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A Study of Sixteen Fatal Cases of Encephalitis-like Disease In North Carolina Children

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The etiology of diseases and deaths reported as encephalitis represents one of the most perplexing problems in the field of infectious disease—to the clinician, the epidemiologist, and the virologist. In 1960 this ill-defined entity, "infectious encephalitis of unknown etiology," accounted for 1335 or 52 per cent of all cases of infectious encephalitis reported to the Encephalitis Surveillance Unit, Communicable Disease Center, Atlanta, Georgia¹. In 1961 encephalitis of unknown etiology was by far the largest category (56.3 per cent of a total of 2143 cases reported by state epidemiologists). Mumps and measles encephalitis represented 31.5 per cent and arthropod-borne, varicella, influenza, post-vaccinial, and unspecified encephalitis represented the balance.

Early in 1962 a rapid increase in the reporting of fatal encephalitis-like disease in North Carolina children was noted. From January 1, 1962, until April 30, 1962, a total of 27 cases involving children 15 years of age and under was reported to the North Carolina State Board of Health. Preliminary evaluation of the cases reduced the number of cases of true encephalitis-like disease in children to 16. The other 11 cases were due to causes rather conclusively not encephalitis, or causes without enough documental information for proper evaluation. A survey of all reported deaths of meningoencephalitic disease of unknown etiology in this age group in the previous five years in North Carolina demonstrated this increase.

The numbers cited in table 1 represent the total number of cases of meningoencephalitis of unknown etiology by year. It

appeared to us that an unprecedented phenomenon, as evidenced by the number of encephalitis-like deaths in this age group, was occurring in North Carolina.

Table 1
Cases of Fatal Meningoencephalitic Disease of Unknown Etiology*

Year	No. Cases
1957	9
1958	15
1959	11
1960	5
1961	9

*International Classification of Diseases. 340.2 meningitis, except meningococcal and tuberculous, due to other specified organism; 340.3 with no specified cause; 343 encephalitis, myelitis, and encephalomyelitis.

We were further stimulated by a letter from the Department of Health, Commonwealth of Pennsylvania², which reported four deaths in children aged 7½, 8, and 10 years, respectively, in January, 1962. These children had a relatively mild upper respiratory disease which was followed by a period of apparent recovery. Three to five days later, however, there was an onset of fever, vomiting, and hyperirritability which progressed to produce drowsiness and coma. In spite of supportive therapy, the course of each patient was described as rapidly downhill, with death occurring approximately 48 hours after the onset of vomiting. These cases seemed remarkably similar to those occurring in North Carolina.

Investigation

We began to investigate each case as rapidly as possible after it was reported. An attempt was made to accumulate all pertinent facts relating to the history, physical and laboratory findings, postmortem examination, and bacteriologic and virologic materials. Inquiries were made of attending and referring physicians, pathologists, hos-

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pitals, and the families of the children, and all the information was carefully appraised.

The 16 cases were broadly distributed geographically, as demonstrated in figure 1. This figure also shows the distribution of cases by month of onset. All but three of the children came from predominantly rural areas. Figure 2 demonstrates the distribution of cases by month of onset and race, sex, and age. It is of particular interest that the peak of the cases reported coincides with that of reported influenza B in North Carolina during 1962.

Case Summaries

Accompanying charts represent all positive information available from each of the 16 cases. Since in many instances there was a delay between the actual death and our notification it was impossible for us to obtain the necessary specimens and studies in every case—which would have been ideal.

Signs and symptoms

Premonitory signs and symptoms were generally similar and almost uniformly mild. In 4 of the cases the onset of the en-

cephalitic syndrome appeared within less than 24 hours after the onset of illness. In 2 other children, premonitory signs and symptoms were less than three days in duration. Similar to the Pennsylvania report, 4 of the patients manifested mild, nonspecific signs and symptoms for three to five days before the onset of severe illness. The remaining 5 had symptoms from five to eight days before the onset of apparent encephalitis. Only 1 of the 16, an 8 year old juvenile diabetic, had a significant past medical history.

