LYMPHOCYTIC CHORIOMENINGITIS

BY

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In 1910 Laubry and Foy described three cases of this disease, occurring in Paris, under the heading of "syndrome méningéal avec lymphocytie rachidienne d'origine indéterminée," and Riét and Rolland (1910) five cases of a similar condition as "méningite bénigne d'allure épidémique." In 1925 Wallgren, in a paper entitled "A New Infectious Disease of the Central Nervous System," reported a Swedish epidemic of 19 cases. J. Gibbens (1931) termed it "acute aseptic meningitis," and described the following characteristics of the condition: (1) An acute onset, with definite meningeal signs. (2) Meningeal changes in the cerebrospinal fluid; there is an increase of pressure and of cells, but the fluid is sterile on culture. (3) A uniform clinical symptomatology. (4) A relatively short benign course without secondary complications. (5) No epidemiological connexion with any known infectious meningeal disease. (6) There is no local infection such as otitis media or sinusitis.

Although it has been suggested that some of the cases described under various headings, such as "benign lymphocytic meningitis," "acute aseptic meningitis," and "lymphocytic choriomeningitis," have been really cases of lethargic encephalitis or poliomyelitis, it is now generally conceded that there is a disease *sui generis*, which is best termed "lymphocytic choriomeningitis."

Clinical Features.—The clinical features of the disease are as follows. The onset is acute, with fever, headache, and meningeal signs. The cerebrospinal fluid is clear or turbid, under increased pressure, and shows a pleocytosis varying from 60 to 1,500 per c.mm.; polymorphonuclears may predominate at the onset, but are rapidly replaced by lymphocytes; the total protein and globulin are increased, the sugar and chlorides usually being unaffected; the fluid is sterile on culture, and direct smears are negative for all organisms, including the tubercle bacillus. The prognosis is good, complete recovery occurring in two or three weeks as a rule.

Aetiology

Armstrong and Lillie (1934) isolated a virus from a case that appeared clinically to be encephalitis lethargica (St. Louis type). It differed from the virus of encephalitis, however, in the following characteristics:

(a) It was not pathogenic for rabbits.

(b) On intracerebral inoculation into mice the animals developed symptoms which are quite different from those produced by encephalitis. The incubation period was 6 to 7 days and fairly constant. "When lifted up by the tail a series of rapid jerky motions with the front and hind legs results, which conveys a pronounced sensation of tremor to the hand, readily distinguishable from that observed with normal mice. These rapid motions often pass into a convulsion, lasting from some seconds to a minute or more, in which the hind legs and toes are strongly extended and rigid, as is also the tail. The seizure may end in death or gradually relax, when the mouse may run about the cage apparently normal. Practically all the mice, however, ultimately die in convulsions, usually in from 1 to 3 days from the onset of symptoms."

(c) On post-mortem examination the mice showed marked cellular infiltration of the meninges, in which lymphocytes predominated, more pronounced on the base of the cerebrum and in the space between the hippocampus and the brain-stem. Also there is often a lymphocytic infiltration of the choroid plexus. No cellular gliosis is seen around the vessel sheaths as in encephalitis.

(d) In monkeys inoculated intracerebrally with the virus it is found to be present in the blood and cerebrospinal fluid.

(e) Intranasal inoculation has no effect.

(f) Cross-neutralization tests indicate that the two viruses are immunologically distinct.

More recently Findlay, Alcock, and Stern (1936) have isolated a virus from cases that correspond clinically with the picture of lymphocytic choriomeningitis and have shown this virus to

be identical with that obtained by Armstrong and Lillie, thus establishing the aetiology of the disease.

Pathology

Viets and Warren (1937) have given the post-mortem findings in one of their cases. The report is here summarized:

The meninges were oedematous, congested, and infiltrated mainly with lymphocytes and also a few endothelial cells. The cerebrum showed a localized oedema of the cortex just below the surface. Perivascular infiltration with lymphocytes and endothelial cells was present. Other cells resembling microglia and a few large cells four or five times the diameter of the lymphocytes with somewhat acidophilic cytoplasm and eccentric, large, and indefinite nuclei were observed. No inclusion bodies were seen. In the midbrain the changes noted were even more evident; in addition, in numerous swollen ganglion cells cytoplasmic inclusion bodies were seen, some of them being rod-like in shape and others round. In the internal capsule the reaction was less intense and no inclusion bodies were found. In the cerebellum and spinal cord perivascular infiltration and gliosis in the white matter were seen and there were no inclusion bodies.

