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Sinusoidal Intrathecal Infusion for Assessment of CSF Dynamics in Kaolin-Induced Hydrocephalus

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Summary

Objective. To evaluate whether changes of CSF outflow resistance and compliance in hydrocephalus can be assessed by an intrathecal infusion which is performed at a sinusoidal varying rate.

Methods. Hydrocephalus was produced in 10 Sprague Dawley rats by instillation of 0.0375 g of kaolin in 0.9% saline into the cisterna magna. Measurements were performed 4 weeks later: With each animal both, three successive constant rate infusions (0–0.02 ml/min) and a sinusoidal infusion (0–0.02 ml/min, frequency 0.006 Hz) were performed. 6 normal animals served as control. The pressure recordings of both infusion techniques were used for the assessment of the CSF outflow resistance. The time constant and the pressure volume index were calculated only from the sinusoidal input testing.

Results. The sinusoidal test as well as the constant rate infusion both demonstrated a severe impairment of CSF absorption. By the sinusoidal input, a decreased compliance was confirmed additionally. Thus, the sinusoidal infusion test demonstrated a high resistance and low compliance hydrocephalus in the kaolin-treated group. A simple graphical procedure is presented which allows an easy assessment of CSF dynamics by the sinusoidal infusion test.

Keywords: Hydrocephalus; rats; CSF dynamics; CSF outflow study.

Introduction

Decision making for treatment of patients presenting with clinical signs of normal pressure hydrocephalus remains a difficult task.

Besides clinical investigations various efforts have been made including CT and MR imaging, continuous intracranial pressure monitoring, and hydrodynamic testing to confirm the diagnosis. Concerning the lumbar or ventricular infusion tests, variable results have been obtained on the diagnostic value of the CSF outflow resistance (Rout). Some investigators found the test reliable if Rout exceeded values of 15–20 mm Hg/ml/min [20, 17, 2]. Others failed to reproduce these results [8, 14]. Also measurement of CSF reabsorption by constant lumbo-ventricular infusion at different pressures turned out to be slightly successful for the clinical use [5, 3, 23].

Despite these conflicting results, measurement of the CSF dynamics is still considered a reasonable diagnostic approach, as impairment of CSF absorption must be regarded as the basic defect in the pathogenesis of NPH [5]. Consequently, the need for a more reliable test has been claimed [22].

Against this background, the value of a hydrodynamic testing with a sinusoidal varying rate was investigated in the present study. The ICP response to a sinusoidal input test has already been studied theoretically as well as experimentally in healthy rats [17]. It was found, that the CSF dynamics can be assessed from evaluation of the ICP recordings and the corresponding infusion rate. A preliminary clinical study indicated the value of the sinusoidal input test also in man [18]. Nevertheless, the value of the sinusoidal input test for diagnosing pathological CSF dynamics is unclear. Therefore, the sinusoidal infusion test was reinvestigated in the present experimental study.

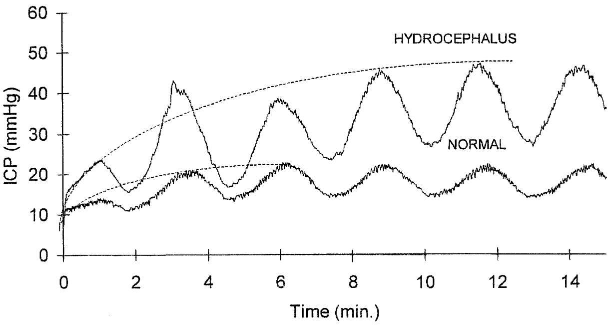

Fig. 1. Pressure recording during a sinusoidal infusion at a rate of 0–0.02 ml/min. In hydrocephalus, the ICP increase and the pressure amplitude is strengthened in comparison with a control animal. In normal animals, the steady state (stable maximum and minimum pressure) is attained much faster than in hydrocephalus

Methods and Material

Animal Experiments

16 adult Sprague Dawley rats (250–350 gr) were studied. The animals were anaesthetised with ketamine and dihydralazine.

6 normal rats served as control. In 10 rats hydrocephalus was produced by instillation of kaolin (aluminium silicate, Nakaraitex Inc., Kyoto Japan, 0.15 ml = 0.0375 g in 0.9% saline) into the cisterna magna.

