LOW CEREBROSPINAL FLUID PROTEIN IN AFRICAN CHILDREN WITH FEBRILE CONVULSIONS

BY

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Febrile convulsions in childhood constitute one of the commonest medical emergencies in paediatric practice. Although the aetiology, clinical picture, treatment and possible sequelae are described and discussed in the standard paediatric literature, little or no mention is made of the exact cerebrospinal fluid (C.S.F.) composition in this condition (Sheldon, 1951; Grulee and Eley, 1952; Collis, 1952; Moncrieff and Evans, 1953; Nelson, 1954; Livingston, 1954; Chao, Druckman and Kellaway, 1958; Dekaban, 1959; Ford, 1960). Wilcox and Lyttle (1925), Wolman (1957) and Ellis (1960) mention that the total C.S.F. protein concentration in convulsions and meningismus may occasionally be raised. Lennox (1949), Moll (1955) and de Chenar (1959) found no C.S.F. abnormalities; Wilcox and Lyttle (1925) and Levinson (1950) found an occasional increase in sugar. Lennox (1960) quotes Zellweger as having done detailed blood, urine and C.S.F. examinations in patients with febrile convulsions, but does not give the results, and Prichard and McGreal (1958) stated that all 'laboratory tests' were normal in their cases, but did not specifically mention C.S.F.

Most authors stress the importance of performing a lumbar puncture on convulsing children to exclude neurological disease, and one is left to conclude that the finding of a normal C.S.F. is to be expected if the convulsions are of the benign febrile type.

The range of normality for total C.S.F. protein concentration in children is generally accepted as 15-45 mg./100 ml. (Moncrieff and Evans, 1953; Nelson, 1954; Moll, 1955; Wolman, 1957), with Levinson (1950) and Cumings (1954) giving the lowest levels of normal as 5 mg., and 10 mg./100 ml. respectively, and Wilcox and Lyttle (1925) giving the highest range of 30-80 mg./100 ml.

The effect of age on the total C.S.F. protein has been noted by Müller, Jaworski, Silverman and Elwood (1954), Wolman (1957) and Widdell (1958). The highest values were found in the neonatal period and the lowest values in the 9-month to 2-year age group.

No normal values are available for African children in Kenya, and the European standards of 15-45 mg./100 ml. have (perhaps wrongly) been accepted as equally applicable to African children.

In the paediatric wards of King George VI Hospital, Nairobi, all children with febrile convulsions have a lumbar puncture performed on admission to hospital, and on several occasions the total C.S.F. protein concentration of those with sub-tropical malaria was noted to be below 5 mg./100 ml., although all other constituents were normal.

As most pathological processes involving the central nervous system are associated with an increase in C.S.F. protein, the significance of a low C.S.F. protein was obscure and was largely ignored as most children made a rapid recovery and the C.S.F. was not re-examined.

No record, however, can be found of this having been described before in connexion with either malaria or febrile convulsions in general.

Although Lennox (1960) comments on the rarity with which convulsions accompany malarial fever, the reverse has been the experience in this hospital and in other paediatric centres in the tropics (Trowell and Jelliffe, 1958). The latter authors state that the C.S.F. is usually normal even in cerebral malaria, but may show an increase in cells and protein.

Gómez, Ramos-Galván, Cravioto and Frenk (1957) found low C.S.F. protein concentrations averaging 11-5 mg./100 ml. in a series of malnourished children. A similar observation has been made in Kenya (L. G. Macdougall, unpublished data), but in no instance was the C.S.F. protein concentration below 5 mg./100 ml. Perera (1959) has also commented on low C.S.F. protein concentrations commonly found in Ceylonese children and attributed to their inferior state of

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* U.R.T.I. = Upper respiratory tract infection.  
† S.T. = Subtertian.
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nutrition. The exact C.S.F. findings, however, are not quoted.

Mention has been made of 'low' C.S.F. protein in adults with epilepsy (Hoch and Chanutin, 1952), but in no instance was the total protein below 18 mg./100 ml. Hohmann (1954) also found low C.S.F. proteins in epilepsy and quoted Demme as having reported similar low values in infectious disease in children. Müller et al. (1954), however, studied the C.S.F. in children with acute respiratory infections and found no child in the 0-4 year age group with a total protein below 15 mg./100 ml.

In view of the few published reports on low C.S.F. protein levels it was decided to investigate the African children more fully and assess whether or not low values were a constant feature of malarial or other febrile convulsions and, if so, whether it bore any relation to their nutritional status.

