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ORIGINAL ARTICLES.

LETHARGIC ENCEPHALITIS.

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DURING the early months of this year there appeared in the medical journals records of groups of cases presenting anomalous nervous symptoms under such titles as "Acute Infective Ophthalmoplegia or Botulism,"[1] "Note on an Epidemic of Toxic Ophthalmoplegia associated with Acute Asthenia and other Nervous Manifestations,"[2] "Epidemic Stupor in Children,"[3] "Epidemic Polio-encephalitis (so-called Botulism),"[4] and "A Case of Cerebral Toxæmia— ? Botulism."[5] Interspersed with these original articles in the various journals are letters and clinical memoranda recording by different observers isolated instances of disease simulating "Botulism," which was the diagnosis suggested by the authors (Harris and Hall) who reported the first cases. The "epidemic" formed the subject of a report by the Medical Department of the Local Government Board under the title "Recent Epidemic of Obscure

Origin,"[6] in which the relationship of the disease to food and poliomyelitis is considered. More recently there appeared in this *Journal*[7] a series of articles from the Glasgow Health Office entitled "On Some Unusual Forms of Nervous Disease," by Drs. Chalmers and Picken, dealing with somewhat similar cases appearing in our own neighbourhood.

From a survey of all these articles there would appear to have been in existence during the early part of this year a mild epidemic of an unusual and peculiar nervous disease characterised by somnolence and ophthalmoplegia or paralysis of any cranial nerve. It was this combination of cranial nerve paralysis with an extreme degree of lethargy which was the striking and unusual feature—so marked was the somnolence or lethargy, and so persistent, that "sleeping sickness" would immediately occur to the mind of anyone observing or reading the clinical data of a case. For the benefit of the reader who has not seen Dr. Harris's communication, I will give an abstract of his composite clinical picture, and at the same time briefly detail three personally observed examples of what I consider the same disease.

Dr. Harris says that "the patient whilst in ordinary health begins to be languid and drowsy, with or without headache and other symptoms of malaise. In a few hours or days the weakness has increased very much, and indeed may amount to complete prostration, so that he lies helpless in bed and can hardly move a muscle. Together with this the drowsiness becomes more marked and develops into real lethargy. Pyrexia may be absent throughout or it may be present from the first, become severe, and persist. Cerebral excitement and delirium has been a prominent feature in some of the cases. In most of them local symptoms pointing to lesions in the bulbo-pontine area are present at some time or other. Of these ptosis, ophthalmoplegias of various extent, nystagmus, facial palsy . . . speech affections, and dysphagia have occurred in different combinations in different cases. Muscular tremors of a curious kind have been noted in some . . . But there has been, as yet, no evidence of a localised limb paralysis such as one commonly sees in acute poliomyelitis."

The following is a record of the three cases which have come under my observation—

CASE I.—A. T., female, æt. 6½ years, admitted to Royal Hospital for Sick Children on 25th March, 1918.

The history is that the child had gone to school in her usual health eighteen days previous to admission. During the afternoon she was sent home by the teacher as she complained of a headache and seemed dull and listless. Since then the mother stated that she had remained in a most apathetic condition, in fact sleeping constantly, taking no interest in her surroundings and requiring to be roused from time to time to be fed and to evacuate the bowel and bladder. If roused and asked questions she would answer "yes" and "no" quite correctly, and would perform simple movements when requested. There had been no vomiting and no complaint of headache since the onset of the illness.

On admission she was described as a small spare child, cyanosed and very drowsy. She slept continuously but could be roused, when she appeared quite *compos mentis* and would answer questions intelligently—*e.g.*, give her name, age, and address, and would perform any movements requested, as clapping her hands, shaking hands, touching her nose, &c., but on the cessation of all interference she would immediately relapse into sleep. While asleep there existed a definite cataleptic state, the limbs being retained in any position in which they were placed. There was also noted a right-sided facial paralysis and nystagmus. The pupils were equal, and reacted normally though sluggishly. Ophthalmoscopic examination revealed slight redness and swelling of both optic discs. The right leg seemed slightly paretic—both knee-jerks were exaggerated and ankle clonus could be elicited in both feet. There was no anæsthesia.

