Published in final edited form as:

J Forensic Leg Med. 2017 January ; 45: 21–28. doi:10.1016/j.jflm.2016.11.006.

Mathematical model in post-mortem estimation of brain edema using morphometric parameters

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Abstract

Current autopsy principles for evaluating the existence of brain edema are based on a macroscopic subjective assessment performed by pathologists. The gold standard is a time-consuming histological verification of the presence of the edema. By measuring the diameters of the cranial cavity, as individually determined morphometric parameters, a mathematical model for rapid evaluation of brain edema was created, based on the brain weight measured during the autopsy. A cohort study was performed on 110 subjects, divided into two groups according to the histological presence or absence of (the – deleted from the text) brain edema. In all subjects, the following measures were determined: the volume and the diameters of the cranial cavity (longitudinal and transverse distance and height), the brain volume, and the brain weight. The complex mathematical algorithm revealed a formula for the coefficient ϵ , which is useful to conclude whether a brain edema is present or not. The average density of non-edematous brain is 0.967

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g/ml, while the average density of edematous brain is 1.148 g/ml. The resulting formula for the coefficient ϵ is $(5.79 \times \text{longitudinal distance} \times \text{transverse distance}) / \text{brain weight}$. Coefficient ϵ can be calculated using measurements of the diameters of the cranial cavity and the brain weight, performed during the autopsy. If the resulting ϵ is less than 0.9484, it could be stated that there is cerebral edema with a reliability of 98.5%. The method discussed in this paper aims to eliminate the burden of relying on subjective assessments when determining the presence of a brain edema.

Graphical abstract

Keywords

brain edema; brain swelling; cranial cavity; autopsy

INTRODUCTION

Brain edema is a pathological entity, which is characterized by an increased amount of fluid (water) in the brain parenchyma [1]. Among several development mechanisms of brain edema, there are two forms that are particularly important in forensic medicine: vasogenic and cytotoxic [2]. However, a mixed form of (the – deleted from the text) brain edema is the one that is encountered most frequently. Necrotic damage to the brain is usually followed by the interstitial and osmotic type of edema [3–5].

Current principles for evaluating brain edema during an autopsy are based on a subjective assessment of several macroscopic characteristics of the brain, such as widened and flattened waves, narrow and shallow grooves, as well as direct contact with the dura matter. Upon inspecting the brain on cross sections, narrowing of lateral ventricles, along with loose and adhesive brain tissue can be noted, depending on the phase of the brain edema. In cases of brain herniation, the presence of a brain edema is evident and its verification is straight forward. Given the fact that there is a wide range of variation of the volume of the cranial cavity, it is very difficult to diagnose a border-line case of brain edema, as well as diffuse brain edema, when the weight of the brain is within (the – deleted from the text) normal ranges. In these cases brain edema can only be diagnosed by pathohistological examination.

A more reliable method of evaluating the presence of a brain edema includes measuring the weight of the brain. The weight of a normal brain is between 1200 and 1800 g [5] or between 1100 and 1700 g according to Dawson and Neal [6]. If the brain weighs above this

range, it is considered a reliable indicator of a brain edema. However, a brain weighing over 1700 g is rarely seen in practice, which makes weight a very unreliable parameter in verification of a brain edema. Additionally, if the brain weighs more than 1700 g, it is likely that craniomegaly is present.

The time-consuming pathohistological examination is the “gold standard” in verifying the presence of brain edema. This is due to the limits of subjective visual assessments and the wide range of baseline weight of the normal brain (particularly in cases of brain edema with previous brain atrophy as seen in the elderly [6,7]). Microscopic examination shows specific halos around bodies of ganglion cells and astrocytes in the cerebral cortex, while increased looseness is seen in the white matter. [8,9]

In (the – deleted from the text) search for a physical quantity or a mathematical formula that could verify the presence of a brain edema, it is necessary to review previous studies that directly measure or estimate the significant parameters. Anthropological / anthropometric research performed by a group from France [10] aimed to determine the volume of the cranial cavity of modern Europeans. This measurement was based on Archimedes’ principles, using water and glass beads. The obtained values were 1676.47 ± 161.26 ml for men and 1476.48 ± 102.49 ml for women.

