NEUROLOGICAL COMPLICATIONS OF RUBEOLA (MEASLES)

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The course of rubeola usually is benign and the patient's recovery rapid. Uncommonly, neurological complications occur which may alter the prognosis drastically. The subsequent course of patients so afflicted has rarely been followed and reported. Moreover, it is difficult to obtain from the literature a critical picture of the various manifestations of the complications and sufficient data on which to base prognosis.

Measles was recognized by Rhazes, an Arabian, in the ninth century, who regarded it as a form of smallpox (51). It was however, first described clearly as a clinical entity by Sydenham (58) in the seventeenth century. Lucas (37) in 1870, described the neurological complications in a 23-year-old female who, on the eighth day of measles, developed paralysis of the legs and retention of urine, which cleared in twelve days. In this patient there was a previous history of a similar episode with an attack of variola.

However, appreciation that neurological complications accompanied or followed rubeola developed when myelitic complications were reported by Barlow and Penrose (5), cerebellar signs by Clapton (12), Schepers (54) and Fox (23) and cerebral signs by Abercrombie (1), Allyn (2), Henoch (30) and Williams (62) in the second half of the last century. The first comprehensive review of the problem was by Boenheim (7) in 1925, who reviewed 5940 cases of measles from the Berlin hospitals over a 25-year period. In these patients he encountered six cases of "encephalitis", eleven unexplained convulsions and eight cases of "serous meningitis". More detailed classification was provided by Ford (18) who, in addition to reporting twelve cases, analyzed the 113 cases that had been reported in the literature up to that time. Though recognizing that a certain degree of overlap inevitably occurred, he divided the manifestations of measles, as they affected the nervous system, into the following main groups: (a) diffuse cerebral symptoms of brief duration, (b) multiple focal cerebral symptoms, (c) hemiplegias and aphasias, (d) cerebellar syndromes, (e) paraplegias and spinal-cord syndromes and, (f) other incidental complications (mental disturbances, optic neuritis, etc.).

During the ensuing years, several large series of cases with "measles encephalitis" have been reported (4, 22, 28, 36, 47, 50, 56). The incidence of neurological complications among these has varied considerably. In some epidemics or years it has been high, in others low (19). Top (59) for example, found only two cases of "encephalitis" in 30,000 cases of measles in Detroit in the 1937–1938 epidemic; whereas, Hoyne and associates (32) reported 20 instances in 12,846 cases of measles. A reasonable statement is that of Merritt (41), that the incidence varies

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from 1 in 400 to 1 in 1000. This is in keeping with the experience of Boenheim (7) that neurological complications appeared in 0.4 per cent of his cases.

There is no definite sex predominance, although in most series, females slightly outnumbered males (59). The youngest patient reported was 27 days old (46), the oldest 40 years (48). Hoyne (31) considered that fewer Negroes are afflicted with neurological complications than would be anticipated, but this has not been substantiated by others.

Most of these articles, however, have appeared in the pediatric literature and the approach was from a general pediatric viewpoint. They create the impression that almost any neurological complication of measles was considered "measles encephalitis", and that little, if any, critical effort had been made to classify various syndromes in terms of history, natural course, residua, and prognosis. One recent review article stated: "... results of physical examination and laboratory tests are so bizarre and inconstant that in respect to them one case has little in common with another, save all results indicate involvement of the central nervous system. No more specific common denominator is available."

It is the aim of this review to consider whether, in fact, more definite characterization of the neurological complications of measles is possible or useful. For this purpose, the case material in the literature has been surveyed and correlated, where possible, with the cases and follow-up studies that form the basis of this report.

From 1919 to 1956, 85 cases of measles with neurological complications were recorded at the Johns Hopkins and Baltimore City Hospitals. Ten of these are known to have died. Forty-seven have been followed-up personally. Eight others were checked by their own physicians. It was impossible to trace 20 patients. However, 7 of these had been observed for periods ranging from 3 to 11 years. The remaining 13 were followed for less than one year because, with two exceptions, all had apparently made complete recoveries. The average period of observation for the entire series (excluding patients who died) was 7.2 years. The shortest period was 20 days, the longest 30 years.

I. MEASLES ENCEPHALOMYELITIS

This condition is commonly referred to as measles "encephalitis", though there is no convincing proof of the presence of an infectious organism; and, certainly, in some cases, myelitic features have predominated. It was first described clinically by Lucas (38). The morbid anatomy has been described by Greenfield (26), Wohlwill (63), Ferraro and Scheffer (15) and others. The intensity of the pathological process varied considerably from case to case. The most striking finding has been perivascular demyelination, with sparing of axis cylinders, predominantly in the white matter but also in the deeper layers of cortex. The whole brain was commonly congested. Petechial hemorrhages, and perivascular cuffing around small veins with microglial cells, lymphocytes and plasma cells were also frequently noted. This cellular proliferation tended to fade gradually into cerebral tissue. Moreover, endothelial swelling of the small veins themselves was often found. Neuronal changes were not prominent. When

present, their appearance could well have been attributed to terminal anoxic damage. Likewise, meningeal infiltration has been insignificant though a few scattered round-cell foci were usually encountered.

Less clear, however, are the pathogenetic features. Clinically, there is good evidence to suggest that in the naturally occurring disease, measles virus may be heterogenous in its cellular tropism. During the pre-exanthematous period, cells of many tissues, including those of the central nervous system, are likely to be involved. Frank skin involvement may represent only one of the later phases of the infectious process. It is quite possible that the neurological complications under consideration are, in fact, due to actual invasion of the central nervous system by the measles virus itself. Major support for this hypothesis came from isolation of measles virus from the brain of a child dying of measles encephalomyelitis (55). Brain suspension, inoculated into monkeys, produced measles rash in 2 animals. One showed transient cerebral symptoms. It must be emphasized, however, that this demonstration has not been confirmed. Until that occurs, the role of actual virus invasion in the pathogenesis of this neurological complication must be considered only tentative.

It is equally reasonable to attribute the changes in the central nervous system to an allergic or immunological reaction instigated in some fashion by the measles infection (17). The similarity, pathologically, amongst vaccinia, rubella, variola, and rubella encephalitides is striking and suggests some common pathogenesis of the neural complications of these four diseases. In addition, Finley (17) has suggested that the constant latent period following the rash, uncommon in other known infectious encephalitides, forms a strong argument in favor of an immunological reaction. However, the strongest evidence in favor of this hypothesis has been the production of similar lesions of the central nervous system in sensitized animals (33, 43, 53); and the isolation of antigen from sensitized brain emulsion (32). It could well be, however, that the antigenic role in such a postulated reaction is played by the measles virus itself, subsequent to invasion of the central nervous system.

Finally, but with little experimental support, it might be argued that in measles encephalomyelitis the measles virus in some manner "activates" a latent virus in the host which, in turn, constitutes the noxious agent (26, 62). In herpes simplex infections, for example, it is well known that a multiplicity of initiating factors—other infections, irradiation, trauma, etc.—may, in some unknown fashion, lead to symptomatic activation of a latent herpetic virus (10). This was clearly demonstrated by Good and Campbell (24) who inoculated rabbits with herpes simplex. Some of their animals developed encephalitis. In those which were clinically affected and recovered, it was possible later to reproduce the encephalitic syndrome by suitable non-specific stimulation. Fowl pox, swine influenza and some tumor-producing viruses have similarly been described in latent phases (14). There is great need for correlative information and further experimentation. Some of the basic observations need additional confirmation. Progress in some fields, especially virology, offers the hope of new techniques in the near future which could be adapted to the problem at hand. On the basis of

available facts, it appears that the pathogenesis of measles encephalomyelitis remains unsettled.

