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Central nervous system complications of measles

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CENTRAL NERVOUS SYSTEM COMPLICATIONS OF MEASLES

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CENTRAL NERVOUS SYSTEM COMPLICATIONS OF MEASLES

Although the incidence of central nervous system complications is rare in almost all of the acute febrile disease of childhood, they occur more commonly in association with rubeola than any other exanthem. Their recognition in the eighteenth century is evidenced by literature appearing as early as 1724, the majority of which was of German or French origin. In 1790 Lucas reported his case findings in the London Medical Journal but those on a pathological basis were made first by Barlow in 1886 in the British Medical Journal. Both Allyn and Hennoch made surveys of existing literature and collected case histories[10] available during the ensuing decade.

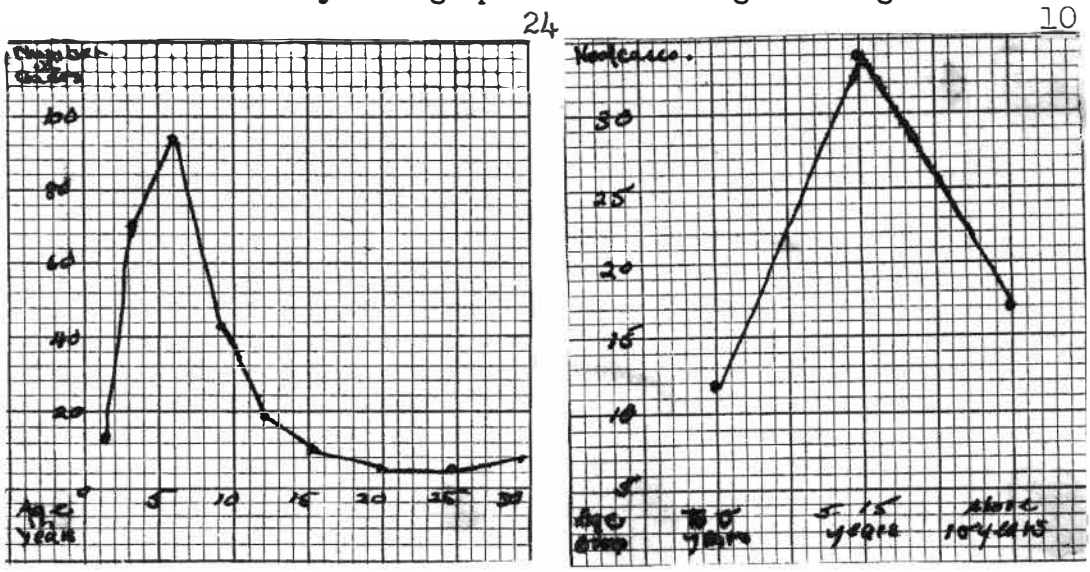
Then the incidence of the affliction was only sporadic and continued to be so until the last twenty-five years. The paucity of cases was paralleled by a dearth of reports in the literature, partly due to the fewness of number and partly due to failure of recognition of cases. That increase in published material has not paralleled the almost epidemic proportions assumed since 1923 is no doubt due in part to this latter factor and in part to the lack of established knowledge regarding the clinical course of the disease, and its cure.

Boeheim between 1905 and 1925 recorded 5940 cases of measles in the German literature, and estimated 0.4% as having central nervous system complications.[29] That the incidence of such complications with the exanthem has risen since then has been postulated as due to

one or both of two factors, namely the periodic change in the virus (assuming its neurotropic factor to be causative), and the environmental or genetic change in the host in the past two and one-half decades when it has been estimated as occurring from 1.2% to 2.0% of those afflicted with the exanthem. Here again must be mentioned possible incidence use on a basis of more accurate recognition of cases.

The age incidence of the complications coincides sharply with the age incidence of measles. Explanation of minimal deviation from this parallel in older age groups is explained by the fact that the central nervous systems of children are more unstable than those of adults and, therefore, more susceptible to the causative factors. No age in which measles may occur is devoid of danger of the complications.

