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ORIGINAL COMMUNICATION

Determinants of lumbar CSF protein concentration

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Abstract *Objective* To determine factors influencing the wide variation of protein concentration in lumbar cerebrospinal fluid (CSF). *Methods* Patient variables with potential influence on spinal CSF flow and resorption were measured in different patient settings and compared with albumin and IgG CSF/serum quotients. *Results* In patients whose diagnostic lumbar puncture produces normal CSF the albumin quotient increased with body mass index (r = 0.408), abdominal circumference (r = 0.399), and body weight (r = 0.317), age-corrected with partial correlation. Body motion before lumbar puncture showed only marginal influence on albumin quotient. In patients with radiculography the albumin quotient decreased with iodine contrast medium elimination from spinal subarachnoid space (r = –0.598) and increased with narrowing of lumbosacral spinal canal (r = 0.515). *Conclusion* Correlation of albumin quotient with body mass index and related variables may be mediated by spinal CSF resorption, which should be impaired in overweight patients with elevated venous pressure. Negative correlation of albumin quotient with iodine resorption from spinal CSF supports this assumption. Correlation of albumin quotient with narrowing of lumbosacral canal should be due to slowed spinal CSF flow which does increase protein concentration. Tested variables explain part of variation of CSF protein concentration. Other variables like blood-CSF barrier permeability and pulsatile spinal CSF flow should have additional influence.

Key words CSF protein concentration · variation · spinal CSF flow · spinal CSF resorption

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Introduction

Albumin and IgG concentrations in lumbar CSF vary widely; even under normal conditions the span is 4–7 fold [22]. Determinants of the wide variation are individual differences of blood protein levels, of permeability of blood-CSF barrier, of CSF flow, and of CSF resorption [7, 23, 28]. Only the first of these can be measured and is accounted for by the CSF/serum quotient of albumin and IgG. To identify further determinants of CSF protein concentration we tested patient variables relating to spinal CSF flow and to spinal CSF resorption. Specifically we measured indicators of length and width of spinal canal, of thoraco-abdominal pressure changes by body motion, and of iodine contrast medium transfer from subarachnoid to venous compartment. Measures were correlated with albumin and IgG quotients. The aim was to better understand the wide variation of CSF protein concentrations, which ultimately could help delineate pathological conditions more precisely.

Patients and methods

Patients in whom a diagnostic lumbar puncture (LP) or lumbosacral radiculography was clinically indicated, were grouped into 4 study settings after giving informed consent. Altogether 144 patients (78 fe-

males, 66 males, age 18–87 years) participated. The university hospital ethical committee had no objection to the study.

Group I patients

In 56 patients with normal CSF the following variables were noted:

a) The distance of the LP site to the foramen magnum was taken as indicator of the length of the spinal CSF path to puncture site. The length of spinal CSF path may influence CSF flow.
b) Body weight has been reported to correlate inversely with spinal canal width [15]. Spinal canal width should influence CSF flow. Body mass index and maximal supine abdominal circumference were included as related variables.
c) Body motion induces spinal CSF flow [4]. Body motion was estimated by inquiring from patients time spans spent lying down, sitting, and standing or walking during six hours before LP. Assuming less CSF motion at rest, lying down was coded with fictitious value 1, sitting with 2, and standing or walking with 3. Motion values were added according to respective time spans.

Lumbar puncture was performed in a relaxed sitting position. CSF was considered normal at cell count 0–4/µl, no more than 200 erythrocytes/µl, albumin < 40 mg/dl, albumin CSF-serum quotient < 6.5 below age 45 years, and < 8 at older age, IgG index < 0.65). CSF was sampled in 3–4 fractions of 3–4 ml, to calculate concentration gradients as further variable [1, 10, 25, 31].

Group II patients

Influence of thoraco-abdominal pressure alterations on CSF protein concentration was also tested with change of body position or with the Valsalva manoeuvre [4, 19, 30] and sequential CSF sampling. Samples were taken without delay. Pathological CSF was included because the point of interest was intraindividual comparison of sequential samples. Patients with CSF containing > 200 erythrocytes/µl were excluded:

a) In 34 patients 2–3 sequential lumbar CSF samples of 3–4 ml were taken in the sitting position, after which the patient lay down in a lateral position, when further 2–3 samples were collected.
b) In 22 patients 2–3 lumbar CSF samples of 3–4 ml were taken in the sitting position. Then patients coughed deeply, after which a further 2–3 samples were collected.

