Measles Antibodies in the Serum and Cerebrospinal Fluid in Subacute Sclerosing Panencephalitis

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SUMMARY

The levels of complement-fixing antibodies to measles antigen in the sera and cerebrospinal fluids of 17 patients with subacute sclerosing panencephalitis seen in a 2-year period, are compared with those in 14 measles patients with or without acute encephalitis and 25 patients with neurological disease.

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Connolly *et al.*[1] established the association of high levels of complement-fixing antibodies to measles antigen in the serum and the cerebrospinal fluid of patients with subacute sclerosing panencephalitis (SSPE). Serology subsequently has had an important place in distinguishing these cases from others with somewhat similar symptomatology.

Complement fixation tests for measles antibodies have been routinely applied in our laboratory to cases of measles encephalitis and SSPE. The investigations included examination of the serum and CSF of a number of other children in whom the diagnosis of SSPE was raised by the clinician but in whom the clinical diagnosis subsequently proved to be other than SSPE.

This communication gives an account of our experience with measles complement fixation tests over the past 2 years.

PATIENTS AND METHODS

The CSF and serum from 56 children and adolescents were examined during this study. Of the group, 17 had a clinical diagnosis of SSPE; 7 were children who were recovering from acute measles encephalitis; 7 had acute uncomplicated measles; 25 had neurological disease as manifest by evidence of either mental retardation, intellectual deterioration, behavioural disorders or impaired motor function.

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Complement fixation tests were performed on dilutions of the patient's serum or CSF using commercial measles virus antigen at optimal dilution, incubated overnight at 4°C with 2,5 units of complement. Fully sensitised sheep red cells were added next morning and the 100% end-point read after 30 minutes. Dilutions of serum and CSF were made by the microtitre technique, but samples with high antibody levels in serum were confirmed by making a series of dilutions using separate pipettes for each transfer.

RESULTS

The results of the measles complement fixation tests on serum and CSF from patients with a variety of clinical illnesses are presented in Figs 1 and 2.

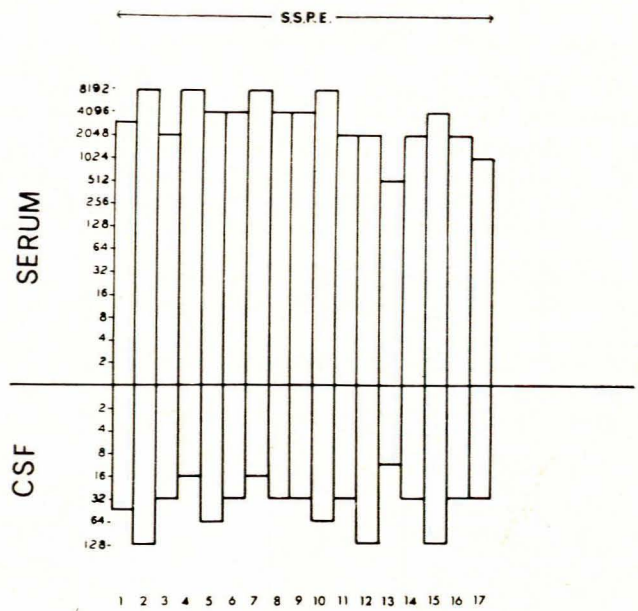

Fig. 1. Measles (CF) antibodies in the serum and CSF of 17 patients with SSPE.

In the 17 patients with clinical features of SSPE the serum antibody titre varied from 512 to 8 192 with a geometric mean of 3 153. In every patient similar antibodies were demonstrable in the CSF, with titres ranging

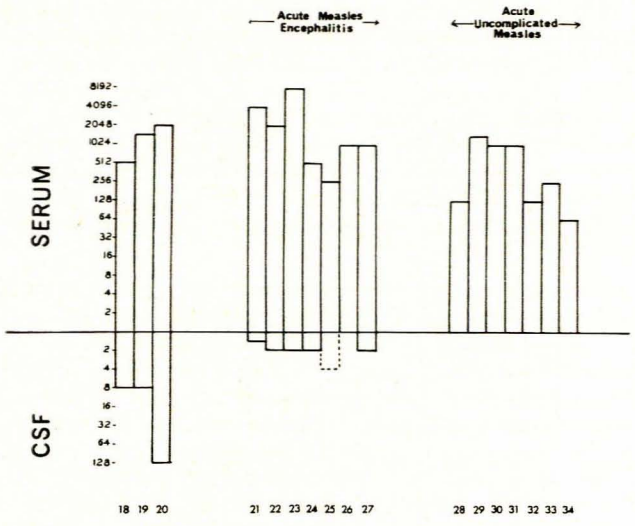

Fig. 2. Measles (CF) antibodies in serum and CSF of a variety of patients (see text). Broken line indicates an anticomplementary effect.

from 12 to 128 with a geometric mean of 40. Three other patients (Nos. 18 - 20) who, on serological grounds at least, appeared to fall into this group are listed separately, because they could not be identified as cases of SSPE at this stage.