Röthig & Schaarschmidt [11] investigated calculating the brain weight using the body height. They determined the expected weight of the brain according to these formulas:

$$\begin{aligned}(\sigma)M_{ERS} &= 554.5 + 5.03 \cdot \text{body height}, \text{ and} \\ (\varphi)M_{ERS} &= 464.2 + 4.95 \cdot \text{body height}\end{aligned}$$

where M_{ERS} represents the expected weight of the brain. However, their calculation was not based on the edematous brain and it can be used only for a normal brain that has not been affected by any pathological process.

Hausmann et al. [12] published a morphometric research of brain edema, graded by measuring the parahypocampal gyrus, the cerebellar basal conus extension, and perivascular distension in 42 subjects with brain edema. The Röthig & Schaarschmidt method was used as a criterion for normal brain weight for these subjects, but the study failed to define these morphometric parameters as reliable for grading or even diagnosing brain edema.

Rapid and reliable assessment of the existence of a brain edema during an autopsy is an everyday challenge faced by medical examiners / forensic pathologists. The aim of this research is to reveal a mathematical relation that will determine the presence of a brain edema (especially in those cases where the edema is not evident macroscopically) using simple measurements of the diameters of the cranial cavity (as morphometric parameters that are individual, age and gender dependent) and the weight of the brain. This method, relying on a mathematical relation, would be able to determine the existence of brain edema with a certain degree of reliability in a fast and easy way without relying on subjective impressions of each examiner.

METHODS

The study covered post mortem measurement of morphometric parameters of the skull and the brain in 200 subjects who underwent a forensic autopsy.

Measurements of morphometric parameters of the skull were related to the determination of the volume and the diameters of the cranial cavity. For the first 20 subjects, measurements were performed three times in order to increase the accuracy. The second and third measurement of the diameters of the skull was no different than the first in every case, and it was concluded that these parameters can be accurately measured by only one measurement. On the other hand, measurement of the volume of the cranial cavity and the volume and weight of the brain were performed three times for all participants and then calculated as the mean value.

Criteria for inclusion / exclusion in the study

The inclusion criteria for this study were fulfilled by considering deceased bodies of both sexes older than 18 years and younger than 80 years. We excluded people older than 80 due to the significantly higher incidence of brain atrophy in this population [7], which could seriously dehomogenize the sample and give false-negative results (that is, show histologically confirmed edematous brains as non-edematous).

Also, we excluded the subjects with:

- fresh skull fracture – due to the inability of accurate measurement of the diameters of the cranial cavity;
- expansive intracranial processes (tumor, epidural / subdural hematoma and subarachnoid hemorrhage) – because of the disturbed volume ratio between intracranial structures;
- hydrocephalus or enlarged brain ventricles;
- calcifications of dura matter;
- Morgagni-Stewart-Morel's syndrome (*hyperostosis frontalis interna* – skull thickness greater than 12 mm in the area of frontal bone's shell, outside the central longitudinal line of the body – common in our Mediterranean region);
- initial and advanced decay changes.

For some subjects, the measured volume of the cranial cavity differed from the actual volume by more than 1% because of deviation from the circular line that occurred during skull cutting. These subjects were also excluded from the study.

In the end, due to the rigorous criteria for inclusion in the study, measurements were made in only 200 bodies out of 1500 available autopsies. However, because of errors that occurred during the measurement (primarily due to improper cutting of the roof of the skull), final evaluation of the data was done in only 110 (respondents – deleted from the text) out of the 200 examined subjects.

Measuring the volume of the cranial cavity

After opening the skull with the electrical saw and precisely following the previously drawn circle with the center front barrel at about 2 cm above glabella and the center posterior barrel at the level of the posterior occipital protuberance, the brain and the dura mater were removed with the usual technique. Then, using the adaptive waterproof rubber, all major foramina in the base of the skull were sealed (*foramen magnum, lacerum, ovale, rotundum and caroticum*). The head and upper body were then placed upright so that the cross-section of the skull lies within the horizontal plane (Figure 1).

