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The CSF-Protein Pattern in Acute Cerebellar Ataxia of Childhood and Intracranial Midline Tumours

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Abstract. CSF-protein profiles of 25 children with acute cerebellar ataxia and of 39 children with intracranial midline tumours at diagnosis were examined by quantitative zone electrophoresis in agarose gel. The profiles were compared with those obtained from a control group of 86 cases, and those from 61 patients with aseptic meningitis and 40 children with bacterial meningitis. The data from the latter groups demonstrated the CSF-protein pattern of moderate or severe disturbance of the blood-CSF barrier (B-CSF-B), respectively. The children with acute cerebellar ataxia showed minor signs of a B-CSF-B impairment and no increase of γ-globulin. These findings point to a slight acute vascular lesion. CSF changes indicative of a moderate-to-severe dysfunction of the B-CSF-B occurred in the majority of the patients with cerebellar astrocytomas, pontine gliomas, tumours around the 3rd ventricle, and medulloblastomas. Therefore acute cerebellar ataxia can be differentiated from intracranial midline tumours in most cases by means of CSF-protein electrophoresis. A striking finding was that 12 out of 14 children with medulloblastomas revealed a marked increase of γ-globulin. Since in 5 of these cases oligoclonal γ-globulin could be detected, this finding means local immunoglobulin synthesis within the CNS. The marked increase of γ-globulin which almost exclusively occurred in association with medulloblastomas allows their seperation from acute cerebellar ataxia and the other tumour groups. Quantitative agarose gel electrophoresis can be a complementary diagnostic test in children with acute ataxia and suspected of having a CNS infection, or in cases with a negative CT brain scan in which intracranial midline tumour is a likely possibility.

Key words: Cerebrospinal fluid – Protein electrophoresis – Acute cerebellar ataxia – Medulloblastoma – Astrocytoma – Pontine glioma

Introduction

Acute cerebellar ataxia is a well-described syndrome characterized by the sudden onset of severe ataxia, often shortly after a non-specific infectious disease. Intention tremor, abnormal eye movements (nystagmus), hypotonia, irritability and vomiting are less frequent manifestations. It affects primarily children between one and five years of age. In most of the cases complete recovery occurs within one week to six months (Weiss and Carter 1959; Bell and McCormick 1975; Weiss and Guberman 1978). The CSF is usually normal although a mild pleocytosis or a modest increase of total protein can occur. The CSF protein pattern has been reported to be normal (Weiss and Guberman 1978).

In patients with intracranial midline tumours the results of electrophoretic CSF studies by agar gel electrophoresis are inconsistent (Wieme 1959; Bauer and Habeck 1963; Lowenthal 1964; Frick 1966; Schmidt 1968). The introduction of computerized tomography (CT brain scan) has brought about a 60% reduction in the use of lumbar puncture as a diagnostic procedure (Ferry 1980). CT has become the diagnostic method of choice since it supplies direct evidence of the tumours in the majority of the cases. Usually the information obtained from the lumbar puncture does not justify exposing the child to the potential hazard of tentorial or tonsillar herniation but lumbar puncture is

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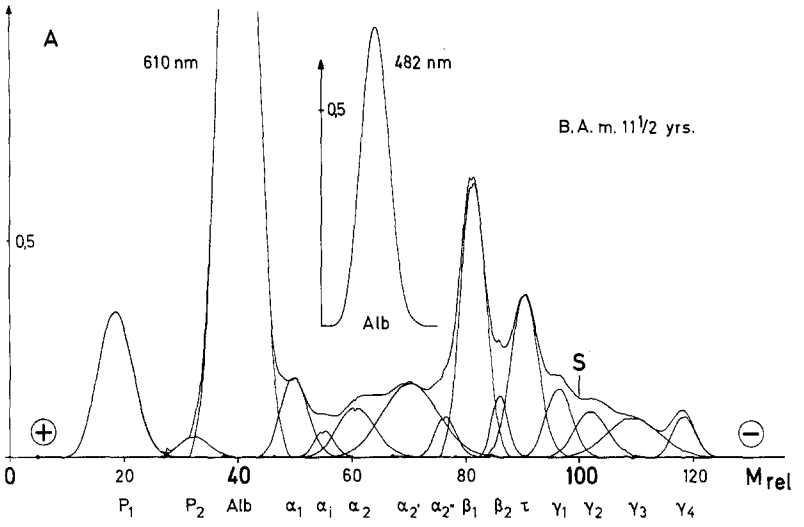

Fig. 1. CSF-protein pattern (absorbance scan and the computer generated contributing protein fractions) in $11\frac{1}{2}$-year-old boy without CNS disease. A = absorption, M_{rel} = relative electrophoretic mobility, P_1, P_2 = prealbumins, *Alb* = albumin, α_1-γ_4 = globulins

