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Value of morphological parameters for grading of brain swelling

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Abstract This study investigated the value of both gross features and histological findings for grading of brain swelling. For this purpose, the grooving of the temporal gyri (unci) as well as the extension of the cones at the basal part of the cerebellum were measured in 42 brains obtained at autopsy. Furthermore, the distension of perivascular spaces in tissue samples from seven different regions of the brains was evaluated histologically, assisted by an automatic image processing and analysis system. In each individual, the normal range of brain weight was calculated on the basis of the body height, using the formulae by Röthig and Schaarschmidt. The difference between this calculated (normal) value and the brain weight evaluated at autopsy was considered as a reliable criterion for the grade of brain swelling. There was no statistical evidence of a positive correlation between the various parameters. Hence, it can be concluded that both gross section and histological findings are of minimal significance for grading of brain swelling.

Keywords Cerebral edema · Brain swelling · Grading · Morphological signs

Introduction

Brain swelling is caused by cerebral edema, which is characterized by abnormally large amounts of fluid in the extracellular compartment of brain tissue, preferentially in the white matter. It is a common phenomenon after traumatic brain injury due to a dysfunction of the blood–brain barrier, failure of the microcirculation, or reactions of the local glial cells [2, 5, 6, 8, 10, 13]. Generalized posttraumatic edema is regularly accompanied by increased intracranial pressure, leading to various degrees of neurological disorders or death [11]. Assessing the grade of cerebral edema at autopsy is of considerable interest in forensic neurotraumatology, especially if focal lesions are absent and cerebral edema is the only intracranial abnormality following blunt head injury. Although the brain swelling is easily recognized by morphological features such as flattening of gyri, narrowing of sulci, or expansion of the white matter with reduction of the ventricular system [9], an accurate determination of mild or moderate degrees of cerebral edema can be very difficult at autopsy [9, 20]. However, it has been reported that gross features of cerebral pressure such as the cone of basal parts of the cerebellum as well as histological findings are of minimal significance for the diagnosis of increased cerebral volume [14, 20]. Against the background of a limited number of systematic investigations in the literature, as well as the inconsistency of the results, this study was performed to evaluate both gross section and histological findings for the grading of cerebral edema in forensic autopsy cases.

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Material and methods

The brains of 42 individuals, 26 males and 16 females, aged between 18 and 81 years (average age 46 years), were obtained at autopsy for postmortem investigations. Of the patients, 24 died of acute cardiac arrest due to myocardial infarction (n=16) or coronary insufficiency (n=8). In the remaining cases, an unnatural cause of death, such as traumatic brain injury (n=10), fatal heroin overdose (n=4), hanging (n=3), or plastic bag suffocation (n=1), was diagnosed. In the individuals who had sustained traumatic head injury, the survival period ranged between 0 and 12 h, whereas in all other cases, death occurred immediately. The postmortem interval before autopsy did not exceed 2 days. The brains were weighed immediately after removal at au-

topsy and then fixed in 4% PBS–formaldehyde solution for 7 days.

Macroscopic measurements

The formalin-fixed brains were rinsed in H_2O for 30 min, and the so-called pressure zones of the basal cerebellum ("cones") as well the grooving of the unci were measured using a precision sliding caliper (Fa. LUX, Basic, 150 mm, Nonius 1/50=0.02 mm, Fig. 1). The grooving of the unci was measured at coronal sections through the medial part of the hippocampal gyrus and determined by the maximum length of line *g*, vertical to the tangent *t* (Fig. 2). Accordingly, the extension of the cerebellar cones was evaluated at coronal sections through the tonsils as shown in Fig. 3. In each case, three independent measurements were performed at both sites of the brain for calculating a mean value of the cone sizes or the extension of the unci grooving.

Histological investigations

Tissue samples, 3 cm^3 in size, were collected from the following regions of each brain: (1) cortex, (2) thalamus, (3) putamen/pallidum, (4) Ammon's horn, (5) uncus, left and right side (6) cerebellum. The tissue samples were embedded in paraffin, and sections (3–5 μm) were stained with hematoxylin and eosin (HE). For histological grading of the cerebral edema, the extension of the perivascular spaces (perivascular distension) was measured microscopically (objective 6.3/0.20, ocular ×20), assisted by an automatic image processing and analysis system (LEICA QWin). In each specimen, ten cerebral arteries up to a diameter of 200 μm showing cross-sectional areas were selected for morphometrical analysis. In addition to the distension of the perivascular spaces, the diameters of the respective blood vessel was measured. To get data independent from the vascular sizes, the ratio *r* was calculated as the values of the vascular diameters divided by the values of the perivascular distensions (Fig. 4).