The volume of the lower half of the cranial cavity was measured by pouring water into the lower half of the cranial cavity all the way to the edge and subsequently pouring it into a graduated cylinder. The same procedure was repeated on the upper half of the skull, and the water was poured into the same cylinder.

Measuring the diameters of the cranial cavity

The measurement of the diameters of the cranial cavity was carried out in the central sagittal plane and the widest level of the transversal plane, as well as the frontal plane for the depth. We measured the largest internal distance (the distance between opposing internal bone plates) using a schubler – slide caliper. While measuring the sagittal (longitudinal) distance, the frontal bone's wrinkles and occipital bone's bumps were avoided. Grooves of the medium meningeal artery were avoided during the measurement of the transverse distance. The "depth" of the skull was determined by the distance between the top of the skull (*apex*) and the middle of the cliff (*clivus*) of the occipital bone. In order to measure the depth, it was necessary to drill a hole at the apex, pull the extracting part of slide caliper through it, and measure the distance to the middle of the cliff (Figure 2).

Measurement of the mass and volume of the brain

To measure the weight of the brain, a digital scale with a precision of ± 1 g was used. The volume of the brain was determined according to the basic principles of measuring the volume of firm bodies with an irregular shape. After sinking the brain into a vessel of water, the volume of the displaced fluid was measured.

Microscopic verification of brain edema

Brain edema is clearly visible by microscope with the use of basic hematoxylin-eosin staining. In order to standardize the test, the clips were taken from the basal side of temporal lobe and lateral side of contralateral parietal lobe of each brain. The diagnosis of the brain edema was confirmed by the standard criteria for brain edema in hematoxylin-eosin stained slides: the slides are paler than normal, with halos around cells in gray matter, as well as the increased looseness of the white matter.

Design of the study

This study was designed as a cohort study. After microscopic examination of all brain slices and confirmation of the diagnosis of brain edema, all subjects were divided into two groups. The first group consisted of 72 patients who had a histologically confirmed brain edema, and

the second group consisted of 38 patients who did not have (a – deleted from the text) brain edema.

The mathematical calculation

By multiplying the measured diameters of the cranial cavity for each subject, we calculated its theoretical volume (as the volume of a parallelepiped), which was then compared with the actual measured volume of the cranial cavity, in order to calculate the coefficient of volume of the cranial cavity. Its mean value will be used as a corrective factor in future, to calculate the corrected estimated volume of the cranium.

$$\begin{aligned} V_{Ce} &= LD \cdot TD \cdot h, \\ \lambda &= \frac{V_{cm}}{V_{ce}}, \\ V_{Cce} &= \lambda \cdot LD \cdot TD \cdot h \end{aligned}$$

V_{Ce} stands for the estimated volume of the cranial cavity, defined by its diameters: LD (longitudinal distance), TD (transverse distance) and h (height, or depth of the skull); V_{Cm} represents the actual volume of the cranial cavity (measured as the volume of poured water); λ is the coefficient of volume of the cranial cavity and V_{Cce} is the corrected estimated volume of the cranium (Figure 3).

According to Troncoso [5], 93% of the volume of the cranial cavity is taken by the brain and the remaining 7% belongs to the meninges and cerebro-spinal fluid. Based on the measurement of the actual volume of the cranial cavity, one can determine the expected theoretical value of the volume of a non-edematous brain (B_V) with a simple formula: $B_V = 93\% \cdot V_{Cm}$. However, since the morphometric examination included the measurement of the brain volume and the volume of the cranial cavity in each case, we were able to determine the ratio of these two values for the tested sample (referring to the second group – subjects who did not have histologically verified brain edema). We obtained the value of 92.4%, which we used in further calculations for estimating the expected volume of non-edematous brain (B_V) instead of the value of 93%, given by Troncoso. By doing this, we increased the accuracy of the calculation:

$$\begin{aligned} B_V &= 0,924 \cdot V_{Cce} \\ B_V &= 0,924 \cdot \lambda \cdot LD \cdot TD \cdot h \end{aligned}$$

After classifying the subjects into two groups based on the histological findings, the mean value of the mass and volume of non-edematous brains (the second group of subjects) were calculated and the mean density of the brain was found using the formula:

$$B_D = \frac{B_W}{B_V},$$

where B_D represents the mean density, B_W – the mean weight of the brain, and B_V – the mean volume of non-edematous brain.