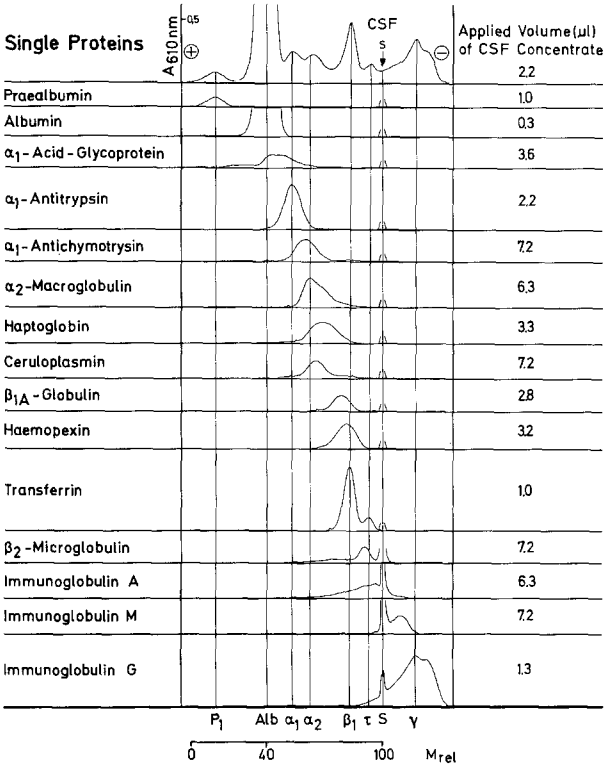

Fig. 2. Identification of the main single plasma proteins of the CSF-phoretogram by the technique of immunofixation electrophoresis (Cawley et al. 1976). The electrophoretic fractions are designated according Fig. 1, S = application slot, M_{rel} = relative electrophoretic mobility referring to the distance of albumin from the application slot. Several electrophoretic fractions are mainly or totally built up by one protein: P_1 *(prealbumin), Alb* (albumin), β_1 *and* τ (transferrins) and γ_3 (IgG), α_1-antitrypsin essentially contributes to the α_1-fraction, α_2-macroglobulin to the α_2 and haptoglobin to α_2'-fraction

indicated when the diagnosis is unclear and when infection is a likely possibility. Intracranial midline tumours and the syndrome of acute cerebellar ataxia of childhood have some symptoms and signs in common, so that problems in differential diagnosis can arise. The purposes of this CSF-study were to:

1. analyse the protein pattern in childhood acute cerebellar ataxia in order to elucidate its pathogenesis;
2. characterize the protein profile in intracranial midline tumours; and
3. compare the patterns of both diseases in the hope that in certain instances some discrimant features could give useful diagnostic information.

Patients and Methods

Clinical Series

Lumbar CSF from 251 patients, 3 months to 15 years of age, was investigated. Twenty-five children suffered from acute cerebellar ataxia of childhood: 18 of these cases were between $1\frac{1}{2}$ and 4 years, 5 between 5 and 8 years of age. The diagnostic criteria according to Bell and McCormick (1975) were:

1. abrupt onset of truncal and gait ataxia several days to several weeks after onset of an exanthem or an nonspecific infectious illness (19 cases, 1 case each after measles and chicken-pox), or no signs of preceding infection (6 cases);
2. no signs of meningeal irration or increased intracranial pressure;
3. dysmetria, intention tremor, hypotonia, decreased muscle stretch reflexes and occasionally nystagmus and slurred speech in addition to ataxia; and
4. normal CSF-findings or only slight elevation of the cell count and total protein concentration.

CT brain scans were performed in 18 children. With the exception of one child who transiently showed a hypodense area in the cerebellum they were all normal. Ataxia lasted 1–4 weeks. In one child it disappeared after 3 days, in two other children it persisted for 6 and 10 weeks, respectively. Only one child did not have total recovery.

In 39 children with an intracranial midline tumour CSF was examined before any treatment was started. Lumbar puncture was performed in the children as a diagnostic procedure when a CSN infection was suspected or when CT brain scan was negative and/or when there was no evidence of increased

Table 1. Determination of the degree of blood-CSF barrier disturbance by changes of the CSF-protein pattern

Protein fractions (%)	Normal range ($\bar{x} \pm 2S$)	Points	
		1 (>2S–3S)	2 (>3S)
Prealbumin (P_1)	8.4– 4.0	< 4.0– 2.8	< 2.8
Albumin	51.9–63.9	>63.9–66.9	>66.9
β_1-globulin	8.9– 5.7	< 5.7– 4.9	< 4.9
τ-globulin	5.6– 2.8	< 2.8– 2.1	< 2.1