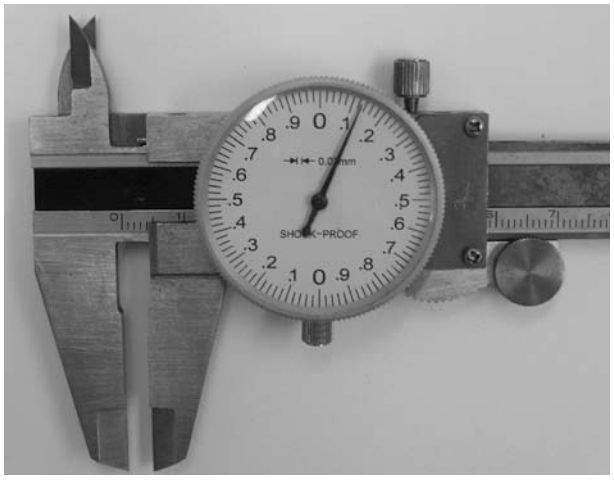

Fig. 1 Precision sliding caliper (Fa. LUX, Basic, 150 mm, Nonius 1/50=0.02 mm), used for measuring of the coning at the basal cerebellum and the temporal grooving

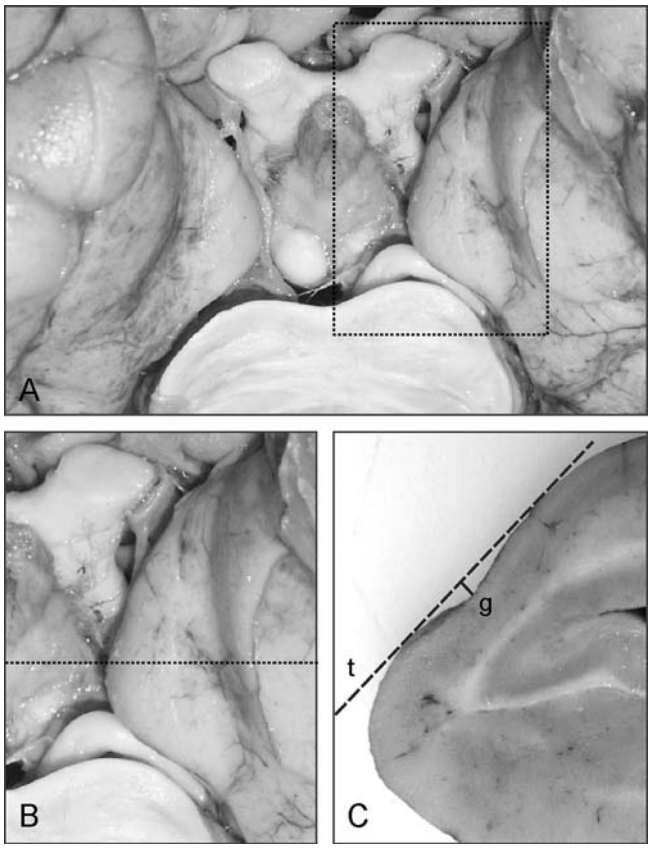

Fig. 2 Basal surface of the brain showing the uncus of the left temporal lobe (**a**). The temporal grooving was measured at a coronal section through the medial part of the uncus (*dashed line*, **b**) and determined by line *g*, vertical to the tangent *t* (**c**)

Reference brain weight

The brain weight evaluated at autopsy was compared to the reference value *x*, which was calculated by a regression analysis according to Röthig and Schaarschmidt [16], using the following formulae (*y*=body height):

$$(1)\ \text{male}: \quad x[g] = 554.5 + 5.03 * y$$

$$(2)\ \text{female}: \quad x[g] = 464.2 + 4.95 * y$$

The standard deviation (SD) was ±115.3 for males and ±107.5 for females.

