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ACUTE ASEPTIC MENINGITIS: A REVIEW

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Experience at the Addington Children's Hospital, Durban, over the last 5 years has made it clear that many cases of the aseptic meningitis syndrome are being misdiagnosed or missed entirely. The latter error is not necessarily a serious one, and may indeed have much to commend it, for it saves the patient and his family not inconsiderable discomfort, worry and expense for an illness which is entirely benign and self-limiting! Confusion with more serious disease, however, is of considerable importance, all the more so because it is so easy. In view of the frequency of the condition, the occasional difficulties in diagnosis, and the light shed during recent years on its aetiology, it appears worth while focussing some attention on this subject and reviewing the present position. Some illustrative case-histories are presented but no analysis of case-material attempted; this will form the subject of a subsequent communication.

Definition. The term aseptic meningitis is a clinical one applying to any condition of meningeal irritation, with cellular response in the CSF and bacteriological sterility. It is evident that such a syndrome may be produced by a wide variety of agents, infective and non-infective, and that, defined as such, the condition would include such serious diseases as poliomyelitis, tuberculous meningitis, malignant meningeal infiltrations, etc. For the sake of completeness, and because in their early stages at least such diseases may readily simulate the clinical picture of aseptic meningitis, these are included in the section dealing with aetiology. Our main interest, however, attaches to the benign forms of the condition, and to limit discussion to these types we must include in the definition two further features—a benign course and full recovery without sequelae. It is with this more restricted concept of the aseptic meningitis syndrome that this paper deals.

History. There appears to be no description of aseptic meningitis earlier than 1907.[1] The first epidemic recorded was in Paris during the years 1910—13, but as this followed an epidemic of poliomyelitis it was largely interpreted as being due to that disease.[2] The second epidemic reported occurred in Sweden in 1922—24, and it was during this time that Wallgren, on the basis of his experience of 6 cases, first postulated that this was a new disease entity.[3] Since that time, and particularly since viral research facilities have become more generally available, thus enabling the aetiology to be established in a high proportion of cases, our concept of the condition has changed, so that today it can hardly be said to exist as an entity at all. It is simply a symptom-complex that happens to be common to several specific diseases.

Aetiology

The following table summarizes the known conditions which may give rise to the clinical picture of aseptic meningitis. It is compounded from that of Bayer and Gear,[4] and that of Steigman[5] modified by Anglin.[6] Full acknowledgement is made to these authors.

- A. Physical trauma—including the encephalitis of pertussis
- B. Chemical irritation:
  - I. Systemic—lead, arsenic
  - II. Local—intrathecal injection of air, antibiotics, sera, radio-opaque contrast media
- C. Metabolic—porphyria
- D. Allergic—serum sickness, ? other allergies, auto-immunization following administration of rabies vaccine, pertussis vaccine
- E. Reactive, to neighbouring pathology—sinusitis, mastoiditis, abscess, thrombosis, haematoma, neoplasia
- F. Post-infectious—measles, rubella, varicella, mumps, vaccinia, variola
- G. Infectious:
  - I. Helminthic—trichinosis, cysticercosis, multiceps
  - II. Protozoal—malaria, toxoplasmosis
  - III. Spirochaetal—syphilis, leptospirosis
  - IV. Fungal—torula
  - V. Bacterial:
    1. Early septic meningitis
    2. Septic meningitis modified by chemo- or antibiotic therapy
    3. Tuberculous meningitis
  - VI. Rickettsial
  - VII. Viral:
    1. Established viral origin, transmitted:
       - (*a*) Man to man:
         Encephalitis lethargica, poliomyelitis, mumps, herpes simplex, herpes zoster, Coxsackie A, Coxsackie B, atypical pneumonia, infectious hepatitis, ECHO viruses types 2, 3, 4, 5, 6, 7, 9, 14 and 16 (especially types 4, 6, 9)
       - (*b*) Dog (and other animals) to man: Rabies
       - (*c*) Rodent to man: Lymphocytic choriomeningitis.
       - (*d*) Arthropod to man: Mosquito—St. Louis, Japanese B., equine group of encephalitides, West Nile fever
         Tick—louping ill, Russian spring-summer encephalitis
    2. Presumed viral origin: Infectious mononucleosis, infectious lymphocytosis, cat-scratch disease.

Seasonal Incidence. The vast majority of cases occur during the summer months, frequently in localized epidemics. Our cases in Durban have been largely confined to the months from October to March.