One further point was added in each case (a) if γ_1 exceeded the normal upper range (>2.4), (b) for disapperance of γ_4-globulin (a microglobulin), and (c) occurrence of additional plasma proteins α_{1A}-, α_{2A}-globulin

$\bar{x}$ = mean, s = standard deviation. For calculation of points, the changes of the main secretory type proteins (prealbumin P_1, τ) and of the most salient plasma proteins (albumin, β_1-globulin) were considered most reliable. If relative concentrations were between two and three standard deviations of the mean (> 2s–3s) 1 point was given and if the valgues were higher (> 3s) 2 points were given. The deviations scored 1 additional point were due to a more severe injury to the B-CSF-B. The maximum possible sum of points was 12. changes of most of the α-globulins and of γ_2- and γ_3-globulin have not been considered, since they were equivocal (see Table 2 and text).

intracranial pressure. The CT-scan was positive in only 21 out of 28 children on the first investigation. This method failed to demonstrate the tumor in some cases of medulloblastoma and pontine glioma (3 out of 9, and 3 out of 6 children, respectively).

A high proportion of positive results was achieved by angiography (36 out of 39 patients).

The final diagnosis of the brain tumour was made by histologic investigation of tumour tissue after craniotomy or by radiological findings alone. Thirty children showed an infratentorial space-occupying mass (medulloblastoma: 14 cases; cerebellar astrocytoma: 7 cases; brain-stem glioma: 9 cases) and 9 children had a tumour located in the region of the 3rd ventricle (hypothalomic tumour: 4 cases; tumour of the pineal body: 3 cases, craniopharyngioma: 2 cases).

Eighty-six children without a CNS-disease in whom lumbar puncture was performed to exclude meningitis served as controls. For details of selection of the cases see Siemes et al. (1975).

For comparison, CSF from another 61 children with aseptic meningitis and 40 children with bacterial meningitis was investigated. The samples were taken on the day of diagnosis. During the initial stage of these diseases, the protein pattern of moderate and severe blood-CSF-barrier (B-CSF-B), respectively, disturbance can be demonstrated (Siemes et al. 1980).

Laboratory Methods

Total CSF protein was determined by the Biuret-method (Biochemica-Test-Combination, Boehringer, Mannheim). Quantitative analysis of the protein fractions was performed in agarose gel as previously described in detail (Siegert and Siemes 1977). The procedure comprised the following steps: concentration of CSF by ultrafiltration in collodion tubes; refractrometric estimation of the protein content of the concentrate; application of about 40 µg protein to the agarose gel film (8 µg/ml); staining of the protein with Amidoblack 10B after electrophoresis; photometric scanning of albumin at the wavelength of 482 nm and of prealbumin and the globulins at 610 nm (wavelength factor 3.7). The phoretograms were evaluated by means of an analogue computer (modified Du Pont Curve resolver 310). Gaussion curves generated by the computer were adjusted successively to the single protein fractions until the superposition curve of all Gaussians fitted the scanning curve. The percentage of each proteins (% of total protein) was calculated automatically. The relative electrophoretic mobility of the protein fractions was determined by comparing their horizontal position to the distance of albumin from application slot. In children without CNS disease 15 regular protein fractions can be characterized in relation to total protein and electrophoretic mobility (Fig. 1). Pathological phoretograms were evaluated on the basis of the normal protein profile: when necessary, additional fractions were introduced.

Hand-drawn Gaussian curves can serve as a substitute for computerized analysis of the phoretograms. The area under the curves are measured by means of an integrator curve. With some experience the normal and abnormal patterns can be differentiated by visual inspection.

Most of the proteins that build up the different fractions of the phoretogram can be identified by immunofixation performed after standard electrophoresis by layering the antiserum over the agarose gel (Cawley et al. 1976). The analysis of 20 pooled CSF-samples is shown by Fig. 2.

For determination of the degree of B-CSF-B disturbance, a scale from 0 to 12 was applied (Table 1). This scale was based on the sterotyped deviations of the protein pattern in a case with a lesion of the B-CSF-B (Siemes et al. 1980).

Results

A) Acute Cerebellar Ataxia

Ten out of the 25 children with acute cerebellar ataxia showed a slightly elevated CSF cell count (8 cases 4–50 cells, one child 93 cells, one child 160 cells per mm^3). In 3 cases total protein concentration was raised (410–900 mg/l, normal 100–350 mg/l). Fig. 3 shows the changes of CSF-protein fractions in a child with acute cerebellar ataxia. The profile in all children is characterized by significant change of 8 fractions: slight decrease of prealbumin (P_1), α_1-, α_2'-, α_2''-, β_2- and γ_1 and γ_4-globulin and marked elevation of albumin (Table 2). However, these deviations mean only a minor abnormality if they are compared with the changes observed in the children with acute aseptic or bacterial meningitis who demonstrate the respective protein patterns of moderate or severe B-CSF-B disturbance. Except for the patients with acute meningitis, there was no elevation of α_2-globulin (mainly built up by the large protein α_2-macroglobulin) and of γ_3-globulin (consisting of IgG, see Fig. 2).