Two case surveys are graphed below in regard to age incidence:



Geographical distribution also correlates fairly well with the incidence of measles and therefore is reported for the most part in large cities of the temperate climate. The Omaha Public Health Department does not record separately cases of the exanthem with central nervous system complications and those without it. Thus, no statistics are available for this area. Such is the condition commonly existing elsewhere so that isolated reports must be used in an attempt to obtain a picture of their incidence in this country. Individual writers in commenting upon these reports feel the statistics are inaccurately low and assert that if all cases were recognized and reported, incidence would be much higher.

Reports include:

1935 - 1936	Long Island	1:2600
1937 - 1938	Detroit	1:1500
1938 epidemic	Chicago	1:1000
1940	Newark	3:6585
1942	San Francisco	1:6000
1946	Southern Survey: incidence	.2%

The complications seem to show a predilection for the white race and some authors have asserted that they never occur in negroes. In my survey of the literature, I found one case reported of a nine year old negro boy.[21] No mention was made of any cases occurring among members of the Mongolian race.

There is a wide difference of opinion as to the cause of the manifestations, most of which has arisen as a result of pathological findings of divergent nature. Because of the evident association with measles itself, many believe that the rubeola virus has a neurotropic factor which sets up an active inflammatory process in the

tissue when carried there via the blood stream. From a known case of fatal measles encephalitis Gay and Holden made sterile broth cultives of the brain. These they injected into monkeys via nasal and subcutaneous routes producing in one, on the fifth day, a measles like exanthem with development, on the eighteenth day, of right sided and transient weakness. In the other, Koplik's spots and an exanthem were transient. Neither, when inoculated with the specific virus six months later, developed measles. Intrathecal injection into the brain of a rabbit failed to produce symptoms. Hearst produced a fibrinous meningitis when injecting the virus intrathecally into experimental animals. Although MacIntosh's results were negative, the above mentioned results suggest cause due to the virus itself.

The virus commonly persists in the blood stream no more than seventy-two hours after onset of exanthem but can persist as long as nine days. If the virus be causative of cerebral symptoms, it may be that its reaction in nervous tissue is due to its' retention there.

However, the lesion found on autopsy is no longer considered a true inflammatory one but rather a toxic degenerative one suggesting that not the virus itself, but the toxin it liberates produces the symptoms in those afflicted with the disease as well as animals inoculated. Of course, in order to produce toxin, the virus must be intially present so this theory is not contradicted

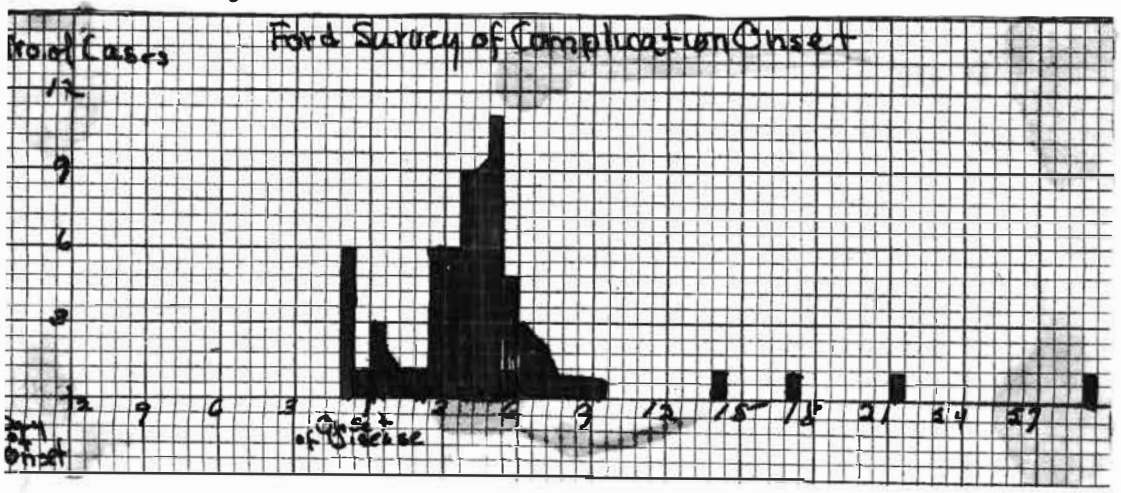
by experiments mentioned above. This toxin is considered very potent and unless there is a rapid defense reaction of the patient, death will occur before specific central nervous system symptoms develop. Damage to cerebral blood vessels seen on autopsy in those fatally afflicted suggests that it is carried by the blood stream.