Group III patients

Elimination of iodine contrast from spinal CSF into brachial venous blood was measured as an indicator of spinal CSF resorption in 32 patients who were undergoing lumbosacral radiculography because of low back pain:

Lumbar puncture was performed in a lateral decubitus position. After collecting 3–5 ml CSF the contrast medium iopamidol (Solutrast® 250M, Byk Gulden, Konstanz, Germany) was injected into the subarachnoid space until there was sufficient filling. Slightly pathological CSF was accepted as inherent in this patient selection (albumin quotient < 15, cell count < 10/µl, IgG index < 0.65). Patients with CSF containing > 200 erythrocytes/µl or with incidental sub- or epidural contrast deposition were excluded from study. Radiculograms were taken in upright postero-anterior and lateral views. Cubital vein blood samples were taken before radiculography and 30, 60, 120, 180 minutes after the injection of contrast medium. Later sample times were not considered because the point of interest was spinal resorption [17]. After x-ray examination patients were kept in a supine position, about 30 degree upright in bed.

CSF samples of all patients were handled in the same way: Cells were counted in a Fuchs-Rosenthal chamber within 40 minutes from sampling. Proteins were determined with a Behring nephelometer analyser (Dade Behring, Marburg, Germany), total protein after TCA precipitation, albumin and IgG after binding to polyclonal antibody and beta-trace protein after binding to polystyrene particles coated with immunoaffinity-purified polyclonal rabbit antibodies against human beta-trace protein. The same proteins were measured in serum samples obtained at time of LP. The mean between run variations of control measures in CSF were 5.2 % for total protein, 4 % for albumin, and 2.8 % for IgG, in serum 4.2 % for total protein, 4.3 % for albumin, and 3.2 % for IgG; for beta-trace protein variation was 7.6 %. CSF albumin and IgG controls were run at medium concentration ranges, serum controls at low, medium, and high ranges.

The relation between CSF protein concentrations and patient variables was analysed with CSF/serum quotients of albumin and IgG concentrations (QAlb, QIgG). CSF protein concentrations themselves are reliable diagnostic measures, while quotients in addition reflect CSF albumin and IgG independent of serum concentrations [24, 28]. Quotients are adequate study parameters, because the aim was to identify influences on CSF protein concentration other than influence of serum proteins.

Blood samples from patients having radiculography were kept frozen at –20 °C until the measuring of iodine concentration with an x ray fluorescence analyzer (Schering AG, Berlin, Germany). Mean between run variation of control measures was < 5 %. Radiculograms were evaluated from lumbar vertebra 2 down to the sacrum for narrowing of subarachnoid space (see Table 3 for measure of narrowing).

Statistics

The relations of patient variables with CSF protein values were tested with correlation and significance test, and with partial correlation to correct for interfering variables. Concentration gradients of sequential samples were assessed with general linear model (glm), and t test. All p values are two-sided. Calculations were done with SPSS.

Results

Patient variables and protein concentrations of 56 patients with normal CSF (group I) are shown in Table 1. Significant relations were found between albumin quotient and age ($r = 0.277$, $p = 0.039$), and age-corrected with partial correlation between QAlb and body mass index ($r = 0.408$, $p = 0.002$), maximal abdominal circumference ($r = 0.399$, $p = 0.009$. Fig. 1), and body weight ($r = 0.317$, $p = 0.019$). Influence of body mass index on variance of albumin quotient amounted to 16 %. No relation was detected between QAlb and body length, lumbar puncture site, distance of LP site to foramen magnum, body motion one and six hours before LP, and between QIgG and patient variables.

Sequential CSF samples in patient group I showed linear decrease of CSF protein concentration ($p < 0.000$, glM), amounting to 1.5 % per ml CSF for albumin and 1.1 % for IgG. Beta-trace protein concentration increased linearly ($p = 0.006$, glM) by 0.4 % per ml CSF. Concentration gradient of albumin quotient in sequential samples did not correlate with albumin quotient, and showed only a tendency towards a negative correlation with body motion during 1 hour (and 6 hours) before LP ($r = –0.296$, $p = 0.07$).

In group II patients change of sitting to lying position (group II a. Table 2) with sequential CSF sampling

Table 1 Patient variables and CSF values in 56 patients with normal CSF (group I).

