Central nervous system manifestations of chickenpox

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Summary: A study of 57 cases of affection of the central nervous system associated with chickenpox diagnosed and treated at The Hospital for Sick Children in Toronto between 1956 and 1967, inclusive, is presented. The commonest type, the cerebellar variety (50%), had an excellent prognosis. In the next commonest, the cerebral type (40%), the mortality rate was 35% but there was a low incidence of permanent sequelae in the surviving patients. A small group classed as aseptic meningitis was defined and one case of myelitis was reviewed.

Involvement of the central nervous system by chickenpox is so rare that it takes many years to accumulate sufficient knowledge of the condition to be able to evaluate a case and treat it wisely. To provide a guide to those called upon to attend such a case we have summarized the experience with such conditions at The Hospital for Sick Children in Toronto over a 12-year period from 1956 to 1967, inclusive.

The cases appeared to be of two major clinical types, with a third and a fourth seen less frequently. The first and more dramatic of the two main types, "cerebral" encephalitis, was characterized by involvement of the cerebral cortex in anything from a mild to a fatal degree. In the second, the "cerebellar" type, the encephalitic process affected that portion of the brain. The third type noted was a form of aseptic meningitis, and the fourth was a single case of myelitis.

A. Cerebral type

The main features of this illness are set forth in Tables I and II. The symptoms began anywhere from one day before eruption of the rash (one case only) to as long as 20 days after the rash appeared, with an average time of 4.6 days. The length of hospital stay ranged from one-half to 26 days, with an average of 6.8 days; the shorter stays usually occurred in the fatal or mild cases. In addition to the symptoms listed one child complained of abdominal pain, and each of the following findings was recorded in one case: high-pitched cry, absent corneal reflex, and unequal pupils.

Ten cases (43%) showed a cerebrospinal fluid cell count of more than 10 per c.mm., all cells being lymphocytes except in two cases where an occasional polymorphonuclear leukocyte was included in the differential count. The protein in the CSF was elevated in five cases (36% of cases where the protein was determined).

In addition to the forms of treatment listed several others were used less frequently. Mannitol was given in three cases to reduce cerebral edema; antibiotics were used prophylactically; two patients received blood transfusion, and one required tracheostomy and the use of curare.

Of the 23 patients, 15 survived. Thirteen of these were described as being improved or normal by the time of discharge from hospital, but two suffered permanent brain damage.

A clinical résumé of five of the eight fatal cases is presented.

Case 1

A 6-year-old boy had a history of chickenpox with headache for five days and vomiting for three days. Six hours before admission he had become semi-comatose and restless when disturbed. On initial examination in hospital he was comatose and moderately dehydrated, with an injected pharynx, enlarged liver, hyperactive reflexes and flexor plantar responses. The optic discs were normal. The CSF pressure was 140 mm. H_2O and the fluid, which showed no cells, had a protein level of 42 mg. per 100 ml.; the sugar was not determined. The blood sugar was 227.8 mg. per 100 ml.; the CO_2 combining power was 8.8 mEq. per litre; the pH was 7.38. His electroencephalogram (EEG) was grossly abnormal with almost no electrical activity. In spite of intravenous fluids, hydrocortisone (Solu-Cortef: Upjohn) and tracheostomy, he died 19 hours after admission. At necropsy, crusted lesions of varicella were noted on the skin of the chest and back. The brain, which weighed 1590 g. (normal: 1260 g.), appeared soft and there was slight herniation of the hippocampal gyrus. Microscopic examination revealed widespread perivascular and perineural edema. In a Hissl stain there were shrunken acidophilic nerve cells in the olivary nucleus. More destruction of nerve cells with quite marked edema was noted in the dentate nucleus. In sections stained for fat occasional fat-filled macrophages were seen around vessels. There was no evidence of encephalitis or extensive demyelinization. The liver was large, pale and yellow, weighing 794 g. (normal: 650 g.). Hematoxylin and eosin sections showed marked destruction of liver cells with fatty infiltration. Fatty infiltration was also demonstrated in the proximal convoluted tubules of the kidneys.