As noted on the case summaries, 2 children complained mainly of leg pain; emesis was prominent in 6, sore throat in 2, lethargy in 2, and cough in 3. Six of the 13 experienced mild respiratory disease that occasioned no particular parental concern. Low-grade fever was noted in only 4 children prior to the beginning of the devastating symptomatology.

At the onset of the encephalitis-like illness, marked elevations of temperature were recorded in 6 children; and tonic-clonic movements, convulsions, or both, were present in 10 of the 16 children. Eleven

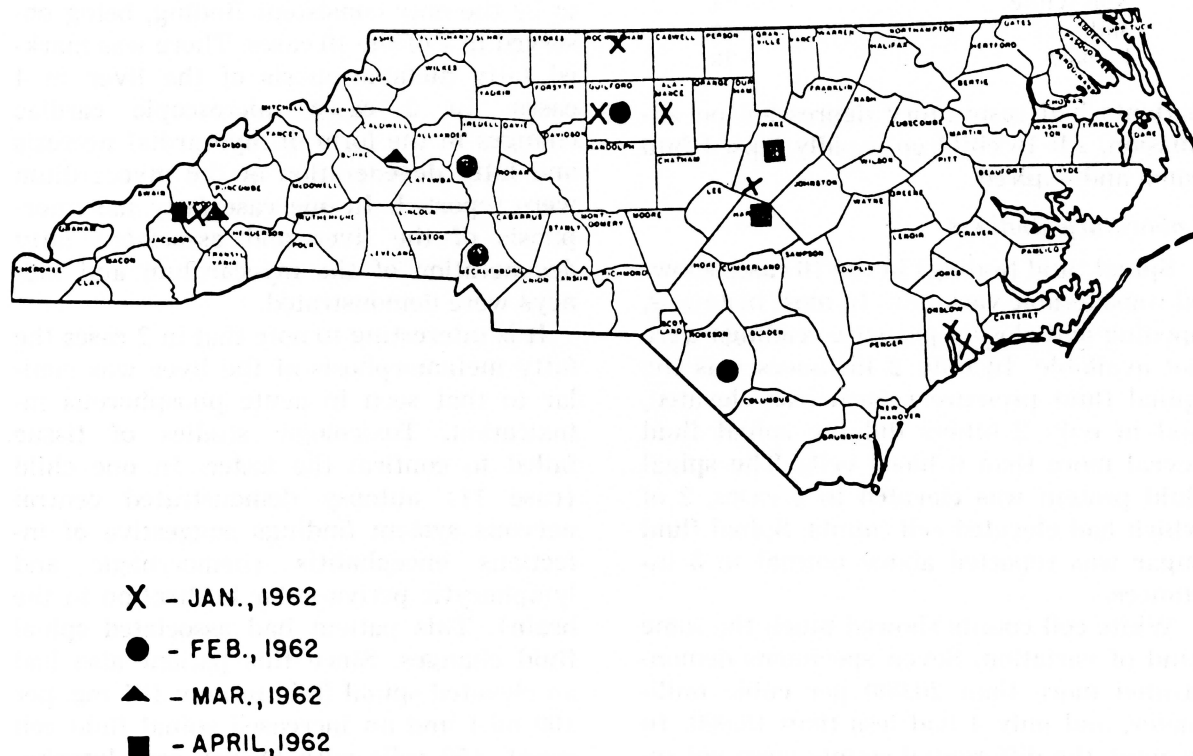


Fig. 1. Geographic location and month of onset.

