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FATAL CASE OF POLIO-ENCEPHALITIS DUE TO POLIOMYELITIS VIRUS

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[WITH PHOTOGRAPHURE PLATE]

The case of fatal polio-encephalitis described in detail below is reported because of its interesting clinical picture and because of the striking proof of the diagnosis by intracerebral inoculation in a monkey. The similarity of the lesions in the cord of the human victim to those in the monkey inoculated with a filtered saline extract from the child's brain and cord can easily be seen by reference to the illustrations.

Case Report

A well-developed child of 3½ years was admitted to Edgware General Hospital on Aug. 3, 1948. He had had pertussis at 1½ years, but had otherwise been well until he began to attend a nursery school one month before his admission. He was not happy at the school, slept irregularly at night, and was sleepy in the mornings. Three weeks before admission he had an illness of influenzal type lasting one day, during which he vomited and was febrile and drowsy. On July 31 he was said to have fallen from a swing, though apparently with no untoward effect. However, the next day he became drowsy and slept through much of it, would not eat, complained of abdominal pains, and vomited twice. During the night he awoke three times and complained of headache and pains in the back of the neck and in the legs. On Aug. 2 he still complained of the pains, and some weakness of the left side of the face developed, the face being drawn to the right. Although he was febrile and eager for fluids, he appeared to swallow with difficulty. He talked normally throughout the day. By evening he was generally stiff and showed a tendency to restlessness and twitching of the limbs. The bowels were constipated from that day to the end, and he again vomited once. On the day of admission he was not easy to rouse and would not speak; the restlessness and twitchings continued.

On admission he was very drowsy, toxic, and cyanosed. His temperature was 102° F. (38.9° C.), pulse 88, respiration 56. His tongue was moist but furred. The throat was not inflamed, but the tonsillar glands were palpable. There was pronounced stiffness of the neck and spine. Kernig's sign was not present and the legs were not stiff. His pupils were equal and reacted to light, though sluggish. The disks were normal. He had slight weakness of the left side of the face. No other apparent abnormality in cranial nerves was observed and no weakness was noted in the limbs. Tendon-jerks were absent in the left lower

limb but brisk on the right side. Plantar response was extensor on the left side and indefinite on the right. No abnormality was noted in other systems.

Lumbar puncture showed clear fluid under normal pressure; total protein, 80 mg. per 100 ml.; Pandey +; white blood cells, 55 per c.mm. (degenerate polymorphs 5%, lymphocytes 20%, large endothelials 75%); chlorides, 710 mg. per 100 ml.; no organisms seen; sterile on culture.

Overnight his condition had deteriorated rapidly, and when seen by one of us (G. H. J.) next morning (Aug. 4) he was almost completely unconscious. He was still toxic and cyanosed; respirations were stertorous, but the rate was only 22. His temperature was 98° F. (36.7° C.) and pulse 80. A tendency to show slight general convulsions was noted. The disks were normal, as were the pupils, apart from the persistent sluggish reaction to light. Neck stiffness was slight and Kernig's sign was negative. The face was now almost expressionless as a result of general weakness. The left side of the body, though still showing voluntary movement, appeared definitely weaker and more flaccid than the right. The tendon-jerks, though sluggish, were all elicited except the right ankle-jerk. The abdominal reflexes were all present. The left plantar response was still definitely extensor, but that on the right remained indefinite.

Lumbar puncture showed C.S.F. under very low pressure; no block; opalescent fluid; fibrin clot formed after 15 minutes; white blood cells, 195 per c.mm. (lymphocytes 86%, polymorphs 14%); red blood cells, 465 per c.mm.; normal sugar content; sterile on culture. A blood count showed: Hb, 90%; red cells, 5,090,000; white cells, 4,700 (polymorphs 68%, lymphocytes 28%, monocytes 4%).

A diagnosis of a neurotropic virus infection was made, and since the prodromal illness three weeks before admission was within the reported maximal incubation period of 35 days for the poliomyelitis virus it was considered that the case was possibly one of polio-encephalitis. The child's condition continued to deteriorate; the temperature became subnormal, the pulse rate increased to 120–136, and the respiration rate remained at 24–26. He died early on the following morning (Aug. 5) after many hours of complete unconsciousness.