Clinical Features

A typical case presents with fairly acute onset—headache, usually frontal and retro-orbital, fever, up to 104°F, drowsiness and irritability, nausea and vomiting, and varying degrees of neck and back stiffness. Some cases give a history of sore throat, general muscular pains, abdominal pains, constipation or diarrhoea, conjunctivitis and photophobia. Convulsions are rare, occurring in only 2 of our 76 cases. At times a biphasic illness, such as occurs not infrequently in poliomyelitis, is observed. Lymphadenopathy and a rubelliform rash are features associated particularly with infection by

ECHO virus type 9. Jaundice has been reported,[7] and a peculiar enanthem consisting of whitish-grey dots opposite the molar teeth was described in some cases during the Sheffield outbreak.[8] Our experience, however, has been that physical examination reveals little apart from fever and neck and back stiffness, the latter are often unconvincing.

The peripheral blood white-cell count is usually normal but may be raised, with a normal differential count. Lumbar puncture reveals the CSF under some increased pressure and with a pleocytosis of up to 5,000, though seldom over 500, cells per c.mm. Initially there may be polymorphonuclear predominance, with a mononuclear swing after a few days. Occasionally the initial CSF is normal. We have encountered this only once, but in the Leicester outbreak Rotem reported 27 of her cases as having an initially normal CSF and in 6 of these a second specimen was also normal.[24] The protein content is frequently raised, but seldom over 100 mg.%, and the CSF sugar is normal. Rarely is vomiting severe or protracted enough—as in tuberculous meningitis—to depress the chloride level significantly. Direct smear examination and culture of the CSF and the blood are, of course, negative for bacteria.

The course of the disease is variable. In most cases the symptoms and fever settle rapidly, whereas a few run a course of up to 10 days or so. Lumbar puncture often produces marked symptomatic relief. We have not encountered relapses, but they are not uncommon in epidemics associated with ECHO viruses types 4[11] and 9.[9, 10] Bayer and Gear[4] found in their series of 100 cases that the CSF remained abnormal for 2 weeks in 60%. Our experience has been similar.

Differential Diagnosis

A full discussion of all the conditions in which the aseptic meningitis syndrome may occur cannot be attempted here. Most of the non-viral conditions can be excluded on the history, but confusion commonly and easily arises with bacterial meningitis, especially if the case is seen early. The failure to demonstrate bacteria on direct examination or culture of the CSF cannot, of course, be relied upon, as in some 25% of cases of septic meningitis the organism is not identified. Likewise, in early cases the CSF sugar level is not a reliable indication. It can only be said that, in general, children with aseptic meningitis appear less ill than one would expect a case of septic meningitis of equivalent duration to be. With experience of the condition one becomes more and more courageous, leaving untreated cases with high CSF cell counts which previously one would have had no hesitation in treating as bacterial meningitis. The following case, which presented with a purpuric rash, illustrates this point.

Case 1. S.N., a 6½-month-old male infant, was admitted on 9 November 1958 with a history of fever, vomiting and irritability, associated with a rash on the face, for less than 24 hours. The mother also volunteered that the baby had screamed when the back of the neck was touched. Examination showed the child to be extremely irritable, with a temperature of 101°F, slight neck stiffness, and a fine purpuric rash on the face and neck. The white-cell count was 16,800 per c.mm., with 51% polymorphs, 44% lymphocytes and 5% monocytes. The CSF was opalescent and contained 142 polymorphs and 32 lymphocytes per c.mm., and protein 35 mg.% with no increase of globulin. No specific therapy was given and the child rapidly improved, the temperature being normal after the 3rd day. On 11 November the CSF contained only 29 polymorphs and 12 lymphocytes per c.mm., and 2 weeks later they had fallen to 2 polymorphs and 2 lymphocytes. No virus was isolated from the stool, CSF or blood; complement-fixation tests for toxoplasma, leptospira, herpes, lymphocytic choriomeningitis and mumps were negative.

The aetiology of this case, therefore, remains obscure. Particular interest attaches to the purpura which, in spite of its localized distribution, could have been mistaken for the rash of meningococcaemia. The child, however, was just not ill enough for this condition.