Case Records

Hughes (1937) states that cases have occurred in Asiatics, but does not describe any. Below are recorded eight fairly typical cases that have been under my care in the third-class male wards of the General Hospital, Singapore. My colleagues and I have seen several other cases at the hospital.

Case 1.—A male Malabari Indian aged 21 was admitted on Oct. 6, 1938, with a history of fever for five days. No further history was obtainable. He was delirious on admission, being quite uncontrollable, and had to be kept under the influence of morphine and hyoscine. The neck was not rigid, and Kernig's sign was negative. There was no evidence of involvement of the cranial nerves or paralysis of the limbs. The temperature on admission was 103° F. (39.4° C.); it came down to normal on Oct. 9, but showed an occasional rise up to 100° F. (37.8° C.) from time to time. The ear-nose-and-throat examination was negative, and the fundi were normal. The blood Kahn test was negative (000). The cerebrospinal fluid showed the following changes: pressure increased, naked-eye appearance turbid; cell count, 542 per c.mm. (polymorphonuclears 65%, lymphocytes 35%); total protein, 80 mg. per 100 ml.; globulin + (Ross-Jones); sugar, 51 mg. per 100 ml.; chlorides, 660 mg. per 100 ml.; W.R. negative, Kahn test negative; direct smears negative for organisms (including T.B.); culture sterile; no clot on standing. On Oct. 11 the cerebrospinal fluid was clear; the cell count was 100 (polymorphonuclears 5%, lymphocytes 95%). On Oct. 23 the cerebrospinal fluid was clear, the cell count being 60 (polymorphonuclears 8%, lymphocytes 92%). The patient was discharged cured on Oct. 28.

Case 2.—A male Hokien aged 19 was admitted on Oct. 31, 1938, with a history of fever, headache, and a feeling of chilliness not amounting to a rigor, for one week. The temperature on admission was 101° F. (38.3° C.). On physical examination no abnormality was found except slight stiffness of the neck and a positive Kernig's sign. Examination of the central nervous system was normal. A lumbar puncture was done on Nov. 1, and the cerebrospinal fluid showed the following changes: cell count, 152 per c.mm. (polymorphonuclears 35%, lymphocytes 65%); total protein, 250 mg. per 100 ml.; globulin + (Ross-Jones); sugar, 10 mg. per 100 ml.; chlorides, 627 mg. per 100 ml.; direct smears negative for organisms (including T.B.); culture sterile; no clot on standing; W.R. negative, Kahn test negative. The blood Kahn test was negative (000), the fundi were normal, and the Mantoux test was positive. Lumbar puncture was repeated almost every day for the relief of headache, and a precipitin test done on the cerebrospinal fluid against the meningococcus was negative. On Nov. 7 the cell count was 155 per c.mm. and all the cells were lymphocytes. On Nov. 16 the cell count was 35 per c.mm., all the cells being lymphocytes; total protein, 150 mg. per 100 ml.; and there was no globulin (Ross-Jones). This man was discharged against medical advice, improved but not cured.

Case 3.—A male Tamil aged 22 was admitted on April 6, 1941, with a history of fever, weakness of the legs, and giddiness for two days. On admission the temperature was 101° F. (38.3° C.), there was rigidity of the neck, and Kernig's sign was positive. Examination of the central nervous system revealed no abnormality. A lumbar puncture was done on April 7, the cerebrospinal fluid showing the following changes: cell count, 900 per c.mm. (polymorphonuclears 4%, lymphocytes 96%); globulin + (Ross-Jones); total protein, 125 mg. per 100 ml.; sugar, 47 mg. per 100 ml.; chlorides, 745 mg. per 100 ml.; direct smears negative for T.B. and other organisms; culture sterile; no clot on standing; W.R. negative. On April 16 the cell count was 22 per c.mm., the total protein 50 mg. per 100 ml., and there was only a trace of globulin. The

fundi were normal, and the blood Kahn test was negative (000); the total white count was 7,500 per c.mm. (polymorphonuclears 60%, lymphocytes 36%, and large hyalines 4%). The patient was treated with repeated lumbar punctures and sulphanilamide 1 g. t.d.s. from April 9 to 15. The temperature came down on April 10 and remained normal. The patient was discharged cured on April 19 and returned to work on May 3.