Post-mortem Examination

This was performed five hours after death. The body was that of a normally developed male child.

Brain (1,350 g.).—Meninges normal. Surface of brain intensely congested. On section the cortex of the hemispheres was plum-coloured, but showed no petechiae; white matter normal except for a few tiny petechial haemorrhages in the occipital lobes. The cerebellum, mid-brain, pons, and medulla were macroscopically normal.

Spinal Cord.—Macroscopically normal.

Skull.—Normal except for a small quantity of yellow glairy fluid in the right mastoid cavity. Films of this fluid showed occasional pus cells, and on culture a few colonies of *Bacterium coli* and *Streptococcus faecalis* were grown.

Comparison of Histological Lesions of Central Nervous System in the Case described and in the Inoculated Monkey

	Human	Monkey
Motor cortex, left	Congestion only	{ Early perivascular cuffing Nil Nil Nil Nil
" " right		
Sensory cortex, left		
" " right		
Olfactory bulb		
Basal nuclei	Few small areas of perivascular cuffing and very early neuronal changes	Perivascular cuffing and early neuronal degeneration
Brain stem		
Cervical cord	Marked perivascular cuffing. Slight cellular infiltration of anterior horns. Early neuronal degeneration	Marked perivascular cuffing. Cellular infiltration of grey matter, most marked in anterior horns. All stages of neuronal degeneration, including neuronophagia by histiocytic cells. The changes increase in severity, progressing from cervical to lumbar region
Thoracic cord	Marked perivascular cuffing. Marked cellular infiltration of anterior horns, particularly on left side. Advanced neuronal degeneration	
Lumbar cord

(i)

(ii)

FIG. A.—Perivascular cuffing in poliomyelitis. (i) Section of lumbar cord (human). H. and E. ($\times 100$). (ii) Section of lumbar cord (monkey). H. and E. ($\times 100$).

The remaining organs were normal macroscopically and microscopically except for some fatty degeneration in the liver cells.

Various pieces of the nervous system were fixed in formal-saline for histological examination. Sections were stained with haematoxylin and eosin, Loyez's haematoxylin, and Mallory's phosphotungstic acid. The detailed changes noted in these tissues are shown in the accompanying Table and are compared with those of an inoculated rhesus monkey (see below) which had been similarly fixed and stained.

Animal Inoculation (Dr. F. O. MacCallum)

The diagnosis of poliomyelitis infection in this case was confirmed by animal inoculation. A suspension of pieces of cerebrum, mid-brain, and pons was prepared within a few hours of necropsy and inoculated intracerebrally and intranasally under ether anaesthesia into one monkey of the species *Cercopithecus aethiops sabaues*. The monkey developed typical signs of poliomyelitis 13 days later and was killed with chloroform. Histological examination of the central nervous system revealed typical lesions of poliomyelitis.

A suspension of cord from this monkey was inoculated intracerebrally into a rhesus monkey, which also developed typical poliomyelitis eight days later; the microscopical lesions are well shown in Figs. A ii and B ii and in the Plate (Figs. 5 and 6). The original C.N.S. tissues of the patient were also inoculated intracerebrally into mice and guinea-pigs, with negative results.

Histological Findings

The histological changes in both the human and the monkey sections were basically the same and varied only in degree. The perivascular cuffing, neuronal degeneration, and cellular infiltration characteristic of poliomyelitis were all found in the spinal cord and brain-stem.

The neuronal degeneration (Plate, Figs. 1–6) showed itself as a loss of the nuclear membrane and of the oxyphil nucleolus (Fig. 2). Next the tigroid substance became granular or showed condensation at the side of the cell (Fig. 3). Eventually the nucleus and the tigroid substance completely disappeared, leaving a structureless eosinophil mass (Fig. 4). This was invaded by histiocytes (neuronophagia), which eventually removed it completely (Figs. 5 and 6). The cellular infiltration

(i)

(ii)

FIG. B.—Cellular infiltration of spinal cord in poliomyelitis. (i) Anterior horn of lumbar cord (human). H. and E. ($\times 100$). (ii) Anterior horn of lumbar cord (monkey). H. and E. ($\times 100$).

of the grey matter (Figs. B i and B ii) showed the same cells as in the perivascular cuffs. No demyelination of the white matter was seen.

