A case of Powassan virus encephalitis

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Summary: A case of encephalitis due to Powassan virus, probably transmitted through tick-bite, is reported in an 8-year-old boy. There was a 50-fold increase in neutralization titre against Powassan virus, but the virus could not be isolated. Other virological investigations were negative.

The patient survived and early physiotherapy and speech re-education could be instituted. Nine months after onset of illness the patient showed moderate sequelae, despite a very severe illness.

Résumé: Les auteurs rapportent un cas d'encéphalite à virus Powassan chez un garçon de 8 ans, probablement transmise par une piqûre de tique. Une augmentation du titre de neutralisation de 50 fois contre le virus Powassan a été observée, mais le virus n'a pu être isolé. Les autres recherches virologiques sont demeurées négatives.

Le patient ayant survécu, physiothérapie et logothérapie ont été instituées précocement. Neuf mois après le début des symptômes, le patient présentait des séquelles modérées malgré la gravité de sa maladie.

Symptomatic arbovirus infections are known to involve the central nervous system and to have a high degree of mortality and morbidity, especially in children. In 1958 McLean and Donohue[1] isolated Powassan virus from the brain of a child who died of encephalitis in northern Ontario. Subsequent studies by those investigators and others showed the virus to be a new member of the group B tick-borne arboviruses, related to the Russian spring-summer encephalitis complex (RSSE). It is the sole serotype isolated in North America so far. This report presents a case of Powassan virus encephalitis, including epidemiological and entomological investigations.

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Materials and methods

Techniques for virus isolation, complement fixation (CF), hemagglutination-inhibition (HI) and neutralization (N) tests were performed according to classical procedures.[2]

Antigens for the viruses of measles, herpes simplex, herpes zoster, mumps, rubella, poliomyelitis, coxsackie B, lymphocytic choriomeningitis and Rocky Mountain spotted fever were obtained from commercial sources. Antigens for leptospira were kindly supplied by Dr. J. A. McKiel, L.C.D.C., Health and Welfare Canada.

Antigens for arboviruses were obtained from commercial sources or kindly supplied by Dr. D. M. McLean, Department of Medical Microbiology, The University of British Columbia, Vancouver. Several antigens were also prepared at the Communicable Disease Center in Atlanta, Georgia, where part of the arbovirus serology was performed.

Case report

G.F., an 8-year-old white boy who lived near Sherbrooke, P.Q., was admitted in early October 1972 to St. Vincent de Paul Hospital in Sherbrooke, because of headache, vomiting and fever.

The family history was irrelevant. The patient had failed his first year at school at the age of 6. Approximately one year prior to his illness he had been submitted to the routine collective psychological evaluation carried out at the primary school in his village. On this occasion he was found to be of below average intellectual ability. Otherwise, his personal history was irrelevant.

He had been well until two days before admission, when a dull headache developed, followed by generalized malaise, anorexia, vomiting and fever. On admission he was somnolent and showed some stiffness of the neck. A lumbar puncture revealed a clear cerebrospinal fluid, containing 495 leukocytes/mm^3 (82% polymorphs and 18% lymphocytes), protein 28 mg/dl and glucose 74 mg/dl. No bacteria were seen in gram-stained smears, and cultures in differential media were negative. Blood sugar was not measured. Hemoglobin was 14 g/dl, hematocrit 42%, leukocyte count 12,000 with 76% polymorphs. Intravenous ampicillin therapy was initiated.

On the fourth day of illness the patient was more obtunded and became progressively stuporous with periods of agitation. His temperature was 40°C. A second lumbar puncture yielded fluid containing 295 leukocytes/mm^3 (5% polymorphs and 49% lymphocytes). The protein and sugar were normal. He was examined the next day by a neurologist because of generalized and focal seizures. The patient was comatose and could respond to painful stimuli by retracting all four extremities, the right more than the left. Both eyes were constantly deviated to the right. A left facial palsy was noted. The optic fundi were normal. The left lower extremity was extended and the left upper extremity was flexed. The right leg was flexed. Bilateral pyramidal tract signs were noted, with moderate nuchal rigidity. A diagnosis of viral meningoencephalitis with predominant involvement of the right hemisphere was suggested. In view of the rapid deterioration, the patient was transferred to the Centre hospitalier universitaire de Sherbrooke.