Finally, we identified the ratios:

- the ratio of the expected (based on B_D and mean value of λ) and the measured weight of the brain: B_{We}/B_{Wm}
- the ratio of the expected weight of the brain according to Röhthig & Schaarschmidt and the measured weight of the brain: B_{WRS}/B_{Wm} ;

where B_{WRS} represents the expected mass of the brain according to the method Röhthig & Schaarschmidt, calculated by the formulas noted in the introduction chapter.

The B_{WRS}/B_{Wm} ratio was calculated in order to compare the results of the study with the known methods performed by other researchers [11].

For the cases where the brain edema had been histologically verified, the borderline values of the brain mass were determined in a way that the ratio of the expected and measured weight of the brain (B_{We}/B_{Wm}) reduced the value of the hypothetical coefficient ϵ (epsilon).

When the value of the coefficient ϵ is higher than the statistically calculated value for specific confidence intervals, there is no brain edema. When it is lower than this value, the brain edema is present. The final result of this research is that the value of the coefficient ϵ , which is based on the brain weight (B_W) and the diameters of the cranial cavity (LD, TD and h, or only AP and LR with known mean value of height) measured during an autopsy, can be used by a pathologist to immediately identify the presence of a brain edema. If the value of ϵ is higher/lower than the statistically calculated limits for a given diameter of the skull, a pathologist will immediately be able to state, with a high certainty, whether or not there is a brain edema without histological verification.

Statistical analysis

The normality of the distribution within the groups was determined for each individual feature using the Shapiro-Wilks's test. Given the fact that in the pairs of compared features one of them belonged to a normal distribution and the other one did not, it was necessary to perform a non-parametric Mann-Whitney U test in the statistical analysis. In only one case both series of data belonged to a normal distribution and the parametric Student's t-test could have been used. A non-parametric Z-test was used in the comparison of proportions. The exact values of probability p is listed, where it has been implied that the statistical significance exists if $p < 0.05$ and that this significance is high if $p < 0.01$.

The ROC (Receiver Operating Characteristic) curve is used in methods of prediction by establishing the cut-off value between positive and negative test results in a given sample. The area under the curve is a measure of the accuracy of the prediction of the test which provides the levels of sensitivity and specificity for a given prediction. In the present examination, the ROC curve was used to determine the threshold value of the coefficient ϵ for which the subject does or does not have a brain edema.

RESULTS

The descriptive statistics

After performing the measurement in over 200 subjects, the final sample size was limited to 110 subjects due to the defined criteria for inclusion in the study. Based on the microscopic examination of the brain clips, they were divided into two groups. The first group consisted of 72 subjects with a histologically verified brain edema, while the second (control) group consisted of 38 subjects who did not have a brain edema. Table 1 provides the basic descriptive data for these two groups of subjects.

The results of morphometric measurement and the mathematical calculation

In all 110 subjects, all three diameters of the cranial cavity were measured. By multiplying their values for each individual, the volume of the parallelepiped (V_{Ce}) was calculated, with the average value of 2645.81 ± 220.33 ml for all subjects. Then the actual volumes of the cranial cavities (V_{Cm}) were measured and the mean value of 1395.59 ± 143.47 ml was calculated. The average value of the coefficient of volume of the cranial cavity (calculated as the ratio of the actual volume and the volume of a parallelepiped) was $\lambda = 0.528 \pm 0.033$.

Then the volume of the cranial cavity was calculated for the value of λ for each respondent, according to the formula:

$$V_{Cce} = \lambda \cdot LD \cdot TD \cdot h$$

The mean density of the brain was then calculated, based on its weight and volume. The mean density of a non-edematous brain (the second group) was found to be $B_{D2} = 0.967 \pm 0.046$, and the mean density of an edematous brain (the first group) was found to be $B_{D1} = 1.148 \pm 0.050$.