Case 4.—A male Tamil aged 32 was admitted on April 22, 1941, with a history of fever, headache, and vomiting for one week. The temperature on admission was 103° F. (39.4° C.); the patient was drowsy and difficult to examine. There was neck rigidity, but Kernig's sign was negative. A complete examination of the central nervous system revealed no abnormality. A lumbar puncture was done on the day of admission, when the cerebrospinal fluid showed the following changes: naked-eye appearance, granular-looking; cell count, 206 per c.mm. (polymorphonuclears 18%, lymphocytes 82%); total protein, 70 mg. per 100 ml.; globulin + (Ross-Jones); sugar, 84 mg. per 100 ml.; chlorides, 705 mg. per 100 ml.; direct smears negative for T.B. and other organisms; culture sterile; no clot on standing; W.R. negative, Kahn test negative. The blood picture was as follows: total red cells, 5,700,000 per c.mm.; haemoglobin, 100% (Sahli); total white cells, 15,000 per c.mm. (polymorphonuclears 79%, lymphocytes 17%, large hyalines 3%, eosinophils 1%). The blood Kahn test was negative (000) and the fundi were normal. On April 29 the cell count in the cerebrospinal fluid was 50 per c.mm., 10% being polymorphonuclears and 90% lymphocytes. The patient was treated with sulphanilamide 1 g. t.d.s. from April 22 to 29. The temperature came down to normal on the 26th and remained so. The patient was discharged cured on May 3.

Case 5.—A male Hokien aged 26 was admitted on July 5, 1937, with headache and vomiting for three weeks. He gave a history of exposure to venereal infection on June 5 and had developed a urethral discharge and buboes on both groins on June 14. Clinically the case was one of lymphogranuloma inguinale, and Frei's intradermal reaction was positive. The blood Kahn test was negative. It was at first considered that the headache and vomiting were due to toxæmia resulting from the buboes. On July 12 the patient still complained of headache, and on examination there were stiffness of the neck and generalized hyperaesthesia. Kernig's sign was negative, and examination of the central nervous system revealed no abnormality. Lumbar puncture showed the following changes in the cerebrospinal fluid: pressure, 70 mm.—no change on compression of the neck veins; colour, yellow; cell count, 220 per c.mm., all the cells being lymphocytes; total protein, 550 mg. per 100 ml.; globulin ++ (Ross-Jones); sugar +; no clot on standing; culture sterile; direct smears negative for T.B. and other organisms. On July 13, on cisternal puncture, the cerebrospinal fluid showed the following changes: pressure, 40 mm. (on jugular compression it rose to 100 mm.); naked-eye appearance, slightly turbid, almost milky; cell count, 290 per c.mm.; total protein, 90 mg. per 100 ml.; globulin + (Ross-Jones); sugar +; chlorides, 675 mg. per 100 ml. There was no clot, and direct smears were negative for T.B. and other organisms. On July 15 lumbar puncture was repeated. The pressure was 140 mm., there being no change on jugular compression; the cell count was 680 per c.mm., all the cells being lymphocytes. By this time the general condition was improved and the buboes had subsided. There was a slight rise of temperature (up to 100° F. (37.8° C.)) from July 14 to 19, the course of the disease being otherwise afebrile. On the 21st slight headache and giddiness were still present, but there was no vomiting, the neck was not rigid, and Kernig's sign was negative. Repeated lumbar and cisternal punctures were performed, and on July 29 a block was still found. The total white count was 6,800 per c.mm. (polymorphonuclears 70%, lymphocytes 22%, large hyalines 5% eosinophils 3%). The W.R. of the cerebrospinal fluid was negative, and the colloidal gold test was also negative (0000000000). The patient was discharged against medical advice on Aug. 3, but was examined again on Aug. 10 and found to be free from all symptoms. Inquiries carried out several months later revealed that the patient had continued to be fit and was carrying on a normal life.