A. Clinical Data

There were 67 patients with measles encephalomyelitis in the present series. The clinical picture was quite varied.

(a). Usually the child was recovering, the rash fading, and the temperature had returned to normal. Rather abruptly the temperature rose, the child became listless, irritable, complained of headache, and became somewhat drowsy. Physical examination revealed no neurological abnormalities, or merely slight meningeal signs. Fortunately, in most instances, the illness was mild and of short duration; after a day or two, there was a return to normal temperature, and the child made a complete recovery. None of the sequelae was seen in these cases. This is probably the most common variant of the neurological complications of measles; but, since these patients were rarely admitted to the hospital, they comprised only a small number of this series.

B.H., a 5-year-old female. Five days after eruption of the measles rash the patient complained of headache. She was listless and somewhat drowsy. The only positive neurological finding was a positive Kernig sign. Lumbar puncture revealed 33 lymphocytes, protein 42, and normal pressure. In 36 hours, the child was asymptomatic. EEG remained diffusely abnormal for three weeks, but it was normal at a three-month follow-up. At the age of 10, the child was completely normal.

R.H., a 3-year-old male. Five days after onset of measles, the patient became anorexic and irritable and complained of headache and pain in the legs. His temperature was 103°, and he became delirious. Meningeal signs appeared, and reflexes were brisk with flexor plantar responses. No cranial nerve or cerebellar signs were noted. Lumbar puncture showed 240 cells, 80% lymphocytes, a protein of 72, and normal pressure. The child was more rational the next morning and by the third day was in good contact with his environment. He was completely normal on the seventh hospital day. Lumbar puncture on the eighth hospital day showed no cells and a protein of 47. Five years later the boy was doing average work in school, and there were no sequelae.

(b). Convulsions often occurred as the fever rose. These were frequently solitary and of little prognostic significance. When repetitive, however, they were of considerably greater importance. Four of our patients died of status epilepticus.

M.S., a 2-year-old male. Four days following onset of measles rash the child had a generalized convulsion and was brought to the hospital. Temperature was 102°. He was drowsy and post ictal, but otherwise the neurological examination was normal. Lumbar puncture showed 20 lymphocytes and protein of 35, and pressure of 100 mm. H_2O. He was completely normal the next morning. Four years later he was normal and doing well in school.

C.G., a 6-year-old male. On the third day following appearance of the rash, the child was listless and drowsy. The next morning he had a convulsion. Physical examination revealed only mild meningeal signs. Lumbar puncture showed a pressure of 100 mm. H_2O, 22 lymphocytes and a protein of 67. Patient was completely well the next evening. Two years later patient remained normal and was doing excellent work in school.

S.K., a 2-year-old female. On the second day of the measles rash the child was very irritable. On the third day the patient had the first of many convulsions. Lumbar puncture showed a pressure of 150 mm. H_2O, 96 lymphocytes and a protein of 34. Death ocurred on

the fourth day without the convulsions being controlled. The patient never regained consciousness. Post-mortem revealed the typical changes of measles encephalomyelitis.

(c). Some patients, after having passed into a drowsy, irritable stage—with or without convulsions—slipped into deep coma from which they could not be roused. Eyes were held open and staring, pupils dilated. Cranial-nerve signs were rare, though minimal papillitis, sixth-nerve palsy, and nystagmus were seen. There was often generalized rigidity and frank decerebrate phenomena. Tendon reflexes were usually increased, plantar responses extensor in type and myoclonic twitches frequently seen.

J.A., a 7-year-old male. Ten days following onset of measles, the patient had a temperature rise and became irritable and drowsy. The next day he was lethargic, responded poorly to questions, and was unable to void. On admission he was unable to answer questions but could be roused. The patient had meningeal signs, normal cranial nerves, brisk reflexes with extensor plantars. On the fifth hospital day lumbar puncture showed no cells, and negative Pandy test for protein. For the next three weeks he remained unresponsive with eyes usually open and pupils wide. On the 29th day, the patient responded by smiling and blinking his eyes; he used his hands on the 34th day and began to speak on the 40th. At this time visual complaints appeared and it was apparent that he had a severe visual loss and was misrepresenting some visual stimuli. On the 60th day the patient had recovered sufficiently to carry on a conversation, but movement was slow and awkward. He had bilateral central scotomata with 20/40–20/50 vision. On the 90th day he was walking and regained bladder and bowel control; he was restless and overactive. Reflexes were increased. One year later the patient had 20/20 vision, normal discs and no scotomata. At age 18, a neurological examination revealed only extremely brisk reflexes with flexor plantars. Patient later graduated from college.

(d). After a period ranging from 1 to 40 days, signs of recovery appeared and coma progressively lightened. Clues of awareness became evident; eyes began to follow the examiner and later indications of cooperation developed. At this point, it was often apparent for the first time that focal neurological damage had occurred—a severe paraplegia, monoplegia, ataxia, blindness or aphasia.

P.M., a 4-year-old female. Two days after a measles rash, the patient did not recognize her parents. The following day her temperature increased to 107° and she became comatose. Her reflexes were hyperactive with bilateral extensor plantar responses. There was nuchal rigidity. Five days later she began to follow people with her eyes. She talked on the ninth day. Cerebellar signs were noted at this time. Three months later she was unkempt, hyperactive, cried and was emotionally labile. Reflexes were increased with a right extensor plantar. Her I.Q. at this time was 111. At age 7, temporal-lobe seizures developed. At age 13, she stated that at first she did poorly at school and just could not learn, but lately she had improved. At the present time, aged 17, the only neurological finding was a right extensor plantar response. She is doing average work in school and notes that she comprehends much more quickly if her lessons are heard rather than read, despite normal vision.

Once recovery set in, it progressed over a period of weeks. Sometimes this phase of continuous improvement was lengthy. In one child, 180 days elapsed before a steady state was reached. On the whole, duration of the recovery process, and its rate, was found important in eventual prognosis. Slow recovery correlated closely with lasting residua, whereas, rapid recovery, even from prolonged coma or stupor had, for the most part, an excellent prognosis. In the

majority of patients a behavioral change was noted in the recovery period. While this was usually transient, it frequently was severe enough to be a problem in management of the patient.

E.A., a 5-year-old female. Seven days following measles rash the patient had a convulsion and became semi-comatose. There was nuchal rigidity. Reflexes were hyperactive with extensor plantars. Lumbar puncture revealed normal pressure, 13 lymphocytes and Pandy negative. On the 10th hospital day she was deeply stuporous, had meningeal signs, brisk tendon reflexes and bilateral extensor plantars. The patient was incontinent; she swallowed with difficulty. On the 37th hospital day she lay quietly in bed and gave evidence that she could hear and understand for the first time. On the 38th day improvement was remarkable and she began to feed herself. On the 40th day she began talking; and EEG showed diffuse slowing. She walked on the 43rd day. The patient was still restless and fretful on the 65th day but was normal by the 120th. Eight years later she was normal neurologically and her EEG was normal. She was doing well in school.

E.B., a 6-year-old female. Seven days after measles the patient was noted to have a personality change and was stuporous. She stopped talking and then was unable to walk. She had "no tendon jerks". She then passed into a coma. When seen for the first time on the sixtieth day, it was stated she had been gradually improving for five weeks. At that time she could talk, but could not walk or stand. The right hand and foot were weaker than the left and she had cerebellar signs on the right. There were bilateral pyramidal tract signs. Her mental status revealed her to be alert, though confused and very emotionally labile. She walked slowly and abnormally by the end of the first year. Two years later she had a cerebellar gait and slurring speech, also intention tremor bilaterally. Eight years later she still had an ataxic gait with persistent cerebellar signs. She had been a severe behavior problem since the illness, was restless, destructive and hard to control. I.Q. was 72 with a wide scatter.