The animals were investigated 4 weeks later after having developed hydrocephalus. For the infusion a 1 mm nylon catheter was introduced into the right lateral ventricle. First, CSF outflow resistance profile was estimated by a series of constant rate infusions of saline. Then, sinusoidal input testing was performed (rate 0–20 µl/min., frequency = 0.006 Hz). A computer controllable infusion pump (505 DU, Watson Marlow, UK) and a standard IBM compatible personal computer for analogue digital signal processing with commercially available laboratory software (Daisy lab, Datalog GmbH, Germany) were used. The sinusoidal infusion rate was calculated as: $I(t) = Io + Io * \sin(2^* pi^* f^* t)$ [ml/min].

The experiments were performed in accord with the institutional approval of the local government (Bezirksregierung Hannover).

Calculation of Resistance

In each experiment CSF outflow resistance was calculated by three successive constant rate infusions first by $Rout = (ICP - ICPo)/Ir$ (ICPo = baseline ICP, Ir = infusion rate). Ir were adjusted within a range of 0.005–0.02 ml/min, values which lead to an ICP increase of approximately 10–40 mm Hg.

Then, a sinusoidal input was performed with a frequency of 0.006 Hz and a rate from 0 to 0.02 ml/min. Rout was calculated from the quotient of ICP increase at maximum and minimum pressure levels and corresponding infusion rates (Fig. 1). The resistance was additionally calculated from the mean pressure and the mean infusion rate.

In rats, CSF outflow resistance is dependent on the ICP in a nonlinear fashion. According to Mann *et al.* [15] the following exponential equation (eq. 1) was used to analyse the experimental results: $R = M * ICP * e^{(-ICP/Pr)} - M * ICPo * e^{(-ICP/Pr)}$ {mm Hg/ml/min}. This equation contains two independent parameters (M and Pr) which determine the individual pressure resistance profile. Both parameters can be obtained from the infusion tests by plotting the ICP increase with the logarithm of the corresponding infusion rate

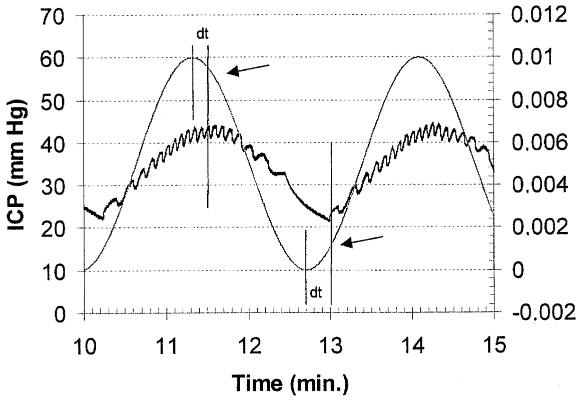

Fig. 2. Graphical evaluation of the sinusoidal infusion: After having determined the maximum and minimum pressure a vertical line is set at these points. The lines indicate the corresponding infusion rates (arrows) at maximum and minimum pressure levels, respectively. The time lag (dt) between the ICP and the infusion rate is taken from the distance between the maximum and minimum values of both curves, respectively

(Fig. 3). M is calculated from the inverse of the x-intercept of the logarithmic regression line and Pr from its steepness.

Calculation of the Time Constant and Intracranial Compliance from the Sinusoidal Input

The ICP recordings during a sinusoidal input showed a considerable phase lag between the pressure recording and the infusion rate (Fig. 2). There was a slight difference in the phase shift at maximum and minimum pressure levels. According to the results of Charlton *et al.* [7] this phase lag enables the calculation of the time constant of the system and the intracranial compliance:

At first, for the maximum and minimum ICP level the phase shift in degrees was calculated by the term $phi = 2^* pi^* f^* \Delta t$ (Δt = measured phase shift in seconds). Thus, the time constant of the system in seconds could be calculated by $tau = tau(phi)/2^* pi^* f$. With given tau and the corresponding R, the compliance of the system could be calculated by $C = tau/R$. This value was then used to calculate the PVI [16]: $PVI = C * ICP/0.4343$ [ml].