Previous administration of antibiotics is another common cause of confusion, and often precludes an exact diagnosis. Difficulty is also encountered in the early case in which the CSF shows only a few cells, but in which one or two bacteria are reported, although the culture proves sterile. One cannot do otherwise than treat these cases as for bacterial meningitis, but a suspicion often lurks at the back of the mind that the pathologist might have been perhaps over-enthusiastic.

The readiness with which early tuberculous meningitis may be simulated by the benign forms of aseptic meningitis is well illustrated by one of Wallgren's original cases,[3] a child with a history of exposure to tuberculosis, a positive tuberculin test, a suggestive chest X-ray, and a CSF which appeared typical. The meningitis resolved completely and spontaneously in a few days. Since the advent of streptomycin, there must be many children who have been subjected to months and years of painful and potentially dangerous therapy—and perhaps lost their hearing in the process—for nothing more than benign aseptic meningitis in the presence of an arrested tuberculous lesion elsewhere. We have to our knowledge been guilty of initiating such unnecessary treatment in more than one case in which the subsequent too-rapid improvement indicated the true diagnosis and anti-tuberculous drugs were discontinued within a few days of their commencement (see case 3).

Leptospirosis, due to *L. icterohaemorrhagiae*, *L. canicola* or *L. pomona*, may produce only the picture of aseptic meningitis without the other features of jaundice, haemorrhages and nephritis. A biphasic illness, conjunctival injection, and muscular pains, especially in the legs, are features suggestive of this condition. Five such cases caused by *L. canicola* were reported recently from the Witwatersrand.[12]

Rickettsial infection occasionally produces the aseptic meningitis syndrome, as evidenced by the following case:

Case 2. M.M., aged 13 years, was admitted on 5 January 1959 with a history of malaise with a painful lump in the left axilla for 4 days, and fever, headache and vomiting for 2 days. He was febrile (103°F) and there was a possible tick bite on the left chest, with tender left axillary lymphadenopathy. The spleen was easily palpable. Slight neck and back stiffness led to a lumbar puncture being performed, and the CSF was found to contain 1 polymorph and 12 lymphocytes per c.mm., with normal chemistry. Tick-bite fever was diagnosed clinically and the patient was treated with chlortetracycline with prompt response, the temperature remaining normal after the 3rd day. On the day following admission the patient developed the typical rash of tick-bite fever.

Viral Infections

Poliomyelitis is a common cause of aseptic meningitis and, particularly during an epidemic, in a case with no paralysis it may be impossible to exclude it without virological investigations. The following case illustrates to what degree confusion can be caused by this virus:

Case 3. H.H., a 5-month-old patient, was admitted on 22 March 1955. Since being returned from a foster home to her parents' care 4 days previously she had been feverish, irritable and generally unwell, refusing most feeds, and she had vomited twice on the day

of admission. It was possible that she had been ill for considerably longer than 4 days. She was an ill-looking, irritable baby with a temperature of 104°F, a bulging fontanelle, and slight neck stiffness. There was no detectable weakness, and the reflexes were normal. The CSF showed 10 polymorphs and 340 lymphocytes per c.mm., protein 70 mg.% with globulin one plus increased, chlorides 688 mg.%, and sugar 78 mg.%. As she seemed really ill, pending further investigations, she was treated with streptomycin, INH and sulphadimidine. The fever promptly subsided, the temperature remaining normal after the 3rd day. Three days after admission the CSF contained 6 polymorphs and 80 lymphocytes per c.mm., protein 55 mg.% with no increase of globulin, chlorides 751 mg.%, and sugar 83 mg.%. Three days later the cells had fallen to 1 polymorph and 13 lymphocytes. All treatment was stopped, and the babe remained well, with no signs of weakness. Subsequently type-1 poliomyelitis virus was isolated from the stools.

Mumps meningo-encephalitis not uncommonly occurs in the absence of other features such as parotitis and orchitis. The following 3 cases occurred in a family of 6 children, 2 of whom had had uncomplicated parotid mumps a short while previously:

Case 4. C.L., aged 2 years, was admitted on 21 September 1958 with a history of fever for 18 hours and copious vomiting for 12 hours. She had a temperature of 102°F and looked ill. There was a small swelling at the angle of the jaw on the left side which was thought to be an enlarged lymph gland rather than parotid. There was no neck stiffness or other CNS abnormality. The spleen was enlarged, being easily palpable 2 cm. below the costal margin. On the day following admission the CSF showed 25 polymorphs and 75 lymphocytes per c.mm., protein 20 mg.%, no excess of globulin, chlorides 700 mg.%, and sugar 59 mg.%. One week later the CSF showed 415 polymorphs and 145 lymphocytes, with normal chemistry; 17 days after admission there were still 20 polymorphs and 97 lymphocytes per c.mm. Symptomatically, the child was better after 3 days, but the temperature settled only after 12 days.