(e). Of the 67 patients in our series, 35 were female and 32 were male. The age incidence of these neurological complications follows the distribution of measles infection in the population. All of our patients were under 12 years of age. All ages were represented, but the mean age was 6. Symptoms usually began from 1 to 7 days following the rash. In the earliest case, central nervous system manifestations appeared 1 day before eruption of the skin lesions. In the latest, neurological complications developed 13 days after the rash. These extremes were, however, uncommon. The average day of onset was the fourth.

Because of their prognostic importance, certain features of this clinical picture of measles encephalomyelitis will be considered in more detail.

1. Convulsions

Of the 67 patients in this series, 38 had a convulsion or a series of convulsions. They were usually generalized, although 4 patients had focal seizures. Mild headache and drowsiness were a frequent prodromata.

B.K., a 6-year-old female. On the third day following measles rash the patient had a convulsion without any prodromata. Up to this time she was felt to be making a normal recovery. When examined, later that day, she was slightly drowsy but no neurological signs were noted. Lumbar puncture showed a pressure of 100 mm. H_2O, 70 lymphocytes, 3 polymorphs, and a protein of 60. The child was normal by evening. When last seen, at age 12, she was doing well in school and had had no further convulsions.

R.M., a 9-year-old male. Four days following rash the patient was noted to be listless. Later that day he developed status epilepticus with a high temperature which was treated with

barbiturates. The patient was normal on the second hospital day. Lumbar puncture revealed normal pressure, 13 lymphocytes and a protein of 44. He remained seizure-free until age 20, when following a severe head injury, he had blackout spells. These were diagnosed elsewhere as "petit mal". The patient is a high-school graduate, and now married.

Four patients had repeated and prolonged convulsions without ever regaining consciousness. In these cases death could reasonably be attributed to the repeated convulsions and secondary anoxia. Post-mortem examination showed the typical pathological picture of measles encephalomyelitis.

M.D., an 8-year-old female. Three days following the appearance of a measles rash the patient complained of a slight headache. She was irrational at times, and her parents noted that her hands "trembled". Lumbar puncture on the day of admission revealed normal pressure, 32 lymphocytes and a protein of 136. On the morning of admission she had a generalized convulsion and was still unresponsive when seen shortly thereafter. Following this she had many generalized convulsions and succumbed the next morning without the seizures ever being adequately controlled. At autopsy the brain appeared hyperemic. There was typical microglial perivascular cuffing and demyelinization throughout the brain stem and both cerebral hemispheres.

In 14 cases, return to normal status following the convulsion was prompt and rapid. In the remaining 24, other evidences of encephalomyelitis developed.

R.S., a 7-year-old male. Five days following the appearance of a measles rash, the patient complained of a headache. Later that day he had two convulsions. Physical examination the next day showed cerebellar signs on the left and a wide based ataxic gait. There was some visual disturbance although no definite scotomata were found. On the sixth hospital day the patient was slightly euphoric and the cerebellar signs were improving. Electroencephalogram showed diffuse slowing. On the 28th day, there was mild residual ataxia. Mental status was normal. Gait was normal two months following the illness. Four years later, at age 11, he was doing excellent school work and physical examination at this time was normal.

A seizure or series of seizures, accompanying a second febrile rise is a common occurrence in measles encephalomyelitis. It should be viewed with considerable alarm and not lightly regarded as a "febrile" seizure of no consequence. It is true that in one-third of our cases, no other objective evidence of central nervous system damage occurred. However, 4 such patients died and over half of the whole group later showed other evidences of encephalomyelitis. Fortunately, however, the mere occurrence of convulsions during the acute stage did not necessarily presage the later appearance of repeated seizures. Of our 14 patients in that category, only one subsequently became epileptic and, in this instance, an unrelated severe head injury may well have been the underlying factor. On the other hand, the 20 patients with seizures and other evidences of acute central nervous system damage fared less well in this regard. Four patients in this group had a subsequent convulsive disorder.

2. Cerebellar Ataxia

Cerebellar signs were found during the acute illness in 22 patients in the present series. In most instances, they constituted only one element of multiple central nervous system changes. They were seldom the predominating feature. Recognition of their importance was easy and the outlook in general good.

N.A., a 4-year-old male. On the sixth day following onset of measles rash the patient became confused, had tremors of his hands, and developed an unsteady gait. The next day he was stuporous and delirious. Lumbar puncture showed no cells, normal pressure and a normal protein. Physical examination revealed meningeal signs, intention tremors and increased tendon reflexes with bilateral extensor plantars. His gait was ataxic. By the fifth hospital day the cerebellar signs and mental changes had improved. On the 12th day the neurological examination was normal. EEG showed diffuse slowing. At age 11, seven years later, the patient was retarded. He was in the lowest grade in school and has made no progress. (His older brother does even more poorly in his school work.) The boy was nervous and fidgeted a lot. Neurologic examination remained negative.

M.P., a 3-year-old female. On the fifth day following measles rash she became drowsy, restless and would not walk. On examination she was found to be delirious with no meningeal signs. Her gait was ataxic. She had bilateral extensor plantars and intention tremors. Lumbar puncture showed no cells, protein 56. She improved over the next two weeks. Her gait was normal on the 20th day and the EEG was normal then. At age 6, three years later, she was "as well as any other 6-year-old". Neurological examination was unremarkable.

In rare instances (in 3 patients in the present series), cerebellar signs were the only objective indication of central nervous system involvement.

B.C., a 6-year-old male. On the fifth day of measles the child became drowsy and vague. Intention tremor, adiadochokinesis, and hypotonia were noted on the right side. Lumbar puncture showed 635 cells, 98% lymphocytes and a protein of 190. The patient was normal by the third hospital day. The electroencephalogram still showed a diffuse slow-wave abnormality. Lumbar puncture showed four cells and 104 protein on the ninth day of illness. Two weeks after leaving the hospital the boy was well and the electroencephalogram was normal.

When the relationship of cerebellar signs to measles is close and clear, and when other manifestations of encephalitis are present, the recognition of their significance is obvious. When the measles itself has gone unrecognized or the interval between the illness and the limited neurological disturbances is unusual, considerable diagnostic difficulties may exist. Cerebellar tumor or abscess or other posterior fossa lesions may be incorrectly suspected. In this connection, it is interesting to speculate on the role of unsuspected measles in the etiology of "acute cerebellar ataxia of childhood". Griffith (27) noted that 8 of his 31 cases followed measles.

3. Myelitis

In 10 cases, likewise, there was evidence of additional spinal involvement in patients with flagrant measles encephalitis. This was manifest by absent reflexes, abnormal bladder control or paraplegia which was noted once the coma had passed. As a rule, the myelitis completely disappeared although in some instances, the patient was left with brisk reflexes.

R.K., a 6-year-old female. Three days after measles rash the patient was unable to void. On the fourth day she had to be catheterized. On the fifth day she developed headache and minimal meningeal signs. She had brisk reflexes with probable extensor plantars in the lower extremity. Lumbar puncture on the fifth day revealed 90 lymphocytes with a protein of 42. She recovered bladder function on the eighth day. On the tenth day there were no cells and 140 protein. The parents recall that when the child left the hospital she had some trouble

walking and some visual complaints, which improved in the first three weeks at home. The girl was seen one year later and was doing well in school at that time. She was seen again at age 11, was noted to have a normal examination and had no further difficulty.