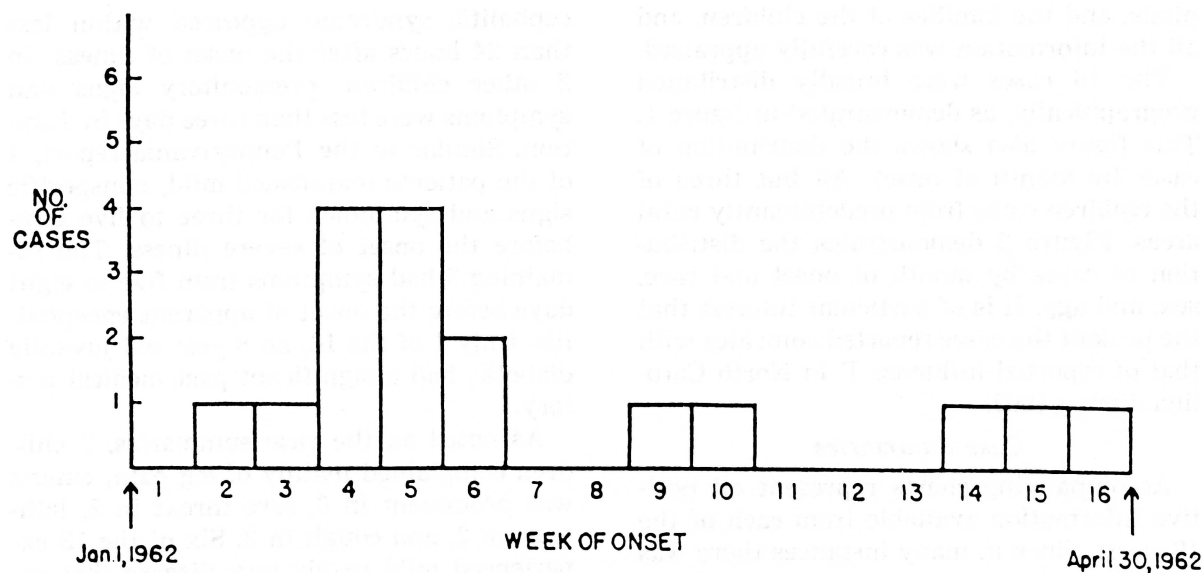


Fig. 2. Cases by week of onset.

Table 2
Age Incidence

Years	No.
0-1	2
1-3	3
6-10	7
6+	3

Table 3
Race and Sex Incidence

White	15
Non-White	1
Male	6
Female	10

patients had respiratory depression on admission. All 16 children rapidly lapsed into coma and expired.

Laboratory findings

Spinal fluid findings in the 16 cases showed considerable variation. In most instances, opening and closing pressure readings were not available. In only 2 instances was the spinal fluid pressure reported as elevated, and in only 2 others did the spinal fluid reveal more than 6 blood cells. The spinal fluid protein was elevated in 4 cases, 2 of which had elevated cell counts. Spinal fluid sugar was reported above normal in 3 instances.

White cell counts showed much the same kind of variation. Seven specimens demonstrated more than 20,000 per cubic millimeter, and only 4 had less than 10,000. In general, the differential counts were not remarkable. Considering the severity of the

cases, the blood chemistry values were not remarkable. The few abnormal blood chemistry studies reported were consistent with the particular cases.

Autopsy findings

Fortunately, postmortem examinations were done immediately following 13 of the 16 deaths. Marked cerebral edema seemed to be the only consistent finding, being observed in 7 of the 10 cases. There was marked fatty metamorphosis of the liver in 4 cases. In 2 cases microscopic cardiac changes in the form of myocardial necrosis and fatty degeneration of the myocardium were reported. In one case fatty metamorphosis of the liver and associated fatty degeneration of the myocardium and kidneys were demonstrated.

It is interesting to note that in 2 cases the fatty metamorphosis of the liver was similar to that seen in acute phosphorous intoxication. Toxicologic studies of tissue failed to confirm the latter. In one child (case 11) autopsy demonstrated central nervous system findings suggestive of infectious encephalitis (hemorrhagic and lymphocytic perivascular infiltration in the brain). This patient had associated spinal fluid changes. Since this patient also had an elevated spinal fluid protein (61 mg. per 100 ml.) and an increased spinal fluid cell count, (56 cells with 88 per cent lymphocytes), it is the only case in the series which

