MEASLES MENINGOENCEPHALOMYELITIS

BY

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Accounts of nervous disorders associated with measles, some of which were presumably meningoencephalitis, can be traced as far back as the beginning of the eighteenth century, according to the historians Comby (1935) and Rolleston (1937).

In this series 10 cases were encountered over a short period—three in the second quarter of 1951, from the Borough of Wembley, and seven between September, 1951, and June, 1953, widely distributed in the boroughs surrounding Neasden Hospital, a further two being from Wembley. The well-known protean character of the disease, and its tendency to occur in little groups, were well illustrated by these cases, but no light was thrown on the pathogenesis of the condition or on prevention and treatment, apart from the failure of A.C.T.H. to influence its course.

Notes of 10 Cases in Present Series

Case 1.—Female, 3½ years; severe measles. Severe encephalitis 5 days after rash; delirium, choreiform movements progressing over 10 days, coma 20 days. Retention of urine and incontinence of faeces. Flaccid quadriplegia. Plantar reflexes extensor and squint. Meningeal signs negative. C.S.F. normal. Complete recovery from paralysis, but personality changes marked: purposeless hyperkinesia, lacks concentration, plantar reflexes extensor.

Case 2.—Male, 5½ years; mild measles. Severe encephalitis 5 days after rash: lethargy, slurred speech, dysphagia, meningeal signs 5 days, left plantar extensor, motor aphasia. C.S.F.: lymphocytes 38. W.B.C. normal. Complete recovery in 3 weeks.

Case 3.—Male, 5 years; mild measles. Moderate encephalitis 3 days pre-eruptive: left facial palsy, meningeal signs 3 days. C.S.F.: lymphocytes 60, protein 40 mg. per 100 ml. W.B.C. normal. Recovery in 4 months.

Case 4.—Female, 6 years; mild measles. Moderate encephalitis 5 days after rash: lethargy, meningeal signs 10 days. Generalized hypotonia, plantar reflex extensor. Recovery in 5 weeks.

Case 5.—Male, 5½ years; moderate measles. Severe encephalitis 2 days after rash: meningeal signs 13 days; coma 14 days; cerebellar ataxia and behaviour problems. C.S.F.: lymphocytes 20, protein 80 mg. per 100 ml. W.B.C. normal. Recovery in 5 weeks.

Case 6.—Male, 20 months; mild measles. Severe encephalitis 3 days after rash: meningeal signs 4 days, convulsion, coma 2 days, cerebellar ataxia. C.S.F.: lymphocytes 80, protein 200 mg. per 100 ml. W.B.C. normal. Recovery in 5 weeks.

Case 7.—Female, 13 years; mild measles. Mild encephalitis 11 days after rash: meningeal signs 10 days. C.S.F.: cells 11,080 (90% lymphocytes). W.B.C. normal. Recovery in 18 days.

Case 8.—Male, 23 years; moderate measles. Mild encephalitis 3 days pre-eruptive: meningeal signs 9 days. C.S.F.: lymphocytes 10. W.B.C.: 4,400 (77% polymorphs). Recovery in 13 days.

Case 9.—Female, 3½ years; moderate measles. Very severe encephalitis 3 days after rash: meningeal signs 2 days; stupor 19 days. Quadriplegia, retention of urine. C.S.F.: lymphocytes 14. W.B.C.: 4,300 (65% polymorphs). Residual cerebellar ataxia and hypotonia. Aphasia. Behaviour problems. Given A.C.T.H. gel, 50 mg. daily I.M. for 8 days without benefit. Complete

recovery from paralysis and almost so from ataxia, but after 6 months personality changes: stubborn, mentally retarded child.

Case 10.—Male, 5½ years; moderate measles. Very severe encephalitis 2 days pre-eruptive: meningeal signs 5 days. Delirium and coma 5 days. Incontinent of urine and faeces. C.S.F.: protein 200 mg. per 100 ml. W.B.C. normal. Given A.C.T.H., 10 mg. I.M. 6-hourly (3 doses) with no effect. Postural drainage and oxygen. Died of pulmonary oedema and anoxia. Post-mortem examination refused. Virus studies: positive complement-fixation reaction 1 in 80 to psittacosis, taken on 8th day, was considered to be a residual titre from a previous illness.

Incidence

It is difficult to determine whether the rising incidence recently recorded is real or is due to better diagnosis and reporting. Three of the present cases occurred in an area in which 795 cases of measles were notified in the same epidemic period—that is, an incidence of 1 in 285. In a series of 30 cases Hoyne and Slotkowski (1947) reported an incidence of 1 in 428, but a figure of the order of 1 in 1,000 more closely represents the overall incidence.

Diagnosis

The sudden onset of nervous symptoms in a patient making an apparently normal recovery from measles should suggest the possibility of meningoencephalitis, but all grades occur from slight or transient headache, drowsiness, and irritability, with or without initial vomiting. Its occurrence seems to be unrelated to the severity of the primary disease or to the presence of its characteristic complications, whether respiratory or gastro-intestinal. Some degree of fever is probably always present, but may be missed or attributed to other causes. Meningism is variable and usually of the mild form common in poliomyelitis, but may be completely absent, especially if the spinal fluid is normal. On the other hand, meningism is not uncommon in post-measles pneumonia, otitis media, and gastro-enteritis, especially in infants and young children. It may occur during the eruptive stage or in early convalescence (up to the fourteenth day from the onset), or even before the appearance of the rash (Cases 3, 8, and 10). These three patients had meningeal signs, one, suffering from delirium and coma, dying of pulmonary oedema and anoxia in five days. This early onset seems to be against the allergic hypothesis of aetiology. No cases appear to have been recorded before the onset of the disease or without the typical rash, in this respect unlike mumps.