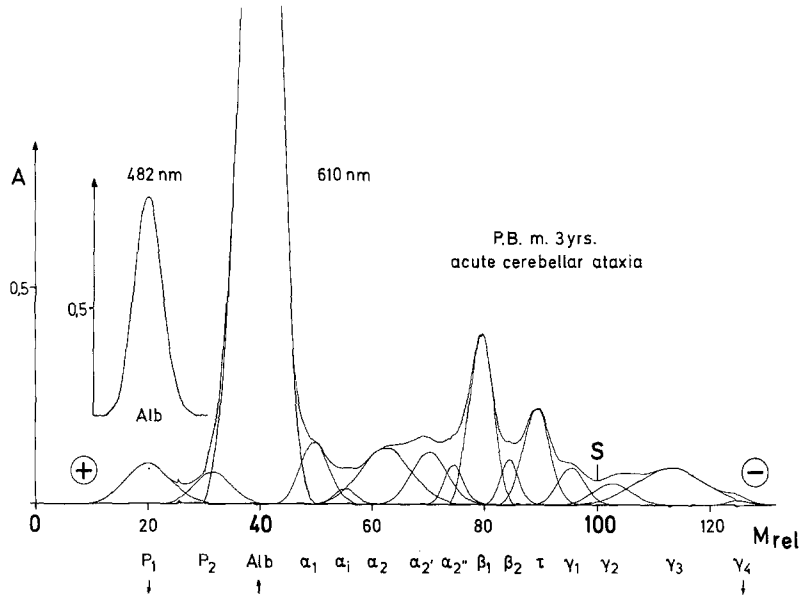

Fig. 3. CSF-protein profile in a 3-year-old boy with acute cerebellar ataxia showing slight disturbance of the B-CSF-B. Increase or decrease from the normal percentage of the total protein is indicated by ↑ or ↓

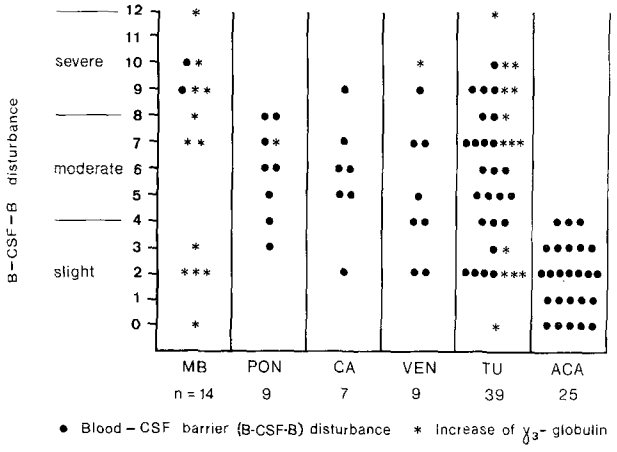

Fig. 4. Degree of B-CSF-B disturbance and frequency of occurrence of increased γ_3-globulin in intracranial midline tumours and acute cerebellar ataxia of childhood; *MB* = medulloblastoma, *PON* = pontine tumour, *CA* = cerebellar astrocytoma, *VEN* = tumours in the region of the 3rd ventricle, *TU* = all tumour patients, *ACA* = acute cerebellar ataxia. Scores refer to the score-system of Table 1

B) Children with Brain Tumours

Cell count was elevated in 10 out of the 14 children with medulloblastomas, in 2 of the 9 children with pontine gliomas and none of the remaining tumour patients. Tumour cells were identified in 6 of the children with a medulloblastoma and none of the other children.

Total protein was frequently increased in association with a medulloblastoma (12 out of the 14 cases), rarely in the other tumour patients (4 out of 25).

The significant changes of the protein pattern in the children with brain tumours as a whole apply to nearly all the fractions, giving a pattern which is similar to that in acute non-bacterial meningitis. However, several proteins are more markedly involved [prealbumin (P_1), albumin, α_1-, α_2'-, β_1-, and τ-globulin] indicating a moderate-to-severe B-CSF-B disturbance. To our surprise the increase of the α_2-fraction (mainly α_2-macroglobulin, see Fig. 2) observed in acute aseptic meningitis was absent in the tumour patients. Its occurrence in cases of acute meningitis could be explained by the strong "acute-phase reaction" in the plasma which is reflected in the CSF. Fig. 4 demonstrates the two most important aspects of the protein profiles: the degree of B-CSF-B disturbance estimated according Table 1, and the frequency of increased γ_3-globulin (IgG). Most of the children with pontine gliomas, cerebellar astrocytomas and tumours around the 3rd ventricle revealed a moderate B-CSF-B disturbance, whereas half the patients with medulloblastomas showed a marked disturbance. Figs. 5 and 6 illustrate the different degree of barrier involvement.