Then, the expected brain volume and weight was calculated for the mean value of the coefficient of volume of the cranial cavity for all subjects, according to following formulas:

$$\begin{aligned} B_V &= 0,924 \cdot \lambda \cdot LD \cdot TD \cdot h \\ B_V &= 0,924 \cdot 0,528 \cdot LD \cdot TD \cdot h \\ B_V &= 0,488 \cdot LD \cdot TD \cdot h \\ B_{We} &= B_V \cdot B_{D2} \end{aligned}$$

The value of the expected weight of the brain for the mean coefficient λ and the mean density of a non-edematous brain, (B_{We}), is the key parameter of this study. After comparing this value with the measured weight of the brain, (B_{Wm}), a set of data was obtained (B_{We}/B_{Wm}) for both groups of subjects. Using the Shapiro-Wilks's test, it was determined that the set of data from the first group did not have the normal distribution ($p = 0.013 < 0.05$), while the set of data from the second group did have the normal distribution ($p = 0.055 > 0.05$), which led to using the non-parametric Mann Whitney's U-test. It was determined that $p < 0.001$, which means that the difference in the B_{We}/B_{Wm} ratio between the first and the second group has high statistical significance.

The ratio of the expected and measured weight of the brain, calculated by the methodology proposed in this research (B_{We}/B_{Wm}), was compared with the ratio calculated by the Röhlig & Schaarschmidt methodology (B_{WRS}/B_{Wm}). Using the non-parametric Mann Whitney's U-test, the obtained p value was less than 0.001 which concludes that there is a significant difference in the results of these two methodological approaches.

The coefficient ϵ

If we refer back to the B_{We}/B_{Wm} ratio, it is clear that B_{We} is a value that contains the mean value of the coefficient λ , the mean density of a non-edematous brain (from the second group of subjects) B_{D2} , and the mean value of the brain's share in the volume of the cranial cavity (92.4%). Multiplying all constant values ($\lambda \cdot B_{D2} \cdot 0.924$) gives the result of 0.475, which leads to the formula for the coefficient ϵ that can be used for the evaluation of the presence of brain edema based on the measured brain weight (B_{Wm}) and the diameters of the roof of the skull (LD, TD and h):

$$\epsilon = \frac{0.475 \cdot LD \cdot TD \cdot h}{B_{wm}}$$

Using this formula, a new set of data was made for the measured morphometric parameters of the cranial cavity and the brain in both groups. After comparing these sets of data between the groups, once again it was found that the set of data from the first group of subjects did not belong to the normal distribution ($p = 0.012 < 0.05$), while the second group did ($p = 0.065 > 0.05$). Therefore the non-parametric Mann Whitney's U-test was applied showing that the p-value in the tested sets of data was less than 0.001 which leads to the conclusion that there is a highly statistically significant difference between the coefficient of ϵ of the first and that of the second group. The ROC curve (Figure 4) reveals that these two sets of ϵ has an area equal to 0.990. For the cut-off value of 0.9792, the sensitivity of the test was 0.972, while the 1-specificity equaled 0.015.

Given the fact that the standard autopsy technique does not involve the measurement of the height of the skull (h), which is a pretty complicated deal that involves the use of non-standard autopsy equipment, it seemed that the previously given formula for the coefficient of ϵ would be useless in practice. Therefore, based on the measurements of the height of the cranial cavity in all 110 subjects, we calculated the average height of the skull and obtained the value of 12.19 cm. Consequently, the final equation that does not depend on the skull height was reached:

$$\epsilon(h) = \frac{5.79 \cdot LD \cdot TD}{B_{wm}}$$

Following the same procedure as the described above using the Shapiro-Wilks's test, it was found that the newly formed sets of data for the coefficient ϵ have the normal distribution in both groups ($p = 0.161 > 0.05$ in the first group and $p = 0.165 > 0.05$ in the second group). Therefore, the parametric Student's t-test was performed in the further analysis. Since the p value was found to be less than 0.001, it was concluded that there is a highly statistically

significant difference between these two sets of coefficient ϵ values. The ROC curve is presented in Figure 5 and has a surface of 0.985. For a cut-off value of 0.9484, the sensitivity of the test was 0.922 and the specificity equaled of 1–0.045.

Mean values of the coefficient ϵ , as well as its minimum and maximum values within the groups, are given in Table 2.