In 7 patients with acute measles encephalitis the serum antibody levels showed a similar range of variation, but the geometric mean titre was 1 579. In the CSF, however, antibody was either not demonstrable at all (on the single occasion it was examined) or only in the undiluted fluid or, at most, in the half-diluted CSF. One CSF sample contained anticomplementary substances to a titre of 4, thus invalidating the reading of the result.

Since the indications for lumbar puncture are infrequent, CSF was available from only 7 children with acute uncomplicated measles infection. The serum antibody titres in these children varied from 128 to 1 536 with a geometric mean of 331. This figure is lower than expected because the single blood sample was taken during the acute stage of the disease and not at the optimal period following convalescence. No antibodies were detectable in any of the 7 samples of CSF, even in the undiluted fluids.

Serum and CSF samples were also examined from a miscellaneous group of 22 children with neurological disease in whom the diagnosis of SSPE was considered at the time of admission to hospital, but later found to be untenable. All of these patients had complement-fixing measles antibodies in their sera with a geometric mean titre of 139. In no single instance was measles antibody detected in the CSF, but in two samples the undiluted fluid was anticomplementary.

DISCUSSION

Of the 17 patients with SSPE listed in Fig. 1 the first 15 (Nos. 1 - 15) are those referred to by McDonald *et al.*[2] in the companion article in this issue of the *Journal*. One patient (No. 16) was 16 years old and was not seen in the paediatric wards; the other (No. 17) aged 11 years and the only White patient, came from outside the Cape Province. Accordingly, neither was included in the earlier article.

The high antibody levels in the serum and CSF in this group of 17 patients are striking. They assume even greater significance and diagnostic importance when compared with the serological findings in other patients suffering from acute measles infection, with or without encephalitis, or in patients with neurological disease with one or more of the signs or symptoms associated with SSPE.

Three children (Nos. 18 - 20), aged 5, 4 and 8 years respectively, appeared, on the basis of the antibody level in the CSF, to fit into this group, but a clinical diagnosis of SSPE could not be upheld. There are four possible explanations for this. First, although there was no visible blood or blood-staining of the CSF samples on arrival at the laboratory, a falsely high antibody figure could be due to some admixture of blood which took place during the lumbar puncture. The second possibility is that the patients were in the early stage of SSPE but the typical clinical features, EEG changes and paretic type of colloidal gold response in the CSF had not yet become manifest. Thirdly, it may be that these children were in the process of recovery from SSPE with a slow reversal of the abnormal CSF antibody changes. In 1 patient at least (No. 19), the complement-fixing antibody titres found on 4 successive examinations were 8, 4, 2 and 4, respectively, and were accompanied by suggestive evidence of some clinical improvement. In this context Legg[3] has recorded 3 patients with SSPE in whom the disease was arrested, plus 1 who made a good recovery. The fourth possible explanation is that there had been a non-specific 'leak' of serum antibody into the CSF, resulting from a disorder of the central nervous system with altered permeability of the blood - brain barrier as occurs in bacterial or viral meningitis,[4] brain injury or some other earlier lesion. It is noteworthy that 1 of the 3 patients in this small group (No. 20) had had serious head injuries in a motor car accident 6 months prior to his admission for the present illness, with a provisional diagnosis of 'myoclonic epilepsy'.

There is satisfying evidence that the high levels of measles antibody in the CSF in SSPE are not due to an anatomical or physiological breech of the intact blood-brain barrier. Clarke *et al.*[5] have demonstrated that even in the presence of high levels of poliovirus antibody in the serum, poliovirus antibody could not be detected in the half-diluted CSF. This suggests that antibody in SSPE patients was produced locally in the central nervous system and that it applies to both measles IgM and IgG.[6]

Three patients had anticomplementary substances in the CSF, either in the undiluted fluid or, in one case, in the quarter-dilution. The nature of the anticomplementary substance was not established, but analytical ultracentrifugation, at velocities adequate to sediment antigen-antibody complexes, failed to reduce or remove the anticomplementary effect.