Physical examination revealed an unconscious, well coloured and hydrated 30 kg boy with the head and both eyes deviated to the right and drooling of the saliva. The lungs, heart and abdomen were normal. No lymph node enlargement was noted. The carotid arteries showed normal pulsation. Neurological findings were as described above except that the nuchal rigidity was more marked and a definite left peripheral nerve palsy and a left hemiparesis were observed. Both pupils measured 3 mm and reacted to light. The corneal reflex was diminished more on the left than on the right. Occasional spasmodic tremors of the head and all four extremities were observed.

The remainder of the neurological examination was negative. On admission the temperature was 40°C, pulse 96, respirations 28/min and blood pressure 140/80. Urinalysis yielded normal findings. The hematocrit was 42%, the leukocyte count 12,600 with 76% neutrophils, and hemoglobin 14 g/dl. The blood glucose was 125 mg and urea nitrogen 9.5 mg/dl. The sedimentation rate was 20 mm/hr. Other biochemical analysis was noncontributory. Three successive hemocultures were negative. Electrocardiography, routine radiography and liver function tests gave normal results. An echoencephalogram showed a third ventricle measuring 2 mm with a slight shift of 2 mm to the left. The electroencephalogram revealed high amplitude, diffuse, polymorphic slow waves with a right centrotemporal predominance. The brain scan was negative. On the same day a third lumbar puncture disclosed a cerebrospinal fluid pressure of 180 mm; the fluid contained 95 leukocytes/mm^3 with 60% polymorphs, 40% lymphocytes and 194 erythrocytes/mm^3; the glucose was 70 mg/dl (simultaneous blood glucose 132 mg/dl) and the protein 69 mg/dl. No bacteria were seen in gram-stained

smears, and cultures remained sterile. Phenobarbital was administered intramuscularly, 5 mg/kg/day. A Levin tube was introduced, salicylates were prescribed, hypothermic blankets were applied and hydration was maintained by parenteral fluids.

On the sixth hospitalization day the patient was still critically ill, but no seizures had been noted. He showed irregular respiration with periods of tachypnea from 32 to 68/min. The temperature was 39°C and the pulse 120. About 350 ml of clotted bloody fluid was obtained by gastric aspiration.

On the seventh day the vital signs were stable and the patient was responding better to stimuli and the pyramidal tract signs were less pronounced, with more spontaneous movements on the right side. The nuchal rigidity was moderate. The electroencephalogram showed a slight improvement and the echoencephalogram no longer showed third ventricle displacement. Improvement continued so that by the eighth day the patient could open and close his eyes spontaneously, although not on command. A week later oral feeding was started. By then the nuchal rigidity was slight. The spasticity had decreased and he was able to move his left side more freely. The conjugated gaze deviation to the right was still present and facial asymmetry was less marked.

During the second week after onset of illness the patient displayed a state of akinetic mutism with episodes of spasmodic crying and laughing, but there was no seizure activity. His general condition gradually improved. A lumbar puncture showed a cerebrospinal fluid pressure of 120 mm; the fluid contained 64 leukocytes/mm^3 (88% lymphocytes and 12% polymorphs), protein 104 mg/dl and glucose 73 mg/dl. A gram-stained smear and cultures were again negative. The electrophoresis of CSF proteins showed an increase of γ-globulin at 31.4%. The liver function tests were normal except for a slight increase of S-LDH and SGOT. The electroencephalogram showed several episodes of drowsiness and sleep despite repeated attempts to alert the patient, and was interpreted as evidence of higher brain stem involvement: otherwise the magnitude of the diffuse abnormalities seen in earlier tracings had decreased. The echoencephalogram showed a third ventricle of 6 mm without displacement.

Physiotherapy was started in the second week as well as an intensive speech therapy program. Gradually his neurological condition improved. By the fourth week the profound anarthria was still present but his degree of comprehension had improved. His visual and auditory acuity were intact. Rigidity and spasticity were noted more on the right than on the left, and more in the lower extremities than in the upper extremities. He was discharged, markedly improved after two months in hospital. Follow-up was conducted in the outpatient pediatric clinic. He attended once a week the speech and physiotherapy clinics. Seven months after the onset of illness further improvement in his motor achievement and particularly in his speech was noted. He had a right hemiplegic gait and could easily perform the wheelbarrow maneuver. He could stand up by himself without aid. The pyramidal tract signs were bilateral, more marked in the right lower extremity and left upper extremity, with bilateral Babinski reflex and ankle clonus. He was able to walk, use his bicycle, attend school in his village and follow the first-year program three mornings a week, although with marked fatiguability. A psychological evaluation carried out nine months after onset of illness showed an I.Q. of 58% (Wechsler test). Although this would be compatible with mental retardation, caution is needed in the interpretation of this result in view of the motor difficulties of the patient and of his below-average intellectual ability prior to his illness. Indeed, it may well be that such a finding only expresses some degree of mental retardation unrelated to the present illness and susceptible of improvement.