The perivascular cuffing (Figs. A i and A ii) consisted of an infiltration of the perivascular space with histiocytic cells and lymphocytes; very few polymorphonuclear cells were seen.

Discussion

This case of polio-encephalitis had several features of interest apart from the confirmation of the diagnosis by animal inoculation. First among them comes the encephalitic nature of the signs, the chief of these being coma and evidence of brain-stem involvement. Kelleher (1947) stated that in his experience 30% of the poliomyelitis cases seen in the first part of the 1947 epidemic were of the bulbar type; of these a few were drowsy, and one became comatose and died after being unconscious for less than 24 hours. This last case had pronounced cranial-nerve disturbances together with mid-brain and cerebellar involvement. Brewis and Neubauer (1948) described a probable case of polio-encephalitis which recovered after showing coma, fits, cerebellar signs, and spastic weakness. Laurent (1947) recounted two similar examples of encephalitis, one of which made a good recovery; the other died 16 hours after admission. Necropsy in the latter case showed only oedema in the cerebral cortex, but small areas of perivascular "cuffing" with mononuclear cells were seen throughout the brain-stem (bulb, pons, mid-brain, and basal ganglia).

These findings correspond to some extent with those in our case, in which the cortex was extremely congested but showed no other lesion. In this case perivascular cuffing was observed in the pons, particularly in its dorsal part below the floor of the fourth ventricle. In this area, too, were cells which showed peripheral concentration of Nissl's granules. Unfortunately, the medulla, cerebral peduncles, and basal ganglia were not examined, but it can be said that the changes in the pons were of a surprisingly mild order: that this was not due to the short history of the case can be seen from the intense motor-cell destruction in the spinal cord.

This sparing of the cortex has been recorded several times by investigators in the United States, including the Collective Committee investigating the New York epidemic of 1907. From their evidence and other evidence at his disposal Rothman (1931) was left in doubt about the reality of polio-encephalitis. In fact, Brown *et al.* (1948) concluded from their investigation of a large series of cases of the bulbar encephalitis type that the cerebral symptoms were in a large measure due to anoxaemia, although in a few cases focal cerebral lesions were found.

Scheinker (1947) also reported no cortical involvement, but Bodian (1947), in 24 necropsies on cases of poliomyelitis, found involvement in the motor cortex alone, usually of mild or moderate degree, in 20 instances. In this series the most severe lesions were found in the brain-stem, where the substantia nigra, the cerebellar roof nuclei, the vestibular nuclei, and the reticular formation were heavily involved. Bodian felt that stupor, disorientation, and coma resulted from these brain-stem lesions, which in some of his cases included focal softening. The series also showed almost consistent involvement of the fifth, seventh, tenth, and twelfth cranial-nerve nuclei, the seventh being slightly more involved than the others. In the cord the anterior horn cells were much more involved than those of the posterior and intermediate horn cells, and were sometimes wiped out over whole segments. These findings again correspond to those in our case.

Scheinker found a distribution of lesions in the C.N.S. comparable with those found by Bodian, the medulla, pons, mid-brain, and cerebellum all being markedly involved in his cases of poliomyelitis. He also described heavy perivascular cuffing in the substantia reticularis, in the floor of the fourth ventricle, in the periaqueductal region of the brain-stem, and in the substantia nigra. But in these regions rarely was there actual destruction of the nerve cells, and complete chromatolysis was the most advanced lesion found. Lesions in the corpus striatum, the globus pallidus, and in the hypothalamic nuclei were likewise of only moderate severity.

Scheinker found numerous foci of lymphocytes in the cranial nerves, particularly in the vagi, and also an especial concentration of cells around the vagal nuclei. Apropos of these findings he quoted the view of Sabin (1942) that the virus may spread up the vagi from the alimentary tract to the central nervous system. A simultaneous cellular inflammatory reaction, including multiplication of microglial cells and degeneration of nerve cells, was a feature of Scheinker's cases. The cellular reaction was most prominent in the medulla and mid-brain, and the cell degeneration was most pronounced in the anterior horn cells of the cord.