Statistical methods

The statistical data analysis was performed using SPSS for Windows release 11.01. Descriptive analysis included means, medians, and SD. Pearson's correlation coefficient

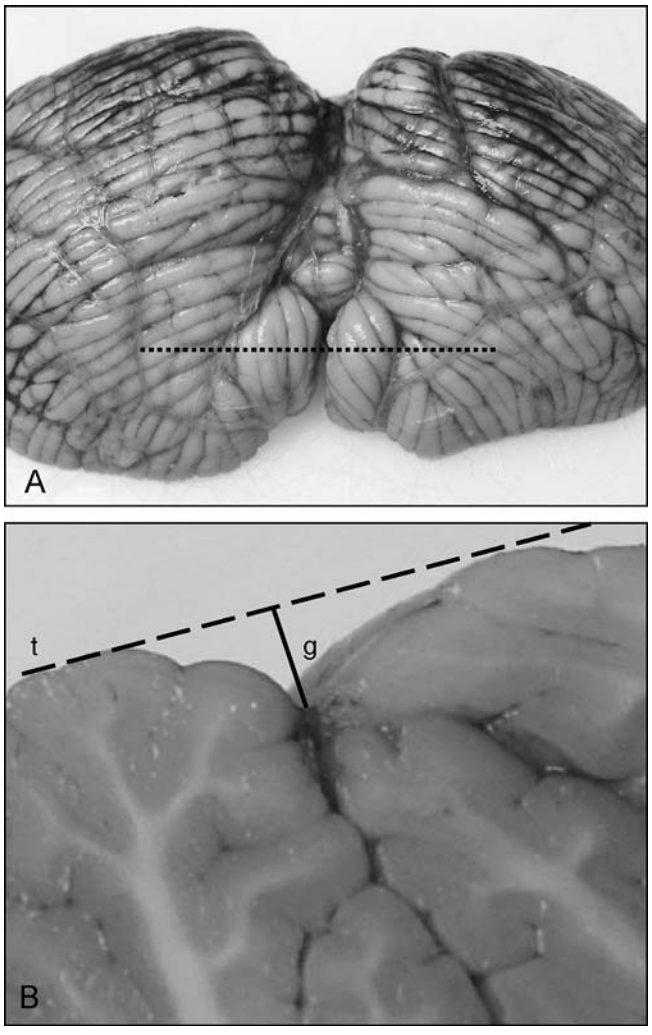

Fig. 3 Basal surface of the cerebellum showing the tonsils (**a**). The extension of the cones was determined by measuring the length of line *g*, vertical to the tangent *t* (**b**)

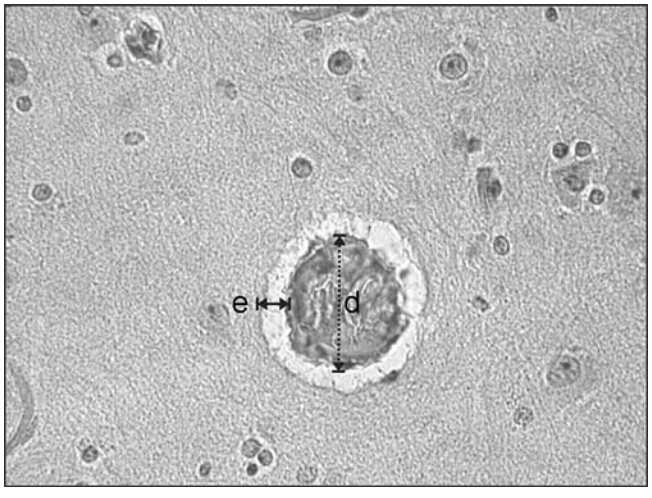

Fig. 4 Distension of the perivascular space *e* and the vascular diameter *d* in a tissue sample from the temporal cortex (hematoxylin and eosin, original magnification ×120)

was calculated to evaluate the relationship between the various gross section and histological data.

Results

Gross findings

The brain weight evaluated at autopsy ranged between 1,090 and 1,810 g. When compared to the calculated values of the reference brain weight, the evaluated values were within the range of the SD in 29 cases (69%). In seven cases (17%), the brain weight was below the calculated minimal value (mean−SD), and in six cases (14%), the brain weight exceeded the maximum reference value (mean+SD). Related to the calculated mean values, the evaluated brain weights were lower in 22 cases (52%) and higher in 19 cases (42%), respectively. In one case, the brain weight evaluated at autopsy was consistent with the calculated mean value.