Because the lesions formed are in many ways similar to those seen in similar complications of variola and varicella, the presence of a latent virus activated by all of these exanthems has been purported. One case following small pox vaccination had a history of measles some months earlier so that it was cited with question as to possible correlation.[36] However, were this a latent virus, why would the condition occur in the early pre-exanthem stage as it sometimes does? Also, the lesion in variola and varicella is marked by more lymphocytic infiltration and by far less complications than that of measles, a factor not explainable if the causative organism were the same.[35] In suggesting the possible neurotropic virus, herpes strains have been suggested. However, broth from autopsied brains when inoculated onto chick embryos fails to produce the characteristic lesion of herpes,[29] although inoculated subcutaneously, it has produced vesicle like lesions.

A fourth factor which at this time is largely discredited is that of an allergic response of the central nervous system at the height of the antibody reaction for symptoms can occur before the

onset of symptoms of the disease when antibody levels are but slightly elevated. Also, no foreign protein has been demonstrated as is present in such reactions as those of antitoxins. Putnam believes the lesions due to spontaneous vessel thrombosis due to an allergic swelling of vessel-walls, but most pathologists now believe this to occur as a result of toxic damage to endothelium and to decreased clotting time of the blood.

When viewed from any aspect, the clinical picture is as bizarre and varied as that of "the great imitator". Litvak considers only those cases which begin no more than fifteen days before or twenty-one days after the onset of acute rubeola symptoms to be part of the disease.[1] The former are rare but Ward has reported two such cases.[26] Neuberger reported one case of complications occurring sixty days after onset of the disease.[7] McCaulen's cases averaged the fifth to fifteenth post-exanthem day in onset and the statistics of Ford cover a range of two days pre-rubeola to six weeks after its acute onset. An overall average of time of onset is considered to be from four to six days after onset of the disease itself.



The symptoms obviously vary with the part of the central nervous system locally involved but these are usually masked early in the disease by several fairly constant generalized findings of abrupt or gradual onset.

Fifty per cent are of the former type of onset marked by increased irritability, convulsions and coma. Forty per cent are of the latter with headache and dullness progressing to drowsiness stupor and coma. The remainder may be restless and delirious, become confused and have characteristic muscle twitchings but never become comatose. Temperatures sometimes previously normal rise abruptly to 102°, 104°, or even 105°. Reflex findings usually positive are the Kernig, Babinski, and Grudzinski. Toxic psychoses are not uncommon.

A classification of symptoms based upon specific area involvements[28] may be divided as follows:

1. Diffuse cerebral symptoms with headache and often vomiting. Spinal fluid pressure is elevated, pupils are dilated, Kernig and Babinskis are positive and there is neck stiffness due to muscle rigidity. There are no focal signs and the symptoms are usually transient.
2. Multiple focal cerebral symptoms early are evidenced by stupor, muscle rigidity, myoclonic twitchings, and dilated fixed pupils with optic nerve edema. As the complications progress, the extremities become spastic. Tremor, choreiform or athetoid movements are seen. There is aphasia, and

stereotyped speech. Mental upset is characterized by excitement, emotional instability and apathy. Physical findings include positive Kernig and Babeniki reflexes, fixed pupils, clonus, and urinary retention. This condition is differentiated from tuberculous meningitis which runs a slow fatal course in which the spinal fluid cell count rises gradually and the spinal fluid pressure and sugar content fall gradually. It is also to be distinguished from epidemic encephalitis which runs a chronic progressive course with new symptoms developing months after disease onset.