B.W., a 3-year-old male. On the eighth day following measles the patient became disoriented. That evening he became steadily more drowsy and was unable to pass urine; he was catheterized. Physical examination revealed some stupor and meningeal signs. There were brisk reflexes in the lower extremities with extensor plantar responses. Sensory examination was unreliable. Lumbar puncture revealed 39 lymphocytes, 3 polymorphs, one-plus Pandy and normal pressure. Electroencephalogram done on the second day showed diffuse slowing; on the third day his mental status was normal. He was walking with a bilaterally spastic gait on the eighth day. The child's arms remained normal. On the 15th day only slight spasticity remained in the left leg. Five months later the electroencephalogram was normal. The child was doing well in school. Reflexes in the legs were brisk and hyperactive but plantar responses were flexor. When last seen, at age four, he was perfectly well except that the hyperactive reflexes had persisted; but they were not clearly pathological. Plantar responses remained flexor.

Isolated myelitis without concurrent cerebral or cerebellar symptoms was much more unusual.

F.K., a 6-year-old male. One week following a measles rash the patient began stumbling. He had some trouble urinating but there were no other complaints. When examined, his sensorium was completely normal. His cranial nerves and upper extremities were normal. There was a diffuse weakness in the lower extremities, greatest proximally. There was blunting to all sensory modalities below T 10, but loss was not complete. Reflexes were increased at the knee and ankle joint. There were ankle clonus and bilateral extensor plantars. Lumbar puncture showed free dynamics, normal pressures, 24 lymphocytes and a protein of 40. Over a 3-week period, the patient gradually improved and when last seen, 2 months later, he had a normal neurological examination.

This was the only instance of isolated spinal involvement encountered in the present series. However, similar cases have been noted by others (3, 4, 6, 9, 26, 34). In the setting of measles, the recognition of etiology was usually simple. In isolated cases reported in the literature (19) the diagnosis has been less evident and differentiation from anterior poliomyelitis, etc. difficult.

4. Retrobulbar Neuritis

Five patients, recovering from acute encephalomyelitis, had visual difficulties. In 4, bilateral central scotomata were found—one was totally blind. In 3, including the latter, some blurring of the optic disc and hyperemia had been noted during the acute stage of the illness. Vision usually improved rapidly, and after 3 months all patients had normal vision. Temporal pallor persisted in the patient with blindness after vision had returned to normal. In the others, the nerve heads regained a normal appearance.

F.S., an 11-year-old female. Two days after measles she became irritable, drowsy. Optic nerves were blurred. She was hospitalized in another hospital where she was in "coma" for twenty days with tonic neck reflex reactions. Lumbar puncture showed 20 lymphocytes and a protein of 39. On the fortieth day it was noted that she could follow light. On the fiftieth day she recovered enough to cooperate for examination and had bilateral central scotomatous defects with 20/200–20/200 vision. Reflexes were very brisk bilaterally. She could not identify objects by sight but could by touch, and was felt to have visual "aphasia". On the 160th day

the girl could read and had 20/20 vision. A year later she was noted to be normal in every way and doing well in school. At age 26, she had a normal neurological examination; she had graduated from junior college and had worked in an office for 4 years before marrying. Vision and optic discs were normal.

These cases are representative of others reported in the literature (36, 60). In all, the neuritis was bilateral and of relatively short duration. Moreover, the outcome has been uniformly favorable regardless of the degree of amblyopia present during the acute stage. Residual pallor of the nerve heads, in some cases, has been of no functional significance.

5. Transient Mental Disturbances

Only 3 patients of the present series showed evidence of transient mental disturbances characterized by active hallucinations during recovery from the encephalomyelitis. Though uncommon, such phenomena have also been noted by other authors (19).

S.M., a 7-year-old female. On the seventh day of measles the patient became drowsy and confused. She did not recognize her mother and did much thrashing and screaming. Later that night she had a convulsion. She convulsed intermittently for 10 days and on the 10th day "picked at imaginary objects in the air and saw objects that were not there", (hallucinations). This lasted 4 days. Lumbar puncture showed 220 lymphocytes with a 1+ Pandy reaction. Thirty days later, the girl had a "bad temper and did not obey", had increased appetite, was very restless and had many tics. Five months later she was completely normal. Thirteen years later she was working, after having been graduated from high school.

As in the above case, many of the patients showed disordered personality traits, emotional instability and even psychotic behavior during the post-encephalitic period. They have, in some instances, accompanied structural changes leading to permanent mental impairment. For the most part, they have been isolated phenomena of no serious prognostic importance, and are discussed further later.

H.A., an 8½-year-old male. The patient had been left back twice in school. Five days after onset of measles rash he became irritable and imagined he saw little animals, such as squirrels and mice. Temperature rose to 105°. He became totally irrational and then had three convulsions. He had meningeal signs and there was generalized weakness with brisk reflexes. Lumbar puncture showed 570 cells (65% lymphocytes) with a protein of 63. On the fifth hospital day the boy again claimed he saw "animals" and he had other hallucinations. On the 13th hospital day a repeat lumbar puncture was normal. He showed general improvement and on the 26th day was walking again. Eight months later he still had a personality change. I.Q. was 71. Eight years later the patient was noted to have explosive behavior. He was not profiting from school and was sent to a state school for defectives.

B. Laboratory Data

Lumbar puncture was performed in 33 of these 67 cases, 4 of which had completely normal cerebrospinal fluid at the time of the procedure. This negative result was of questionable validity in 2 of the cases since they had only one puncture in the second week of illness. Of more significance were the other 2, where the fluid was examined on the third and fourth day following onset of neurologi-

cal symptoms. It is noteworthy that these patients with normal cerebrospinal fluids, as so assessed, were otherwise completely typical of measles encephalomyelitis.

In the remaining 29 cases the cellular count or the protein in the cerebrospinal fluid was increased. In all instances the cells were overwhelmingly lymphocytic. The highest number of cells in our cases was 650/mm.^{3}, whereas the usual number has been 7–250. The cell count fell to normal within a few days. Although in one patient an initial count of 587 was followed by a normal fluid 3 days later, the usual period for a complete return to normal was from 5 to 12 days. There was no relation between cellular response and eventual prognosis. The possibility of bacterial infection must always be considered in these cases especially in the presence of polymorphonuclear cells. We have encountered one such case.

N.D., a 2-year-old male. Measles rash developed 7 days prior to meningeal signs, fever, nystagmus and left-sided pyramidal tract signs. Lumbar puncture showed 2000 cells (polymorphs), 2+ Pandy. Culture revealed staphylococcus aureus. Two days later the child could not walk, talk or feed himself. He had marked generalized spasticity; he remained in a vegetative state with decorticate postures. Eight years later he died of recurrent meningitis in a state hospital. The patient had remained unchanged during the intervening years.

The protein, elevated in 17 cases, took a few days longer to return to normal than the cell count. Colloidal gold curves were most often normal, or showed a a minimal "first-zone" curve, i.e., 11221110000. The spinal fluid pressure was essentially normal.

Electroencephalography was performed on 18 patients. The tracings were abnormal in all instances. The most common change lay in increased numbers of slow frequencies, and often 4 to 6 per second waves became prominent. The records were, for the most part, fairly symmetrical, although a preponderance of abnormal activity on one side was not rare, as Levy and Roseman (35) have noted. These authors observed no relation during the acute stage between electroencephalography changes and severity of encephalomyelitis. The tracings usually remained abnormal well after the patient had made good clinical recovery; in most cases it was 3 to 8 weeks before the record returned toward normal. Persisting abnormality in the record correlated well with permanent neurologic damage or convulsive disorders.