The measurements of the so-called pressure zones revealed values between 0.248 and 2.658 mm for the unci and values between 0.0 and 3.294 mm for the cones, respectively. In the majority of cases, the difference between the left and the right site was less than 0.5 mm at both locations (Table 1).

Histological findings

The ratio of the perivascular distentions and the vascular diameters obtained by the morphometrical analysis ranged between 0.106 and 0.404 with a standard deviation of 0.043 up to 0.055 (Table 2).

Statistical analysis

Comparing the data obtained for the temporal grooving (unci) with the sizes of the cerebellar cones and with the perivascular distension in histological sections, a positive correlation could not be found statistically (Fig. 5). The calculated Pearson values are shown in Table 3. Furthermore, the data obtained in cases with significantly increased brain weights were selected for statistical evaluation, and the values are plotted in Fig. 6. It is evident that there was no correlation between the so-called pressure signs and the extent of brain weight increase: the maximum values for temporal grooving as well as for cerebellar coning were observed in cases in which brain weights were within the calculated range of mean value ±SD (Fig. 6a,b). The maximum perivascular distension was found in tissue sections from a brain with a weight 5% less than the calculated minimal value (Fig. 6c).

Table 1 Gross-sectional data of the 42 brains obtained at autopsy

Number	Sex	Age	Cause of death	Height (cm)	Brain weight (g)	Reference brain weight		Difference of the brain weight from		Uncus (mm)	Cone (mm)
						Mean	Range	Mean	Mean±SD		
1	F	30	TBI	166	1,210	1,286	1,178.5–1,393.5	−76	0	1.985	2.489
2	M	60	MI	177	1,440	1,445	1,329.7–1,560.3	−5	0	1.778	2.830
3	M	41	CI	177	1,502	1,445	1,329.7–1,560.3	+57	0	2.182	0.00
4	F	27	Hanging	178	1,364	1,345	1,237.5–1,452.5	+9	0	1.630	1.193
5	M	38	Heroin intoxication	174	1,250	1,430	1,314.7–1,545.3	−180	−64.7	0.881	2.373
6	M	39	TBI	189	1,450	1,505	1,389.7–1,620.3	−55	0	1.000	1.956
7	F	22	Heroin intoxication	155	1,350	1,232	1,124.5–1,339.5	+118	+10.5	1.061	1.183
8	F	49	Heroin intoxication	170	1,250	1,306	1,198.5–1,413.5	−56	0	1.367	1.345
9	F	37	MI	173	1,280	1,321	1,213.5–1,428.5	−41	0	1.169	1.361
10	M	48	MI	187	1,400	1,495	1,379.7–1,610.3	−95	0	0.492	3.294
11	M	40	MI	178	1,450	1,450	1,334.7–1,565.3	0	0	1.452	0.832
12	F	26	CI	178	1,450	1,345	1,237.5–1,452.5	+105	0	0.968	1.002
13	M	52	TBI	182	1,125	1,470	1,354.7–1,585.3	−345	−229.7	1.328	2.624
14	M	33	CI	188	1,630	1,500	1,384.7–1,615.3	+130	+14.7	0.850	1.062
15	M	18	MI	191	1,580	1,515	1,399.7–1,630.3	+65	0	0.849	1.445
16	F	36	Suffocation	165	1,410	1,281	1,173.5–1,388.5	+129	+21.5	0.659	1.937
17	F	78	MI	161	1,210	1,261	1,153.5–1,368.5	−51	0	0.481	2.276
18	F	18	MI	166	1,370	1,296	1,188.5–1,403.5	+74	0	1.181	2.732
19	M	23	MI	186	1,560	1,490	1,374.7–1,605.3	+70	0	0.814	1.820
20	F	81	CI	158	1,250	1,246	1,138.5–1,353.5	+4	0	1.234	1.280
21	M	58	TBI	170	1,380	1,410	1,294.7–1,525.3	−30	0	0.299	0.780
22	F	62	MI	162	1,200	1,266	1,158.5–1,373.5	−66	0	1.206	2.280
23	F	52	CI	153	1,260	1,222	1,114.5–1,329.5	+38	0	0.726	2.147
24	M	57	CI	176	1,456	1,440	1,324.7–1,555.3	+16	0	0.438	0.893
25	M	57	Hanging	171	1,540	1,415	1,299.7–1,530.3	+125	+9.7	1.367	2.345
26	M	76	TBI	174	1,250	1,430	1,314.7–1,545.3	−180	−64.7	0.687	1.206
27	M	45	MI	178	1,270	1,450	1,334.7–1,565.3	−180	−64.7	1.473	2.361
28	M	37	MI	174	1,470	1,430	1,314.7–1,545.3	+40	0	2.658	1.113
29	M	71	CI	154	1,260	1,329	1,213.7–1,444.3	−69	0	1.925	0.534
30	M	47	MI	179	1,560	1,455	1,339.7–1,570.3	+105	0	1.273	1.349
31	F	49	TBI	167	1,115	1,291	1,183.5–1,398.5	−176	−68.5	0.791	0.499
32	M	39	MI	168	1,300	1,400	1,284.7–1,515.3	−100	0	1.429	0.308
33	M	40	MI	176	1,220	1,440	1,324.7–1,555.3	−220	−104.7	0.650	1.830
34	M	38	TBI	183	1,810	1,475	1,359.7–1,590.3	+335	+219.7	1.708	2.067
35	F	67	TBI	157	1,270	1,241	1,133.5–1,348.5	+29	0	0.594	1.306
36	M	43	TBI	188	1,400	1,500	1,384.7–1,615.3	−100	0	0.488	1.687
37	M	48	MI	170	1,367	1,410	1,294.7–1,525.3	−43	0	2.426	3.194
38	F	53	Hanging	179	1,320	1,350	1,242.5–1,457.5	−30	0	0.838	2.411
39	M	54	CI	177	1,480	1,445	1,329.7–1,560.3	+35	0	0.248	1.139
40	M	30	Heroin intoxication	164	1,200	1,379	1,263.7–1,494.3	−179	−63.7	1.203	1.632
41	F	79	TBI	146	1,090	1,187	1,079.5–1,294.5	−97	0	1.644	2.175
42	M	22	MI	190	1,710	1,510	1,394.7–1,625.3	+200	+84.7	1.047	1.749