3. Single focal cerebral involvement often is not seen until years later and may then be a residium of a widespread brief process such as hemiplegia or aphasia. If it develops early and abruptly it is characterized by focal symptoms and unconsciousness of brief duration.

4. Cerebellar involvement is marked by unconsciousness at onset and localization is revealed in convalescence by ataxia, intention tremor, nystagmus, loss of equilibrium and head tremor which tend to be residual. Differentiation from neoplasm as well as from epidemic encephalitis is to be made in diagnosis.

5. The cord syndrome produced by transverse myelitis is early covered by stupor, or convulsions due to fever and toxins.

Early there is an ascending flaccid paralysis with absence of all reflexes. Sensory loss and sphincter loss also occur at this time. Later reflexes become hyperactive, paralysis is spastic and sensory recovery occurs. Some cases may simulate poliomeyelitis, especially if bulbar paralysis occurs.

6. Other complications include optic neuritis, (one case of which occurred two days before the appearance of Koplik's spots and five days before the eruption of the rash) which is due to the toxic effects of the virus and to retinal thrombosis. The toxin and the fever produce a transient delirium which may be variously characterized by excitement, mania, depression, auditory and visual hallucinations and by somnolence. Intoxication too produces convulsions which rarely occur beyond the acute stage.

It is doubtful that true meningitis ever occurs. If the spinal fluid is found to be cloudy, secondary infection should be suspected.

Laboratory findings are in themselves not diagnostic, but may be of confirmatory aid. White blood counts range from 5,500 to 25,000 with a relative lymphocytosis (counts as high as 50,000 have been observed). Spinal fluid findings do not correlate with the severity of the disease and are no key to its prognosis. Fluid pressure is usually moderately elevated. Since sugar content is

normal or slightly decreased, the Pandy test is usually negative. Protein levels may be elevated or normal. Cell counts in spinal fluid are in an average range of one hundred to five hundred, but have been reported as low as twenty and as high as six hundred.[19]

Encephalograms done early in the course of the disease show definite pathological anatomy when the process is cerebral. The lateral ventricles are dilated, but there is no brain shift. This procedure is a definite aid in differentiation from tumor and hydrocephalus.[30]

Electroencephalograms in the acute phase of the disease show slow spiking waves of high voltage which may be focal or general. In the subacute stage, the pattern is less abnormal. Scattered slow waves are interspersed with periods of normal pattern. Where convulsions occur interseizure discharges like those in seizures are seen and there have been found petit mal patterns. If recovery is satisfactory, the pattern returns to normal, but does not do so where there is residual damage.[23]

The prognosis is not dependent upon the severity of the measles or the severity of onset of complications. It becomes increasingly grave as symptoms are prolonged. As compared with similar complications in other contagious diseases,[15] it has a better prognosis than pertussis in which thirty per cent of the cases are fatal, and varicella in which twenty-five per cent are fatal. Scarlet Fever complications are less serious carrying only a five per cent mortality

8,30

while those due to rubella (reported in one survey to be twenty per cent) and mumps are usually negligible.