Complement-fixation tests and isolation of the virus are so far inapplicable in forming a diagnosis, although Shaffer, Rake, and Hodes succeeded in growing the virus from the brain tissues of a fatal case as long ago as 1942. The coincidental prevalence of acute poliomyelitis may sometimes introduce an element of uncertainty, and occasionally the final diagnosis may depend on the subsequent development of mental and behaviour changes, in this respect resembling encephalitis lethargica.

Aetiology

In the cerebral disorders associated with infectious diseases and the prophylactic administration of their antigens, two varieties are differentiated:

(1) Post-infectious—that is, after virus diseases such as measles, rubella, smallpox, chicken-pox, and mumps, as well as after inoculations in which the antigen is living although attenuated, such as vaccination and rabies. The typical changes are diffuse demyelination and perivascular infiltration with small round cells, occurring in haphazard fashion more or less after the pattern of poliomyelitis. The damage is assumedly inflicted by the virus, probably a highly neurotropic variant, and, at least in the case of mumps, can be readily isolated from the cerebrospinal fluid.

(2) After inoculations in which the antigen is killed and usually modified in some way. *Haemophilus pertussis*

vaccines seem to be the commonest source of these accidents (Byers and Moll, 1948), but similar sequelae have been recorded after inoculation of diphtheria, typhoid, and other bacterial antigens as after the disease itself, again notably whooping-cough. These cerebral accidents are commonly regarded as allergic or protein-shock phenomena, the predominating changes being vascular thrombosis. The hypoxia accompanying severe paroxysms is regarded as an important factor in the causation of whooping-cough encephalopathy, which tends to leave permanent residua (Levy and Perry, 1948). The frequent occurrence of convulsions raises the question of an epileptic diathesis or like predisposition, or a trigger mechanism in cerebation which may be released by fever, from whatever cause.

Another theory, which receives less support than formerly, involves the existence of an unidentified encephalitis virus, which in some way is activated by these diseases or by the products of bacterial or viral metabolism. The sporadic appearance of "idiopathic" encephalitis lends some support to this theory (Brain and Hunter, 1929).

Prognosis and Treatment

The case mortality in the present series was 10% (the same as in Ford's (1928) series); delirium and coma were sudden in the fatal case and continued to the end five days later. Complicating features were terminal pulmonary oedema and the presence of psittacosis agglutinins in significant titre, but unfortunately a necropsy was refused. The higher fatality rates recorded by some workers were probably due in part to the omission of mild or doubtful cases; Hamilton and Hanna (1941), in their review of 241 from the literature and 44 of their own, recorded a case mortality of 20% and a residua rate of 40%.

There were no cases of permanent physical residua in the cases now reported, but two severe cases (Nos. 1 and 9) showed the worst sequelae—behaviour problems and maladjustment. The assessment of the latter is difficult, especially regarding the extent to which the environment perpetuates or improves the condition. The prognosis should always be guarded.

Treatment is largely symptomatic and anticipatory, involving oxygen and chemotherapy, especially when pulmonary or bulbar features are present. When cerebral oedema is suspected, concentrated albumin, plasma, or dextran may be given intravenously—usually three to four times the normal strength. Convalescent serum or gamma globulin may also be tried in the spreading forms of the disease; but little benefit can be expected in the ordinary forms as the initial cerebral assault appears to be maximal in degree and extent, the later changes being biochemical or reactionary and cumulative in their lethal effect. A.C.T.H. was given to two cases (one fatal) on the basis of an allergic aetiology, but seems to have had no effect on the course of the disease or in the prevention of residua, as the case which recovered became severely ataxic and paralysed, with pronounced personality changes.

Summary

Ten cases of measles meningoencephalomyelitis, three occurring in the pre-eruptive stage, were encountered in a localized area of North-west London between September, 1951, and June, 1953.

The average age of the patients was 5 years, the limits being 20 months and 23 years.

No correlation was observed between the incidence and severity of the disease and the character of the primary disease.

Of the three pre-eruptive cases, one was fatal. This early appearance, and in fact the lack of a fixed time-relationship to the rash, seem to be against the allergic hypothesis of aetiology; moreover, there was no eosinophilia.

Coma and severe paralyses are unfavourable features, especially if prolonged, but complete recovery may follow.

Predominantly meningitic forms tend to show pronounced fluid changes and encephalitic forms show slight changes, but a high pleocytosis is not incompatible with severe attacks.

Treatment is symptomatic and anticipatory, involving the use of oxygen and chemotherapy for severe forms. Immune sera and concentrated plasma given intravenously may turn the scale in selected cases, especially when cerebral oedema is a prominent feature. The failure of A.C.T.H. to influence the course of the disease (two cases) supports the virus rather than the allergic hypothesis of aetiology; but the drug was given rather late and in very severe cases.

The case mortality, 10%, equals the lowest recorded in a comparable series.

While physical residua were negligible or absent among the nine recoveries, two patients, both 3½ years old, showed undoubted mental and behaviour deterioration—in one so pronounced as to require institutional care.

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ANTAGONISTIC EFFECT OF A.C.T.H. AND CORTISONE ON THE ANTICOAGULANT ACTIVITY OF ETHYL BISCOUMACETATE

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In agreement with the observations of Cosgriff *et al.* (1950) and Cosgriff (1951), we have noticed a higher incidence of thrombo-embolic complications during administration of A.C.T.H. and cortisone. While treating these complications with the anticoagulant ethyl biscoumacetate ("tromexan") we observed that patients on hormonal therapy would often need a larger dosage to maintain an optimum level of plasma prothrombin activity. On withdrawal of hormonal therapy the requirement of ethyl biscoumacetate decreased considerably.

Two patients were studied—one a case of idiopathic acquired haemolytic anaemia and the other a case of

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