There was usually a leukocytosis between 10,000–20,000 in the peripheral blood with a shift to the left. Urinalysis usually revealed no abnormalities.

C. Mortality and Sequelae

Forty-two patients were restored to normal. Four patients died in status epilepticus at the time of the initial illness. One patient who developed a convulsive disorder died of status epilepticus eight years later. In 47 patients the length of coma or stupor was known. Eleven of these patients had severe residua. The relation of the length of coma in these patients is given in Table I. Coma or stupor lasting less than 2–3 days had an excellent prognosis. A rapid recovery from coma likewise was a good prognostic sign. A lengthy duration of

TABLE I

Length of Coma or Stupor	Severe Residua	Recovery
0–3 days	1	32
3–10 days	4	4
10–20 days	3	3
20–30 days	2	2
30–40 days	1	2

coma or stupor did not preclude complete recovery. Fifteen patients had some permanent neurological residua following their illness. The distribution is shown in Table II.

Seven patients (10%) had a history of subsequent convulsive disorders. In one patient it was the cause of death, 8 years after the initial encephalomyelitis. It should be noted that in 2 cases spells began as late as 5 years following illness and in one case they began 15 years later. One patient developed petit mal 11 years after his illness, following an automobile accident. Of the remaining 6 patients, 4 had convulsions at the time of the initial encephalomyelitis and 2 developed seizures for the first time following it. All patients had been deeply stuporous or comatose with their initial illness. There was no direct relationship, therefore, between convulsions during the encephalomyelitis and an eventual convulsive disorder. The following case serves as an example.

S.S., a 6-year-old female. On the seventh day of the measles rash her temperature increased and the patient had a typical measles encephalomyelitis with convulsions. She remained unconscious for three weeks. Since then she had been mentally retarded. Four months following her illness she had a generalized convulsion. When seen at this time she was showing signs of sexual development. She had 4 to 6 seizures a year. At age 14, the patient died in status epilepticus. No post-mortem was performed.

Three female cases showed precocious puberty following their encephalomyelitis. Similar instances have been reported by Ford and Guild (20) and Boenheim (7) in females and by Apley (3) in a male.

Fifteen patients were mentally retarded following the encephalomyelitis. Five of these had neurological evidences of severe brain damage. There were 8 other patients whose intelligence, although still in normal ranges, was lower than expected. Severe personality disorders of a permanent nature were seen only in

TABLE II

Restlessness and fidgetiness	8
Cerebellar signs	7
Hyperactive reflexes	7
Pyramidal tract signs	5
Tremor of hands	3
Athetosis	2
Diabetes Insipidus	1
Paramyoclonus Multiplex	1

the mentally retarded group; they were felt to be due, in all probability, to the fact that the illness had resulted in a defective intelligence in the patients. All patients whose personality "changed" after infection showed steady improvement to a "normal" personality within 1 to 3 years after the illness, provided that intelligence was relatively normal. It should be noted that in no instance was post-encephalitic Parkinsonism seen. Narcolepsy was not seen, although Lust (38) reported such a case. In general, patients with measles encephalomyelitis in the first 2 years of life had more severe residua and more permanent sequelae then would be anticipated. These facts were noted by Gordon (25) in discussing the paper of Litvak, et al. (36), who commented on the high frequency of mental retardation if the illness ocurred before age 3. Hamilton and Hanna (28) also noted "very young patients seem to have the poorer prognosis."

D. Summary

We have attempted to show that measles encephalomyelitis may be manifest by a variety of symptoms and signs which can only be understood if one regards the total clinical picture as part of a wide spectrum. The signs and symptoms in any case are determined by the relative intensity of the pathological process in various portions of the neural axis. One can usually find some clues to the diffuseness of the process even in the face of signs which are apparently focal. Mortality is most often the result of the convulsive disorder in the acute stages. Sequelae are much more prone to occur in the more severe cases, the cases with prolonged coma, and in the patients below age 2.

II. HEMIPLEGIA

Ten patients in this series developed sudden hemiplegia. Thirty cases have been reported in the literature. It is notable that the age distribution is younger than that for measles encephalomyelitis. In 5 patients the hemiplegia occurred before the rash, whereas the others occurred as late as 28 days following the rash. There appears to be no relationship between the day of onset of neurological signs and the measles rash, as is so frequent in measles encephalomyelitis. Likewise, there was little tendency for the cases to be grouped in the second to fifth day period as the patients with measles encephalomyelitis. Most often the hemiplegia was ushered in by a focal seizure. Lumbar puncture was normal in our cases in contrast to the high percentage of abnormalities noted in the measles encephalomyelitis group. The electroencephalogram demonstrated a diffusely abnormal record with marked focal accentuation in the hemisphere contralateral to the hemiplegia. After the acute phase had passed, the abnormality usually consisted of occasional slow waves and spikes which arise from the pathologic hemisphere. The opposite hemisphere also showed some minor abnormalities.

Noteworthy also was the persistence of the hemiplegia in 23 out of 30 cases in the literature and in each of our cases. This tendency for a permanent residua was unlike the spontaneous improvement characteristic of most of the cases of measles encephalomyelitis. The electroencephalogram in these cases almost

always remained abnormal, and it was rare to see a normal electroencephalogram in a patient who had a hemiplegia in relation to measles. This was the only group with a high incidence of "post-encephalopathy" seizures. In our series these approached 50 per cent, which was 5 times the incidence noted in patients with measles encephalomyelitis.

W.K., a 5-year-old male. Five days after onset of measles rash the patient had a left-sided convulsion followed by a left hemiplegia. EEG showed a focus in the right hemisphere. Lumbar puncture showed 5 cells, protein 25. There were behavioral difficulties for three months following the hemiplegia. Two years later seizures started but had been controlled with anticonvulsant medication. Four years later the patient still had a slight left hemiplegia. His I.Q. was 90; schoolwork was poor.

S.J., a 2-year-old female. One day after a measles rash the patient had a right-sided convulsion followed by a right hemiparesis. Lumbar puncture showed no cells and a negative Pandy. She was seen 2 months later and had a mild hemiplegic residua.

R.F., a 15-month-old male. Four days before onset of measles rash patient was "cross" with a high fever. He had a left-sided convulsion followed by a permanent left hemiplegia. Lumbar puncture showed no cells and a negative Pandy. At age 14, he still had signs of a slight left hemiplegia. He had grand mal seizures, starting at age 15, but has had none in the last 4 years on anti-convulsant medication.

E.M., a 1½-year-old female. One week before measles rash the patient had onset of a left hemiplegia. She is now, at age 29, severely retarded, has convulsions and residual hemiparesis.

One patient was of unusual interest as she apparently had both a typical measles encephalomyelitis and, shortly after recovery, also developed a hemiplegia. The course of events in this patient strongly suggested that there were 2 distinct pathological processes relating to the measles infection.

K.A., a 4-year-old female. Four days following a measles rash the child became lethargic. She was admitted to another hospital where she was described as deeply stuporous, with meningeal signs and bilateral pyramidal tract signs. Lumbar puncture showed 150 cells, 85% lymphocytes, normal pressure and normal protein. The child began to respond on the third day. She was discharged on the eighth hospital day with a normal neurological examination, except for some mild personality changes. Two weeks later, or 28 days following the measles rash, the patient had a sudden onset of left-sided convulsions, resulting in a permanent left hemiplegia. Lumbar puncture revealed no cells, negative Pandy. Eighteen months later she showed persisting hemiplegia. Air study at this time showed enlarged lateral ventricle, right greater than left.