Case 2

A 6-year-old girl presented with a history of chickenpox for six days and vomiting, headache and listlessness for two days. On admission she was lethargic and had the typical crusted lesions of chickenpox. Her optic discs were normal. The liver was slightly enlarged. No cells were found in the

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TABLE I
Clinical Findings in Chickenpox Encephalitis

		Cerebral type	*Cerebellar type*
No. of cases		23	29
Sex: Males		12 (52%)	15 (52%)
Females		11 (48%)	14 (48%)
Age at onset: Average		5.0 years	5.0 years
Range		9 mos.—8.5 yrs.	8 mos.—8.5 yrs.
Symptoms			
General:	Vomiting	13	21
	Fever	11	6
Neurological:	Lethargy	10	13
	Convulsions	9	0
	Headaches	7	10
	Delirium	2	0
	Ataxia	0	24
	Dizziness	0	6
	Slurred speech	0	3
Physical findings			
Sensorium:	Semi-coma	12	0
	Coma	4	0
	Lethargy	0	8
	Delirium	4	0
	Hyperventilation	4	0
	Irritability	2	7
Cranial nerve involvement:	Dilated pupils	3	0
	Sluggish pupils	2	1
	Nystagmus	0	7
	Slurred speech	0	3
Motor system:	Nuchal rigidity	9	5
	Ataxia or incoordination	0	25
	Increased muscle tone	4	0
	Convulsion on admission	2	0
Sensory involvement		None recorded	None recorded
Reflexes:	Hyperactive tendon reflexes	8	10
	Extensor plantar responses	6	0
	Clonus (ankle)	2	0

CSF; pressure, protein and sugar values were not recorded. She was treated with intravenous fluids and chloramphenicol but died three hours after admission.

At necropsy, congestion of the liver and spleen, patchy bronchopneumonia and atelectasis were found. The brain was reported as being "tight with moderate Kernohan's notching". Representative sections showed only perivascular edema indicated by spaces about some of the vessels in the white matter. No perivascular cells or demyelinization was demonstrated.

Case 3

A 6½-year-old girl had had chickenpox for five days and vomiting and lethargy on the day of admission. She was moderately dehydrated and slightly disorientated. The optic discs were normal. Cerebrospinal fluid pressure was 170 mm. H_2O and the protein was 14.5 mg. per 100 ml.; there were no cells. No CSF or blood sugar estimations were made. She was given intravenous fluids, phenobarbital and calcium gluconate but had a convulsion, became comatose and died nine hours after admission.

At necropsy the brain which weighed 1475 g. (normal: 1243-1273 g.) crowded the cranial cavity and appeared large and tense. Slight meningeal congestion was noted. The gyri showed slight flattening, and minor hippocampal herniation was noted. There was also slight coning of the cerebellar tonsils. Multiple sections revealed only cerebral edema. The liver was normal in size, shape and colour.

Case 4

A 5½-year-old boy presented with a history of chickenpox and fever for five days, vomiting, drowsiness and restlessness for two days, and on the day of admission a convulsion for which he was given Sodium Luminal (Winthrop) 2 grains intramuscularly. On examination he was drowsy and lethargic, and his pupils were dilated. The optic discs showed slight blurring on the nasal side. Cerebrospinal fluid pressure was 160 mm. H_2O; the fluid contained 3 lymphocytes per c.mm., protein 21.4 mg. per 100 ml., and sugar 12 mg. per 100 ml. Blood sugar was reported as less than 5 mg. per 100 ml. and serum proteins as 5.2 g. per 100 ml. On the day of admission he became unconscious and hyperpneic, and assisted ventilation was begun. On the second day the optic discs showed early papilledema. His temperature rose and fell for five days. He was given intravenous fluids, including 50% glucose, 20 ml., Levophed (Winthrop), Solu-Cortef and a blood transfusion, and his acidosis was corrected. Four days after admission the blood sugar rose to 226 mg. per 100 ml. and remained elevated until death on the seventh hospital day in spite of the use of insulin.

At necropsy the brain weighed 1589 g. (normal: 1260 g.). The lungs were congested, the heart grossly enlarged and the liver large and pale yellow. Sections from the cerebral cortex, thalamus, cerebellum and medulla were normal. The hepatic cells contained much fat, some bile and little glycogen. Inflammatory cells were present in the pancreatic ducts and there were some lymphocytes in the acini.

Case 5

A 6-year-old boy with a history of chickenpox for five days and vomiting for two days was admitted unconscious, with hyperreflexia and extensor plantar responses. The optic discs were normal but became slightly blurred on the second day. Cerebrospinal fluid pressure was 290 mm. H_2O; there were 8 to 9 lymphocytes per c.mm.; the protein was 25.5 mg. per 100 ml., sugar 76 mg. per 100

TABLE II
Laboratory Findings

	Cerebral type		*Cerebellar type*	
	Range	*No. of cases*	*Range*	*No. of cases*
Cerebrospinal fluid				
Cells	0 - 260 c.mm.	23	0 - 68/c.mm.	29
Protein	5.2 - 75.8 mg.%	14*	16.3 - 52.0 mg.%	19*
Viral culture	Negative	16*	Negative	16*
Electroencephalogram	12 cases 10 diffusely abnormal 2 normal		21 cases 4 abnormal 17 normal	