Results

Resistance

To evaluate the reliability of the sinusoidal input for the calculation of Rout, the pressure increases from the constant rate infusions (in the equilibrium state) and the sinusoidal input (at maximum, minimum and mean ICP levels) were plotted against the corresponding infusion rates.

The logarithmic regression lines, obtained from both infusion techniques, were comparable as there was found to be a close correlation. The correlation was found as well in control animals as in hydrocephalic rats. The regression lines of the hydrocephalic

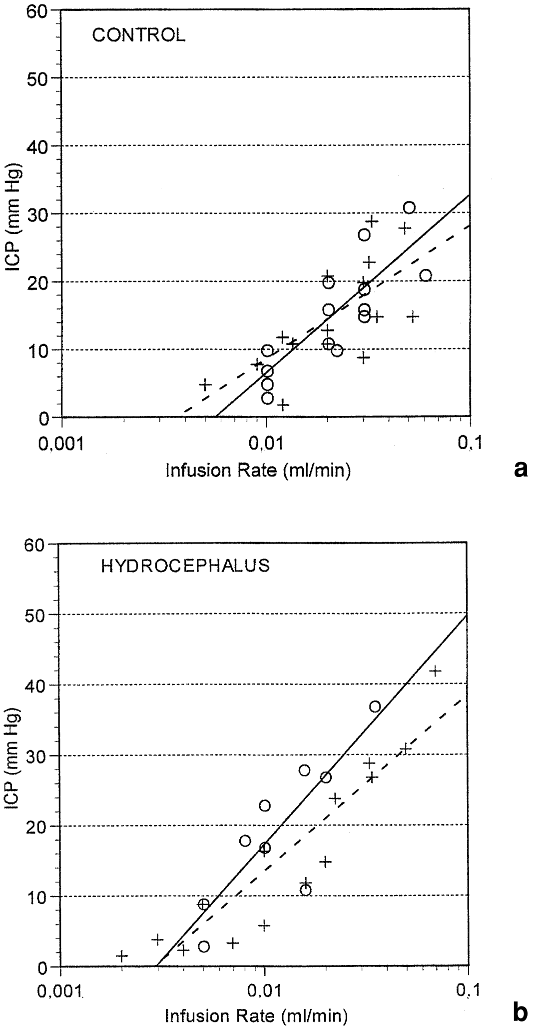

Fig. 3. The ICP increase during the constant (_____o) and sinusoidal (– – +) infusion is each plotted with the logarithm of the infusion rate. A logarithmic regression analysis is performed. The Parameter M can be assessed from the inverse of the X-intercept, the parameter Pr from the steepness of the regression line. There was no significant difference between results of the infusion techniques neither in normal nor in hydrocephalic animals. (a) Control animals, $R^2 = 0.62$ constant rate infusion, $R^2 = 0.48$ sinusoidal infusion. (b) Hydrocephalic animals, $R^2 = 0.85$ constant rate infusion, $R^2 = 0.71$ sinusoidal infusion

animals were significantly different from that of the control animals (Fig. 3).

In the hydrocephalus group a significant increase of M ($p < 0.05$, t-test) was found as compared with control animals whereas the values for Pr, however, were not statistically different in both groups. These results could be confirmed with both measurement techniques (Table 1).

Comparable results of both measurement techniques were also seen by plotting the resistance/pressure values. Furthermore, marked differences between the control and the hydrocephalic group were found (Fig. 4).

Table 1. *Comparison of CSF Outflow Parameter (M and Pr) Obtained by Constant Rate (C) and Sinusoidal Input (S). Asterisks Indicate Significant Differences ($P < 0.05$, t test, mean ± SD). M and Pr are the Parameters Necessary to Describe the Nonlinear Relationship Between ICP and the CSF Outflow Resistance According to Equation 1*

Group	M (C)	M (S)	Pr (C)	Pr (S)
Control	181 ± 72,8	200 ± 94,7	26 ± 2,5	23 ± 6,8
Hydrocephalus	288 ± 76,7*	444 ± 96,4*	31,6 ± 9,7	22,6 ± 6,1