Patient group I	Number	Median	Range
Gender	32 female, 24 male		
Age in years	56	50.5	18–80
Lumbar puncture site	44		L3/4 in 5 patients L4/5 in 20 patients L5/S1 in 19 patients
Body length (cm)	55	169	151–188
Distance LP site – occiput (cm)	44	65	55–84
Body weight (kg)	56	65.85	52–116
Body mass index (kg/m^2)	55	23.3	17.4–34.7
Abdominal circumference (cm)	43	81	64–118
Body motion 1 hour before LP	44	2.14	1–3
CSF total protein (mg/dl)	56	40.0	16.8–69.1
CSF albumin (mg/dl)	56	22.3	8.3–39.6
QAlb x 10^{-3}, age < 45 years	19	4.9	3.4–6.4
QAlb x 10^{-3}, age > = 45 years	37	6.1	2.5–7.8
QAlb gradient*	56	0.09	–0.17–0.38
CSF IgG (mg/dl)	56	2.4	1.1–8.4
IgG index	56	0.45	0.31–0.63
CSF beta trace protein (mg/dl)	56	1.6	0.9–3
CSF total protein-(albumin+IgG+ beta-trace protein) (mg/dl)	56	14.2	1.2–37.2
CSF cells /µl	56	1	0–4

* QAlb gradient is QAlb of sample 1 – sample 2/sample volume.

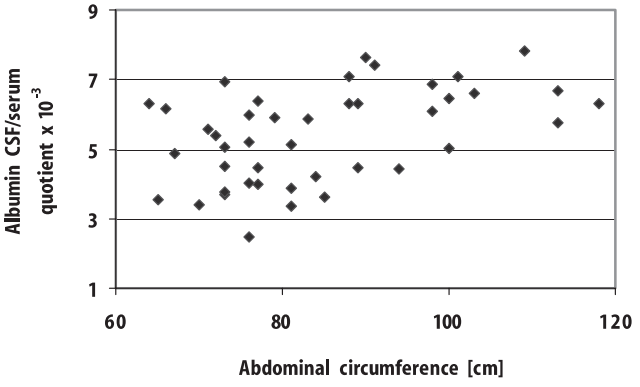

Fig. 1 Relation of QAlb and abdominal circumference (cm) in 43 patients (group I) with normal CSF (correlation coefficient r = 0.479, p = 0.0002. Corrected for age with partial correlation r = 0.399).

caused a small but significant increase of albumin quotient only in the sample after lying down (p < 0.000, glm). Valsalva manoeuvre by coughing (group II b. Table 2) with sequential CSF sampling flattened gradient of albumin quotient significantly between samples before and after cough (p = 0.002, glm).

In radiculography patients (group III. Table 3) albumin quotient correlated negatively with iodine concentration in venous blood at 60 minutes (r = –0.396, p = 0.03), at 120 minutes (r = –0.404, p = 0.027), and at 180 minutes (r = –0.598, p = 0.002. Fig. 2), corrected for influence of spinal canal narrowing with partial correlation. At 30 minutes correlation was not significant

Table 2 Decrease of albumin quotient in sequential CSF samples, collected without delay. In 34 patients (group II a) CSF samples 1–3 were taken in sitting position and samples 4–6 in lateral decubitus position. In 22 patients (group II b) all CSF samples were taken in sitting position, patients coughed deeply after third sample. Linear decrease of QAlb is reverted in group II a between samples 3 and 4 after lying down (p = 0.000, glm), and flattened in group II b between samples 3 and 4 after coughing (p = 0.002, glm). Effect is limited to one sample.

	Patient group II a	Patient group II b
Number, Gender	19 female, 15 male	14 female, 8 male
Age in years (Median, Range)	44, 21–86	44.5, 26–87
CSF	Mean ± SD	Mean ± SD
QAlb x 10^{-3}, sample 1	7.3 ± 3.6	7.6 ± 2.4
QAlb x 10^{-3}, sample 2	6.9 ± 3.4	6.6 ± 2.0
QAlb x 10^{-3}, sample 3	6.4 ± 3.3	6.0 ± 1.9
QAlb x 10^{-3}, sample 4	6.7 ± 3.3	5.8 ± 1.8
QAlb x 10^{-3}, sample 5	6.2 ± 3.1	5.2 ± 1.5
QAlb x 10^{-3}, sample 6	6.1 ± 3.0	4.4 ± 1.3
IgG index	0.57 ± 0.32	0.6 ± 0.42
Cells/µl (median, range)	4 ± 4	4 ± 7

Table 3 Patient variables in 32 patients with radiculography (group III). Venous iodine concentration is at 180 minutes after lumbar subarachnoid iopamidol application, normalized to 180 minutes. Venous iopamidol concentration is calculated from iodine concentration, then extrapolated to total blood volume (using a nomogram based on age, gender, and body weight [11]) and related to iopamidol dose applied into lumbosacral subarachnoid space, to give an impression of iopamidol transfer. Lumbosacral canal narrowing is maximal narrowing divided by width of neighbouring normal contrast band, so that 0 is no narrowing and 1 is contrast stop, values of multiple narrow sites are added up.