The temperature was normal; the pulse numbered 84 per minute and was regular; the heart, lungs and abdominal viscera revealed nothing abnormal.

Lumbar puncture disclosed a clear fluid under low pressure, which on centrifugalisation was found to contain only an occasional lymphocyte; no organisms were detected and it remained sterile on culture.

The child remained in the same lethargic state till the end of April—*i.e.*, for five weeks. About the middle of April (14th) double ptosis with almost complete paralysis of both third

nerves was detected. The paralysis was more severe on the left side, there being a marked external squint of the left eye. About 4th May—*i.e.*, six weeks after admission and almost nine weeks after the onset of the illness—the patient commenced to get a little brighter, and by 10th May seemed quite alert, and could sit up in bed and talk with the nursing staff and the rest of the patients in the ward; but the double ptosis and external squint of the left eye and the right-sided facial paralysis persisted. The temperature continued normal during the whole time she was under observation; there had been no headache, and from the disappearance of the lethargy she had taken her food well and had attended to the calls of nature.

She was dismissed from hospital after twelve weeks' residence, the right-sided facial paralysis and left external squint persisting and to a lesser extent the ptosis, but otherwise she seemed quite well. It was learned later that her parents noticed on her return home a marked change in her disposition. She had become simple in her ways and was easily led astray, and her memory had deteriorated.

On being seen again on 20th August—*i.e.*, five months after the onset of the illness—the right-sided facial paralysis, ptosis of right upper eyelid, and left external squint were still apparent. Otherwise nothing abnormal was detected, though her mother stated that mentally she was not so acute as she had been prior to her illness.

CASE II.—C. M., male, æt. $10\frac{4}{12}$ years, admitted to Royal Hospital for Sick Children on 13th June, 1918.

The parents gave the history that the child had been quite well until six days previously. On that day he complained of double vision, and it was noticed that he was squinting. Next day, however, he seemed quite well, and remained so for twenty-four hours, when he became very drowsy, and for four days had lain in bed with his eyes closed, sleeping constantly. He was never unconscious and could be roused, when he would answer questions quite intelligently. There had been no complaint of headache, no vomiting, and squint had not been noticed since the onset of the illness.

On admission it was noted that he was a well developed boy

with flushed cheeks, and that he was very drowsy. He could be roused, however, when he would answer questions. There was some rigidity of the neck, and spasticity of both legs, with positive Kernig. No paralysis was detected. The movements of the eyes were normal; the pupils were unequal, the left being slightly larger, but both reacted normally. The pulse numbered 88 per minute and was regular. Examination of the heart, lungs, and abdominal viscera revealed nothing abnormal.

By lumbar puncture a clear fluid, under great pressure and devoid of any sediment on centrifugalising, was obtained; on culture it remained sterile.

On 17th June, four days after admission, it was noted that the drowsiness from which he could be roused persisted with varying spasticity of the limbs, that both optic discs were reddened, and that with the exception of one observation, viz., on the day after admission, the temperature had been within normal limits.

On the morning of the 18th June he seemed a little brighter, but during the afternoon he suddenly became cyanosed, the respirations shallow and irregular, the pulse feeble, and he died soon afterwards. This seizure was probably evidence of bulbar implication.

Unfortunately permission for a *post-mortem* examination was not granted, but clinically the case seems to be similar to the one recorded above.

CASE III.—H. C., male, æt. $4\frac{10}{12}$ years, admitted to Royal Hospital for Sick Children on 20th June, 1918.

Patient had taken ill suddenly ten days previously, with vomiting. In the evening he had had a typical epileptiform convulsion lasting thirty minutes, followed by five others, each of only a few minutes duration. From then until admission he is said to have lain in a lethargic condition, not taking any interest in his surroundings, and to have complained occasionally of headache.

On admission he was described as a fair-sized and well-nourished boy, very drowsy but able to be roused, when he spoke intelligently though slowly. The temperature was

normal. The pulse numbered 64 per minute, and was occasionally irregular. Physical examination was negative.

During his residence of five weeks nothing abnormal was detected except the drowsiness, with slow articulation during the first ten to fourteen days. He ultimately made a complete recovery, comporting himself in the ward as a normal child.