The range of the brain weight was calculated as mean value±SD according to formula recommended by Röthig and Schaarschmidt [16]
TBI Traumatic brain injury, *MI* myocardial infarction, *CI* coronary insufficiency

Table 2 Ratio of the perivascular distension and the vascular diameters in different regions of the brain

Criteria	Cortex	Thalamus	Putamen/pallidum	Ammon's horn	Cerebellum	Uncus
Range	0.187–0.379	0.106–0.404	0.113–0.305	0.146–0.367	0.135–0.402	0.181–0.373
SD	0.054	0.055	0.043	0.052	0.063	0.043
Mean	0.284	0.229	0.210	0.236	0.276	0.261
Median	0.281	0.218	0.216	0.239	0.269	0.262

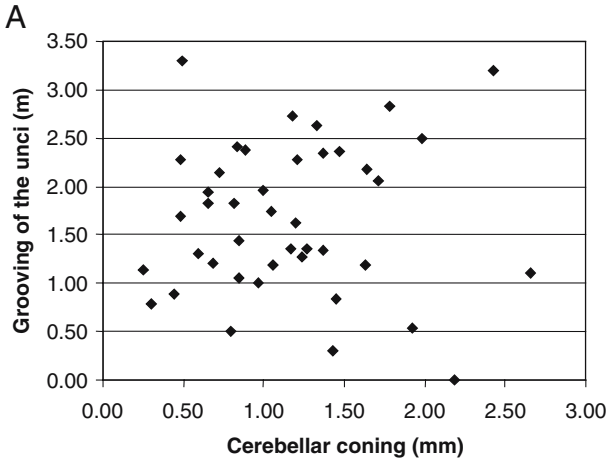

Fig. 5 Relationship of the various gross section and histological parameters

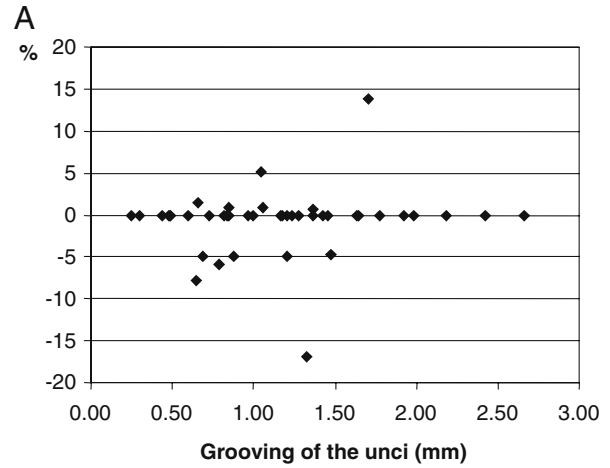

Fig. 6 Individual values of temporal grooving (**a**), cerebellar coning (**b**) and perivascular distension (**c**) against the brain weight (n=42), plotted as the percentage deviation of the brain weight from the calculated statistical range (mean±SD)