Epidemiological and virological investigations

On September 2, 1972 the patient had spent a day cutting wood in the forest with his father about 10 miles from Sherbrooke. At home, that night, his mother noticed a "hard large bug" trapped in the skin of his right shoulder and which required considerable scratching to remove. His father also noticed that it could not easily be squashed. The shoulder felt sore for a day or so but there was no subsequent local swelling, malaise or fever. The onset of symptoms was not until 34 days later. He was not bitten by any insect in the interval, apart from mosquitoes, which were very abundant in the area.

At that same time several horses died of eastern equine encephalitis (EEE) in the Eastern Townships of Quebec.[3] The possibility that this might be a case of human EEE was considered and extensive virological investigations were carried out. Specimens of feces, throat secretions and CSF, obtained one week after the onset of symptoms, were negative in tissue cultures of Wi_{38}, African green-monkey kidneys and Hep_2. The results were also negative following intracerebral inoculation of CSF in 2- to 3-day-old mice, including several blind passages. Paired sera obtained on the 6th and 19th days after onset of illness showed a modest increase in CF titre from 1:4 to 1:8 for EEE. Otherwise the CF titres were negative or unchanged for viruses of measles, herpes simplex, herpes zoster, mumps V and S, rubella, poliomyelitis types I-III, coxsackie B_1-B_6, lymphocytic choriomeningitis, western equine encephalitis, St. Louis encephalitis, California encephalitis, Powassan encephalitis, Colorado tick fever, Rocky Mountain spotted fever, *Leptospira canicola, Leptospira pomona* and *Leptospira icterohaemorrhagiae.*

A third serum sample, obtained 27 days after the onset of symptoms, provided the first evidence of a rising CF titre for Powassan virus. This led to further testing by HI and neutralization tests for Powassan virus and other arboviruses in the patient's serum as well

as in that of close members of his family. The results, summarized in Table I, confirmed that the patient was infected by Powassan virus. Both parents, two sisters and two aunts who lived in the same household were all found to be negative when tested by CF and HI with the same antigen.

Ticks in the Eastern Townships, Province of Quebec

Although no large-scale study of the tick population has been carried out in this area, the following species have been identified on one or several occasions: *Dermacentor variabilis,* Say (American dog tick), *Dermacentor albipictus,* Pack (winter tick), *Haemaphysalis leporis palustris,* Pack (rabbit tick), *Rhipicephalus sanguineus,* Latr. (brown dog tick) and *Ixodes cookei,* Pack. This latter species has been shown by other investigators to be one of the vectors of Powassan virus.[1,4-11]

The forest where the patient had been bitten in early September 1972 was revisited late in May 1973. Several attempts at collecting ticks from the ground, using appropriate entomological techniques, were unsuccessful. A chipmunk shot at that time was found parasitized by fleas, but carried no ticks. Both parents of the patient claimed that the insect which had bitten their son nine months earlier was certainly larger than the specimen of unfed *Ixodes cookei* when this was shown to them. This suggests that the tick was engorged with blood when removed from the patient's skin.

Discussion

Following the original isolation of Powassan virus,[1] extensive epidemiological and ecological studies carried out by McLean and his associates in northern Ontario[4-7] showed that man appears to be a tangential host in the natural tick-rodent cycle involving groundhogs and squirrels as the main reservoirs and ticks *(Ixodes cookei* and *Ixodes marxi)* as the main vectors. Similar natural foci of Powassan virus infections have been described in Colorado,[8] southern Dakota,[9] New York State[10] and British Columbia.[11] Serological confirmation of Powassan infection in a 57-year-old patient in New Jersey was reported in 1970.[12] Three other cases occurred in children in New York State in 1971 and 1972.[13,14]

The case presented here is the second proved case of Powassan virus encephalitis in Canada. It also provides some evidence of transmission through tick-bite. Although our attempts to isolate the virus from the CSF were unsuccessful, the significant rise in CF and N titres in properly timed blood specimens, a high HI titre and the negative serological findings for more common viruses, as well as other arboviruses frequently associated with encephalitis, exclude another etiological agent. There is also little doubt that the patient was bitten by a tick though the transmission through a tick-bite sustained a month prior to illness would imply an unusually long incubation period. In the tick-borne encephalitides of Europe and Russia associated with group B arboviruses the average incubation period has been reported to be 8 to 14 days after exposure[15] with a frequent biphasic course.

