Aseptic Meningitis and Meningoencephalitis in Cold-agglutinin-positive Infections

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The syndromes of aseptic meningitis and meningoencephalitis have a varied aetiology. They are most often caused by a virus—in Sweden, so far as we know at present, mostly by parotitis virus, several types of enterovirus (polio, Coxsackie, E.C.H.O.), and tick-borne encephalitis virus. In patients at the Stockholm Hospital for Infectious Diseases different enteroviruses have dominated at different periods in the past decade (Svedmyr, 1963), and some of them have caused major epidemics: polio type 1 in 1953-4 (Ström, 1956), E.C.H.O. 6 in 1954-5 (von Zeipel and Svedmyr, 1957), E.C.H.O. 9 in 1957 (Kahlmeter, 1961), Coxsackie B5 in 1961-2. To a fairly large extent, however, the aetiology remains unknown.

Similar experience has been reported from elsewhere. For example, 407 cases of aseptic meningitis were reported from Cleveland during the years 1955-8 (Lepow *et al.*, 1962). In 54% a viral cause was discovered, 17 different enteroviruses being isolated.

Meningoencephalitis has also been reported on a few occasions in cold-agglutinin-positive infections (Keizer, 1949; Sterner, 1956). Chanock *et al.* (1960) observed aseptic meningitis in a child infected with Eaton's agent (*Mycoplasma pneumoniae*). Museteanu *et al.* (1963) published a report of six fatal cases of primary atypical pneumonia and encephalitis in children aged 6 to 7 months. Necropsies of these cases revealed the presence of a large virus in nerve and glia tissue of the brain and in blood-vessels.

At the Stockholm Hospital for Infectious Diseases additional cases have been observed in the past few years with temporal association between cold-agglutinin-positive infection and aseptic meningoencephalitis or meningitis. These cases are reported here.

Case 1

A 14-year-old girl, who had parotitis in 1955, fell ill on 19 October 1962 with fever (40° C.), headache, and general malaise. After a few days she had a cold and an intense racking cough, and on 24 October pain occurred in the left thorax. She was admitted to hospital on 30 October with a diagnosis of unknown febrile illness.

On admission she was mildly dyspnoeic, had a cold and cough, and a temperature of 40.5° C. Pea-sized tender lymph nodes were present in the right maxillary angle and small tender lymph nodes in the armpits. Bronchial respiratory sounds and rales over the base of the right lung were heard. Lung x-ray pictures on the second and sixth days in hospital were normal. Neurological examination showed low psychomotor activity, moderate nuchal rigidity, Lasègue's sign positive 60-70 degrees bilaterally, lively reflexes, and patellar and foot clonus. E.E.G. showed diffuse non-specific dysfunction.

During her first week in hospital the headache, stiffness of the neck, and cough diminished and she became afebrile. E.E.G. showed a regression on the 14th day in hospital. She was discharged after 17 days, subjectively and objectively free from symptoms. At a follow-up three weeks later she was normal.

Laboratory Tests.—Cerebrospinal fluid (11th day after onset): 32 white cells/c.mm. (38% polynuclear, 62% mononuclear); protein 43 mg./100 ml. E.S.R. (12th, 24th, 45th days), 90, 48, 10 mm./hr. White blood cells (12th day): 6,600 c.mm., with normal differential

count. Faeces (23rd day): no cytopathogenic agent. Sera (12th and 24th days): no complement-fixing antibodies to herpes simplex; parotitis 32 and 32; in serum 1, non-specific fixation to dead polio-virus antigen and tick-borne encephalitis virus; in serum 2, polio type 1, negative; polio type 2, 16; polio type 3, 8; and tick-borne encephalitis virus, ≤ 4 . Cold agglutination (12th and 24th days): 64 and 4. C.F. titre to Eaton's agent: 1024, 1024, 128. Normal findings from nasopharyngeal swabs. Normal antistreptolysin and antistaphylolysin titres.