DISCUSSION

Although this study had primarily been focused on the determination of a mathematical formula that would quickly and simply verify the presence of a brain edema, other important results were obtained during this research, which could serve other purposes. Specifically, the ratio of the volume of the brain and cranial cavity volume given by Troncoso [5] as 93%, showed little variation in the present study, yielding a value of 92.4%. Since the measurement of the volume of the brain and the cranial cavity had been repeated 3 times in each subject, a reliable result was obtained.

Furthermore, the coefficients of volume of many different organs are well known in medicine and have a routine use especially in ultrasound, CT, and MRI examination of parenchymal organs. The research showed that the mean coefficient of the volume of cranial cavity equals 0.528 ± 0.033 . The low value of the standard deviation in this case (6.25%) indicates that the diameters of the roof of the skull can predict the volume of the cranial cavity very well.

In addition, some other morphometric values were obtained in this study. The mean volume of the cranial cavity is 1395 ± 143 ml, regardless of gender, i.e. 1451 ± 127 ml in men and 1249 ± 102 ml in women. Quattrehomme et al. [10] got significantly higher values of the volume of the cranial cavity: 1676.47 ± 161.26 ml for men and 1476.48 ± 102.49 ml for women. The difference of almost 200 ml is not clear. Whitwell et al (13), using MR imaging, got the mean total intracranial volumes of $1382 \text{ mL} \pm 144$ and $1374 \text{ mL} \pm 150$ when measured on T1- and T2-weighted images, which is close to the values referred by our study.

The mean weight of a non-edematous brain is 1254 ± 107 g in men, and 1107 ± 87 g in women. The obtained values are lower than the ones published by Dawson and Neal [6] which state that the mean value of brain weight is 1400 g for men and 1275 g for women. One possible explanation for these variations may be the difference between the mean ages of the subjects in our study (46.68 years) and that of the aforementioned study (33.5 years). It is a known fact that the brain mass decreases with age.

The mean density of the brain was also obtained in this study: 0.967 g/ml for a non-edematous brain and 1.148 g/ml for an edematous brain. The standard deviations of these quantities were 4.81% and 4.35%, respectively.

The complex mathematical algorithm we applied has shown that we can determine parameters associated with the skull size: the diameters of the cranial cavity, the volume, as well as the weight and volume of the brain. Deviations from these expected values indicate

an edema or atrophy of the brain. Since the evaluation of atrophic brains was not the aim of this study, the brains that had a greater than typical mass were researched.

One of the key variables of the study on the path to the required coefficient ϵ is the value of the expected mass of the brain for the mean coefficient λ and the mean density of a non-edematous brain. By comparing this value with the actual weight of the brain measured for each subject according to defined groups, we found a high statistically significant difference ($p < 0.001$). Thus, the ratio of the expected mass of an edematous brain and the actual measured mass of the brain (the first group) was significantly different than the ratio of the mass of a non-edematous brain and the actual measured brain (second group). Using the ROC curve, we obtained a cut-off value of 0.9989 with a very high sensitivity (97.5%) and specificity (98.6%) with a predictive accuracy of 99%. If this ratio is greater than 0.9989, the brain is classified as having no edema. If the ratio is lower than 0.9989, then the brain is classified as having an edema. With this method, 97.5% of the sampled brains would be correctly classified as edematous and 1.4% would be incorrectly classified as edematous.

By performing the same calculation using the literature-known method of determining the expected mass of the brain by Röthig & Schaarschmidt [11], we also obtained the results that were highly statistically significant in the groups regarding the difference in the ratio of expected brain weight and the actual measured brain weight ($p < 0.001$). Applying this approach in determining the expected mass of the brain, the ROC curve defines the ideal cut-off value of 1.0063 with a sensitivity of 98.7%, a specificity of 98.4%, and a predictive accuracy of 98.3%. As in the previous calculation, if the value of the ratio is lower than the cut-off value, a brain edema exists. If it is greater, a brain edema does not exist. By using this methodological approach, 98.7% of the brains would be correctly classified as edematous, and 1.6% would be incorrectly classified as edematous.