Ford (19) noted that "hemiplegias with apoplectic onset bear a somewhat less direct relationship to the measles than exists in other groups of cases." He believed that they resulted from the non-specific effect on vessel walls which occurs in any febrile illness (21). That they represent a significant group is shown by the fact that at least 24 out of 125 cases presented and reviewed by Ford fall into this category. Most authors do not attempt to separate them from measles "encephalitis", and in most series, at least one such case is noted (36, 39, 47). In a recent case where a post-mortem has been described (19), an infarction in the distribution of the middle cerebral artery was found. Similar findings were noted in the cases of Calmeil (11) (quoted in reference 18) and Malamud (39). Walsh (60) described a patient who, on recovery from an acute

hemiplegia during measles, was left with a complete homonomous hemianopsia. It is likely that a similar vascular pathology affecting the posterior cerebral artery was responsible.

The clinical picture in no way differed from the acute infantile hemiplegia seen in other childhood illnesses. These patients should not be considered to have measles encephalomyelitis, as the onset, course of disease, prognosis and pathology appeared to be entirely different. The hemiplegias that may be seen as part of measles encephalomyelitis are usually gradual in onset, preceded by days of stupor or coma. There are other signs present and usually the "hemiplegia" is only relative, i.e., reflexes on one side are brisker than the other. There is a great tendency for rapid improvement. Frequently, there is a spinal fluid leukocytosis and the electroencephalogram is rarely as localizing as in these patients.

III. TOXIC ENCEPHALOPATHY

Three of the patients developed acute cerebral edema without focal signs. The syndromes occurred on the third, fifth, and seventh days of illness. These patients had an encephalopathy that could be distinguished from the usual "measles encephalomyelitis". The onset of neurologic symptoms was characteristically more abrupt, the child obviously sicker. The signs were those of acute increase in intracranial pressure and of temporal pressure cones compressing the brain stem. The spinal fluid showed elevated cerebro-spinal fluid pressure with normal protein and normal cell count. All of the patients died.

N.M., a 4½-year-old female. One week after onset of typical measles, the patient became incontinent of urine and feces and had some twitching of individual muscles. She was comatose and unresponsive to all stimuli. There was bilateral papilledema. The pupils were dilated and fixed to light. Lumbar puncture showed increased pressure (greater than 300), and no cells; protein 16. The patient remained in coma for 12 days. At one time she had seizures of the right face and arm. She died on the 12th day. Autopsy showed marked cerebral congestion and edema. There was a petechial hemorrhage in the hypothalamus. Some spotting with subarachnoid blood was seen. There was no perivascular cuffing, or demyelination. There were bilateral uncal herniations with compression and downward shift of the brain stem. Dural sinuses were all patent.

L.P., an 8-year-old female. The patient was exposed to measles and received gamma globulin. Three days later she developed a measles rash. Three days following this she rapidly became comatose and decerebrate with meningeal signs. There was bilateral papilledema and both pupils were dilated and fixed to light. Lumbar puncture pressure was greater than 300. There were no cells and the Pandy was negative. The patient had respiratory difficulties and expired on the second day. No autopsy was performed.

W.G., a 2-year-old female. Five days after measles the child became ill and would not talk. She lay quietly in bed and seemed to have had difficulty breathing. On admission to the hospital, she was comatose. The discs were blurred and there was little response to noxious stimuli. Her reflexes were brisk. Plantars were extensor. She quickly passed into deeper coma and became decerebrate. Lumbar puncture showed elevated pressure, no cells, protein 60. She died of respiratory failure. No post-mortem was performed.

The appearance of this disorder is not restricted to measles and has often been seen after other illnesses in childhood; little, if anything, is known of its pathogenesis. It is usually described under the name toxic encephalopathy (19). Similar instances in relation to measles have been reported (16, 45, 52).

IV. ISOLATED RETROBULBAR NEURITIS

One rarely sees bilateral retrobulbar neuritis developing with measles in the absence of any other symptoms or signs of neurological involvement. There were 2 such cases in our series. Symptoms were noted on the tenth and twelfth day following the measles rash, which would be unusually late if they were manifestations of a diffuse measles encephalomyelitis. The patients improved rapidly; one was left with a slight residual pallor of the discs.

J.H., an 8-year-old male. At age 7 his vision was known to be 20/20 in both eyes. At age 8 he had measles and on the 12th day suffered from rapid failing of vision to 1/500 bilaterally. A pallor of the papula macular bundle was noted and a large bilateral central scotoma. Two weeks later, vision was 20/20 left and 20/40 right, with a small right central scotoma. Two months later vision was normal bilaterally despite a slight pallor of the discs.

This was, in all probability, the same type of case as described by Meadows (40) which occurs sporadically and with other infections of childhood and not specifically related to measles. It has been seen by the author following varicella and influenza-like illnesses. Strom (57) and Wiegelin (61) described such cases following measles. Meadows (40) and Wiegelin (61) described cases having severe permanent visual loss. Etiology was unknown. Wiegelin believed that bilateral retinal artery embolism was a possible etiology in his case. These cases must be separated from those where there appears to be a primary retinal lesion.

J.D., a 3-year-old female. The patient was noted to become blind three days following measles rash. Ten years later she had 3/800 right, 6/800 left vision. There was bilateral old choreoretinitis, strabismus and an ocular nystagmus. The child had normal optic discs. Her neurological examination was otherwise normal.

Walsh (60) (1947) described a patient who developed blindness 5 days following measles with severe visual loss persisting; examination showed a fundus picture like retinitis pigmentosa. Other cases with retinal and choroidal lesions have been recently reviewed (61).

V. TOXIC PSYCHOSIS

In severe cases of measles, particularly when the child has evidences of pneumonitis and fever, one may see a toxic psychosis. It commences while the child is ill and febrile and is not associated with any reaction in the spinal fluid. This would suggest that toxic psychosis is a non-specific reaction to the illness rather than due to a specific lesion characteristic of measles. This is similar to a toxic psychosis seen in other severe febrile illnesses; and, according to several pediatricians, it is common. It has been seen much more frequently than encephalomyelitis by practicing pediatricians and causes little, if any, concern. Indeed, most of them regard toxic psychosis as an expected occurrence with severer cases.

D.J., a 2-year-old female. At onset of measles temperature was 105. The child was delirious and completely disoriented. She had measles pneumonia, which subsided in 2 days. Her

mental status also returned to normal at this time. There were no residua and lumbar puncture was completely normal.

B.R., a 5-year-old male. On the second day of measles, with a fever of 105, the patient became hyperactive, talked of mice and rats in his bed and was definitely paranoid and confused. Neurological examination and lumbar puncture were both negative. On the fifth day, with subsidence of fever, the patient's mental status returned to normal.

VI. THROMBOPHLEBITIS OF THE CEREBRAL VEINS

This complication, while rare, occurs especially in the markedly dehydrated infant. The neurological aspect was fairly characteristic: seizures, evidence of increased cranial pressure and venous engorgement of superficial scalp veins. It left severe spastic diplegia in its wake. No patients in this series had this complication.

VII. PERIPHERAL NEUROPATHY

There were no cases of this complication in our series. Morton (44) reported a case of peripheral neuropathy following measles, but some question had arisen as to the possibility of an unrecognized diphtheria infection (21). Miller (42) noted 10 reported instances of peripheral neuritis following measles but no details were given. In our opinion, a specific peripheral neuropathy clearly related to measles infection has yet to be demonstrated.