Patient group III	Number	Median	Range
Gender	13 female, 19 male		
Age (years)	32	56	31–82
Lumbar puncture site	32		L1/2 in 2 patients L2/3 in 6 patients L3/4 in 22 patients L4/5 in 2 patients
Applied Iopamidol (ml)	32	17.75	14–20
Venous iodine concentration at 180 min (mg/l)	31	16.5	0–62.7
Venous iopamidol concentration at 180 minutes (ml/l)	31	61.8	0–229.7
Venous iopamidol at 180 minutes as percentage of applied dose (%)	31	1.4	0–7.4
Lumbosacral canal narrowing	32	0.775	0.01–1.61
Body mass index (kg/m^2)	32	25.5	16.9–40.6
CSF albumin (mg/dl)	32	30.9	15.6–58.5
QAlb x 10^{-3}	32	7.6	3.9–13.8
CSF IgG (mg/dl)	32	3.2	1.7–9.5
IgG index	32	0.45	0.36–0.63
CSF cells /ml	32	1	0–7

(r = –0.254). Albumin quotient correlated positively with narrowing of lumbosacral spinal canal (r = 0.428, p = 0.014. Fig. 3). The influence of iodine- related CSF resorption, corrected for spinal canal narrowing, on variance of albumin quotient amounted to 35 %. Albumin quotient in this group, in which patients with pathological CSF are included, did not correlate with age, body

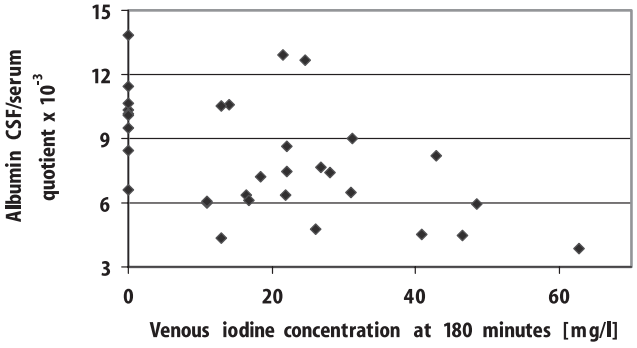

Fig. 2 Relation of QAlb and iodine concentration in venous whole blood (mg/l) at 180 minutes after lumbar subarachnoid iopamidol application in 31 patients (group III) with radiculography (correlation coefficient, r = –0.472, p = 0.006. Corrected for spinal canal narrowing by partial correlation, r = –0.598).

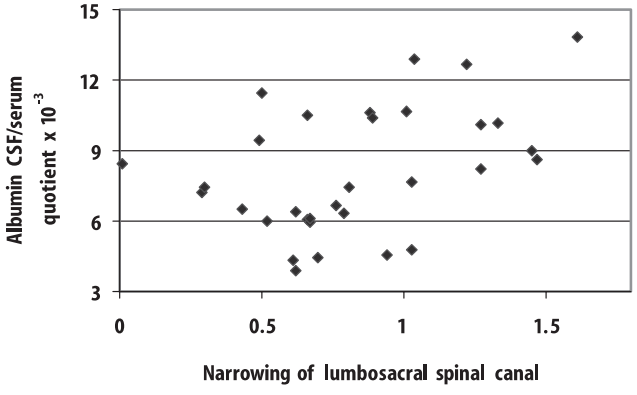

Fig. 3 Relation of QAlb and narrowing of lumbosacral spinal canal on lateral view radiculogram (narrowing is expressed as maximal narrowing divided by width of neighbouring normal contrast band, so that 0 is no narrowing and 1 is contrast stop, values of multiple narrow sites are added up) in 32 patients (group III) with radiculography (correlation coefficient r = 0.428, p = 0.014)

weight, or body mass index. The above correlations were therefore not corrected for these variables.

Discussion

Conclusions in this study refer to the sample area in lumbosacral CSF space, because sample volume was small compared with total spinal CSF volume [9, 15] and because lumbosacral CSF flow rate is low [6, 21]. The results nevertheless show that some tested variables influence local CSF albumin concentration significantly.