Case 6.—A male Cantonese aged 42 was admitted on Oct. 19, 1938, with a history of fever, headache, and pain in the bones for four days. Physical examination, including the central nervous system, revealed no abnormality; there was no rigidity of the neck and Kernig's sign was negative. As several cases of lymphocytic choriomeningitis had been encountered at this time, and as some of them had evinced few or no pointers to meningeal affection, a lumbar puncture was done, though neck rigidity and Kernig's sign were absent on repeated examination. The cerebrospinal fluid showed the following: pressure not increased; naked-eye appearance clear; cell count, 563 per c.mm., practically all the cells being lymphocytes; total protein, 120 mg. per 100 ml.; globulin + (Ross-Jones); direct smears negative to T.B. and other organisms; culture sterile; W.R. negative, Kahn test negative. On Oct. 29 slight congestion of the pharynx was noticed. On the 31st lumbar puncture was repeated, with the following findings in the cerebrospinal fluid: naked-eye appearance clear; chlorides, 643 mg. per 100 ml.; sugar

51 mg. per 100 ml.; direct smears, no T.B. or other organisms; all the cells were lymphocytes; culture sterile; precipitin test for meningococci, negative. The Widal and Weil-Felix reactions were negative, and the blood culture was sterile; examination of the ear, nose, and throat revealed nothing abnormal except a deflected nasal septum; the Kahn test on the blood was positive (444). There was irregular fever between Oct. 19 and Nov. 3, after which date the temperature remained normal. The total white count was 7,600 per c.mm. (polymorphonuclears 60%, lymphocytes 40%). The patient was given sulphanilamide 1 g. t.d.s. from Nov. 2 to 9. He was discharged cured on Nov. 9.

Case 7.—A male Tamil aged 23 was admitted on Oct. 22, 1938, with fever and stiffness of the neck for seven days but no headache. There was rigidity of the neck, but Kernig's sign was negative. Examination of the ear, nose, and throat revealed opacity of the antra on transillumination, but skiagrams showed no abnormality; the ethmoid cells were unusually large and numerous. The central nervous system was normal. The fundi were also normal. The blood Kahn test was positive (444). The temperature was 102° F. (38.9° C.) on admission, and there was irregular fever till Oct. 26, after which date the temperature remained normal. On Oct. 23 the cerebrospinal fluid showed the following changes: pressure increased (on jugular compression there was a definite increase); naked-eye appearance slightly turbid; cell count, 831 per c.mm. (polymorphonuclears 90%, lymphocytes 10%); total protein, 150 mg. per 100 ml.; globulin + (Ross-Jones); sugar, 11 mg. per 100 ml.; chlorides, 643 mg. per 100 ml.; W.R. negative, Kahn test negative; direct smears negative for T.B. and other organisms; culture sterile; no clot on standing. On Oct. 27 the cerebrospinal fluid was sterile on culture; the precipitin test for the meningococcus was negative; the cell count was 576 per c.mm., 6% being polymorphonuclears and 94% lymphocytes. The patient was given sulphanilamide 1 g. t.d.s. from Oct. 24 to Nov. 2, and was discharged cured on Nov. 9.

Case 8.—A male Tamil aged 30 was admitted on April 17, 1941, with a history of vertigo for two days. There were no other symptoms; the ear, nose, and throat were normal, the neck was not rigid, and Kernig's sign was negative. On standing or walking there was a tendency to fall to either side; this did not increase on closing the eyes. Otherwise, examination of the central nervous system revealed no abnormality. The blood picture was as follows: total red cells, 4,850,000 per c.mm.; haemoglobin, 83% (Sahli); total white cells, 6,800 per c.mm. (polymorphonuclears 60%, lymphocytes 18%, large hyalines 2%, eosinophils 20%). There were ancylostoma ova in the stools. Blood: April 18—W.R. ±, Kahn test ± (111); April 24—Kahn test + (333); April 30—W.R. +, Kahn test + (344). On April 21 the cerebrospinal fluid showed the following changes: naked-eye appearance slightly turbid; cell count, 280 per c.mm. (polymorphonuclears 94%, lymphocytes 6%); total protein, 75 mg. per 100 ml.; globulin + (Ross-Jones); sugar, 57 mg. per 100 ml.; chlorides, 715 mg. per 100 ml.; direct smears negative for T.B. and other organisms; culture sterile; no clot on standing; W.R. negative. On May 5 the cell count was 20 per c.mm., all the cells being lymphocytes. The patient was given sulphanilamide 1 g. t.d.s. from April 22 to 27, and was discharged cured on May 5.

