

Discussion

In children acute viral CNS infections, such as meningoencephalitis and encephalitis, have many causes. A presumptive diagnosis is usually possible when other, more life-threatening diseases, such as bacterial meningitis, brain abscess and tuberculosis have been ruled out. Examination and culture of CSF is the most useful way of differentiating acute viral CNS infection from other diseases.

The leukocyte count in the CSF of patients with acute viral CNS infections is usually low; 85% of our patients had counts of $50 \times 10^7/l$ or less. However, isolated cases with cell counts of more than $100 \times$

$10^7/l$ ($104.7 \times 10^7/l$, $280 \times 10^7/l$ and $778 \times 10^7/l$ respectively) have been reported from reviews of aseptic meningitis.^{4,6} Although mononuclear cells usually predominate, neutrophils may do so early in the disease,⁷ as was noted in five of our patients and the one of Torphy and associates⁴ who had a high leukocyte count; however, mononuclear cells predominated in the CSF of four of our five patients 12 to 24 hours later. Repeat lumbar puncture is therefore recommended when the diagnosis is unclear. Other laboratory investigations, such as determinations of the glucose and protein levels in the CSF, are helpful and usually reassuring to the physician. All of our patients but two had normal CSF glucose levels. The four patients with CSF protein concentrations exceeding 1 g/l had mumps meningoencephalitis.

The cause of viral encephalitis or meningoencephalitis is not usually known until a virus is isolated from CSF or a fourfold increase in the titre of antibody in the serum is noted. Coxsackieviruses and echoviruses have been reported to be the most common causes of acute viral CNS infection.⁸ In addition to meningoencephalitis, they may cause myelitis, cranial nerve palsy, hemiplegia or the Guillain-Barré syndrome.⁹⁻¹¹ In our series these viruses were identified in only 11% of the patients for whom the cause was determined. Herpes simplex encephalitis carries a mortality of 53% to 90%.^{12,13} Among our eight patients with this condition one died. The infection tends to be localized in the temporal and orbitofrontal lobes, though this is not pathognomonic. Aside from cases in which there was a classic viral exanthem or classic mumps, the diagnosis was most often made serologically. Paired serum samples were helpful in establishing the diagnosis in 63% of the cases in which they were obtained, so the usefulness of this procedure cannot be overestimated. The proportion of our cases in which the cause was undetermined, 64%, is similar to the figures in other reports (61% to 70%).^{1,14}

Signs and symptoms of CNS involvement are often difficult to interpret in young infants. Apnea was the sole clinical manifestation in three of our infants under 3 months of age. Viral CNS infection should be considered in all infants who apparently nearly suffered the sudden infant death syndrome. We found that when the clinical picture was that of encephalitis but the CSF was normal a CT scan and an EEG were helpful in making a diagnosis.

More complete investigation of acute viral CNS infection is required. Throat swabs and specimens of CSF and stool should be obtained in all patients for viral culture. Serum should be obtained during the acute phase of the illness and during convalescence and examined for a significant increase in the antibody titre. A search for viral antibody in the CSF has been advocated to provide supportive evidence since antibody may appear in the CSF before the serum titre rises.¹⁵ Steps such as these are vital for determining the cause of viral CNS infection.

We estimated the yearly incidence of acute viral CNS infection in the children in our area to be 19.5/100 000. This estimate differs markedly from the in-

Table III—Protein concentrations in the CSF of 156 of the patients

Concentration (g/l)	No. (and %) of patients		
	Cause of infection		Total
	Undetermined	Determined	
≤ 0.40	31 (30)	24 (45)	55 (35)
0.41-0.80	60 (58)	17 (32)	77 (49)
0.81-1.00	12 (12)	8 (15)	20 (13)
1.01-1.50	0	2 (4)	2 (1)
1.51-2.00	0	2 (4)	2 (1)
Total	103	53	156

cidence calculated from nationwide reports of such infection in all age groups in Canada, 2.87/100 000. This suggests that reporting of acute viral CNS infection is incomplete.² The incidence in our study appeared to be highest among young infants, at 94/100 000. A prospective study employing strict diagnostic criteria and uniform laboratory investigations is indicated to establish the incidence of this disease in the various age groups.

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Pyometra

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Pyometra is a potentially lethal disease. Eighteen cases, all but one in postmenopausal women, were diagnosed at the Ottawa General and Ottawa Civic hospitals between 1974 and 1978 inclusive. A review of this series and of the literature demonstrates that a large proportion of cases (72% in this series) are associated with or follow radiotherapy for a malignant disease of the uterus and that anaerobic bacteria are frequently isolated from the uterine cavity (in 56% of the patients in this series). Because pyometra is potentially lethal (one patient in our series died) it should be considered as an abscess and treated promptly and vigorously by evacuation and continued drainage of the uterine cavity. Curettage of the cavity and the endocervical canal after dilatation is essential to rule out associated malignant disease as well as to debride the necrotic tissue. Antibiotics effective against aerobic and anaerobic bacteria should be given to all patients with signs of systemic infection. Once the infection is controlled, the underlying problem can be treated.

La pyométrie est une maladie qui peut être létale. Entre 1974 et 1978 inclusivement 18 cas ont été diagnostiqués à l'hôpital Général d'Ottawa et à l'hôpital Civic d'Ottawa;

dans tous les cas sauf un il s'agissait de femmes en postménopause. L'étude de cette série et une revue de la littérature démontrent qu'une grande partie des cas (72% dans cette série) est associée ou consécutive à une radiothérapie pour un cancer de l'utérus et que des bactéries anaérobiques sont souvent isolées de la cavité utérine (chez 56% des patientes de cette série). Parce que la pyométrie peut être létale (une des patientes de cette série est décédée), elle devrait être considérée comme un abcès et traitée promptement et vigoureusement par évacuation et drainage continu de la cavité utérine. Le curetage après dilatation de la cavité et du canal endocervical est essentiel pour exclure la présence d'un cancer, de même que pour débrider les tissus nécrotiques. Des antibiotiques efficaces contre les bactéries aérobies et anaérobies doivent être administrés chez toute patiente présentant des signes d'infection générale. Une fois l'infection jugulée, le problème sous-jacent peut être traité.

Pyometra is the accumulation of pus in the uterine cavity resulting from interference with its natural drainage. The most common cause is a malignant lesion of the uterus.¹⁻³ In postmenopausal women the reported incidence is 0.2%, but among those with malignant lesions of the uterus pyometra is more common, the reported incidence being 1.5% to 4.0%.^{2,3} In the premenopausal female pyometra is rare; usually the cause is traumatic damage to the cervix⁴ or a congenital anomaly of the genital tract.⁵

In the past, no bacteria could be cultured in 15%

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