DISCUSSION

The neurological complications associated with measles may be separated into four major groups:

1. A diffuse encephalomyelopathy characterized by perivascular demyelination and perivenous microglial proliferation.
2. Infarctions in the distribution of major arterial channels.
3. Acute cerebral edema often associated with some mild vascular changes and neuronal changes.
4. Rarer complications (retrobulbar neuritis, toxic psychosis, sinus thrombosis, etc.).

Some confusion has arisen in the literature because of the attempt to consider each of the complications of measles as "encephalitis". Since there appears to be general acceptance of the term measles "encephalitis" (while remaining noncommital concerning the etiology) it is believed that the term should be retained but restricted to that illness which has the diffuse disseminated demyelinating pathology as its basis.

An attempt has been made in this paper to show that the clinical picture which can be associated with such pathology may vary from a patient with mild delirium or a single convulsion, to a deeply comatose patient with or without focal signs. An effort has been made to emphasize that these really represent a continuous spectrum and the symptoms will only vary in terms of the severity of the pathologic process, and the tendency for it to be more severe in certain areas, i.e., giving more cerebellar signs in one patient, more myelitic signs in

another. The important point to note is not the focal signs as such, but the presence of abnormalities elsewhere in the neural axis, i.e., minimal mental changes in association with the myelitis, behavioral and personality changes in the presence of cerebellar signs. Electroencephalography may be of help in suggesting the diffuseness of the process. The spinal fluid almost always is under normal pressure, and the presence of a lymphocytic cellular reaction or raised protein is present in over 89 per cent of the cases in this series.

The second group—the infarctions in the distribution of the major arterial channels—is represented clinically by the acute hemiplegias. These can be distinguished from the first group by their onset at an earlier age, their lack of time relationship to the rash, the permanency of the hemiplegia and the high incidence of seizures. The cerebrospinal fluid is normal. These infarctions account for many of the so-called cases of measles "encephalitis" that occur before the onset of the rash, or unusually long after measles. They are important to identify because the prognosis is so different from measles encephalomyelitis.

The patients with acute cerebral edema or "toxic encephalopathy" are acutely ill individuals. They present the signs of acutely increased intracranial pressure. Papilledema is marked. Most often there is a profound disturbance of mental status and most neurological signs that can be elicited are probably on the basis of the swollen hemispheres displacing the mesial portions of the temporal lobe down through the tentorium and compressing the brain stem. The third nerves are frequently compressed or angulated over the posterior cerebral arteries. These two phenomena probably explain the dilated, fixed pupils, the heightened reflexes and the decerebrate phenomena seen in these patients. Lumber puncture shows an increased cerebrospinal fluid pressure. Protein and cytology are usually normal. If these patients can be recognized clinically, lumbar puncture probably should be avoided. The best treatment would be conservative handling or ventricular drainage from above. Death occurs usually as a result of the tentorial and cerebellar pressure cones. Lumbar puncture could aggravate the condition.

A convulsion ocurring during the course of measles often presents a difficult diagnostic problem. The history of previous convulsions or the occurrence of the convulsion with the initial rise of fever or before the rash, all were taken as strong evidence against the underlying pathology being measles encephalomyelitis and highly suggestive of idiopathic epilepsy. If a lumbar puncture fails to show an excessive amount of lymphocytes, or protein elevation, and the electroencephalogram a normal or paroxysmal pattern, then one can be quite confident of the diagnosis. Long-term follow-up of these patients usually confirmed the clinical impression of an idiopathic epileptic disorder. Convulsions occurring after the rash or late in the course of measles were usually associated with lymphocytic reaction and/or an increased protein in the spinal fluid and diffuse slow-wave disturbances in the electroencephalogram. They were felt to be symptomatic of underlying measles encephalomyelitis. Four patients who died as a result of them had diffuse disseminated demyelinating pathology with perivenous microglial proliferations typical of measles encephalomyelitis.

Twenty-four others revealed or soon developed other clinical signs of a diffuse neurological disease.

The isolated cases of retrobulbar neuritis, without any evidence of the involvement of the rest of the nervous system, were felt to be on a different pathological basis from the encephalomyelitides. It is likely that some of the reports of isolated myelitis during the course of measles infection also represent a distinct entity. Instances of such symptomatology have followed other illnesses and their relation to measles is probably non-specific.

CONCLUSIONS

The neurologic complications of measles may be divided into several groups. Most important, in terms of prognosis and in understanding the illness, is the basic premise that they are not *all* due to so-called measles "encephalitis"; there are numerous types of pathology which can be seen as a result of measles infection and its neurologic complications.

The usual measles encephalomyelitis is not fatal *per se*; the convulsive disorder causes most of the fatalities. If this can be controlled successfully, prognosis is excellent. In terms of recovery, the worst prognosis appears to be in infants; none that have been followed here has emerged unscathed. However, one can still be optimistic in most cases, despite the overwhelming signs, as time has a great tendency to bring improvement. The behavioral disorder so commonly seen after the illness usually disappears provided that the patient's I.Q. remains normal. The prognosis is poor for behavioral improvement in the presence of a low I.Q. Convulsive disorders frequently occur a number of years after measles encephalomyelitis.

The infantile hemiplegias are usually on the basis of vascular infarction and tend to be permanent with a high incidence of seizures developing in later years. "Toxic encephalopathy" has a high mortality. Each of our 3 patients died.

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REFERENCES

1. Abercrombie, J.: Diseases of the Brain and Spinal Cord, 1845, 4th Edition, Edinburgh, Waugh and Innes, p. 158.
2. Allyn, H. B.: "Paralysis Following Measles," Med. News, **59**: 617, 1891.
3. Apley, J.: "Sex Precosity in a Boy after Measles Encephalitis," Arch. Dis. Childh., **27**: 584, 1952.
4. Appelbaum, E.: "Measles Encephalitis," Dologopol, V. B., and Dolgin, J., Amer. J. Dis. Child., **77**: 25, 1949.
5. Barlow, T. and Penrose, F.: "On a Case of early disseminated myelitis occurring in the Exanthum Stage of Measles and Fatal on the 11th Day of that Disease.", Med.-Chir. Trans., **70**: 77, 1887.
6. Bergenfeldt, E.: "Myelitis as a Complication of Measles," Acta. Med. Scand., **61**: 281, 1924.