*All cases in which determination was made.

ml. and chloride 124 mEq. per litre. Blood sugar was 87 mg. per 100 ml. He was treated with intravenous fluids, Solu-Cortef, mannitol, curare, calcium gluconate, transfusion and assisted ventilation. The blood pressure rose to 180/80, spasticity developed, his pupils became dilated; the temperature rose; hyperventilation developed and the child seemed decerebrate. Death occurred after two days. At necropsy the brain was hyperemic and there was some herniation of the cerebellar tonsils. There were lipid droplets in the endothelial cells of the capillaries of the brain. Some cortical neurons showed considerable swelling, with fading nuclei and eosinophilic cytoplasm. The walls of a few arterioles or capillaries were infiltrated with mononucleocytes. The liver was enlarged and yellowish. There was marked fatty infiltration of the liver and the kidney tubules.

B. Cerebellar type

The main findings in this form of illness are also listed in Tables I and II.

The symptoms of central nervous system involvement began anywhere from four days before the eruption (reported in one case) to as long as 14 days after its appearance, the average length of time being 5.5 days. Hospital admission occurred anywhere from two to 30 days after onset of the rash, the average being 10.1 days. The length of stay in hospital ranged from two to 21 days, the average being 7.4 days.

Nine cases (32%) showed a CSF cell count above 10 per c.mm. and lymphocytes were the only type of cell noted. The protein was elevated in four cases (21%).

Where the electroencephalograms were abnormal they showed excess slow wave activity. In a second test 11 days after the first, one child had a normal tracing.

Bed rest was used in varying degrees in all cases, and treatment was generally simpler than for patients with the cerebral type lesion. Fewer drugs were used. Seven patients were discharged as cured and the remainder as improved.

Of the 20 patients who had ataxia only two were followed up in this clinic; they were normal in four weeks. One child who had slurred speech was improved. Transient personality change was noted in two cases.

C. Aseptic meningitis

The details of four cases which seem to fit best this classification are briefly described below.

Case 6

A 4-year-old boy developed a chickenpox rash 12 hours before admission, and fever and delirium six hours later. He was admitted with a rectal temperature of 104° F. and congestion of ears, nose and throat. Though he was alert and well oriented, he had signs of meningismus. The CSF contained 20 cells per c.mm., all lymphocytes; the Pandy test was negative. He improved rapidly with acetylsalicylic acid and phenobarbital and was discharged after two days.

Case 7

An 18-month-old boy was admitted with chickenpox rash and fever of three days' duration. He had had a convulsion on the day of admission. On examination he was lethargic but awake. The rectal temperature was 104° F. and the ears and throat were infected. Peripheral leukocyte count was 20,000 per c.mm. The CSF contained 30 lymphocytes per c.mm.; protein was 76.0 mg. per 100 ml., sugar 78.5 mg. per 100 ml.; viral culture was negative. The patient was treated with erythromycin and discharged as cured one week later. No EEG was taken.

Case 8

A 6-year-old boy had had a chickenpox rash for six days. He became restless and irritable, and complained of headache for a day and a half before admission. On admission the oral temperature was 100° F. Eczema, healing chickenpox lesions and meningismus were noted (Kernig's sign positive). In the CSF were 8 lymphocytes per c.mm.; sugar was 68.8 mg. per 100 ml.; protein was 56.5 mg. per 100 ml. and culture for virus was negative. No EEG was recorded. The child gradually improved during his seven days in hospital.

Case 9

An 11-month-old infant was feverish and irritable for one day and developed a convulsion on the day of admission. He was known to have had contact with chickenpox one week earlier. On admission the rectal temperature was 102.8° F. On examination he was sleepy and irritable and had a questionable rash on the upper chest. Lumbar puncture revealed 80 lymphocytes per c.mm. and a negative Pandy test. Viral culture produced no growth. Peripheral leukocyte count was 6000 per c.mm. The rash was not diagnosed as chickenpox for three days, during which time the fever gradually subsided. No treatment was given other than supportive measures and he was discharged home in quarantine.

In each of these cases the history of a convulsion or the finding of meningismus warranted a lumbar puncture and this resulted in the discovery of pleocytosis and, in two cases, increased protein in the spinal fluid. The illnesses ran a benign course and the children were all discharged as cured as far as the central nervous system was concerned.

D. Myelitis

One case belonged in this category.