Case 2

A 14-year-old boy fell ill on 26 October 1962 with a severe cough. He had no fever. Headache started on 3 November and next day was worse; this was accompanied by vomiting and dizziness provoked by movement and position; he could not eat. The dizziness increased and he wanted simply to lie still. He was admitted to hospital on 6 November with a diagnosis of questionable meningoencephalitis.

On admission he was at times confused, and vomited on change of position; there was no fever. The tongue had a greyish-white coating and the tonsils were inflamed. Bean-sized rather tender lymph nodes were found in the maxillary angles. Occasional rales were heard over the bases of the lungs. The lung x-ray picture was normal. Neurological examination showed nystagmus of the left eye and an indication of dysmetria. E.E.G. showed slow base rhythm and a non-specific slow dysfunction with a suspect focus post-centrally on the right side. The otological and ophthalmological condition was normal.

During the first week in hospital he was severely ill; the dizziness persisted, as did the vomiting on change of posture. His temperature was normal throughout. During the second week the symptoms abated, and after three weeks his condition was entirely normal. E.E.G. showed unchanged findings on the ninth day in hospital, thereafter regression; only a slow base rhythm occurred on the 17th and 31st days. At the follow-up one month later the E.E.G. and his condition were normal.

Laboratory Tests.—Cerebrospinal fluid (19th day after onset): 5 white cells/c.mm. (all mononuclear); protein 37 mg./100 ml. E.S.R. (12th and 24th days), 48 and 10 mm./hr. White blood cells (12th day), 5,300, with normal differential count. Faeces (15th day), no cytopathogenic agent. Sera (27th day): complement-fixing antibodies to polio types 1 and 2, 2; to polio type 3, 4; to parotitis and tick-borne encephalitis virus, 4 (the serum was anticomplementary on the 12th day). Cold agglutination (days 12, 17, 27, 34, and 49), 16, 64, 16, 16, and 4. Normal findings in culture from nasopharyngeal secretion. Normal and unchanged antistreptolysin, antistaphylolysin, and antipneumolysin titres.

Case 3

A 7-year-old boy fell ill on 24 February 1963 with headache, vomiting, and fatigue. There were no catarrhal symptoms. The next day his headache was worse and his vomiting increased, particularly on change of posture. He was admitted to the hospital on the same day with a diagnosis of questionable acute meningitis.

On admission he was listless and pale, with a temperature of 38.9° C. The pharyngeal mucosa and tonsils were reddened; there were lymph nodes the size of grains of rice in the maxillary angles, along the sternocleidomastoid muscle, and occipitally. Lung and sinus x-ray pictures were normal. Neurological examination showed nuchal rigidity, otherwise no abnormal symptoms. E.E.G. showed fairly widespread slow dysfunction.

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During the first week in hospital he was stiff in the neck, listless, and had slow cerebration. During the second to fourth days he was subfebrile, on the fifth day afebrile. The stiffness of the neck and listlessness diminished during the second week. E.E.G. showed regression on the 12th day and was unchanged on the 20th day. He was discharged after three weeks, subjectively and objectively free from symptoms. At a follow-up three weeks later the E.E.G. and general condition were normal.

Laboratory Tests.—Cerebrospinal fluid (first day after onset): 44 white cells/c.mm.; protein 32 mg./100 ml. E.S.R. (days 2 and 10), 17 and 7 mm./hr. White blood cells (day 2), 16,400 (84% neutrophils). Cerebrospinal fluid and faeces (days 1 and 2): no cytopathogenic agent. Sera (days 2, 17, and 40): complement-fixation reactions to enterovirus showed non-specific fixation; to parotitis virus, 4, negative, and 2. Cold agglutination (days 2, 10, 17, and 40), negative, 128, 16, and negative. Two throat-swab cultures showed growth of β -haemolytic streptococci. The anti-streptolysin titre was 1,600 three weeks after the onset and 800 after another three weeks. Serological reactions to Weil's disease, toxoplasmosis, and listeriosis were negative.