7. Boenheim, C.: Über nervöse Komplikationen bei Spezifisch Infektions Krankheiten Kindlichen," Ergebn. inn. Med. Kinderheilk, **28:** 598, 1925.
8. Boenheim, C.: "Ueber Nervöse Komplikationen bei Spezifisch-Kindlichen Infektious-Krankheiten and Vaccination", Berl. Klin. Wschr., **6:** 1552, 1927.
9. Box, C. R.: "A Case of Acute Ascending Paralysis," Lancet, **1,** 222, 1921.
10. Burnet, F. M.: Principles of Animal Virology, 1955, New York, (Academic Press Inc.).
11. Calmeil, L. F.: Traité des maladies inflammatoires du cerveau, 1859, Paris, J. B. Bailliere et Fils, T.2, p. 411.
12. Clapton, E.: "Atrophy of the Cerebellum," Trans. Path. Soc. Lond., **22:** 20, 1871.
13. Davidoff, L., and Epstein, B. S.: The Abnormal Pneumoencephalogram, 1950, Philadelphia, Lea and Febiger.
14. Dilbecco, R.: "Interaction of Viruses and Animal Cells," Physiol. Rev., **35:** 301, 1955.
15. Ferraro, A., and Scheffer, I. H.: "Encephalitis and Encephalomyelitis in Measles," Arch. Neurol. Psychiat., Chicago, **25:** 748, 1931.
16. Ferraro, A., and Scheffer, I. H.: "Toxic Encephalopathy in Measles," Arch. Neurol. Psychiat., Chicago, **27:** 1209, 1932.
17. Finley, K. H.: "Pathogenesis of Encephalitis occurring with Vaccination, Variola, and Measles," Arch. Neurol. Psychiat., Chicago, **39:** 1047, 1938.
18. Ford, F. R.: "The Nervous Complications of Measles with a Summary of the Literature and Publication of 12 Additional Case Reports," Bull. John. Hopk. Univ., **43:** 140, 1928.
19. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, 1952, 3 ed., Springfield, Charles C. Thomas.
20. Ford, F. R., and Guild, H.: "Precocious Puberty Following Measles Encephalomyelitis, and Epidemic Encephalitis," Bull. John. Hopk. Univ., **60:** 192, 1937.
21. Ford, F. R., and Schaffer, A.: "The Etiology of Infantile Acquired Hemiplegia," Arch. Neurol. Psychiat., Chicago, **18:** 323, 1927.
22. Fox, M. J., Kuzma, J. F., and Stuhler, J. D.: "Measles Encephalomyelitis," Amer. J. Dis. Child., **85:** 444, 1953.
23. Fox, T. C.: "An affection of the Nervous System During the Exanthum Stage of Measles," Lancet, **1:** 771, 1887.
24. Good, R. A., and Campbell, B.: "The Precipitation of Latent Herpes Simplex Encephalitis by Anaphylactic Shock," Proc. Soc. Exptl. Biol. Med., **68:** 82, 1948.
25. Gordon, M.: "Discussion," Amer. J. Dis. Child., **65:** 293, 1943.
26. Greenfield, J. G.: "The Pathology of Measles Encephalomyelitis," Brain, **52:** 171, 1929.
27. Griffith, J.: "Acute Cerebellar Encephalitis," Amer. J. Med. Sci., **162:** 781, 1921.
28. Hamilton, P. M., and Hanna, R. J.: "Encephalitis Complicating Measles," Amer. J. Dis. Child., **61:** 483, 1941.
29. Hegler, C.: Jochmanns Lehrbuch der Infectionskrankheiten, 1924, 2nd Auf., Berlin, J. Springer, p. 760.
30. Henoch, E.: Lectures on Childrens Diseases, A Handbook for Practitioners and Students, 1889, Translated by J. Thompson, London, New Sydenham Society, vol. 2, 255.
31. Hoyne, A. L.: "Measles in 1938," Illinois Med. J., **76:** 136, 1939.
32. Hoyne, A. L.: and Slotkowski, E. L., "Frequency of Encephalitis as a Complication of Measles," Amer. J. Dis. Child., **73:** 554, 1947.
33. Kabot, E. A.: Wolfe, A., Bezer, A. E., "The Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Heterologous and Homologous Brain Tissue with Adjuvants," J. Exp. Med., **85:** 117, 1947.
34. Ker, C.: Infectious Diseases, 1920, 2nd. ed., Henry Froures, p. 51.
35. Levy, L. and Roseman, E.: "Electroencephalographic Studies of Encephalopathies," Amer. J. Dis. Child., **88:** 5, 1954.
36. Litvak, A. M., Sands, I. J., Gibels, H.: "Encephalitis Complicating Measles," Amer. J. Dis. Child., **65:** 265, 1943.
37. Lucas, J.: "An Account of Uncommon Symptoms Following the Measles," London Med. J., 11, 325, 1790.

38. LUST, F.: Münch. Medwschr., 74, 1927.
39. MALAMUD, N.: "Sequelae of Post Measles Encephalomyelitis," Arch. Neurol. Psychiat., Chicago, **41**: 943, 1939.
40. MEADOWS, S. P.: "Discussion on the Neuro-ophthalmological Aspects of Failure of Vision in Children," Proc. Roy. Soc. Med., **42**: 494, 1954.
41. MERRITT, H.: Textbook of Neurology, 1955, Philadelphia, Lea and Febiger.
42. MILLER, H.: "Discussion on the Neurological Complications of the Acute Specific Fevers," Proc. Roy. Soc. Med., **49**: 139, 1955.
43. MORGAN, I. M.: "Allergic Encephalomyelitis in Monkeys in Response to Injection of Normal Monkey Nervous Tissue," J. Exp. Med., **85**: 131, 1947.
44. MORTON: Univ. Penn. Med. Mag., **9**: 740, 1897.
45. MOSSE, K.: Jb. Kinderheilk., **112**: 272, 1926.
46. MUSSER, J. H., AND HAUSER, G. H.: "Encephalitis as a Complication of Measles," J. Amer. Med. Ass., **90**: 1267, 1928.
47. NEAL, J. B. AND APPLEBAUM, E.: "Encephalitis associated with Measles," J. Amer. Med. Ass., **88**: 1552, 1927.
48. NEBEL, E.: Acta. phys. Med. Acad. Caesarea naturae curiosorum, p. 296, Obs. CXL, quoted by Ford, 1928.
49. ODESSKY, L., BEVO, A. V., JENNINGS, K. G., SANDS, I. J., ROSENBLATT, P., WEISTER, H., AND NEWMAN, B.: "Therapeutic Doses of Gamma Globulin in Treatment of Measles Encephalitis and Encephalomyelitis," J. Pediat., **43**: 536, 1953.
50. PETERMAN, M. G. AND FOX, M. S.: "Post Measles Encephalitis," Amer. J. Dis. Child., **57**: 1253, 1939.
51. RAKE, G.: Virus and Rickettsial Diseases of Man, 1948, Philadelphia, J. B. Lippincott, ch. **18**: p. 370.
52. REDLICH, F., Z. Kinderheilk.: **43**: 178, 1927.
53. RIVERS, T. M.: "Relation of Filterable Viruses to Diseases of the Nervous System," Arch. Neurol. Psychiat., Chicago, **28**: 757, 1932.
54. SCHEPERS, M. A.: "Ein Fall von Nervenaffectionen bei Masern," Berl. Klin. Wschr., **9**: 517, 1872.
55. SCHAFFER, M. F., RAKE, G., AND HODES, H. L.: Amer. J. Dis. Child., **64**: 815, 1942.
56. SOLOMAN, G., MARKMAN, C. A., AND WEST, E. J.: "Measles Encephalitis," Pediatrics, N. Y., **11**: 473, 1953.
57. STROM, T.: "Acute Blindness as Post Measles Complications," Acta Paediat. Stockh., **42**: 60, 1953.
58. SYDENHAM, T.: The Works of Thomas Sydenham, 1850, translated by R. G. Latham, London, Sydenham Society, vol. 2, pg. 250.
59. TOP, F. H., and others: Handbook of Communicable Diseases, 1941, St. Louis, C. V. Mosby Company.
60. WALSH, F. R.: Clinical Neuro-ophthalmology, 1947, Baltimore, The Williams and Wilkins Company.
61. WIEGELIN, S.: "Masern durch Verschluss Zentralarterien der Netshaut," Klin. mbl. Augenheilk., **71**: 692, 1923.
62. WILLIAMS, D.: "A Case of 'False Disseminated Sclerosis Due to Measles'," Med. Chir. Trans., **77**: 57, 1894.
63. WOHLWILL: "Ueber Encephalomyelitis bei Masern," Z. ges. Neurol. Psychiat., **112**: 20, 1929.