A 9-year-old boy presented with a history of chickenpox three weeks before admission. A week later he was feverish and vomited. Ten days before admission he developed headaches and weakness of both lower limbs. Examination revealed weakness in both legs and feet, with bilateral ankle clonus, and he dragged his right leg. Tendon reflexes, plantar responses and co-ordination were normal. The CSF contained 31 lymphocytes per c.mm.; sugar was 58.3 mg. per 100 ml.; protein was 40.6 mg. per 100 ml. The Pandy test was positive. Viral culture was negative. The peripheral leukocyte count was 4600 per c.mm. and the electroencephalogram was normal. The patient remained in hospital 11 days and was discharged improved. Three weeks later he complained of a slight limp when he was tired, but examination revealed no abnormalities. In another six months' time there were no complaints.

Clinical picture

Our study shows that a typical case of "cerebral" encephalitis would have an equal chance of being a boy or girl of about 5 years of age who had been ill with chickenpox for approximately four and a half days before the symptoms or signs of encephalitis began to appear and in two more days would be admitted to hospital. The length of time in hospital would be brief if the child died, or if the case was mild; otherwise the patient would remain for one week. Vomiting, fever, lethargy, convulsions and

headaches would be the likely complaints, and specific physical findings would be noted if the sensorium was involved, with less clearly defined or variable signs if the cranial nerves or motor or reflex neurological systems were affected. A mild lymphocytosis in the spinal fluid might be noted and the protein would less likely be elevated. No virus would be cultured from this fluid. An electroencephalogram would be abnormal, showing usually diffuse slow-wave activity. Treatment would be supportive. Two out of three cases with the cerebral type of lesion would survive and most likely recover completely. If the child died, cerebral edema would be the main finding at necropsy.

A typical case with cerebellar involvement would have an equal chance of being a boy or a girl, would be about 5 years of age and would begin to develop symptoms or signs of this complication about five and a half days after the eruption had begun. The patient would likely be admitted to hospital in another four and a half to five days and would remain there a week, during which time the signs and symptoms would regress. The most frequent complaints on admission would be staggering, vomiting, listlessness or drowsiness, and headache, and the main physical finding from examination of the nervous system would be ataxia. A lymphocytosis might be present in the spinal fluid, and elevation of the protein, though unlikely, would be mild. Culture of the fluid for virus would be negative. The electroencephalogram would be normal and treatment would consist chiefly of bed rest. All cases would survive and recover completely.

The aseptic meningitis cases also would run a brief benign course requiring only supportive therapy. Because of its rarity in our series it is impossible to define a typical clinical picture of myelitis.

TABLE III
Treatment and Results

	Cerebral type	*Cerebellar type*
Treatment		
Bed rest	23	29
Intravenous fluids	18	10
Sedation*	18	63***
Steroids**	9	0
Acetylsalicylic acid	4	5
Assisted ventilation	3	0
Results		
Fatalities	8 — 5 males — 3 females	0
Survivors	15 — 7 males — 8 females	29

*Paraldehyde, phenobarbital, diphenylhydantoin sodium, reserpine.
**Solu-Cortef (Upjohn), dexamethasone, prednisone.
***Chlorpromazine, phenobarbital.

Discussion

The presenting signs and symptoms indicate that more than one area of the brain may be involved in the encephalitic process. In some of the cerebellar cases the cerebral cortex was also affected though less seriously and for a shorter time, indicating that the clinical picture is not always clear-cut. By separating the two major types the prognosis becomes easier. Appelbaum, Rachelson and Dolgopol[1] list the mortality in their series as 5%. In our experience the mortality in the cerebellar type was nil and in the cerebral 35%.

Standard texts usually refer to neurological complications in passing but in the small space allotted to the subject can give only the briefest outline of characteristic features. Also, most papers deal with an isolated case or two, and these usually fall into the two main clinical patterns outlined above.[2-5] The major studies of central nervous system involvement have been conducted by Underwood[6] in Britain before 1935, Appelbaum and his colleagues[1] in New York before 1953, Gibbs *et al.*,[7] who studied common types of childhood encephalitis and reported their findings early in 1964, and Boughton[8] of Australia who reviewed a series of 39 cases of chickenpox with neurological complications. The importance of the encephalogram,[7] of the development of hyperpyrexia, coma or ascending paralysis[8] in determining the prognosis requires emphasis. The outlook is most serious for patients with coma. Our management of cerebral encephalitis varied depending on the individual findings, but in severe cases it was aimed primarily at reduction of cerebral edema (Table III).

Necropsy was performed in five cases, and in one, a male, the findings approximated those of classical Reye's syndrome. Two other males showed the visceral changes, but one had an elevated blood sugar and the other had normal levels of sugar in the spinal fluid and blood.

The main findings of cerebral edema and vascular engorgement in the brain with lack of cellular involvement and negative viral cultures of brain and spinal fluid provide no answer to the question whether there is actual direct invasion of the tissue by chickenpox virus or merely a form of tissue reaction prompted by the presence of virus elsewhere.

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