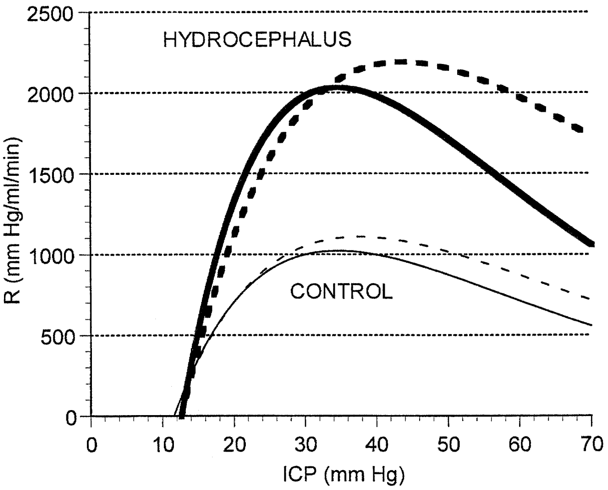

Fig. 4. Pressure/resistance plot as calculated by equation 1. By both measurement techniques (constant rate = dashed lines, sinusoidal input = solid lines) a marked impairment of CSF absorption was found in the hydrocephalic animals

Time Constant and Compliance

The time constant was calculated from the time lag (dt) between ICP and infusion rate at maximum and minimum ICP levels. With the given resistance value, calculated from each pressure level, the compliance and the PVI could be assessed as described above ($C = tau/R$). The results are shown in Table 2.

There was no difference between the time constant of the control and the hydrocephalic rats, whereas the compliance and the PVI values were statistically decreased ($P < 0.05$, t-test). Within each group, however, there was a statistically significant difference between the time constant measured at maximum and minimum pressure levels, while the corresponding values for Rout and C have not shown a statistical difference, respectively.

Table 2. *CSF Dynamics as Estimated by Sinusoidal Input in Normal and Hydrocephalic Animals Asterisks Indicate Significant Differences Between Corresponding Values* ($p < 0.05$, *t test*)

Control		ICP	dt	Ir	Rout	tau	C	PVI
		mm Hg	sec	ml/min	mmHg/ml/min	sec	ml/mm Hg	ml
Maximum ICP	Mean	33,6	20	0,04	579	25	0,00085	0,062
	SD	8,3	3,9	0,01	233	3,9	0,00045	0,029
Mean ICP	Mean	26,4		0,024	646			
	SD	6,3		0,006	266			
Minimum ICP	Mean	19,2	24	0,01	774	34	0,001	0,056
	SD	4,7	5,7	0,003	348	5,8	0,0014	0,055
Hydrocephalus		ICP	dt	Ir	Rout*	tau	C*	PVI*
		mm Hg	sec	ml/min	mmHg/ml/min	sec	ml/mm Hg	ml
Maximum ICP	Mean	38	22	0,02	1352	21,4	0,0004	0,027
	SD	13,8	9,2	0,01	665	8,7	0,0003	0,007
Mean ICP	Mean	31,5		0,011	2286			
	SD	11,7		0,0085	986			
Minimum ICP	Mean	24,6	28	0,0056	2551	35,4	0,0002	0,01
	SD	9,5	7	0,003	682	5	0,0002	0,003

Graphical Analysis of the Sinusoidal Input

The original ICP recordings obtained from the sinusoidal input differ in the extent of the ICP increase and amplitude at identical infusion rates (Fig. 1). By plotting the ICP increase against the corresponding infusion rate much more information was obtained from graphic visualisation (Fig. 5). This plot contains information on the impairment of CSF absorption in one hand and information on the intracranial compliance on the other hand:

Under the condition of normal CSF dynamics a flat ellipse is formed. This was different in the hydrocephalic group: The centre of the ellipse was shifted to higher ICP values as an expression of the increased Rout. Furthermore, the ellipse became broader and the longitudinal axis steeper which indicated decreased compliance. Thus, essential information on the individual CSF dynamics was easily assessable by graphic evaluation of the sinusoidal input test.

The infusion-rate/pressure plot provides further information which helps to distinguish the controls from hydrocephalic animals: The period before the steady state (stable maximum and minimum pressure levels) is reached during the sinusoidal input, is marked by a distinct spiral that runs out into the ellipse at the moment when the equilibrium state is attained. This spiral is only outlined in control animals, whereas it is pronounced in the hydrocephalic rats. In the animals with the highest Rout-values no equilibrium state was reached during the infusion period of 15 minutes (Fig. 5).