The case presents several interesting

Table I—Arbovirus serology in the 8-year-old male patient

Virus		Time after onset of symptoms 6 days	19 days	27 days	7 months
Powassan	CF	<1:4	<1:4	1:32	1:64
	HI	ND	ND	1:320	1:40
	N	1:100	ND	1:5000	ND
Eastern equine encephalitis	CF	<1:4	1:8	<1:8	<1:8
	HI	ND	ND	<1:10	<1:10
Western equine encephalitis	CF	<1:4	ND	<1:8	<1:8
	HI	ND	ND	<1:10	<1:10
Venezuelan equine encephalitis	CF	<1:4	ND	<1:8	<1:8
	HI	ND	ND	<1:10	<1:10
St. Louis encephalitis	CF	<1:4	ND	<1:8	<1:8
	HI	ND	ND	<1:10	<1:10
California La Crosse	CF	<1:8	ND	<1:8	<1:8
	HI	ND	ND	ND	<1:10
Dengue 2	CF	ND	ND	ND	1:16
	HI	ND	ND	<1:10	<1:10
Yellow fever	CF	ND	ND	ND	<1:16
	HI	ND	ND	<1:10	<1:10

CF = Complement-fixation test; HI = Hemagglutination-inhibition test; N = Neutralization test
ND = Not done

clinical features. The systemic and CNS involvement are consistent with an arbovirus infection as seen in Russian spring-summer encephalitis and Murray Valley encephalitis. Our patient showed an unusual onset of a severe viral meningoencephalitis with a mixture of diffuse and, as often seen in children, focal CNS involvement. The severity of symptoms reached a peak on the fourth day of the illness, when unstable vital signs were associated with a profound comatose state. This period seems to be a critical one since the first patient described by McLean and Donohue[1] died at that time from sudden respiratory failure. Although often seen in some viral encephalitides, the high cell count in the CSF, with predominance of polymorphonuclear cells, was disturbing and different from the slower rise in cell count in the patient of McLean *et al* despite similar manifestations in time and severity. The clinical as well as EEG findings suggest an involvement of the diencephalomesencephalic area. According to Osetowska,[16] this site of predilection is characteristic of arbovirus infections. The neuropathological findings of the first case reported by McLean *et al* revealed a diffuse involvement with some sparing of the cord and cerebellum. Also, histologically the lesions were indistinguishable from those described in published accounts of St. Louis, Murray Valley and Japanese B encephalitis. The importance of the treatment of a patient with a viral encephalitis, in regard to the control of seizures, maintenance of the airway, control of temperature, nutritional status, and early physical therapy must be emphasized. The maintenance of joint mobility and a relatively short hospitalization with early return to the family atmosphere contributed to the partial recovery of our patient. The cognitive and behavioural sequelae after seven months can be expected to improve, on the basis of the near maturity of our patient's CNS. As shown by Finley *et al*,[17] because the cerebral ontogenesis was sufficiently advanced at the time of his illness, when all levels of his neuraxis were influencing behaviour and cognition, one can measure the sequelae from the time of the acute illness. Therefore progressive or delayed clinical sequelae are unlikely.

Conclusions

The risk of Canadians contracting arbovirus infections on the Prairies, in the Caribbean region and the southern parts of the continent has long been realized. Sporadic and isolated cases may occur also in other parts of Canada where supporting cycles of infection for pathogenic arboviruses may be present. Such a diagnosis can be established only by means of close cooperation with the virus laboratory. From that point of view the case reported was a challenging one since it occurred during a local epidemic of EEE in horses, a disease unheard of until then in eastern Canada. There lies ahead the important task of measuring the extent of the infection in the wild cycle and determining the species of rodents, birds, insects and arachnids that serve as arbovirus reservoirs for Powassan and EEE virus in the Province of Quebec.

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