S U D D E N D E A T H S I N C H I L D R E N

NO.	AGE	RACE	SEX	CLINICAL SIGNS AND SYMPTOMS	LABORATORY FINDINGS		POST-MORTEM FINDINGS		VIROLOGY FINDINGS	
					LABORATORY FINDINGS		POST-MORTEM FINDINGS		Specimens Available	Results
1.	M.T.	7	W	F	Few aches and pains in back of legs for two days. Sudden onset of Jacksonian type convulsion. Afebrile on admission. Fever to 106° developed shortly. Decorticate rigidity developed and 20 hours after admission another seizure occurred followed shortly by respiratory arrest.	WBC - 30,250 with 70% segs CSF - Normal, protein -45.5mg.% BUN - 8.25mg.%; Blood sugar - 231mg.% Blood culture - no growth	Cerebral edema both grossly and microscopically. No evidence of septic meningitis. There was damage to brain mainly in area of pons, characterized histologically by vacuolization of the myelin and loss of staining quality. Marked pulmonary edema and intra-alveolar hemorrhage.	Serum specimens obtained three days apart. Brain	ECHO B isolated from brain. The pt's sera did not neutralize virus isolated from brain.	
2.	R.Y.	9	W	M	Vomiting for three days. Admitted to hospital dehydrated. Shortly after admission had a generalized convulsion. Followed by thrashing about in bed and intermittent tonic-clonic seizures. Afebrile, on Adm., Coma ensued, Temp. rose to 104°, and respirations became labored. Pt. expired 28 hours after admission.	WBC - 9200 with 70% segs CSF - Protein and sugar normal, pressure - 130 mm.	No autopsy.			
3.	M.McL.	13	W	F	History of lethargy, headache, mild gastric pain, regessing and exacerbating; 4 days pta she began vomiting. One day pta - disoriented with purposeless movements. Tracheotomy on admission failed to halt respiratory distress. She was maintained on a respirator and levo-phed for the next few days until death.	WBC - 17,350 with 85% polys CSF - Protein - 134 Blood sugar-140mg%; BUN-37mg% Na-143, K-57, Cl-105, CO ₂ -20. meq/l Cold agglutinins-1:40 CSF culture, rectal swab, urine culture - neg. EKG-paroxysmal tachycardia with variable block EEG-profusely abnormal with disturbance of cortical rhythm over both hemispheres.	Brain showed wide-spread neuronal necrosis, early degeneration of myelin, but no inflammatory reaction in either the brain or meninges. Pituitary shows infarction of anterior lobe. Heart-spotty myo-cardial necrosis. Liver-marked fatty metamorphosis.	Blood, spinal fluid, stool, throat swab.	Negative	
4.	S.M.	8	W	F	Intermittent upper respiratory symptoms for eight days pta. Lethargy began 2-3 days pta. Vomiting frequently during the 24 hours pta. On admission child restless and confused. Became increasingly groggy, reacting only to deep, painful stimuli. Despite digitalization and endotracheal suction, the child died two days after admission.	WBC - 47,300 with 35% neutrophils CSF - negative CO ₂ -19.4; K-5.5; Cl-111; Na-150 meq/l; BUN-14.2mg%; Transaminase-392 SGT units; Total bilirubin-0.8mg%	Marked cerebral edema with herniation of cerebellar tonsils through the foramen magnum, focal hemorrhages--cerebral cortex, broncho-pneumonia, pulmonary edema, vascular congestion, marked fatty change of the liver.	None		

pta - Prior to Adm.

CLINICAL SIGNS AND SYMPTOMS

LABORATORY FINDINGS

POST-MORTEM FINDINGS

Specimens Available

VIROLOGY FINDINGS

Results

5. W.G. 12 W F Two days pta felt tired and listless, intermittent vomiting began. Shortly before admission became completely uncoordinated, inattentive and unresponsive, going into coma with carpo-pedal spasm, muscular tremor, and tightness of extremities. Temperature 102° on admission. Pupils fixed and dilated, not responsive to pain, child rapidly became more deeply comatose with respiratory depression and expired 13 hours after admission.

6. H.T. 10 W M Sore throat for 3-4 days pta. Vomiting one day pta. Became delirious and semi-comatose shortly pta. On admission did not respond to oral communication, withdrew and rotated head upon physical stimulation. Pupils dilated but responded to light. TM's injected and pharynx inflamed. Patient rapidly became decerebrate. He died 13 hours after admission.

7. H.T. 13Mo. W M Six days pta rhinorrhea was noted. Two days pta coughing and coryza. One day pta mild respiratory distress. This was more severe on admission. Immediate transferral to referral hospital was made. Here he appeared moribund, moderate cyanosis and marked respiratory depression were noted. Temperature 103°. Reflexes were hyperactive. Shortly after admission, respirations ceased.