These main lesions of fatal poliomyelitis correspond to those in the fatal encephalitic type of case described by us. In the less severe cases which recover it is probable that the lesions are of simultaneous type and distribution but of less intensity. The extensor plantar responses in our case and the spastic paresis seen during recovery in their case by Brewis and Neubauer are evidence of a pyramidal involvement, an involvement which McAlpine (1947) has described as occurring, albeit uncommonly, in the spinal form of the disease. But it is a matter for comment that, apart from occasional motor-cortical lesions in Bodian's series, upper motor neurone lesions have not been a prominent feature to the histologist: not even pyramidal demyelination was seen in our case, and no cortical or pyramidal lesions were observed by Scheinker.

It is of course possible that the intense cortical congestion in the present case was responsible for depression of upper motor neurone function, and though cord oedema was thought of little consequence by Bodian it might be associated with the transitory Babinski responses seen in some of the spinal cases. The initial flaccidity which may be associated with these responses in some cases (e.g., that of Brewis and Neubauer) was attributed by Toomey (1940) to "cord shock," a state certainly more intangible than that of congestion or oedema. As Scheinker pointed out in describing the inflammatory response of the nervous tissues, the *whole* nervous system is invaded by the virus of poliomyelitis. It is therefore not improbable that where a pyramidal lesion occurs and recovers in a more protracted case of poliomyelitis there has been some degree of demyelination of the tracts. Such changes did not develop in our case, possibly because of its short course.

A final feature of interest is in the comparison of this case with a series of cases observed in the same district (Jennings, 1947) during the spring, summer, and autumn of 1946. These cases included eight with encephalitic symptoms (apathy, twitchings, severe drowsiness, and delirium); four with facial palsies and other cranial-nerve lesions as well as cerebral symptoms; and a number of cases, some with largely meningitic signs and symptoms, in which there were temporary Babinski responses. Although only one of these cases, and that at school, had proved contact with poliomyelitis, it now seems possible, in retrospect, that at least some of them were cases of poliomyelitis in which only the brain-stem and upper motor neurones appeared to

be involved. This likelihood was mentioned by MacAlpine (1947) after the 1947 period of poliomyelitis had included similar cases; our present case, though affording no proof, does give this concept further support.

Summary

A fatal case of infection by the virus of poliomyelitis has been described.

Although the case clinically showed a mainly encephalitic and brain-stem involvement the cerebral changes were merely those of cortical congestion, and the pons showed only a mild inflammatory reaction. The spinal cord, on the other hand, showed gross and widespread destruction of anterior horn cells. No really satisfactory histological explanation was forthcoming from either cord or brain to account for the definite clinical evidence of upper motor neurone involvement. Congestion, oedema, or very slight early changes in these neurones might be adduced as causes of the signs. Inoculation of the nervous tissues of this case in monkeys resulted in symptoms and histological lesions closely akin to those in the human subject.

This seemingly encephalitic case was thus proved to be due to an infection by poliomyelitis virus, and its features are compared briefly with those shown by possible atypical cases of the same infection seen in the same district two years previously.

Our thanks are due to Miss M. H. Shaw for the photomicrographs of the sections.

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FATAL CASE OF ACUTE ENCEPHALOMYELITIS DUE TO POLIOMYELITIS VIRUS

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The number of instances in which poliomyelitis virus affects the fore-brain and brain-stem seems to vary in different epidemics. Reports dealing with the 1947 epidemic in this country indicated a higher proportion than usual of cerebral and bulbar lesions with or without spinal involvement (Kelleher, 1947; MacAlpine *et al.*, 1947). The picture has been confused by the occurrence, just before the poliomyelitis outbreak of 1947, of minor and localized outbreaks of virus encephalomyelitis recorded by Jennings (1947) and Laurent (1947) and regarded by them as a disease or group of diseases in which no relation to poliomyelitis was probable. On the other hand both Critchley (1948) and MacAlpine *et al.* (1947) believe that the virus responsible was probably identical with that of acute poliomyelitis.