The children with medulloblastomas revealed a marked increase of γ_3 which comprises most of the IgG (Table 2). In 5 cases, oligoclonal γ-fractions appeared (Fig. 6). In one child, 1 fraction; in 3 children, 3 fractions; and in 1 child, 6 fractions were found. Oligoclonal γ-globulin amounted to 1.9–12.4% of total protein. Four of these children were erroneously considered to have aseptic meningitis for several weeks since they had meningism and a moderate pleocytosis (100–220 cells per mm^3) on admission to hospital.

The tumours located around the 3rd ventricle caused a more severe decrease of prealbumin, compared with the other tumour groups (Table 2).

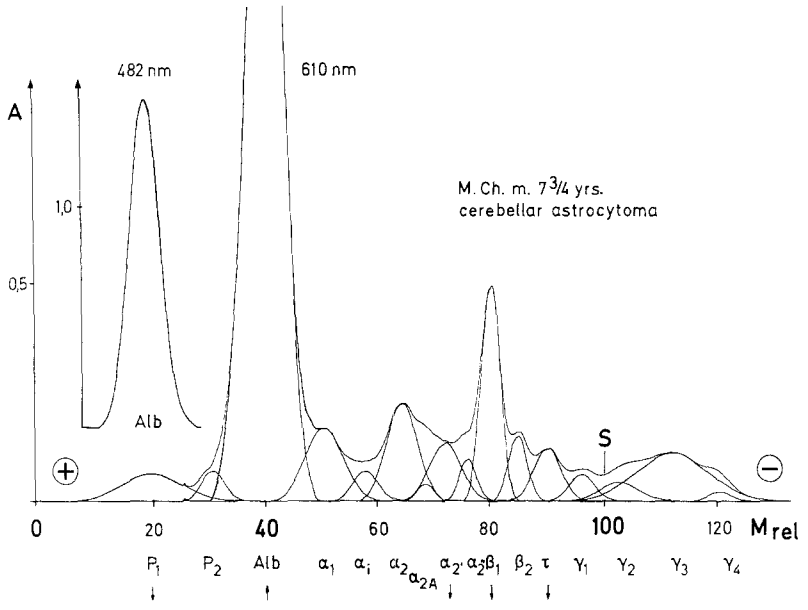

Fig. 5. CSF-protein profile in a $7\frac{3}{4}$-year-old boy with a cerebellar astrocytoma revaling marked B-CSF-B disturbance; there is no increase in γ-globulin. For explanation of the symbols see Figs. 1 and 2; α_{2A} is an additional plasma protein fraction due to a more marked disturbance of the B-CSF-B

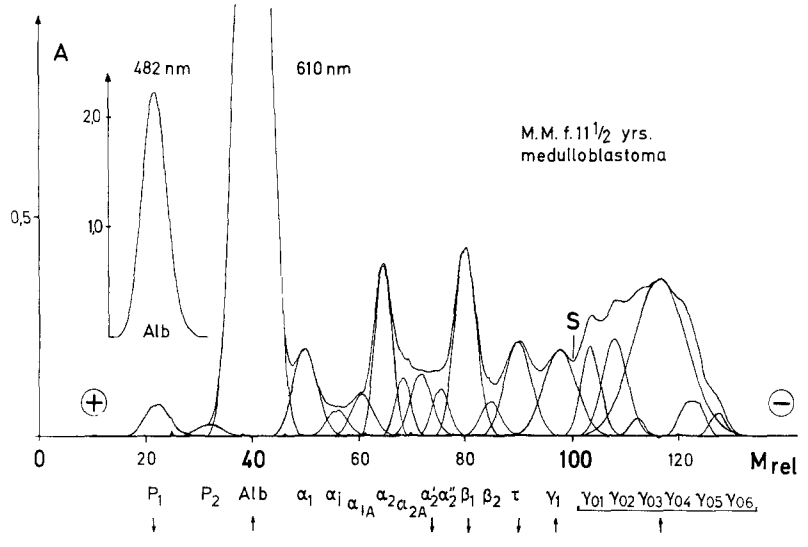

Fig. 6. CSF-protein profile in a $11\frac{1}{2}$-year-old girl with a medulloblastoma showing a severe disturbance of the B-CSF-B and a marked increase of γ-globulin associated with the occurrence of oligoclonal γ-globulins; these fractions consist of IgG (identification by immunofixation electrophoresis according to Cawley et al. 1976); for explanation of the symbols see Figs. 1 and 2: α_{1A} and α_{2A} are additional plasma protein fractions due to severe disturbance of the B-CSF-B

C) Differentiating Acute Cerebellar Ataxia and Brain Tumours by CSF-Protein Analysis

The slight changes of the protein profile in the children with acute cerebellar ataxia and the marked deviations in the children with brain tumours result in significant differences of prealbumin (P_1), albumin, α_{2A}-, β_1-, τ- and γ_3-fraction between these disease groups (Table 2).