The question that naturally arose in the minds of the various observers was the nature of this unusual disease. It was soon apparent, as pointed out by the Local Government Board Report, that examples of more common maladies had been mistaken for the rarer disease. There remained, however, a goodly number with a somewhat characteristic clinical picture such as depicted above, and in which no definite diagnosis nor cause for the condition could be given.

The first cases had been admitted to hospital as suffering from meningitis, but the negative findings on examination of the cerebrospinal fluid disposed of that assumption.

Hall and Harris then suggested *Botulism,* and the latter states in his report that in the first case observed by him Captain Harrison, R.A.M.C., isolated from the stools an organism closely resembling in its morphological characters those of *Bacillus botulinus.* Later workers were unable to confirm this finding, and, not observing any association with the ingestion of particular or suspicious articles of food, inclined to a diagnosis of polio-encephalitis, and as suggested by Melland perhaps an aberrant form of poliomyelitis.

At the same time as these cases were being observed in England and Scotland patients presenting similar symptoms were being admitted to the hospitals in Paris. These cases formed the subject of communications by Professor Netter to the Societé Médicale des Hopitaux of 22nd March, 12th, 19th, and 26th April, and 3rd May, 1918. In view of the importance of the question, he made a longer and more comprehensive communication on the subject to L'Académie de Medécine,[8] in which he reviewed the whole condition, and took cognisance of the cases recorded in England up till that time. He concluded that the condition was probably a disease *sui generis,* viz., epidemic lethargic encephalitis.

In the introductory paragraph of this communication he

remarks that about the beginning of March a certain number of cases were admitted to hospital as examples of cerebro-spinal or tubercular meningitis. The characteristic symptoms were fever, somnolence, and troubles of the motor system of the eye, and, as lumbar puncture revealed a normal cerebrospinal fluid, the initial diagnosis of meningitis, just as in the cases observed in England, could not be maintained.

Many of the Paris physicians had seen cases, and it was quite apparent that they were in the presence of a veritable epidemic the true nature of which, however, was at first obscure. In all 71 cases had been met with when Netter wrote—34 in France and 37 in England. The first one observed had sickened in London on 27th February, and was recorded by Batten and Still[3] on 5th May.

As Netter's clinical picture, like those of his fellow countrymen, is so excellent, and as he seems to have solved the mystery surrounding the malady under discussion, I propose to record in some detail his observations, clinical, historical and otherwise.

He states that the somnolence which is responsible for the name of the disease is generally accompanied at the beginning by headache and vomiting. The patient soon develops an inordinate lassitude, and resists with difficulty the desire to sleep. Nevertheless he may be roused, when he will answer questions, perform movements, and even walk, but immediately on being left alone he once more falls asleep. In the more marked cases the patient lies like a log in bed incapable of performing the slightest movement. Sometimes he wakens voluntarily every two or three days to take food, while in other cases he must be roused not only to be fed but to evacuate the bowel and bladder. At other times absolute coma develops, so that it is quite impossible to rouse him. This state of somnolence may continue for weeks, or even months, and may be complicated by paralysis of the sphincters and bed sores. Occasionally the drowsiness is interrupted by delirium.

Almost as constant a symptom as the lethargy is paralysis of the ocular (external or internal) muscles. There may be bilateral ptosis, complete paralysis of the external muscles with immobility of the eyeballs or partial paralysis with squint. Nystagmus is common.

There may also be paralysis of the muscles of the face, of the palate, of the tongue, larynx or pharynx; but the limbs are seldom involved, though inco-ordination, tremor, and occasionally clonus and contractures are noticed.

Aphasia and paralysis of the sphincters have been observed. Anæsthesia is usually absent. The reflexes show no constant change.

Fever has usually been present, but as a rule it was limited to the commencement or termination of the illness.

The cerebrospinal fluid is normal, so that this finding, along with the absence of nuchal rigidity, any irregularity of the pulse, and Kernig's sign, differentiate the condition from meningitis for which, as previously mentioned, it has usually been mistaken.