Material and Methods

Thirty consecutive children with febrile convulsions admitted to King George VI Hospital, Nairobi, between February and October 1960, provided the material for the study. All had had a convulsion on the day of admission or were convulsing at the time of admission. Children with obvious meningeal infection or neurological disease were not included in the study.

The age range of the children was 5 months to 4 years and 2 months with an average of 1 year and 6 months.

A full physical examination was made to determine the nature of the febrile illness, and particular attention was paid to the general nutritional status which was graded as excellent, good, fair or poor.

Laboratory investigations included the following:

1. C.S.F. examination for cells, protein, sugar and chloride content (obtained by lumbar puncture).
2. Total serum protein and serum albumin estimation.
4. Urine, stool, blood sugar or haemoglobin estimation only if these examinations seemed pertinent.
5. Repeat C.S.F. examination on discharge.

The total C.S.F. protein was estimated by the sulphosalicylic acid method (Denis and Ayer, 1920) and the serum proteins by the Biuret method using 22.6% sodium sulphate. Facilities were not available at the time for the fractionation of either C.S.F. or serum proteins.

Results

The results are summarized in the Table. Of the 30 children studied 23 were male and seven female; 12 were considered to be in an excellent state of nutrition, 13 were good, two were fair and three were poor.

The temperature on admission varied from 97° to 102° F. (36 to 39° C.) and is of doubtful significance as it gives no indication of the degree of fever at the time of the convulsion if this occurred at home.

C.S.F. Findings

Cells. 21 children had no cells in the C.S.F., eight had 2 to 4 per cm. and one had 14 per cm. —all lymphocytes. The latter child was suffering from cerebral malaria and subsequently died.

Chloride.* The C.S.F. chloride ranged from 680-720 mg./100 ml. in all children and was considered to be within normal limits.

Sugars.* The C.S.F. sugar was within the normal range of 40-80 mg./100 ml. in all but four children. One child with salmonellosis had a C.S.F. sugar concentration of 14 mg./100 ml., but no evidence of meningeal infection or hypoglycaemia (blood sugar 92 mg./100 ml.).

Of the three children with a C.S.F. sugar concentration of 90-143 mg./100 ml., two had simple upper respiratory infections and made a rapid recovery, one had a secondarily infected amoebic liver abscess and died. None of these children had glycosuria or ketonuria and the blood sugar was not estimated.

C.S.F. and Serum Protein on Admission. Total C.S.F. protein below 5 mg./100 ml. was recorded in 16 and levels of 5-10 mg./100 ml. were found in 14 children. In the former group 12 had a total serum protein range of 6·30-8·10 g./100 ml. (mean 7·43 g./100 ml.) and serum albumin 3·25-5·05 g./100 ml. (mean 4·12 g./100 ml.). Only one child was considered to be in a poor state of nutrition clinically. Of the children with C.S.F. protein concentrations of 5-10 mg./100 ml., 10 had a total serum protein range of 5·30-7·80 g./100 ml. (mean 6·89 g./100 ml.) and serum albumin 3·00-4·35 g./100 ml. (mean 3·95 g./100 ml.). Two were poorly nourished and three were classified as 'fair'.

C.S.F. Protein on Discharge. A repeat lumbar puncture was performed on 15 children before discharge (two to 10 days after the original convulsion). Their initial C.S.F. protein levels had ranged from 3·8 mg./100 ml. with an average of 4·6 mg./100 ml., and the final range was 7-15 mg./100 ml. with an average of 11·4 mg./100 ml. No child failed to show an increase in the C.S.F. protein content.

* The methods for chloride and sugar estimations were those described by King (1931).
Final Diagnoses. Fourteen children were suffering from upper respiratory tract infections (common cold, otitis media and pharyngitis), eight had subtertian malaria, three had salmonella or shigella enteritis, two had pneumonia and one each had whooping cough, measles and a salmonella-infected amoebic liver abscess.

There were five deaths in the series due to pneumonia (two), salmonellosis and cerebral thrombosis (one), secondarily infected amoebic liver abscess (one) and cerebral malaria (one).

The total C.S.F. protein of those with uncomplicated upper respiratory infections, malaria and measles accounted for the remaining 20%.

A low total C.S.F. protein concentration was a common accompaniment, and the average for the series was 5·1 mg./100 ml., with a range of 3-10 mg./100 ml.

A lumbar puncture performed before discharge on 15 children showed an increase in the total C.S.F. protein concentration in all cases.

No relation could be found between the initial low C.S.F. protein concentration and the total serum protein, serum albumin or general nutritional status of the children. Brock (1961) comments on the ‘marginal range of hypoalbuminaemia which can be used as evidence of impending or early protein deficiency’. This range is given as 2·75-3·52 g./100 ml. Only three children in the present series fell into this category and none of these exhibited the lowest C.S.F. protein concentrations.