However, using the Mann-Whitney's U-test, we compared these two methodological approaches to the prediction of the presence of a brain edema and obtained high statistical significance ($p < 0.001$). In other words, although both methodological approaches are good for the prediction of the presence of a brain edema using morphometric parameters (ours based on the diameter of the cranial cavity, and the other on the basis of body height), the significant difference indicates that the methodological approach defined in our study is more reliable. This claim is based on the finding that the mean deviation of the expected mass of a non-edematous brain obtained in this calculation is 57 g and the mean deviation of expected mass of a non-edematous brain obtained by Röthig & Schaarschmidt is 186 g. This is confirmed by the accuracy of the prediction ROC curves for the Röthig & Schaarschmidt's method (98.3%) being lower than the prediction accuracy of the ROC curve for our methodological approach (99%).

In the Results paragraph, it has already been noted that the value of the expected mass of a non-edematous brain depends on a number of constant values such as the mean value of the coefficient of volume, the mean density of a non-edematous brain and the mean value of the share of brain in the volume of cranial cavity (92.4%). Therefore, all constant values can be multiplied in order to obtain a unique constant parameter in the formula for the coefficient ϵ , which has a value of 0.475. The coefficient ϵ represents the ratio of the product of

multiplication of the diameters of the skull and the measured brain mass multiplied by the value of the constant parameter 0.475. Comparing the coefficient of ϵ among respondents in both groups, a statistically significant difference was found ($p < 0.001$). The ROC curve showed that if the cut-off value of the coefficient ϵ is 0.9792, there is a test sensitivity of 97.2% and specificity of 98.5% with an accuracy of prediction of 99%. Thus, using this formula for the coefficient ϵ , 97.2% of respondents would be correctly diagnosed with a cerebral edema, while 1.5% would be incorrectly diagnosed with a cerebral edema if the value of the coefficient ϵ is less than 0.9792.

Although a number of subjects had been excluded from the study because of imprecise cutting of the skull, it is important to note that, in the routine use, strictly precise cutting of the skull is not necessary and that the diameters of the skull can simply be measured after applying standard cutting methods. Precise cutting was only needed during the analysis in order to increase the accuracy of the measurements of the volume of the cranial cavity. Bearing in mind that only the measurement of the longitudinal and transverse diameter of the skull represents a part of the routine autopsy procedure, it was necessary to adjust the formula for the coefficient ϵ , in order to avoid the measurement of the height of cranial cavity. Measuring the height of the cranial cavity requires a step-out from the standard autopsy technique, which makes this calculation unnecessarily complex. If the mean height of the cranial cavity obtained in this research is multiplied by the other constant parameters, a new constant value of 5.79 is obtained which results in the formula:

$$\epsilon(h) = \frac{5.79 \cdot LD \cdot TD}{B_{wm}}$$

When the results of the coefficient ϵ obtained by this approach were compared in groups, a highly statistically significant difference was noted ($p < 0.001$). The ROC curve shows that the ideal cut-off value of the coefficient ϵ is 0.9484 with a sensitivity of 92.2% and a specificity of 95.5%, with the accuracy of prediction of 98.5%. Therefore, with a probability of 98.5%, we can state that 92.2% of the examined brains will be properly classified as edematous and 4.5% will be incorrectly classified as edematous if the value of the coefficient ϵ is lower than 0.9484. The accuracy of prediction, as well as the sensitivity and specificity of the coefficient ϵ , is worse than the results for the coefficient ϵ that involved measuring all three diameters of the cranial cavity. However, the use of the coefficient ϵ is still preferable for routine use due to its simplicity.

In Table 2, we can see that the maximum value of the coefficient ϵ for an edematous brain is 0.985, and the minimum value of ϵ for a non-edematous brain is 0.913. In order to increase the reliability of the given formula for all values of the coefficient ϵ in the interval below, the diagnosis of brain edema should be confirmed by microscopic examination.

$$0.913 < \epsilon(h) < 0.985$$

Microscopic examination would increase the accuracy of the prediction, the sensitivity, and specificity to 100%. For values of the coefficient ϵ (which involves measuring all three

diameters of the cranial cavity), the boundary of the non-absolute reliability is from 0.852 to 0.953.