Undoubtedly the lack of facilities for the isolation and identification of virus in this country has accentuated the confusion, and, whereas Toomey (1941) recognizes eight clinical types of poliomyelitis, doubts about the existence of types other than spinal and brain-stem are held by many authorities in this country—for example, Walshe (1947), who states: "It is probable, however, that only the spinal type and a few cases of brain-stem type really belong to this [poliomyelitis] infection." Baker and his colleagues (1947), in a comprehensive review in which the word "bulbar" has been used "with some degree of licence" to denote involvement of the entire brain-stem, including the medulla, pons, and mid-brain, present an acceptable classification of all forms of bulbar poliomyelitis. They include a "diffuse encephalitic" and a "focal encephalitic" group, and, in connexion with the latter, state that aphasic disorders have been reported rather infrequently. They quote one case of visual verbal agnosia from the literature.

The following record is a description of a case of acute polio-encephalomyelitis in which during life it was not possible to make a clear clinical distinction between poliomyelitis or other virus aetiology, but in which histological evidence and ultimately virus isolation established the aetiological agent.

Case Report

A man aged 25 with a record of excellent health was admitted to the Western Hospital on Oct. 12, 1947, with a history of illness which had begun six days earlier with a sense of fatigue and malaise, followed 48 hours later by headache and giddiness. On the following day (Oct. 9) he vomited once and, because of increasing malaise and the onset of giddiness, tremors, and blurring of vision, had to take to bed. On the fourth day after the onset feverishness and thirst were pronounced. He was restless and unable to sleep, and had difficulty in hearing. His condition rapidly worsened, until on Oct. 12 he was found by his relatives to be unable to move, to be generally rigid rather than weak or flaccid, and, though conscious, to be unable to speak.

On admission at 5 p.m. on the same day he had a temperature of 101° F. (38.3° C.) and a pulse rate of 82. He was conscious, and there was some cyanosis of the extremities. He was unable to speak. A fine tremor of the outstretched hands was noted. There was moderate neck rigidity and hamstring spasm. He moved his limbs very slowly. Movements were stiff, jerky, and apparently uncoordinated, and passive movements of the limbs further revealed the general rigidity and tonic spasm. The facial muscles were involved in the general hypertonicity, and commands were obeyed incompletely and with great difficulty and delay in execution. There was fine nystagmus in all directions but most pronounced to the right. Apart from a possible weakness of the left sternomastoid muscle there were no obvious cranial-nerve palsies. All tendon reflexes were present but depressed, and the abdominal reflexes were normal. There was a doubtful Babinski sign on the right; the left plantar reflex was flexor. The respiratory muscles were unaffected and the pharynx functioned. There was no retention of urine, but he was incontinent.

A few hours later the tendon reflexes in the right lower extremity were very sluggish, but apart from the dysfunction, which was apparently due to tonic spasm, there was still no apparent paresis or paralysis; the dysarthria might also be ascribed to tonic spasm, although possibly it may have been a true motor aphasia. Lumbar puncture showed a clear fluid containing 18 lymphocytes per c.mm. and 55 mg. of protein per 100 ml.; colloidal gold test, 0111210000; Wassermann reaction negative.

On the following day (Oct. 13) there was little change, but some weakness of the right lower extremity, with greatly diminished reflexes, was noted. Consciousness appeared to be clouding and ultimately all response to stimuli failed. The tonic rigidity persisted and a fine tremor of the upper lids was

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FIG. 1.—Normal anterior horn cell. H. & E. ($\times 1200$.)

FIG. 2.—Anterior horn cell showing loss of nuclear membrane and nucleolus; partial granulation of tigroid substance. H. and E. ($\times 1200$.)

FIG. 3.—Complete loss of nucleus and complete granulation of tigroid substance. H. and E. ($\times 1200$.)

FIG. 4.—Complete chromatolysis, leaving a structureless eosinophil mass. H. and E. ($\times 1200$.)

FIG. 5.—Commencing invasion of degenerated cell by histiocytes (monkey). H. and E. ($\times 1200$.)

FIG. 6.—Degenerated neurone undergoing phagocytosis (monkey). H. and E. ($\times 1200$.)

BERNARD SCHLESINGER: RHEUMATOID ARTHRITIS IN THE YOUNG

FIG. 1.—Normal bone-marrow section at necropsy.

FIG. 2.—Section of bone marrow from femur of Case 1. Hypocellular, with areas of necrobiosis.

FIG. 3.—Section of liver of Case 11 showing perlobular fibrosis and infiltration of inflammatory cells.