Case 5. S.L., aged 9 years, sister of case 4, was admitted on 9 October 1958, having developed left parotid mumps 4 days previously, with a history of fever, vomiting and unsteady gait for 1 day. She was afebrile, slightly drowsy and slightly ataxic. She had some residual left parotid swelling and bilateral cervical lymphadenopathy. The spleen was readily palpable. (Splenomegaly is not an uncommon feature of mumps, rarely mentioned in text-books.) The CSF contained 210 polymorphs and 490 lymphocytes per c.mm., protein 45 mg.% with one plus increase of globulin, chlorides 660 mg.%, and sugar 60 mg.%. A week later the cells had decreased to 65 polymorphs and 355 lymphocytes per c.mm., and 2 weeks after admission numbered 3 polymorphs and 40 lymphocytes. The drowsiness and ataxia disappeared after the 2nd day. No virus was isolated, but the complement-fixation test was positive for mumps (+at 1 : 10, ± at 1 : 100).

Case 6. A.L., aged 1 year, brother of cases 4 and 5, was also admitted on 9 October 1958, with a 2-hour history of fever and vomiting. His temperature on admission was 100°F, subsequently rising to 103°F. He was irritable and had some cervical lymphadenopathy, but there was no neck stiffness or other sign of meningitis. The spleen was easily palpable. Because of the family history, lumbar puncture was performed and the CSF was found to contain 1,035 polymorphs and 700 lymphocytes per c.mm., protein 45 mg.% with one plus increase of globulin, and a sugar content of 59 mg.%. He was given no specific treatment and recovered rapidly, the temperature being normal after the 4th day. A week after admission there were still 20 polymorphs and 29 lymphocytes per c.mm. in the CSF. The mumps complement-fixation test proved positive (1 : 10), and to complicate matters a Coxsackie A virus was isolated from the stools.

There is little doubt that case 6, if seen out of the family context, and if diagnosed at all, would have been regarded as an early purulent meningitis and treated—with great success—with powerful antibiotic combinations.

Both herpes simplex and herpes zoster may produce the picture of aseptic meningitis; the following case is probably an example of herpes simplex:

Case 7. G.W., aged 12 years, was admitted on 16 January 1956 with complaints of fever and general body pains for 4 days and nausea, but no vomiting, for 2 days. The positive findings on examination were a temperature of 102°F, fairly extensive herpes on the lips and chin, and doubtful neck stiffness. The CSF contained 17 polymorphs and 265 lymphocytes per c.mm., protein 40 mg.% with a trace of globulin, chlorides 730 mg.%, and sugar 48 mg.%. Symptoms subsided after one day and the temperature was normal after the 3rd day. No virus was isolated from the stools, blood or CSF; complement-fixation tests, unfortunately, were not performed.

The enteroviruses—which include the polioviruses, Coxsackie viruses A and B, and the ECHO (enteric cytopathogenic human orphan) viruses—are with little doubt the commonest cause of the aseptic meningitis syndrome. Coxsackie viruses[13] have been implicated in several epidemics and, in this country, were the most frequently encountered identifiable cause in Bayer and Gear's series of 100 cases (group A isolated 11 times, group B 20 times).[4] The Coxsackie A viruses, of which there are 19 immunological types,[14] besides their aetiological relationship to aseptic meningitis, are the cause of herpangina and acute febrile lymphadenitis; they have been isolated in association with poliovirus, and in some cases of the Guillain-Barré syndrome, and are thought possibly to play a role in the causation of Bell's palsy, 'myositis', and summer diarrhoea.[15] The ECHO virus type 9 is closely related to the Coxsackie A viruses, producing the same changes in suckling mice, though usually only after preliminary isolation in tissue culture.