In association with measles, approximately ten to fifteen per cent will die, approximately fifty per cent will show central nervous system damage and thirty-five per cent will recover completely. Of the fatal cases, about half have overwhelming toxemia and hyperpyrexia, and more are in the younger age groups than others. Of those with sequelae, the principle site of involvement is a factor to be considered. When cerebral symptoms are brief and diffuse sequelae are rare. Where multiple and focal, they are much more severe. In one series of forty-two such cases, fourteen were mentally defective, four had epilepsy, eleven had motor weakness, one narcolepsy and two died. In cerebellar involvement, there is tendency to gradual recovery over a period of years but permanent ataxia and epilepsy do occur and late life Parkinsonism has been noted. Cord involvement probably carries the most serious prognosis, the majority of the afflicted having infantile hemiplegia, some having speech defects, and a few having epilepsy or chorioathetoid movements. Patients with optic neuritis have no residual blindness from the local process, but one case of cerebral blindness has been recorded.

Over a period of years, there is usually a progressive reduction in neurological findings and an increase in personality disturbances. Commonest overall residuum is decreased intelligence. 28 Personality changes include irritability, emotional lability, destructiveness

and asocial behavior. Neurological changes include weakness, convulsions, choreiform movements and paresis. Rare are pupillary changes, aphasia, speech defects, sensory changes and endocrine and autonic disturbances.

Only two cases are on record in University Hospital. Neither were fatal, but both carried severe residual damage. One, a one-year-old Indian male was comatose when brought here three weeks after an acute case of measles. His head was retracted, neck rigid, feet plantar flexed and his extremities spastic. Pupils failed to react to light and accommodation. Babinski and Kernig were positive. After a month in the hospital he had less muscle rigidity, but facial assymmetry was marked. He continued in a vegetative unresponding state and no hope was given for further recovery upon dismissal.

The second, an eight-year-old girl, had convulsive seizures four days after the exanthem developed. For ten days she remained comatose. Her left leg was spastic, she had left ankle clonus and spastic flexion of the left side. Two months later, upon dismissal from the hospital, she was conscious but completely disoriented. Her parents were advised that intelligence impairment, emotional instability and spastic paralysis of the left side would persist.

In the writings of Barlow in 1886, the autopsy findings described were of extensive inflammatory lesions occurring throughout the white matter of the central nervous system.[28] Since the turn

of the century, however, pathologists agree that the lesions found are a toxic degenerative process. The degree of degeneration correlates with the degree of advancement of the disease when the material was obtained.

Grossly only marked congestion and edema causing flattening of brain sulci are visualized. There is involvement of the white matter of brain, or cord, or both. Meningeal congestion occurs.

Microscopically, the white matter shows patchy and coalescing foci of perivascular demyelination with involvement of the axis cylinders of some neural cells.[11,12] The endothelium of the small venulesis swollen, hyperplastic and containing red thromlic, (formed by stasis). There is proliferation of microglial cells swollen with lipoid disintegration products of destroyed nerve fibers. Fat granules also are loaded in the vessel walls. Some astrocytes and neurocytes may be seen with clarity. In all the picture is one of venous congestion and gliosis which is similar to that in vaccinia and variola, except that the latter are characterized by lymphocytic infiltration not seen here.[5] This toxic degenerative lesion is not considered to be completely specific but nevertheless due to the effect of measles toxin.

Since the incidence of central nervous system complications unlike the death rate closely parallels disease incidence prevention of measles by isolation, gamma globulin, and convalescent serum may be attempted especially in the more susceptible younger

age groups. Since the severity of the measles does not parallel severity of complications, the treatment of the more acute active cases of rubella is less effective.

Until recently, treatment of complications has been non-specific and symptomatic as they tend to run a self-limited course regardless of therapy, or time at which it is begun. Symptomatic treatment includes:

1. For increased intracranial pressure

    a) lumbar puncture (done with caution)
    b) magnesium sulfate
    c) hypertonic glucose

2. Convulsions:

    a) chloroform
    b) ether
    c) magnesium sulfate (oral, rectal, intramuscular, intravenous)

3. Fever:

    a) hydrotherapy

4. General condition:

    a) electrolyte balance - Ringer's solution intravenous
    b) protein deficiency - plasma: amino acids
    c) aenemia - whole blood

5. To prevent infection by secondary invaders:

    a) penicillin
    b) sulfathiozole, sulfadiezene

6. For bulbar paralysis

    a) Trendelenberg position
    b) gavage feeding
    c) aspiration of mucous

7. Urinary retention:

    a) catheter and irrigation

8. Spastic extremities:

    a) supports: muscle packs: casts to prevent deformity later physical therapy.