With the exception of one case, all children with a brain tumour showed the protein profile of a B-CSF-B lesion (Fig. 4). The values representing different degrees of disturbance of the B-CSF-B partially overlap in the tumour patients and the children with acute cerebellar ataxia. Since the changes were only slight in the latter, a moderate or severe deviation indicate that a tumour is more likely.

The γ_3-fraction was above the upper limit of normal in nearly all cases of medulloblastoma, but rarely in the other tumour patients. Oligoclonal γ-fractions only occurred in association with medullablastomas. Therefore, a protein pattern with the signs of moderate-to-severe B-CSF-B disturbance without increase of γ-globulin characterizes the children with pontine gliomas, cerebellar astrocytomas, and tumours around the 3rd ventricle.

In 9 out of the 14 cases with medulloblastomas there was a moderate to severe disturbance of the B-CSF-B. On the other hand, a marked increase of γ_3-globulin

Table 2. Results of CSF-electrophoresis: Relative concentration and electrophoretic mobility of protein fractions

Protein fractions	I. Controls ($n = 86$) $\bar{x}$, (SD)	II. Acute aseptic meningitis, encephalitis ($n = 61$) $\bar{x}$, (SD)	III. Acute bacterial meningitis ($n = 40$) $\bar{x}$, (SD)	IV. Acute cerebellar ataxia ($n = 25$) $\bar{x}$, (SD)	Significant difference[a] I – IV	Significant difference[a] II – IV	V. Tumours ($n = 39$) $\bar{x}$, (SD)	Significant difference[a] I – V	Significant difference[a] II – V	Significant difference[a] IV – V
Prealbumins										
P_1	6.2 (1.3)	2.9 (1.5)	1.3 (1.2)	4.3 (1.8)	+	+	2.0 (1.7)	+	+	+
P_2	1.2 (0.5)	1.0 (0.6)	0.8 (0.5)	1.0 (0.4)			0.8 (0.5)	+		
Albumin	58.5 (3.2)	65.2 (6.4)	61.7 (7.2)	65.5 (5.2)	+		70.3 (7.0)	+	+	+
Globulins[b]										
α_1	3.8 (0.7)	3.2 (1.0)	3.8 (1.2)	2.8 (0.6)	+		2.5 (0.8)	+	+	
α_i	0.9 (0.2)	0.9 (0.3)	1.2 (0.5)	0.8 (0.3)			0.9 (0.3)			
α_{iA}	0.0 (0.0)	0.0 (0.1)	0.2 (0.3)	0.0 (0.0)			0.1 (0.2)	+		
α_2	3.6 (0.8)	4.3 (1.1)	5.7 (2.1)	3.6 (1.2)			3.4 (1.3)		+	
α_{2A}	0.0 (0.0)	0.3 (0.4)	0.7 (0.7)	0.0 (0.0)		+	0.2 (0.3)	+		+
α_2'	3.9 (0.8)	2.8 (1.0)	3.1 (1.6)	2.6 (1.0)	+		2.3 (1.2)	+	+	
α_2''	1.5 (0.4)	1.1 (0.3)	1.4 (0.4)	1.0 (0.3)	+		1.0 (0.3)	+		
β_1	7.5 (0.8)	6.3 (1.0)	6.0 (1.4)	7.4 (1.4)		+	5.6 (1.2)	+	+	+
β_2	1.8 (0.6)	1.5 (1.1)	1.3 (0.5)	1.2 (0.5)	+		1.2 (0.5)	+		
τ	4.5 (0.8)	3.1 (1.0)	2.5 (1.3)	4.0 (1.1)		+	2.5 (1.1)	+	+	+
γ_1	1.6 (0.4)	1.3 (0.4)	2.3 (1.2)	1.3 (0.4)	+		1.1 (0.6)	+		
γ_2	1.4 (0.5)	1.6 (0.7)	1.8 (0.8)	1.3 (0.4)			1.1 (0.6)	+	+	
γ_3	2.8 (0.9)	4.2 (1.2)	5.7 (3.6)	2.6 (1.0)		+	4.7 (2.6)	+		+
γ_4	0.8 (0.4)	0.3 (0.3)	0.2 (0.3)	0.5 (0.5)	+		0.3 (0.5)	+		

$\bar{x}$ = mean value; SD = standard deviation of the mean; n = number of patients

[a] Significant difference ($P < 0.01$, U-test of Mann-Whitney)

[b] α_{iA} and A_{2A} = additional plasma proteins due to B-CSF-B disturbance, oligoclonal γ-globulins are included in γ_3

occurred in association with only a slight disturbance of the B-CSF-B. An elevated γ_3-fraction was observed in only two patients in the other tumour groups and in none of the cases of acute cerebellar ataxia. Therefore this finding—and even more important, the occurrence of oligoclonal γ-globulin—strongly points to a medulloblastoma.