According to Wikoff and Kazdan (1951) the methods of C.S.F. protein estimation described by Denis and Ayer (1920), using sulphosalicylic acid, and Johnston and Gibson (1938), using trichloracetic acid, show extremely good correlation with the standard micro-Kjeldahl method. There is no reason to believe, therefore, that the method used in the present series should give different results from those commonly used in other centres.

Stewart (1928) using a similar technique to ours found normal C.S.F. protein concentrations of 15-55 mg./100 ml. and Müller et al. (1954) gave values of 15-50 mg./100 ml. for the 0-4 year age group. Widdell (1958) using a modified trichloracetic acid and sulphuric acid method found the lower limit of normal to be 13 mg./100 ml.

Levinson (1950) and Cumings (1954), who quoted the lowest values of 5 mg. and 10 mg./100 ml. respectively, did not mention the technique of estimation.

In the absence of any normal C.S.F. standards for Kenya African children the present results were compared with the C.S.F. findings in apparently healthy African children of a similar age group who had recovered from malnutrition. The total C.S.F. protein concentration of 18 such children ranged from 15-22 mg./100 ml. with an average of 17·5 mg./100 ml.

By all comparable standards, therefore, the total C.S.F. protein concentration of the children with convulsions was still below the normal range, and the fact that the protein concentration rose after recovery seems to exclude the possibility of the low initial values being ‘normal’ for these particular children.

The reason for this unexpected finding is difficult to explain and the majority of possible explanations should apply equally to centres where low C.S.F. protein concentrations do not appear to be a feature of febrile convulsions.

It is known that ventricular C.S.F. contains a lower protein concentration than lumbar (Stewart, 1928; Widdell, 1958; de Chenar, 1959; Best and Taylor, 1961) and that convulsions due to any cause will lead to an increase in both amount and pressure of the C.S.F. (Levinson, 1950; Ellis, 1960). As this increase in fluid is derived mainly from the ventricles, a fall in the total protein concentration might be expected, together with an increase in the pre-albumin concentration. This, in fact, is the explanation given by Widdell (1958) for the relatively low C.S.F. protein concentrations found in adult epileptics by Hoch and Chanutin (1952). These latter authors also noted a possible association between X1 fraction which migrated faster than pre-albumin (X) and the development of convulsions in adults. Although this finding was not confirmed by Inesi, Tonini and de Risio (1956) it raises the point that the C.S.F. protein constituents may show some variation from normal during convulsive episodes when the total concentration is in the low-normal range.

Geiger (1958) has shown experimentally that during a convulsion non-carbohydrate oxidation in
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...the brain is predominant, and he suggests that the utilization and turnover of amino acids, protein and lipids may be greatly accelerated during this period of abnormal brain activity. These studies, however, were done on brain tissue, and the effect on the circulating C.S.F. was not assessed.

That any of these factors should apply solely to African children seems unlikely unless this is yet another facet of the precocious nitrogen balance which so many of this age group exhibit and which is so easily upset by any intercurrent stress or infection (Scrimshaw, Wilson and Bressani, 1960).

In view of recent developments in the detailed analysis of C.S.F. protein fractions (Goldstein, Hill, McKenzie, McGuckin and Svien, 1960) it seems timely to review the 'normality' of the C.S.F. findings in febrile convulsions.

It is possible that the present finding in respect of the total C.S.F. protein concentration is merely one of degree and that if detailed serial studies were done on both African and European children, during and after convulsive episodes, comparable alterations in the individual protein fractions might be found.

Summary

Thirty African children with febrile convulsions were studied and in all cases the total C.S.F. protein concentration was low during, or shortly after, the convulsive episode (mean 5-1 mg./100 ml.); 15 children had a repeat C.S.F. examination two to 10 days later, and all showed an increase in the total protein concentration.

No relation could be found between the C.S.F. protein, total serum protein, serum albumin or clinical nutritional status.

The convulsions were associated with respiratory or malarial infections in 80% of the children. Those with uncomplicated upper respiratory infections and malaria, who presented the most typical picture of benign febrile convulsions, tended to have the lowest C.S.F. protein concentrations.

There were five deaths, four due to bacterial infections not primarily involving the central nervous system and one due to cerebral malaria.

The literature relating to convulsions is reviewed and the possible reasons for low C.S.F. protein concentrations are discussed.

References


Low Cerebrospinal Fluid Protein in African Children with Febrile Convulsions
Lorna G. Macdougall

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