8. J.S. 6 W F Low-grade fever for three days pta. Then onset of tender muscles in the thighs was noted. Child returned home, however, was alert and playful and went to bed that evening. Her only complaint at bedtime was a headache. Father awakened by a noise during the night. Child had stopped breathing and entire body was cold. Moribund on arrival at hospital. Blood pressure maintained for short time with Soluortef drip but she expired shortly.

WBC - 10,900 with 61% segs
 CSF - 6 cells, 12 segs, 4 small monos, Protein-32.5 mgm, Sugar-93 mgm.
 Na-140; CO₂-18.6; Cl-112 meq/l; BUN-42.5 mgm; Transaminase - 1270 SGOT units
 Lung culture-positive Staph Albus
 Spinal fluid culture-no growth
 Blood culture - no growth
 Liver - negative for phosphorous, heavy metals, lead

WBC - 8,100 - 76% segs
 CSF - 4 WBCs, Sugar-92 mgm, Protein-70 mgm;
 Spinal fluid culture-negative

WBC - 9,900 with 80% segs
 CSF - normal
 Blood, tracheal and stool cultures were negative, both for bacteria and viruses.

WBC - 8,000 with a normal differential

Edema of the brain. Small focal hemorrhages in the brain. Meningo-encephalitis and meningo-myelitis (small amount inflammation in a few small foci). Intra-pulmonary hemorrhage and acute bronchitis. Fatty degeneration of the myocardium. Marked fatty metamorphosis of the liver. Fatty degeneration of kidney.

Evidences of infection were lacking in the heart, lungs, adrenals, meninges, anterior horns, and spinal cord, etc. The only morphologic diagnosis from this necropsy was acute splenitis.

No autopsy.

Cerebral edema, bilateral atelectasis with rather marked pulmonary edema, and intra-alveolar hemorrhage. A moderate laryngitis was noted. Rest of autopsy negative.

Liver, lung, heart, feces, brain from patient. ECHO B from brain and lung. Coxsackie B₄ from feces of patient. Stool specimens and sera from parents. Sera obtained from parents did not neutralize isolates from patient.

Heart Kidney Liver Brain
 Coxsackie B₄ isolated from brain.

See laboratory findings.

None

NO.	AGE	RACE	SEX	CLINICAL SIGNS AND SYMPTOMS	LABORATORY FINDINGS		POST-MORTEM FINDINGS		VIROLOGY FINDINGS	
					Specimens Available	Results	Specimens Available	Results		
9.	S.B.	9Mo.	W	M	Rhinorrhea and slight cough 3 days pta.-- vomiting and low-grade fever. Morning after admission patient could not be aroused. Seemed unresponsive. Was transferred to a University hospital. Tonic-clonic movements noted on arrival. Also breathing rapidly, marked chest retraction, palpable liver, hyperactive reflexes. Bright light was avoided. Left pupil larger than right, but both reacted to light. Began having generalized tonic-clonic convulsions on second hospital day and became more rigid, pupils dilated. On 4th day he became apneic and his pulse slowed. He expired on the 5th day.	WBC - 23,000 - 40 polys. 15 stabs and the rest small lymphs CSF - 140 mm. pressure, no white cells BUN-25mgm.; Na-141; K-6; Cl-107; CO ₂ -8 meq/L Throat culture - negative Urine culture - negative EEG - abnormal - consisting of a focalization involving the left parietal area as well as what appeared to be a mesencephalic movement.	Acute encephalopathy with anoxic neuronal degeneration, acute bronchitis with minimal broncho-pneumonia, acute pancreatitis with fat necrosis.	Blood, throat swabs	Negative	
10.	J.E.	6	W	F	Slight fever, nausea, vomiting 24 hours duration pta. One week prior to this had had a sore throat treated with antibiotics. Began vomiting one day pta and continued despite anti-emetics. Shortly after admission began convulsing. Respirations began to be labored and suddenly ceased. Emergency tracheotomy and respiratory apparatus maintained patient until her death 18 hours after admission.	WBC - 14,900 with 63% segs CSF - 1 WBC. Sugar-89mgm; Cl-132meq/L Protein-44mgm BUN-17.9; CO ₂ -10meq/L Tracheal aspirant cultured negative. Blood culture - negative Spinal fluid culture - negative	Marked brain swelling, no evidence of inflammatory change, moderate fatty hepatomegaly, basilar pulmonary hyperemia and edema, renal cortical pallor.	None		
11.	D.L.C.	6	W	F	Child had a "cold" for week pta - treated with aspirin. Onset of fever one day pta with some quivering, shaking and anorexia. On day of admission she complained of pain in her chest, cough and didn't seem to recognize her mother. She later vomited. On admission she was semi-comatose but could be roused by painful stimuli. Neurologic exam and optic fundi were negative. Temperature 101.8°. Morning after admission, generalized convulsion with twitching of the arms and legs was noted. Respirations became very labored. Tonic-clonic movements began and continued until her death five hours later.	WBC - 26,400 segs 65% CSF - 56 white cells per cubic mm with 88% polys and 11% lymphocytes noted on spinal tap; Protein - 61 CO ₂ -15; Cl-106; K-51; Na-132meq/L Spinal fluid blood culture - no growth	Largely limited to the brain. Lymphocytic and hemorrhagic infiltration of the perivascular (Virchow spaces). Pathologists impression: influenza encephalitis.	None		
12.	T.T.	1	W	H	Coughing and fever intermittently for one week pta. Anorexia for the day pta. Listlessness and twitching 4 hours pta. Admission temperature 101°. Responded only to painful stimuli, weakness of left arm and leg were evident--head was turned to right. Neck flaccid, lungs filled with moist rales in the lower lobes, hyper-reflexia was noted. Twitching and semi-comatose state continued intermittently for next 4 days. On fifth day, left hemiplegia noted, on sixth day inability to swallow and tonic-clonic movements continued. On ninth day heart sounds irregular, respiratory depression noted and child died shortly thereafter.	WBC - 22,300 with 89% segs CSF - cells 0. Protein-19mgm; Sugar-80mgm; Pressure - 260 mm/ 340 mm on separate occasions	Autopsy not granted.			