Further Cases

In an attempt to throw further light on the question of meningitis in conjunction with a cold-agglutinin-positive infection, I have gone through the records of the Stockholm Hospital for Infectious Diseases for the period January 1962 to June 1963. Altogether 126 patients (69 females and 57 males) had a cold-agglutinin-positive infection. Five of these, apart from the three whose case histories are given, had pleocytosis

Fig. 1.—Age incidence of patients (69 females, 57 males) with cold-agglutinin-positive infection treated at the Stockholm Hospital for Infectious Diseases between January 1962 and June 1963.

Fig. 2.—Monthly incidence of patients (69 females, 57 males) with cold-agglutinin-positive infection treated at Stockholm Hospital for Infectious Diseases between January 1962 and June 1963.

of the cerebrospinal fluid with or without E.E.G. dysfunction. Seventy-five of the 126 patients were in the 5 to 29 age-group, and six of the eight with meningoencephalitis or meningitis (Fig. 1). Most of the cold-agglutinin-positive infections (72 of 126) and of the meningoencephalitis and meningitis cases (six out of eight) occurred in the period October 1962 to February 1963 (Fig. 2).

Details of the five remaining cases with meningitis are given here. All except Case 7 had changes in the chest x-ray picture.

Case 4.—Fell ill with fever, muscular ache, very slight cough. On the fifth day of illness erythema, nodosa exanthema, conjunctivitis, buccal enanthema and sores, redness and swelling of the nasal septum appeared without known provocative agent in the form of a drug or food. Neurological condition normal. E.E.G. normal. Spinal fluid contained 14 leucocytes/c.mm. Maximum cold-antibody titre 1/32 on day 21.

Case 5.—Fell ill with fever, headache, vomiting, and, on the fifth day of illness, cough. Neurological condition: nuchal rigidity, Lasègue-positive. E.E.G.: slow dysfunction, which showed regression at follow-up. Spinal fluid contained 16 leucocytes/c.mm. Cold-antibody titre 1/16 on days 10 and 20. C.F. titre to Eaton's agent: neg., 256.

Case 6.—Fell ill with high fever, headache, nausea, and cough. The patient was given penicillin and chloramphenicol. Purpura on trunk and extremities on 12th day of illness. Neurological condition normal. E.E.G.: non-specific, diffuse, slow dysfunction, which showed regression at follow-up. Spinal fluid contained 3 leucocytes/c.mm. Cold-antibody titre more than 1/1,024 on days 14 and 21. C.F. titre to Eaton's agent: 512, 512, >1,024.

Case 7.—Fell ill with cough, headache, nausea, and subfebrility. Neurological condition: nuchal rigidity, Lasègue-positive 80 degrees bilaterally. E.E.G. normal. Spinal fluid contained 136 leucocytes/c.mm. Cold-antibody titre 1/128 on day 12, but negative on days 16 and 32. Neutralizing antibodies to E.C.H.O. 3 virus present. C.F. titre to Eaton's agent: 8, 16, 4.

Case 8.—Fell ill with high fever, cough, sore throat, headache. Was given penicillin and sulpha drugs. Haemorrhagic exanthema, conjunctivitis, gingival enanthema on 11th day of illness. Neurological condition normal. E.E.G. normal. Spinal fluid contained 32 leucocytes/c.mm. Cold-antibody titre 1/256 on days 15 and 22.