Discussion

The protein changes in the CSF which we observed in children with acute cerebellar ataxia and intracranial tumours may be explained as:

1. the result of a blood-CSF barrier (B-CSF-B) disturbance;
2. secondary to reduced CSF-flow caused by a mechanical obstruction of the CSF-pathways; or
3. the consequence of abnormal local production of proteins within the CSN.

Under normal physiological conditions the CSF-protein pattern is characterized by 3 specific fractions: prealbumin, τ-globulin and γ_4 (γ-trace)-globulin (Fig. 1). Prealbumin is actively secreted into the CSF, the τ-globulin is a locally produced transferrin variant, and the γ_4-fraction is built up by a microglobulin that cannot be separated in the serum profile (Siemes et al. 1975).

Most lesions of the CNS are associated with a disturbed function of the blood-CSF barrier (B-CSF-B), the regulatory interface which separates the blood from the brain and the CSF. In acute infectious diseases and malignant tumours of the CNS, the permeability of the B-CSF-B for proteins is increased, resulting in an elevated protein concentration of the CSF. A concomitant change in the CSF-protein pattern to one more akin to the serum type is a characteristic finding in these disorders (Schultze and Heremans 1966). It can easily be observed that the above mentioned protein fractions which characterize the CSF decrease gradual-

VI. Medullo-blastomas ($n = 14$) $\bar{x}$, (SD)	Significant difference[a] IV – VI	VII. Pontine tumours + cerebellar astrocytomas ($n = 16$) $\bar{x}$, (SD)	Significant difference[a] I – VII	Significant difference[a] IV – (VI + VII)	VIII. Tumours around 3rd ventricle ($n = 9$) $\bar{x}$, (SD)	Electrophoretic mobility Mrel (all children) $\bar{x}$, (SD)
2.2 (1.8)	+	2.5 (1.6)	+	+	0.7 (0.4)	19.7 (1.2)
0.9 (0.6)		0.8 (0.5)	+		0.8 (0.3)	30.0 (1.0)
68.8 (8.6)		71.3 (5.0)	+	+	70.7 (7.7)	40
2.7 (0.9)		2.6 (0.7)	+		2.2 (0.5)	49.7 (0.9)
0.8 (0.3)		0.9 (0.4)			0.9 (0.3)	56.4 (1.0)
0.1 (0.3)		0.0 (0.2)		+	0.0 (0.0)	
3.4 (1.2)		3.4 (1.2)			3.2 (1.5)	63.1 (1.1)
0.3 (0.4)	+	0.1 (0.2)	+		0.1 (0.2)	
2.0 (1.2)		2.2 (1.0)	+		2.8 (1.4)	68.3 (1.2)
1.0 (0.3)		0.9 (0.3)	+		1.1 (0.3)	75.8 (0.7)
5.1 (1.2)	+	5.7 (0.7)	+	+	6.3 (1.7)	80.1 (1.0)
1.1 (0.4)		1.0 (0.3)	+		1.6 (0.6)	85.0 (1.0)
2.4 (1.1)	+	2.4 (0.8)	+	+	2.9 (1.5)	90.2 (0.9)
1.2 (0.7)		1.0 (0.3)	+		1.3 (0.6)	96.6 (1.1)
1.1 (0.9)		1.1 (0.4)	+		1.3 (0.6)	103.6 (1.2)
6.7 (2.9)	+	3.6 (1.2)		+	3.5 (2.1)	113.5 (1.7)
0.2 (0.3)	+	0.3 (0.4)	+	+ .	0.6 (0.8)	124.3 (2.2)

ly according to the intensity of the lesion (Siemes et al. 1980). With mechanical obstruction of CSF-flow the barrier sites located distally to the obstruction are in prolonged contact with the CSF, leading to higher CSF-protein levels and a change in the protein pattern to one more similar to that in the plasma (Matiar-Vahar 1968). At present it is impossible to determine from the changes of the protein profile whether increased barrier permeability or impeded CSF-flow is responsible for the abnormality.

Subacute or chronic CNS infections are associated with an increase of γ-globulin in relation to the other fractions. In cases with a simultaneous B-CSF-B disturbance the elevation is out of proportion to that which might be expected by this mechanism alone. The occurrence of oligoclonal γ-globulin in the CSF is a most important feature of local immuno-globulin synthesis within the CNS (Siemes et al. 1977).