POST-MORTEM FINDINGS

LABORATORY FINDINGS

CLINICAL SIGNS AND SYMPTOMS

NO. AGE RACE SEX

Specimens Available

Results

NO.	AGE	RACE	SEX	CLINICAL SIGNS AND SYMPTOMS	LABORATORY FINDINGS	POST-MORTEM FINDINGS	Specimens Available	Results
13.	G.D. 8	W	F	Patient a juvenile diabetic, normally under good control. One day pta started vomiting. Vomited all day, retaining nothing. She was talkative and hyper-irritable at admission. Diabetic acidosis was treated. Approximately 8 hours after admission, although acidosis seemed to be under good control, respirations became very slow and she suddenly stopped breathing. Fever to 103. She was maintained on a Bennett respirator for 4 days, along with supportive therapy. She died shortly thereafter, however.	Blood sugar - 500mgm% on admission. 300mgm% 6 hours after adm. "electrolytes normal" on second day of hospitalization CSF - within normal limits	Brain extremely soft and edematous, swelling throughout. Focal hemorrhages were noted within the pons and mid-brain. No purulent meningitis or abscess was present. Mild bronchitis and peri-bronchitis was noted. Otherwise, autopsy findings not remarkable.	Brain Spinal fluid Lung Liver Stool Spleen Throat washings and stool specimens obtained from the pt's siblings.	ECHO 8 obtained from the pt's feces and lung. Also obtained from throat washings of mother, 1 sibling and from stools from the pt's siblings.
14.	D.P. 18Mo.	W	F	Child found in crib with open bottle of APCs. Three and one-half hours later was noted to be lethargic and unstable on her feet. Had had a mild upper respiratory infection and low-grade fever for two days previous to this incident. Admitted to the hospital where exam revealed lethargic infant with respiratory rate of 40 per minute. CO ₂ was 14.4 meq and salicylate level reported as normal. Child appeared much improved after fluid treatment. Also, electrolytes returned to normal after fluid treatment. However, 36 hours after admission a generalized convulsion occurred. Reflexes hyperactive, then disappeared. The patient expired 42 hours after admission after progressive respiratory depression.	WBC - 25,800 with 68% neutrophils CSF - no significant abnormality CO ₂ - 14.4; Na-134; Cl-110meq/L Blood salicylate level - within normal limits on two occasions	Marked cerebral edema. Liver was deep yellow in color although histologic study failed to reveal anything remarkable. Terminal edema and vascular congestion noted.	None	None
15.	B.M. 4Mo.	C	F	7-10 days pta - upper respiratory infection. 3 days pta - drainage from ear. 1 day pta irritable, vomiting. On adm. temperature 99, comatose and unresponsive to pain. Respirations rapid, pupils reacted sluggishly. Hyperactive deep tendon reflexes. Cheyne Stokes respiration began. Hypertonic dehydration was corrected. Generalized convulsions began. Died 3 days after admission.	WBC - 10,800, 51% PMN's CSF - No WBC's, Sugar - 65mgm% BUN-26mgm%, CO ₂ -15.3 meq/L, Na-155, K-4.7	Mucositis, early, neurons of hippocampus, acute otitis media, interstitial pneumonia, acute bronchitis.	From patient No results to date. Stool specs. from 5 sibs and parents. Polio 1 isolated from stool of one sib.	ECHO 8 isolated from stools of 2 sibs and 1 parent. Polio 1 isolated from stool of one sib.