Discussion

The "urgent need for a simple, cheap, and accurate test for selecting the right patients for a shunt" [22] has motivated us to study the diagnostic value of the sinusoidal input test. The sinusoidal input had been introduced years before [7, 18], but was never used in hydrocephalic animals.

Resistance

In comparison to constant rate infusions, the sinusoidal test turned out to have the same accuracy in determining the impairment of CSF outflow as well in normal as in hydrocephalic animals. It was demonstrated, that one sinusoidal test provides three pressure/resistance data pairs that sufficiently describe the definitive pressure/resistance profile of each animal.

A marked impairment of CSF outflow was expected in the kaolin hydrocephalic animals. However, analysis of the experimental measurements with calculation of the parameter M and Pr yielded a surprising finding: In hydrocephalus only M but not Pr was statistically increased.

This finding might be important as M has been regarded as a parameter indicating a carrier mediated outflow of CSF e.g. through the arachnoid villi. Pr in-

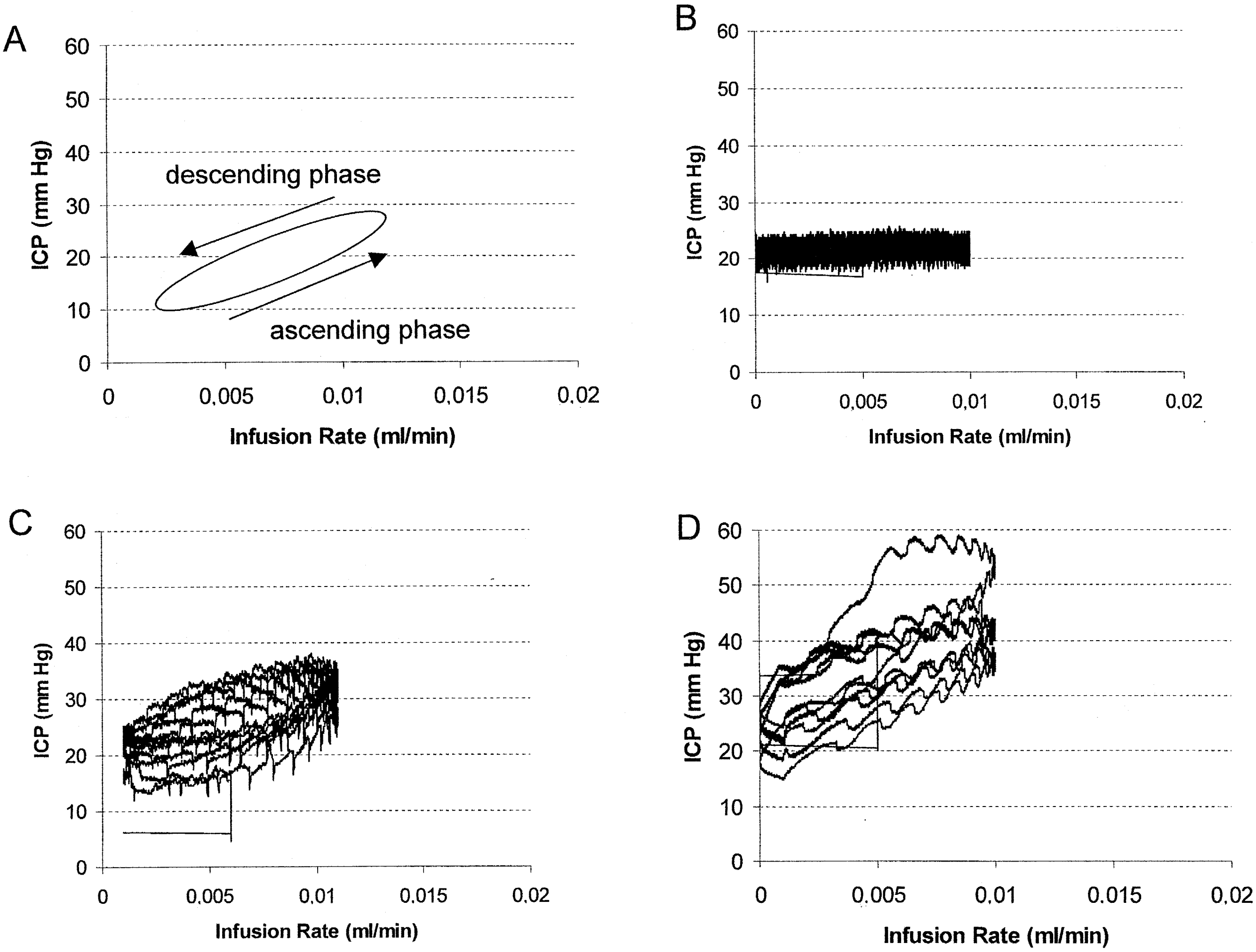

Fig. 5. Graphical evaluation of the sinusoidal infusion: The ICP is plotted against the infusion rate. (A) A hysteresis was found due to a different ICP response during the ascending and descending phase of the infusion rate. The hysteresis was distinct in the hydrocephalus group. (B) Control animal; the ellipse is flat and small. (C) Moderate Hydrocephalus; the centre of the ellipse was shifted to higher ICP, the ellipse was broader and steeper. Furthermore, in hydrocephalus a distinct spiral was seen until the definitive ellipse was attained. (D) Marked hydrocephalus; no steady state was attained during the infusion period as indicated by the spiral body

dicates a second valve-like mechanism of CSF outflow [13] e.g. into the lymphatic system [6] or directly into brain capillaries [11]. Against this background our experimental findings indicate disturbed outflow of CSF among the arachnoid villi but an intact drainage among the second pathway. Our findings furthermore support the suggestions of Johnson *et al.* [13], considering that Pr-linked CSF outflow pathways act predominantly as a protective mechanism at increased ICP levels. It should be mentioned, that this interpretation among significance of M and Pr remains speculative as long as the biological nature of the valve like mechanism is unclear.

Nevertheless, the selective increase of M in comparison to Pr in the hydrocephalic animals in our study should be pointed out: This indicates, that the impairment of CSF absorption in hydrocephalus is not only related to a quantitative increase of the CSF outflow resistance but it is also the result of changed CSF outflow pathways.