Remarks

Case 5 was complicated by lymphogranuloma inguinale, and though one case of meningo-encephalitis (Rajam, 1936) has been described in this disease, the features of the present case seem to correspond to lymphocytic choriomeningitis rather than to meningitis of lymphogranulomatous origin. The only case of meningo-encephalitis recorded (referred to above) was accompanied by coma, fits, a temperature of 104.4° F. (40.2° C.), and proved fatal; the cerebrospinal fluid showed 90% of polymorphonuclears.

Cases 6, 7, and 8 had a positive blood Kahn reaction; but in my mind there is no doubt that these were cases of lymphocytic choriomeningitis and not syphilitic meningitis, in view of the following facts: (a) The histories were short; otherwise the clinical picture was typical of lymphocytic choriomeningitis. (b) The cases showed clinical cure without any antisyphilitic treatment. (c) The W.R. was negative in the cerebrospinal fluid in all those three cases; this is a very unusual finding in meningeal syphilis. In fact, I have seen hundreds of cases of meningeal syphilis and have never encountered one with a negative W.R. in the cerebrospinal fluid. (d) In Cases 7 and 8 the cell picture showed 90% and 94% of polymorphonuclears, respectively, on the first examination, and subsequently became predominantly lymphocytic. This is typical of lymphocytic choriomeningitis. A marked preponderance of polymorphonuclears is never found in meningeal syphilis at any time. (e) In Cases 7 and 8 there was a marked drop in the cell count in the cerebrospinal fluid without any antisyphilitic treatment.

Findings

The findings may be briefly summarized as follows:

1. Duration of illness: 2 to 21 days (average 7).
2. Race incidence: 5 Indians, 3 Chinese.
3. Age incidence: 19 to 42 years (average 27). It must be recorded here that only adults, as a rule, were admitted to these wards.
4. Number of days in hospital: 11 to 29 (average 19).
5. Fever: present in 6 cases.
6. Headache: present in 4 cases.
7. Giddiness: present in 2 cases.
8. Vomiting: present in 1 case.
9. Weakness of legs: present in 1 case.
10. Mental symptoms: present in 2 cases.
11. Hyperaesthesia: present in 1 case.
12. Neck rigidity: present in 5 cases.
13. Kernig's sign: positive in 2 cases.
14. Cerebrospinal fluid: (a) Cell count varied from 152 to 900 per c.mm. (b) Sugar varied from 10 to 84 mg. per 100 ml. 5 out of the 8 cases were between 45 and 60 mg. per 100 ml. (c) Chlorides varied from 627 to 745 mg. per 100 ml.

15. Cases not treated with sulphanilamide spent an average of 22 days in hospital, whereas those treated with it stayed there for an average of 16 days. From these figures it is impossible to draw any definite conclusion as to the therapeutic value of sulphanilamide, but the clinical impression was that cases seemed to benefit from its use.

Conclusions

Lymphocytic choriomeningitis is a disease that occurs not uncommonly in Singapore, and, unless one is on the look-out for it, cases might easily be missed. Headache was complained of in only 4 cases and neck rigidity in but 5 cases out of 8; only 2 had a positive Kernig's sign. One of the cases was simply a pyrexia of unknown origin, and there was no symptom or sign pointing to the central nervous system; this case would certainly have been missed if a lumbar puncture had not been done. It would therefore be advisable to bear this disease in mind when dealing with any obscure case with fever, headache, giddiness, or vomiting. There was no history of a similar illness occurring in the household or intimate contacts of these cases; none of them showed any evidence of infection of the ear, nose, or throat; and there were no sequelae.