16.	D.W. 13	W	M	One day pta - nauseated with headaches, generalized aches and pains. Somewhat confused the following morning. On admission, talkative, throat was red, stiff neck with sluggish reflexes. Became incoherent. Next day emesis of coffee ground material. Temp. 103. Reacted only to pin-prick. Pupils dilated but reacted sluggishly. Despite tracheostomy became cyanotic. 3 days after admission seizures occurred. Remained semi-comatose until expired 10 days after admission.	WBC - 25,750, 65% segs CSF - 91 cells (lymphs 58%, monos 20%) protein - 52 mgm-% Na-147 meq/L, K-3.7, CO ₂ -25 Blood culture and CSF culture - neg.	Findings largely localized to the brain. Brain of marked red-purple color. Almost jelly-like in consistency. Hemorrhages (petechial to few mm. in size) throughout. Marked perivascular hemorrhages throughout. Little, if any, evidence of meningeal reaction.	Urine, throat washings, nasal swab	ECHO 8 isolated from urine.

had three features commonly associated with infectious encephalitis.

There were no remarkable bacteriologic findings. In 8 of the 16 cases materials for virologic study were available from the patients, and in 1 case specimens from the family were available. In three cases ECHO 8 was isolated from the brain, lung, feces, and urine respectively. In one case Coxsackie B₁ was isolated from the brain. In one case ECHO 8 was demonstrated in the brain and the lung, and Coxsackie B₁ in the feces. In the case in which ECHO 8 was isolated from the lung and feces it was also isolated from the throat washing of the mother and one sibling, and from the stools of two other siblings. In one case in which no virologic specimens from the patient were available, ECHO 8 was isolated from the stools of two siblings and one parent, and polio 1 was isolated from the stools of another sibling. In the 2 cases in which sera from either the patient or the family were available, we could not demonstrate neutralization of the virus isolated.

Virology Technique

Specimens collected for virologic studies included stools, swabs, blood, urine, cerebrospinal fluid, and tissues taken at autopsy.

Processing of specimens: Stool and tissue specimens were extracted to make a 20 per cent suspension in neutral Hank's solution. The suspensions were centrifuged and antibiotics were added to the final supernatants. Swabs were shaken vigorously in 2 ml. of the same diluent. Fluid specimens were processed by addition of antibiotics. All specimens, extractions, and cultures were stored at 20°C.

Isolation and identification: Each specimen (0.2 ml.) was inoculated into three tubes each of Rhesus kidney (MK) and Hela Gey (H) tissue culture. A growth media used for MK cell culture consisted of 5 per cent calf serum, 0.5 per cent lacto albumin hydrolysate in Hank's base, and for Hela, 10 per cent calf serum in Media 199, both with antibiotics. The cell cultures were inoculated as soon as a monolayer was established and the growth media exchanged for

maintenance media (same as growth except for MK 2 per cent calf serum and for H 4 per cent calf serum was used).