In SSPE it is now known that, despite the high levels of measles antibody in the blood and CSF, the virus is

not eliminated from the body, since viral antigen can be demonstrated in the brain[1] as well as in lymph nodes and other non-neuronal tissues.[7] Further, measles-like virus has been isolated from the brain by many workers and recently also from lymph glands.[8] Persistence of intracellular virus in the presence of circulating antibodies is a well-known phenomenon in infections caused by herpes simplex, varicella, rubella, cytomegaloviruses and many other viruses. It may be that persistence of measles virus in the brain of healthy, immune individuals is the rule rather than the exception.[9]

What determines the development of the progressive lesions of the central nervous system in these particular individuals? Perhaps the virus persists intracellularly in an incomplete or latent form, which becomes reactivated by circumstances as yet unknown. Reports of SSPE occurring in more than one member of a family and even simultaneously in twin siblings[10] do give some support to the possibility that an environmental factor may be responsible for renewed viral activity. Attention has been drawn to a lower incidence of SSPE in urban areas than in rural areas where contact with animals may result in co-infection with a zoonotic agent.[11] Under such circumstances reinfection with measles virus or some related virus such as that causing canine distemper is a possibility. A papova virus has been isolated from the brain of a child with SSPE[12] but the significance of this and the extent of any possible interaction between the two agents have not been established.

Alternatively, at the time of the primary measles infection there may have been some grade of immunological inadequacy which resulted in a failure to impart to the child the benefits of complete recovery and long-lasting immunity. There are two aspects to this consideration, one being the effect of the measles virus itself, and the other the effect of malnutrition upon the efficacy of the immunological response. Although antibody production is generally a prominent feature of the immune response to measles virus it is apparently not essential, since the agammaglobulinaemic child in natural measles infection may suffer a disease that is not unduly severe, and experience an uneventful recovery followed by effective immunity.[13] While they do not play an important role in recovery from the first infection, the antibodies are almost certainly important in preventing a second attack of measles. This part of the immune response is apparently not impaired in SSPE or in malnutrition.

Measles itself has serious effects upon the immunological responses. It is well known that the cell-mediated hypersensitivity mechanisms are vigorously suppressed so that tuberculin hypersensitivity, for instance, may be absent for several weeks but occasionally for many months.[14] White and Boyd[15] have indicated that patients with measles of duration greater than 4 days showed a loss of all discernible cortex of the thymus for up to 64 days. They suggest that the resulting deficiency of thymus-dependent lymphocytes may possibly allow the persistence of large amounts of virus in immunologically privileged sites such as the thymus and the brain, inducing a state of specific immunological non-responsiveness to measles antigen in the presence of a normal antibody response.[16]

In another primary virus infection, caused by herpes simplex virus, widespread visceral lesions and high mortality are common results if the infection occurs during the stage of immunosuppression induced by acute measles,[17] or when the diminution in cell-mediated responses is caused by severe thymolymphatic depletion associated with kwashiorkor or other forms of protein calorie malnutrition.[17,18] Measles infection in the severely protein calorie-deprived child is notoriously serious and carries a high mortality.[19]

While it is not possible to establish the nutritional state of our patients at the time of their first measles infections, it may be relevant to record that all but 1 of our 17 patients were either Coloured or Bantu, some from a rural area and many of them of lowly socio-economic circumstances. This is a segment of the community in which it would be unwise to ignore the possibility of one or other of the ill effects of protein calorie deprivation upon the efficacy of the immunological responses. It would have been very valuable to have known something about the clinical course of the primary measles infections in these children, since some reports have indicated that the first infection was in no way unusual.[20] However, Gajdusek[21] claims that many SSPE patients have atypical measles, measles without a rash, or measles exposure not diagnosed as measles.

In geographical areas where SSPE appears to occur more frequently than in others, such as the Cape Province, the south-eastern states of the USA[22] and the North Island of New Zealand,[23] it is important to gather and to record all possibly relevant data. This is particularly so in respect of age, sex, and race, as well as the environmental, nutritional, immunological and familial factors which may have a bearing on the outcome of the primary measles infection or on the pathogenesis of SSPE.

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