Specific treatments tried and found without value have been foreign protein therapy with mixed typhoid vaccine, convalescent serum,chemotherapy and inoculation with Herpes F. encephalitis vaccine. However, Kramer in a series of thirty-three cases gave thirty to one hundred seventy c.c. of convalescent serum in thirteen cases with only two deaths. In twenty untreated cases, he reported eight deaths, and suggests such treatment be given further trial.

Recently, Thenebe reported four cases which were specifically treated with plasma and supportive electrolytes. Two had initial fevers of 105°, two 102°. All had been stuporous when therapy was initiated, yet no later than the fourth day all four were almost completely recovered, all had normal temperatures, and in all response to therapy had begun within twenty-four to thirty-six hours. The routine advocated includes at least 500 c.c. of plasma every twelve hours until a total of 2500 c.c. has been given. To supply electrolyte needs of the cerebral cortex 5% glucose solution containing 2.2 molar lactate, 1.0 molar potassium chloride, .6 molar chloride, and .5 molar potassium diphosphate should be administered,

one liter per day.

While too few cases have been reported for definite conclusions, successful results here in the absence of any other specific therapy merits its further trial with the hope that the tragically high incidence of fatalities and sequelae in this decreasingly rare complication of one of the most common diseases of childhood may be at least in part reduced.

SUMMARY:

1. Central nervous system complications are more common with measles than any other exanthem.

2. The incidence, sporadic until 1923, has become almost epidemic since. This may be due to recognition of more cases, to neurotropic changes in the virus and to environmental or genetic changes in the host. Age and geographical incidence closely parallel that of the exanthem.

3. There is much difference of opinion regarding the causative agent but the most widely accepted opinion is that the toxin produced by the measles virus produce the complications.

4. Complications can occur at any stage of the disease but usually average four to six days following development of the acute symptoms of the exanthem.

5. Early findings are usually fairly constant in all cases but vary as the complications progress depending on the area specifically involved.

6. Laboratory findings are not consistent. Early encephalograms are of diagnostic aid. Electroencephalograms are a guide in prognosis.

7. Prognosis becomes grave as symptoms are prolonged. Approximately fifteen per cent die and half will have sequelae. Site of involvement is a determining factor in residual damage.

8. Pathology is a toxic degenerative process marked by endothelial damage of the vessels by gliosis and swelling of microglial cells.

9. Treatment of the self limited process is largely symptomatic but plasma and electrolyte therapy which have recently been successfully tried merit further trial.

BIBLIOGRAPHY:

1. M. F. Shaffer; G. Rake; H. L. Hodes; Isolation of Virus from a Patient with Fatal Encephalitis Complicating Measles. American Journal of Diseases of Children. November 1942.

2. Roos, Bertil; Kompli Kationen seit ens des Zentralnervensystems bei Morbilli. Act a Paediatrica 7: X 1942.

3. Senseman, Lawrence A.; Myelitis Complicating Measles. Archives of Neurology and Psychiatry. September 1941.

4. Finley Knox; M. D. Bated; Pathology of Encephalitis in Vaccination, Varidla and Measles. Archives of Neurology and Psychiatry. May 1938.

5. Finley Knox; M. D. Bated. Pathology of Encephalitis in Vaccination, Varidla and Measles. Archives of Neurology and Psychiatry. March 1949.

6. C. L. Thenebe; Plasma in Post Measles Encephalitis. Archives of Pediatrics. June 1948.

7. K. T. Neuberger; Post Measles Encephalopathy, American Journal of Pathology. September 1947.

8. Spurgeon Wingo; Encephalitis Complicating Rubella: U. S. Naval Medical Bulletin. September 1941.

9. M. G. Peterman M.D; Convulsions in Childhood. American Journal of Diseases of Children.

10. Paul Hamilton; Ralph Hanna; Encephalitis Complicating Measles. American Journal of Diseases of Childhood. March 1941.