The course of the disease is most variable. In some cases the duration has only been of a few days, terminating either in complete recovery or death from bulbar implication. As a rule, however, the condition lasts for some weeks, even two or three months or longer, when complete recovery may supervene, although the condition had seemed desperate, and large bed sores had made their appearance.

Improvement usually sets in abruptly, but psychic and motor troubles may persist for a long time with incapacity for mental and bodily exertion, troubles of accommodation, and langour.

The mortality-rate is about 50 per cent of those attacked.

Examination of the brain in cases which have died reveals little abnormal to the naked eye except meningeal congestion and punctate hæmorrhages in the grey and white matter. On microscopic examination cellular accumulations around the vessels, especially in the vicinity of the bulb and pons and nuclei at the base of the brain, have been found. The cases presenting the symptoms of superior polio-encephalitis have the lesions correspondingly situated; in fact, the lesion may be present in any part of the brain, and the symptomatology is in accordance with the localisation of the pathological changes.

The type of lesion indicates a diffuse interstitial encephalitis, the etiological agent of which, however, is as yet unknown, but apparently it travels by the blood-stream. The pathological picture resembles that observed by Mott and others in cases of

sleeping sickness, a disease which, as will have been noted, presents many clinical similarities to the one under consideration.

Netter points out that, although the disease is new to the present observers, it had already been described, and that on two occasions previously it had manifested itself in epidemic fashion. In the spring of 1890, just as the pandemic of influenza was abating, the lay and medical press announced the appearance in Northern Italy and Hungary of a new epidemic, and one that was not less grave. *Nona*, as the new disease was called at the time, attacked within a few days or even hours many inhabitants of the town of Mantua, in the province of Lombardy, causing lethargy or delirium.

Apparently also cases of a similar nature were noticed during the spring of 1895 in France, England, Switzerland, Germany, Denmark, Austria, Bulgaria, Italy, and the United States. And, although no mention is made in the clinical records of the association of ocular paralysis with the lethargy, Virchow and Fürbringer at the same time were publishing *post-mortem* findings of hæmorrhagic encephalitis in cases which had presented during life serious cerebral phenomena.

Ebstein and others during the epidemic of *Nona* drew attention to the fact that records were extant of a similar condition having been epidemic in Tübingen in 1712, when it was given the name of *Schlafkrankheit.* Camerarius, who apparently recorded the cases at the time, also notes the association of ocular paralysis.

It would also appear that an epidemic of an apparently similar affection prevailed in Vienna during the winter of 1916 and 1917, the symptomatology being characterised by somnolence and ocular paralysis, and, as in the recent epidemic, the majority of the cases were observed during the month of March. The descriptions, too, of the pathological findings are in complete accord with those of the recent cases. Von Wiesner[9] inoculated a monkey (*Macacus rhesus*) intradurally with an emulsion of the brain of one case, and found that the animal succumbed forty-six hours later after presenting for several hours a somnolence which gradually deepened. Another monkey inoculated in the same manner, but with an emulsion which had been passed through a porcelain filter, remained well. From

the brain of the monkey which succumbed, and also from the brain of fatal cases, Wiesner reported that he cultivated a gram-positive coccus.

Netter, from want of experimental animals, has unfortunately been unable to verify Wiesner's results, and his bacteriological researches are not far enough advanced for publication.

It would seem quite apparent, then, in view of these clinical, pathological, and experimental findings, that the condition is one *sui generis* as maintained by Netter, and that it is neither an aberrant form of poliomyelitis nor of the nature of *Botulism.*

A. Botulism is a food intoxication due to the ingestion of food infected by the *Bacillus botulinus*, and was described for the first time by Van Ermengen.[10] Uncooked ham and sausage are the two classes of food usually contaminated. The symptoms usually set in suddenly twelve to thirty-six hours after partaking of the food, and consist of thirst, a feeling of constriction of the throat, and later paralysis of the intrinsic and extrinsic muscles of the eye. Unless in fatal cases anæsthesia or general nervous symptoms are absent. In the fatal cases, where death usually occurs within three or four days, coma sets in and exitus results from bulbar paralysis. In the cases which recover ophthalmoplegia may persist for months, but the weakness gradually recovers within a matter of weeks. As in all examples of food poisoning, several cases occur in one household. In the epidemic described by Van Ermengen 34 persons, all members of a musical society, were attacked.