Coxsackie B viruses have been reported in several epidemics of aseptic meningitis, often in association with Bornholm disease,[14, 16-19] although, strangely, the combination of aseptic meningitis and pleurodynia in the same patient seems to be rare. In Bayer and Gear's series of 100 cases, Coxsackie B virus was the commonest identifiable causative agent, being isolated in the stools of 20 cases and in 9 of these in the CSF as well.[4] Besides causing Bornholm disease and aseptic meningitis, Coxsackie B viruses have been implicated in epidemics of myocarditis neonatorum.[20, 21]

Of the ECHO viruses, types 2, 3, 4, 6, 7, 9, 14 and 16 have been isolated from cases of aseptic meningitis,[22] though types 4, 6 and 9 are most commonly involved in epidemics. These are characterized by a high infectivity rate among a small, often fairly closed, community. Such an outbreak, for example, caused by ECHO virus type 4, occurred in a Johannesburg children's home causing 58 cases among the 121 children.[11] A feature of this outbreak was the high relapse rate—10 cases, one of which relapsed 3 times, and 2 of which relapsed twice—ascribed by the authors to poor antibody production. Relapses have been observed, too, in aseptic meningitis caused by ECHO virus type 9.[9, 10]

An outbreak caused by ECHO virus type 6 produced 24 cases from 16 homes in a small village (Holland, N.Y.) of 500 people.[23] Gastro-intestinal symptoms occurred in 100% of cases, and a few showed depression of reflexes and some muscle weakness, particularly of the neck. In general, however, it is not possible to determine clinically between the various viral causes of the aseptic meningitis syndrome, with the possible exception of the Coxsackie A-like ECHO virus type 9.

There have been numerous reports of recovery of this virus from CSF and stools of cases of aseptic meningitis, occurring usually in localized epidemics.[6-10, 24, 25] The distinguishing feature of these cases is the high incidence of a maculopapular rubelliform rash, involving usually the face and at times

spreading down to the neck, shoulders and trunk. Such a rash has been seen in anything from 18%[24] to 60%[6] of cases. Occasionally it has been petechial. In South Africa 8 cases of aseptic meningitis due to ECHO virus type 9 have been reported;[26] 2 of them occurred in Durban.

Case 8. A.R., aged 5 years, was admitted on 16 January 1956 with a history of headache, fever, vomiting, listlessness and irritability for 2 days, and sore eyes and photophobia on the day of admission. Her temperature on admission was 104°F; there was neck stiffness and positive Kernig's and Brudzinski's signs. The CSF contained 30 polymorphs and 29 lymphocytes per c.mm., and protein 30 mg.%, the remainder of the chemistry being normal. Two days later she was symptom-free and the temperature was normal, and remained so. The CSF on 18 January contained 2 polymorphs and 35 lymphocytes per c.mm.

Case 9. J.R., aged 2½ years, sister of case 8, was admitted on 23 January 1956 with a 1-day history of headache, fever and vomiting, a temperature of 101°F, neck stiffness, and a positive Kernig's sign. The CSF contained 2 polymorphs and 17 lymphocytes per c.mm., with normal chemistry. She improved rapidly after lumbar puncture and her temperature was normal from the 3rd day.

From the CSF of both these cases an ECHO virus type 9 was isolated.

Probably related to 'ECHO 9 disease' is the condition described in infants characterized by fever, irritability, a maculopapular rash on the face, trunk, extensor surface of the limbs and soles of the feet, lasting 3—14 days (petechial in 4 out of 10 cases), superficial lymphadenopathy and faucial reddening, associated with CSF pleocytosis, in which an ECHO virus was isolated from the stools of half the cases.[27]

There appears to be no relationship between the forms of aseptic meningitis discussed in this paper and the several outbreaks of 'myalgic encephalomyelitis' characterized by paresis (without depression of reflexes), sensory changes, mental depression, and often a prolonged, relapsing course.[28,31] The CSF in these cases is normal and, though a viral infection would seem to be the most likely cause, no aetiological agent has yet been discovered. Such an outbreak occurred in Durban towards the end of a poliomyelitis epidemic and was described by Hill.[32]

Frequency of the Condition

During the 6 years 1953–58, 133 cases of acute meningitis were admitted to the Addington Children's Hospital. Of these, 76 (57%) were of the aseptic variety. In this community of Durban European children, therefore, aseptic meningitis is commoner than all the other forms of meningitis combined. Curiously enough, it apparently is not common in non-European children, and is rarely seen in adults.

SUMMARY

The condition of aseptic meningitis is reviewed, with emphasis on its multiple aetiology. The viral infections producing this syndrome are discussed in some detail, and some illustrative case histories are presented. This is the commonest form of meningitis encountered in European children in Durban.

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