In group I patients with normal CSF, albumin quotient correlated positively with body mass index and related variables, independent of age. This finding was unexpected and there is no obvious explanation. Lumbosacral CSF volume has been reported to correlate inversely with body mass index, partly due to epidural fat storage [15]. A decrease of CSF volume may be expected to increase CSF turnover [20], which could lower protein concentration. However, weighty patients also have increased central and retroperitoneal venous pressure [15, 27]. Pressure gradient between CSF and venous compartment, the driving force behind CSF bulk resorption [2, 3], may then be reduced, which may lower CSF resorption, lessen CSF turnover and thus increase CSF protein concentration. This sequence seems a possible explanation for our finding. Influence on variance of albumin quotient, e. g. 16 % for body mass index, was limited. Length of spinal CSF path in this study had no significant relation to CSF albumin concentration, as demonstrated by lack of correlation of albumin quotient with LP site and distance of LP site to head.

Albumin, IgG, and beta-trace protein constitute a major part of CSF proteins. Measuring total protein, however, often leads to considerably higher values than the sum of these proteins. The difference amounts to a median of 33 % of total protein (range 5–60 %) in this study and contributes correspondingly to variation of total protein concentration. An exhaustive analysis of this gap is not known, although several further CSF proteins derived from plasma or from nervous system have been described [14, 28]. Furthermore, methods for measuring defined proteins and for total protein in CSF are different which may account partly for the gap. The concentration gradient of this protein gap taken as a whole was found to be not different from that of albumin, suggesting mainly plasma derived proteins in this fraction (t test).

Concentration gradients of albumin and IgG in sequential samples corresponded to reported values [1, 10, 25, 31]. Albumin quotient gradient showed a tendency towards being lower if there was more body motion before LP. Concentration gradients are the consequence of protein inflow from meningeal extracellular space along CSF flow path [8, 29] and of fading systolic CSF flow towards the lumbosacral space [6, 13, 21]. Additional CSF flow is induced by thoraco-abdominal pressure changes transmitted to the CSF space [4, 26], and by hydrostatic CSF pressure changes [19], caused by body motions and alterations of body position. The direction of this CSF flow component changes according to body motion, which should promote CSF mixing and diminish concentration gradient. It is assumed that this effect is marginal in this study. Manoeuvres in group II patients tested same effects and again showed that the influence on albumin quotient gradient is small. Change of body position from sitting to lying led to slight increase of protein concentration, caused presumably by admixture of higher protein CSF from the sacral space shifted upwards following change of hydrostatic pressure [19]. Valsalva manoeuvre by coughing influenced protein concentration still weaker, presumably by CSF shifting that follows a cough induced spinal epidural pressure peak [4, 30]. Albumin gradient alterations were limited to one

CSF sample after manoeuvre, indicating small shifted CSF volume.

In group III patients with radiculography the finding of negative correlation of albumin quotient with venous iodine concentration after lumbosacral subarachnoid iopamidol application suggests a partly shared exit path of iopamidol and albumin from spinal CSF into venous blood. Marked size difference of both molecules favours a size-independent shared path, for example a CSF bulk resorption way through spinal arachnoid villi and granulations [5, 16, 18]. Ascension of iopamidol in CSF into the cranial cavity and resorption there may have occurred in few patients, but amount should have been small [17]. It ought to be remembered that finding of negative correlation of albumin quotient with venous iodine concentration is from patients with lumbosacral extradural disease and partly pathological CSF, so that extrapolation to normal CSF is questionable. However, the subgroup of 17 patients with normal CSF had similar negative correlation of QAlb and venous iodine ($r = -0.484$, $p = 0.05$), which suggests validity also for less pathologic conditions. Venous iodine concentration 180 minutes after iopamidol application correlated marginally and negatively with body weight in patient group III ($r = -0.369$, $p = 0.041$). This finding supports the assumption from group I results, that body weight related variables may influence CSF albumin concentration by altering CSF resorption.

Group III patients also showed a positive correlation of albumin quotient with spinal canal narrowing. This finding was expected, and would be caused by reduced CSF flow below narrowing, leading to less admixture of CSF with lower protein concentration from a higher spinal level and to more albumin transfer from plasma [23]. The influence of iodine-related CSF resorption, corrected for spinal canal narrowing, on variance of albumin quotient amounts to 35 % in this patient group. It corresponds to large variation of CSF production, as reported from ventriculo-lumbar perfusion [2] and from MRI studies [12].

This study shows a sizeable influence of spinal CSF resorption and some influence of body weight-related variables like body mass index and abdominal circumference on lumbar CSF albumin concentration. Body motion before LP has only marginal effect on albumin concentration gradient. Other variables like blood-CSF barrier permeability and systolic pulsatile spinal CSF flow should have an additional important influence on variation of lumbosacral CSF protein concentration.

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