11. Amando F. Ferraro; I. H. Schiffer; Encephalitis and Encephalomyelitis in Measles. Archives of Neurology and Psychiatry. April 1931.

12. Amando F. Ferraro; I. H. Shiffer: Toxic Encephalopathy in Measles. Archives of Neurology and Psychiatry. May 1932.

13. Fredrick J. Margolis; James L. Wilson; Franklin Top; Post Rubella Encephalitis. Journal of Pediatrics. August 1943.

14.B. Meyer; Encephalitis after Measles with Parkinsonian Rigidity and Recovery. British Medical Journal. April 24, 1943.

15. Abram M. Litvak; Irving J. Sands; Harry Gibel; Encephalitis Complicating Measles. American Journal of Diseases of Children. February 1943.

16. Abram M. Litvak; Irving J. Sands; Harry Gibel; Encephalitis Complicating Measles. May 1942.

17. Hoyne A. L.; Measles in 1938 Illinois Medical Journal. August 1939.

18. J. D. Geiger; Emmet Sappington; Encephalitis Complicating Measles. Archives of Pediatrics. May 1940.

19. Karl H. Beck; Benjamin Clock; Aid to Interpretation of Changes in the Cerebraspinal Fluid in Pediatrics Cases. American Journal of Diseases of Children. December 1947.

20. Harold Faber; Cerebral Damage in Infants and Children. American Journal of Diseases of Children. July 1947.

21. Jay M. Arena; Pre-Measles Encephalitis. Southern Medical Journal. June 1946.

22. Abram M. Litvak, M.D.; Encephalitis and Encephalomyelitis Complicating Measles. Archaeves of Pediatrics. October 1947.

23. F. A. Gibbs; E. L. Gibbs; Electroencephalogram in Encephalitis. Archives of Neurology and Psychiatry. March 1947.

24. Archibald Hoyne; Eugene Slotkowski; Frequency of Encephalitis as a Complication of Measles. American Journal of Diseases of Childhood. 1947.

25. Harry H. Clemens; Pre-Measles Encephalitis. Journal of Pediatrics. June 1943.

26. Chauncey P. Ward; Paraplegia Due to Measles Encephalitis. Archives of Pediatrics. Volume 58, 1941.

27. Harold Price; Measles Encephalitis. Canadian Medical Association Journal. January 1937.

28. Frank Ford; The Nervous Complications of Measles. Bulletin of Johns Hopkins Hospital. September 1928.

29. Weston Hurst; Barbara Cooke; Experimental Measles, Transmission to Monkeys, Failure of Transmission to Rabbits, Cultivation of the Virus of the Chorio-Allantoic Membrane. Medical Journal of Australia. March 1941.

30. A. M. McClausland; S. J. McClendon; Encephalomyelitis Following Measles. Archives of Pediatrics. March 1934.

31. M. G. Peterman; M. J. Fox; Encephalitis as a Complication of Measles. American Journal of Diseases of Children. September 1943.

32. H. M. Zimmerman; H. Yannet; Encephalitis Complicating Measles. Archives of Neurology and Psychiatry. November 1930.

33. N. Malamund; Sequelae of Post Measles Encephalitis. Archives of Neurology and Psychiatry. May 1939.

34. J. Ziskind; H. J. Shattenberg; Post Measles Encephalitis. Archives of Pathology. January 1939.

35. F. R. Ford; R. E. Wilson; The Nervous Complications of Variola, Vaccinia and Varicella. Bulletin of Johns Hopkins Hospital 1927.

36. Pauline St. George; Post Infectious Encephalitis. American Journal of Diseases of Children. April 1943.