Discussion

The question arises whether the cause of these eight cases of meningoencephalitis or meningitis should be sought in the general infection even if it was fairly widespread in Stockholm at the time. The most common cause of aseptic meningoencephalitis is infection with enterovirus, but such cases were not found. Case 7 (cold agglutinin 128 on 12th day, negative on 16th and 32nd days), however, had neutralizing antibodies to E.C.H.O. 3 without rise of titre; the patient's wife had fallen ill with serous meningitis a few weeks previously. E.C.H.O. 3 was isolated from her faeces, and neutralizing antibodies to E.C.H.O. 3 with titre rise were found in her acute-phase and convalescent-phase sera. Another common cause is parotitis, but this was excluded epidemiologically, clinically, and, in five of the eight cases, serologically. Owing to the season of the year an infection with tick-borne encephalitis virus can also be excluded. Certain bacteria, leptospira, and listeria, as also toxoplasma, may produce meningitis of serous type, but were excluded clinically and in one case also serologically. In Case 3 there was bacteriological and serological evidence of infection with β -haemolytic streptococci; the patient therefore had a double infection, which is a common occurrence (Tunevall *et al.*, 1963).

Clinically, Cases 2 and 3 exhibited distinct encephalitic symptoms with severe dizziness and vomiting following on change of posture. Like Case 1 they did not develop pneumonia and had only mild upper respiratory symptoms. Apart from pneumonia, Cases 4 and 8 had a febrile mucocutaneous syndrome and Case 6 had purpura. According to Ström (1962, 1963) this syndrome of allergic origin is not uncommon in

primary atypical pneumonia, but does not cause the meningitis. Of the two remaining cases one had right-sided pneumonia and the other pharyngotracheitis.

The temporal association between cold-agglutinin-positive infection and aseptic meningoencephalitis or meningitis in the eight cases described is not definite evidence of an aetiological relation. The cases should, however, be noted in respect of the possibility of mycoplasma infection in aseptic meningoencephalitis or meningitis, especially in cases without sign of atypical pneumonia.

Summary

From January 1962 to June 1963 126 patients (69 females and 57 males) with cold-agglutinin-positive infection were treated at the Stockholm Hospital for Infectious Diseases. Eight of them (2 females and 6 males) had aseptic meningoencephalitis or meningitis. Six of the eight patients were aged 5 to 29 years (75 of the total number of patients were in this

age-group) and were among the 72 patients who fell ill between October 1962 and February 1963.

It is suggested that *Mycoplasma pneumoniae* may be a cause of aseptic meningitis.

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Effect of Clofibrate and Androsterone on Hypercholesterolaemic Xanthomatosis

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When the claim was made that the oral administration of clofibrate in combination with androsterone (Atromid) led to a lowering of serum cholesterol in patients with hypercholesterolaemia and coronary artery disease (Oliver, 1962) it appeared desirable to determine the effect of this therapy in patients with other manifestations of hypercholesterolaemia. Seven such patients have now been treated for two years with 2 g. of Atromid daily in three divided doses. These patients fall into four groups.

Group A consisted of three male patients aged 30, 40, and 46 with xanthoma tuberosum on the knees and elbows. The xanthomata had been noted for 18 months, 3 years, and 15 years respectively. The two elder patients had suffered inter-

mittent claudication in one leg for eight and three years respectively. All three had impalpable dorsalis pedis pulses in one or both feet. Before treatment their serum cholesterol was 460, 325, and 500 mg./100 ml. respectively. These levels fell to below 250 mg. in two cases within a month of starting treatment. The other fell promptly to 300 mg. in six weeks and then fell still further to 250 mg. or below over the next three months. All have remained below 250 mg. for the rest of the two years. Total serum lipids before treatment ranged from 2.9 to 3.05 g./100 ml., and after treatment from 1.35 to 1.85 g. In all three the xanthomata have disappeared. They appeared to be diminishing three to five months after starting treatment and had completely disappeared in 11 to 13 months. The patient with the shorter history of intermittent claudication insists that he can now walk about four times as far before getting pain.

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Photographs of elbow of patient in group B. Left, photograph taken on 14 August 1962, before starting treatment. Right, photograph taken on 16 July 1964, after 23 months' treatment, showing disappearance of xanthomata.