Microscopic verification remains the method of choice in specific pathological conditions listed in the Introduction paragraph (fresh skull fractures, brain tumors, hydrocephalus, etc.), as well as in older senescent individuals (brain atrophy), due to high individual variability, which makes a universal mathematical approach practically impossible.

CONCLUSION

This research led to several important conclusions:

1. The average volume of the cranial cavity is 1395 ml; 1451 ml for men and 1249 ml for women.
2. The coefficient of volume of the cranial cavity is 0.528.
3. The average density of a non-edematous brain is 0.967 g/ml.
4. The average density of an edematous brain is 1.148 g/ml.
5. The formula for calculating the coefficient ϵ , which includes constant parameters that account for the mean value of the height of the cranial cavity, was obtained:

$$\epsilon(h) = \frac{5.79 \cdot LD \cdot TD}{B_{wm}}$$

(LD – longitudinal distance, TD – transversal distance and B_{wm} – measured weight of the brain).

6. When the diameters of the skull and brain weight are measured during the autopsy and then incorporated into the formula, if the result is less than 0.9484, with a confidence level of 98.5%, it can be stated that there is an edema in the brain. If you want to achieve the reliability of 100%, it is necessary to confirm the diagnosis by microscopic examination in all subjects with the coefficient ϵ between 0.913 and 0.985.
7. The study results will greatly facilitate the daily routine macroscopic assessment of the existence of a brain edema based on scientifically determined principle that nullifies an inaccurate subjective assessment of a pathologist.

Acknowledgments

No part of this paper has been published, or submitted for publication elsewhere in this or in any other language. The paper has been presented as poster presentation on 23rd Congress of the International Academy of Legal Medicine, January 19–21, Dubai (UAE).

During the research, Dr Radojevic was a fellow of Fogarty International Center of the National Institutes of Health's "Research Ethics Education in the Balkans and Black Sea Countries" (Award Number R25TW008171), provided by Icahn School of Medicine at Mount Sinai New York USA and School of Medicine University of

Belgrade Serbia. As so, ethical principles conducted during the research were influenced by the education acquired. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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HIGHLIGHTS

- Mathematical model for rapid evaluation of a brain edema during the autopsy is presented.
- The method aims to eliminate subjective assessments when determining the presence of a brain edema.
- The coefficient ϵ links intracranial diameters, brain volume and brain weight, and gives very high reliability to determine brain edema.
- Some other morphometric parameters are also presented.

Figure 1.
The head and upper body are arranged upright so that the cross-section of the skull lay within the horizontal plane of the skull before pouring the water.

Figure 2.
Measurement of the cranial cavity depth.

Figure 3. Schematic representation of the relationship between V_{Ce} and the actual volume of the cranial cavity.

Figure 4.
ROC curve for the coefficient ϵ by groups.

Figure 5.
ROC curve for the coefficient ϵ by groups, with the abstracted mean skull height H_S .

Table 1

Age statistics by groups (n – number of subjects in each group).

		First group (with brain edema)	Second group (without brain edema)	Total
n		72	38	110
Age (in years)	Mean value	45.93	48.11	46.68
	Standard deviation	14.22	16.08	14.85
	Median	46	50	47
	Minimum	19	18	18
	Maximum	70	72	72

Table 2

The values of the coefficient ϵ by groups (ϵ – the value of the coefficient used to evaluate the presence of brain edema; LD – longitudinal distance; TD – transversal distance; h – height; B_{wm} – measured weight of the brain; $\epsilon_{(h)}$ – the value of the coefficient used to evaluate the presence of brain edema after incorporating the average value of h into the formula).

	First group		Second group	
	$\epsilon = \frac{LD \cdot TD \cdot h}{B_{wm}} \cdot 0.475$	$\epsilon_{(h)} = \frac{LD \cdot TD}{B_{wm}} \cdot 5.79$	$\epsilon = \frac{LD \cdot TD \cdot h}{B_{wm}} \cdot 0.475$	$\epsilon_{(h)} = \frac{LD \cdot TD}{B_{wm}} \cdot 5.79$
Mean value	0.836	0.837	1.022	1.023
Median	0.841	0.838	1.018	1.026
Minimum	0.612	0.627	0.852	0.913
Maximum	0.953	0.985	1.126	1.113