These cultures were incubated at 36° C and examined each day for an eight-day period. Tubes showing cytopathic effect were harvested when 75-100 per cent of the tissue was disrupted. Tubes of culture were frozen overnight, thawed, cooled, and stored. Each of the specimens was inoculated into 24 hour old mice. Each specimen that was suitable was inoculated into egg embryo by the amniotic route. All viral isolations were identified by neutralization tests in monkey kidney.

Six to nine months later, tests of identification of these viral isolates were repeated. At the same time re-isolation was attempted using the original extractions of the specimens included in the study. The isolates obtained from this re-isolation procedure were also identified by neutralization tests in monkey kidney.

Discussion

It is well recognized that a serious perplexing clinical problem is posed by the infant or child who becomes acutely ill with fever, stupor, or coma and convulsions. Recently, Lyon, Dodge, and Adams² have recognized the difficulty in terminology and differential diagnosis in children with this sort of nervous syndrome. They identify these clinical states as being distinguished by generally negative laboratory results and refer to them as acute encephalopathies of obscure origin. These are the syndromes which are associated with febrile illness, generalized convulsions, and neurologic disorders which occur without evidence of spinal fluid changes and are associated with swelling of the brain as a prominent finding.

Flewett and Houl¹ divided into four groups a collection of cases in which influenza virus has been associated with neurologic disturbances. The most dramatic group initially presented confusion and flaccidity, and showed little response to stimuli three days to two weeks following influenza. Their diagnosis was based on commonly accepted laboratory data.

Eli Gold and others³ recently studied the

entire problem of sudden deaths in infants. Among other things, they investigated a group of deaths which were associated with the isolation of Coxsackie virus, Group A₁. Even though histologic confirmation was lacking in these cases, the authors felt that their studies raised important questions concerning the pathogenesis of enterovirus infections and pointed out the need for further study.

It has been interesting to see the continuing evidence of a wide variety of clinical manifestations of Coxsackie and EMCO virus disease in infants and children. The serious nature of these illnesses is becoming more and more apparent. Current⁶ and McAllister⁷ have classified Coxsackie and ECHO virus by their association with symptomatic disease. Coxsackie B₁ has been associated with pleurodynia, aseptic meningitis, paralysis, myocarditis, and meningoencephalitis of the newborn, pericarditis, and undifferentiated febrile disease. ECHO 8 has been associated with diarrheal and respiratory disease. To our knowledge, there have been no series associating fatal encephalitic disease with Coxsackie and ECHO virus other than in infants. Recently, Walker and Togo⁸ reported a case of acute diffuse encephalitis associated with isolation of Coxsackie B₃ virus in a 9 year old child. They cite cases of encephalitis in a 16 year old boy, a 22 year old woman, and a 54 year old woman who demonstrated encephalitis-like disease due to Coxsackie B₁ and B₂. They also make reference to a case of fatal meningoencephalitis which was considered to be due to Coxsackie, Group A₅. Sabin⁹ has attributed encephalitis in older people to ECHO type 9.

Considering the review of literature, what then is the true relationship of the viruses isolated in 5 of our 16 cases with the true cause of disease in each case? If there is an association, it might indicate that in these 5 cases the virus was the etiologic agent. If this is true, then might it not also be true that the other 11 cases represent a similar type of disease in which the viruses were not isolated? The obvious alternative is that the virus isolations are coincidental and possibly unrelated to the true cause of dis-

ease. If enteroviruses do play a role in the etiology of fatal encephalitic disease, we feel that this series brings the question into sharp focus.

What then should be done to clarify this situation? We believe that it is imperative that every physician who faces such a problem should make every effort to identify the possible etiology. This effort should include intensive study of each case, allied with all available laboratory techniques, so that a collective study and analysis of such cases may reveal the true cause of this type of disease. This, of course, would mean that we cannot limit our investigation to the child, but must extend it to the family as well. Surely as we progress we must utilize methods of communication so that episodes such as we have experienced can be properly correlated with the experience of other investigators throughout the country.

Summary

We have presented the information which accumulated during the study of 16 deaths due to encephalitis-like disease in North Carolina. It is our hope that others will share our experience, that this presentation will add to the literature, and that it may contribute to the eventual clarification of the etiology of such cases.

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