Summary

A brief account of the literature on lymphocytic choriomeningitis is given, with reference to the clinical picture, aetiology, and pathology of the condition.

As no cases have so far been actually reported in Asiatics, 8 instances of the disease are described.

All the cases were seen at the General Hospital, Singapore.

The cases conformed to the characteristics described by Gibbens (1931).

There was no death, and no sequelae occurred.

A warning is given that unless one keeps on the look out for such cases they might be missed.

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PATHOGENICITY OF GROUP C (LANCEFIELD)
HAEMOLYTIC STREPTOCOCCUS

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Until recently it was believed that Group C (Lancefield) haemolytic streptococci were not frequent in human disease (Evans, 1944), and that when they did occur mild infections only were produced. Harper and Williams (1944), in reviewing the frequency of streptococci in the healthy nose and throat, found them in about 47% of their cultures, and of these only 1.6% belonged to the Lancefield Group C. The Cardiff Public Health Laboratory (1943), analysing the pathogens from acute cases of upper respiratory infection, found Group C streptococci in 7.2%. In a summary of cases of puerperal infection associated with streptococci that were not Group A, Ramsay and Gillespie (1941) reported 12 in which the Lancefield Group C was found. The pyrexia was mild and the infection low-grade. Cases have, however, recently been reported in which these streptococci were associated with severe infections. Thus Portnoy and Reitter (1944) isolated such an organism in an outbreak of acute cellulitis in which 27 people were affected and 4 died. Fatal puerperal infection has also been recorded (Rosenthal and Stone, 1940).

During a period of two years in a very small Public Health Laboratory 105 strains of Group C haemolytic streptococci were isolated. They came from cases of disease and from routine swabbings of maternity staffs and patients and of children in residential nurseries. The comparative frequency of this group compared with the other Lancefield groups isolated during the same period (to a total of 970) was as follows: Group A, 618 cases; Group B, 69; Group C, 105; Group D, 71; Group G, 107. It will therefore be seen that the occurrence is approximately one-sixth of that of the Lancefield Group A streptococcus—frequent enough, if they are pathogenic, to warrant consideration.

Distribution of Group C Streptococci

Of these 105 strains 32 were found in routine swabbings of throats and 4 in routine vaginal swabbings of pregnant women. In these cases they appeared to be saprophytic. The remaining 69 strains originated as follows: Acutely ill cases, 9; mild tonsillitis, 33; suppuration of soft tissues, 12; puerperal genital tract, 12; sputum (chronic bronchitis), 3.

Analysis of Cases.—The most acutely ill case was that of a middle-aged man who developed bronchitis which led within 10 days to a basal pneumonia with pleural effusion. A severe toxæmia, swinging temperature, and tympanites later set in, and suggested a typhoid or other septicaemia. The blood culture yielded a Group C haemolytic streptococcus. Recovery ensued with penicillin therapy. One case of severe cellulitis occurred after a septic soft-tissue lesion. Infection spread down to the bone, and amputation of the terminal phalanx had to be performed. A dental abscess resulting in osteomyelitis of the zygoma also yielded a pure growth of haemolytic streptococci of Group C.

Six of the strains came from septic throats, in which the patient was very ill with a raised temperature, enlarged glands, and sloughing foul necrotic debris on the tonsils. Swabs were sent in for differential diagnosis between Vincent's angina and diphtheria. Neither of these was present, but an almost pure culture of Group C haemolytic streptococci was obtained in each case. It is interesting that the somewhat large number of cases of mild tonsillitis came from widely separated sources from general practitioners who had been consulted with a complaint of sore throat. The presence of a congested red throat and lack of any membrane or debris were always noted. No other pathogenic organisms were present in any of these cases, so that the Group C streptococcus was held to be responsible.

The 12 strains from soft-tissue lesions were from cellulitis, gunshot wounds, abscesses, and ulcers. A Group C streptococcus was the only organism present, except in the case of the gunshot wounds and ulcers of leg. In these a mixed flora of

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