Thus in three very important features the cases forming the subject of this article differ from Botulism, viz.—(1) The presence of drowsiness; (2) the fact that only isolated examples occurred in any one household; and (3) the failure to discover the etiological organism.

B. Polio-encephalitis or Poliomyelitis.—Owing to the several epidemics of this disease within recent years, our ideas regarding its pathology and symptomatology have undergone radical changes. We now know that the *contagium vivum*, whether it be a diplococcus as held by Flexner and Noguchi,[11] [12] or some other unknown parasite, may attack the grey matter of any part of the cerebrospinal axis, so that cases may be classified as—

(1) Encephalitis, superior or inferior, depending on whether it is the cortex or base of the brain that is affected.

(2) Medullary or bulbar.

(3) Cerebellar.

(4) Spinal.

The nuclei of the cranial nerves are not infrequently attacked, and delirium and unconsciousness may be present at the onset, but never simply somnolence, so that here we see one important difference between lethargic encephalitis and poliomyelitis.

It has been shown by many workers (Flexner, Levaditi, and Landsteiner) that the disease can be transmitted to apes by intradural injection of emulsions of the diseased brain or spinal cord, and that the disease is still communicable after filtration of the emulsion through a Chamberland filter, so that the *contagium vivum* is spoken of as being ultra-microscopic. Here again we see a contrast to the state of matters in lethargic encephalitis where, at least in the only known experiment recorded above, filtration of the cerebral emulsion removed its potency.

Poliomyelitis has always shown a predilection for infants and children, and, even though adults during epidemics may be attacked, the synonym infantile paralysis is most appropriate. Of 54 cases of lethargic encephalitis recorded by Netter, and in which the age was noted, 77 per cent were over 15 years of age, and of the cases observed in London[6] 86 per cent were over 10 years of age, whereas in the case of poliomyelitis practically 90 per cent of the patients are under 10 years of age. Thus also so far as the age incidence is concerned there is a marked difference between lethargic encephalitis and poliomyelitis.

And, finally, there is a dissimilarity in the seasonal incidence of lethargic encephalitis and poliomyelitis. All the hitherto known epidemics of the former have occurred during the cold months of the year, reaching their acme in March, whereas in the case of poliomyelitis it is during the warm months of the year (July, August, September) that the great majority of the cases occur.

Conclusions:—

1. During the spring of this year (1918) there occurred in France and England an epidemic of a peculiar nervous disease.

2. The chief symptoms of the condition are lethargy and ophthalmoplegia or paralysis of a cranial nerve.

3. Pathologically the condition is characterised by perivascular cellular accumulations in the grey matter at the base of the brain; the virus is filterable.

4. It would seem to be a disease *sui generis* due to some unknown cause, and to which the name lethargic encephalitis has been given.

5. There is absolutely no evidence that it is of the nature of *Botulism.*

6. It would also seem to be quite distinct from poliomyelitis or polio-encephalitis (infantile paralysis) on the ground of a different age incidence, of a different seasonal incidence, and of the fact that the virus is not filterable.

REFERENCES.

[1] Wilfred Harris, *Lancet*, 20th April, 1918, p. 568.

[2] Arthur J. Hall, *Lancet*, 20th April, 1918, p. 568.

[3] Batten and Still, *Lancet*, 4th May, 1918, p. 636.

[4] C. H. Melland, *British Medical Journal*, 18th May, 1918, p. 559; and 25th May, 1918, p. 587.

[5] J. L. Brownlie, *British Medical Journal*, 1st June, 1918, p. 617.

[6] *British Medical Journal*, 18th May, 1918, p. 573.

[7] *Glasgow Medical Journal*, August, 1918, p. 79.

[8] *Bulletin de L'Académie de Medécine*, No. 18, 7th May, 1918, p. 337.

[9] *Wiener klin. Wochenschrift*, 26th July, 1917.

[10] *Archives de pharmacodynamie*, 1897 (Quoted by Netter).

[11] *Journal of Experimental Medicine*, 1913, xviii, p. 461.

[12] Harold L. Amos, *Journal of Experimental Medicine*, 1914, xix, p. 212.