Table 3 Correlation analysis, p values (Pearson) in all cases investigated (n=42)

Criteria	Brain weight	Grooving of the unci	Cerebellar coning	Perivascular extension
Brain weight		0.035	−0.102	−0.011
Grooving of the unci	0.035		0.0333	0.004
Cerebellar coning	−0.102	0.0333		0.178
Perivascular extension	−0.011	0.004	0.178	

Discussion

The several sites of brain herniation complicating expanding intracranial processes were originally described in the first half of the last century [12, 18]. Gross features such as the grooving of the temporal uncus as well as the extension of the cones at the basal part of the cerebellum belong to the generally accepted morphological signs of cerebral edema. However, it has been pointed out that the differentiation from normal anatomical findings may be difficult [7, 14, 16]. In addition, pathological studies on these cones revealed no correlation between the cone height and the clinically detected state of cerebral pressure [3, 15]. Thus, it has been doubted whether these morphological findings may be regarded as a result of brain swelling [4]. The occurrence of a cerebellum basal cone should rather be considered as a "normal filling up process of any space in the skull during brain acceleration" [15]. Only in exceptional cases with cone sizes of 10 mm and more did the author discuss a possible significance of the cone formation for the diagnosis of a cerebral volume increase.

The data obtained in this study are basically in accordance with the findings of Röthig [15]. No correlation could be found between the sizes of the cerebellar cones and the extent of brain weight increase and between the histological states of perivascular distension. However, the cone sizes did not achieve the maximum values observed in the abovementioned study. This may be due to different measurement procedures: Röthig argues that the cones are formed with participation of cerebellum parts adjacent to the tonsils, such as the Lobulus biventer and the Lobulus gracilis. In contrast, the herniated tonsils without adjacent parts of the cerebellum have separately been considered as a sign of cerebral edema [17] and were measured in the presented study.

The data obtained in this study for the unci indicate that there is no correlation between the temporal grooving and other morphological parameters of brain swelling such as increased brain weight and distension of perivascular spaces in histological preparations. Similar findings have been reported by Röthig [15], who found temporal grooving in a high percentage of unselected autopsy cases (about 80%).

On the basis of the presented results, it can be concluded that gross features such as the uncus grooving as well as the presence of cerebellar cones are of limited value for the grading of brain swelling. Thus, the histological signs of brain swelling due to cerebral edema might be of particular interest. The generally accepted criteria include pallor of myelin staining, distension of perivascular and pericellular spaces, a loose, sieve-like or spongy appearance of the myelinated areas, rarefication of subpial spaces, a vacuolar appearance of the gray matter neuropil, and pools of protein-rich fluid [1, 2, 10, 17, 19]. Among these, the distension of perivascular and pericellular spaces is particularly suitable for morphometrical analysis and was evaluated in this study. The data obtained in the gray matter did not statistically correlate to the brain weight or to the macroscopic findings. Thus, the value of this histological criterion must be interpreted cautiously as confirmed by the studies of Yates et al. [20]. It has been shown both in human and animal tissue that no correlation exists between the chemical estimation of the water content and the histological assessment of cerebral edema [9]. These findings were discussed to be caused by changes in the water and ion content during the first hours after death. Such changes can be considered to be the result of postmortem plasma diffusion in brain tissue, as demonstrated immunohistochemically by Oehmichen et al. [14].

A major problem in analyzing the value of various morphological parameters for the grading of cerebral edema is the lack of reliable reference criteria such as clinical data of intracranial pressure measurements. The most appropriate morphological criterion might be the normal range of brain weight, which can be calculated using the formula of Röthig and Schaarschmidt [16]; however, the value of this method is restricted by the wide statistical range.

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