The pathogenesis of acute cerebellar ataxia is unknown. It may occur spontaneously or follow a recognized viral or non-viral illness: varicella, ECHO, or Coxsackie infections, mycoplasma pneumoniae infection, or a non-specific infectious disease. The anatomico-pathological correlates are unknown, since virtually all patients recover but it has been ascribed to aseptic encephalitis with primary involvement of the cerebellum. A toxic or an autoimmune reaction has also been proposed (Bell and McCormick 1975). In acute bacterial and viral infections of the CNS the increased vascular permeability to proteins is induced by a vasculitis. The finding of only a slight impairment of the B-CSF-B in our patients with acute cerebellar ataxia suggests that the cerebral blood vessels are involved to a lesser degree than is the case in acute aseptic meningitis. Since symptoms and signs point to the cerebellum as the main site of the illness, a more localized infection of the CNS seems to be the most probable cause of acute cerebellar ataxia. Peters et al. (1978) reported that in two cases of varicella-associated acute cerebellar ataxia varicella-zoster antigens were

found in CSF cells. The authors concluded that direct viral invasion of the CNS plays an important part in the pathogenesis of varicella cerebellar ataxia and that their data rule out a single immune-medicated mechanism. In our patients there is no evidence of local immunoglobulin production within the CNS, pointing against a hyperimmune reaction: the concentration of γ-globulin in relation to the other fractions was within normal limits and no oligoclonal γ-globulin was present.

In human malignant brain tumours there are three potential routes for vascular leakage of protein: i.e., interendothelial gaps, transport by cytoplasmatic vesicles, and fenestrae. Long (1970) found a number of widely patent endothelial cell-junctions which would allow free passage of proteins. He also observed an elevation in the number of cytoplasmatic vesicles. According to the findings of Waggener and Beggs (1976) fenestrae also appear to play a role. Extravasated serum accumulates within the extracellular space of the tumours and the surrounding white tissue (Hossmann et al. 1979). The CSF reflects the protein composition of the brain extracellular fluid since the exchange between both fluids is not restricted by a barrier (Brightman and Reese 1969). On the other hand a decreased CSF-turnover due to partial or total obstruction of the CSF-pathways by the tumour can lead to an elevated concentration of CSF-protein and to a concomitant change of the protein pattern. Depending on the type and localization of the tumour, one of the two factors probably plays a major role. In our study the B-CSF-B was most severely impaired in some of the patients with medulloblastomas. This can easily be explained by the histologic features of this rapid growing tumour (Long 1970; Waggener and Beggs 1976). The permeability of the B-CSF-B for proteins is moderately increased in the majority of the children with pontine gliomas, cerebellar astrocytomas and tumours around the 3rd ventricle.

At present the questions as to why some of the patients with medulloblastoma reveal only a slight B-CSF-B disturbance but show a marked increase of γ_3-globulin (IgG), and why oligoclonal γ-globulins occur in some of the patients with medulloblastoma, cannot be answered. These abnormal immunoglobulins may reflect hyperimmunization due to persistance of viruses inducing a prolonged viral infection. The fact that in some of these cases the associated CSF pleocytosis was more marked than in the other children without oligoclonal γ-globulins could support this assumption. On the other hand, the occurrence of oligoclonal gammaglobulins in medulloblastomas could mean local synthesis of antibodies caused by tumour tissue components without secondary viral infection.

The observation that prealbumin was markedly lower in cases with a tumour located around the 3rd ventricle than in the other tumour groups could be explained by partial obstruction of the CSF-pathway in that region since prealbumin is actively secreted by the choroid plexus, mainly into the CSF of the lateral ventricles.

Problems in differential diagnosis can arise in children with acute ataxia which is a cardinal sign both in patients with acute cerebellar ataxia and those with intracranial midline tumours. Only on rare occasions is ataxia the presenting manifestation of acute bacterial or aseptic meningits, and other more characteristic signs soon develop (Schwarz 1972; Yabeck 1973; Bell and McCormick 1975). If lumbar puncture is considered necessary despite the potential hazards, CSF-protein electrophoresis should be performed in addition to investigation of cells and total protein content. Distinction between the syndrome of acute cerebellar ataxia and intracranial midline tumours can be made by CSF-electrophoresis in a high percentage of cases. Several of our children with a brain tumour revealed an abnormal CSF-protein pattern though CT brain scan was considered normal at the first investigation. In doubtful cases the electrophoretic findings can be helpful in deciding how far diagnostic procedures should go. In the case of a negative CT brain scan, a CSF pattern of a moderate or severe B-CSF-B disturbance could support the decision for a more invasive diagnostic procedure. In a child with acute ataxia the detection of oligoclonal γ-globulin strongly points to a medulloblastoma, since this is an uncommon finding during the acute stage of a CNS-infection. On the other hand, a normal CSF-pattern would point away from a brain tumour.

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