Compliance

In hydrocephalus, intracranial compliance was decreased 4 weeks after instillation of kaolin. This experimental finding confirms the observation of Gonzalez-Darder *et al.* [10] who studied kaolin induced hydrocephalus in dogs. They found two successive phases: An initial acute hypertensive hydrocephalus with high resistance and low compliance and a chronic low pressure stage with a slightly increased resistance and normal compliance. The study of

Gonzalez-Darder *et al.* and several experimental and clinical studies [12, 9, 4, 21] demonstrate complex changes of the resistive and capacitive parameters in the course of hydrocephalus. In this respect the sinusoidal input test might improve the diagnostics, as it provides a synchronous estimation of compliance and resistance. An otherwise similar synchronous assessment of CSF outflow resistance and compliance is only provided by the bolus injection technique [16]. This method, however, was shown to be sometimes inaccurate in clinical terms. A poor correlation was reported between the resistance values either obtained from constant rate infusions or bolus injections [19]. Whether the sinusoidal input test is more reliable under clinical conditions, must be confirmed by appropriate investigations

Graphical Analysis

The sinusoidal input test is best described graphically by plotting the ICP in relation to the infusion rate. By these means, distinction of normal and hydrocephalic rats was made visible and thus served for an easy qualitative assessment of CSF dynamics. It even seems that the graphical evaluation was even more sensitive and more reliable than the mathematical calculation of R and PVI. Therefore one may hope that application of the presented technique in patients would provide more information on CSF dynamics than is available so far.

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Comment

This paper describes a new method for determining the effects of acute, kaolin induced hydrocephalus in animals on cerebro spinal fluid dynamics, specially resistance to outflow and compliance. The technique has been describes earlier, but never been applied in experimental animals (or man).

The finding of a very characteristic response to infusion into the subarachnoid space and sinusoidal changing infusion rates is very interesting and convincing. As might be expected, the technique gives information on both the resorption rate and on the compliance of the total system.

The paper is purely experimental, includes no patient material.

I hope that the study will be followed up by clinical research on patients with normal pressure hydrocephalus, as it is in this group that the real problems concerning selection of patients for CSF shunting exists.

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