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The Significance of the Amount of Fluid Surrounding the Brain to the Recognition of Brain Swelling (or Atrophy) at Autopsy: A New and Routinely Applicable Method of Diagnosing Abnormal Brain Size

ABSTRACT: A new method of measuring relative brain size (relative to the skull cavity) at autopsy is presented. It is convenient and accurate and may be applied almost routinely. It consists of measuring the volume of the brain and the fluids surrounding it. These two volumes together must equal the intracranial volume. An abbreviated method consists of relating the fluid volume to the brain weight. This abbreviated method should not be routinely relied on when the brain size deviates slightly from normal. A review of the pertinent literature shows that other existing methods of determining relative brain size are impractical. The significance of measuring peri-brain fluids at the time of brain removal has not been appreciated prior to this report.

KEY WORDS: pathology and biology, brain, postmortem examinations

Inherent in most discussions and considerations of the sequelae of head trauma is the contribution that brain swelling, usually mediated by brain herniations and often arterial compressions, might make towards the death of the patient. Answering such medicolegal questions as Was the severe fatal cerebellar tonsillar herniation found at autopsy caused by the head trauma that occurred only 3 min prior to death? is usually scientifically impossible, and will remain so, until human brain swelling can be studied more methodically than is presently possible. Standard autopsy methods do not allow easy and accurate recognition of brain swelling, and they should be updated.

The purposes of this report are (1) to familiarize the forensic pathologist with the cumbersome and inaccurate methods of quantitating brain swelling or atrophy reported to date, (2) to introduce a new, practical, and accurate method devised by the author and presently used at the Office of the Medical Investigator in New Mexico, and (3) to review the related literature. This article will be followed by others reporting the data from forensic science autopsies employing the new method.

Preliminary Discussion

One of the most important steps in the autopsy is the measurement of the weights and dimensions of the various organs. This allows the pathologist to make gross diagnoses, such as atrophy or hypertrophy, of abnormal organs and is followed by further study for more specific diagnoses. Norms of organ weights, based on height, weight, age, and other factors, allow probable diagnoses of abnormal organ size in individual cases.

The brain is unique in that it is located within a fixed bony cavity (except during infancy), whereas the other organs are invested by nonbony and moderately distensible sheaths, capsules, or other tissue formations. There is a normal relationship between the brain size and the skull cavity size at all ages, and so the pathologist can assess the normalcy of the size of the brain [1] more accurately than other organs in each individual case. Thus the pathologist can elect to compare the skull cavity volume with the brain volume BV and quantitate any deviations from the normal brain size in each individual case. Ideally, this has a diagnostic accuracy far exceeding visual methods of evaluating swelling or atrophy, which are often highly subjective, and exceeding the accuracy of norms of brain weights for various ages, heights, and body weights. A brain may be quantitatively swollen but visually appear normal [1,2], and the norms for adult brain weight BW for various heights have a spread of 300 g (two standard deviations) per given height [3], a variation too great to be useful in individual cases.

The volume of the brain includes several components or compartments, which include cerebrospinal fluid, better termed cerebral fluid CF, located within the subarachnoid space and ventricles; the vascular system, including intravascular blood; and the nervous tissue parenchyma exclusive of the above compartments. There is normally a dynamic relationship between the several brain compartments such that volume variations in one are compensated for by reciprocal variations in the others, with the optimal result that the brain volume remains rather constant. In the case of an inexorable progressive enlargement of one compartment, as in a brain tumor enlarging the parenchymal compartment, compensation by shrinkage of the other compartments ends and is followed by decompensation and brain swelling. As the brain enlarges the subarachnoid CF ($SACF$) decreases [4], and when the brain fills the skull cavity there is little or no $SACF$. At that point the surfaces of the brain are compressed against bony surfaces (with gyral flattening) and tentorial margins (with uncal and hippocampal herniation), and the brain is forced out the skull cavity through the only available exit, the foramen magnum (with cerebellar tonsillar herniation). These end stages of brain swelling have their well-known clinical correlates [5-8].

Brain swelling is a very general and nonspecific term that can be further defined in each case by dissection and study. It is often rapid in humans [9,10] and experimentally [11-16], but its chronological course obviously depends on the basic neuropathologic and systemic process.

Although brain swelling is extremely common in forensic pathology [17], and its measurement is the commonest purpose of the method to be described, brain atrophy is also encountered. It is defined as a decrease in brain volume and is almost always accompanied by loss of parenchyma and a large increase in the $SACF$. When diffuse it is usually, but not always [1], recognized by gyral atrophy, widened sulci, and increased subarachnoid space. The ventricular system is usually secondarily enlarged. It may be focal (for example, infarct or surgery) or diffuse (for example, organic dementia). Hydrocephalus may complicate any atrophic condition to produce a swollen brain that also shows enormous loss of parenchyma. Quantitative studies of atrophic brains should record the volumes of skull cavity, brain with full ventricles, and brain with empty ventricles to better indicate tissue loss.

Because of factors already mentioned, acute brain swelling has not been systematically studied at autopsy. Pathologists and clinicians are aware that it may occur rapidly [9,18-22] on occasion, but the reports are rather anecdotal. There are no good incidence reports other than one concurrent with this report [17] and deriving from the new method reported herein.

In addition, the nature of acute brain swelling is not well understood [4,23,24]. There is probably loss of cerebrovascular autoregulation [25], but the subsequent relationship between increased blood volume and the formation of hydrostatic edema is complex [26]. This lack of understanding of these processes in the human partly results from the lack of appropriate methods to allow accurate recognition of brain swelling. It is hoped that the new method will allow more concentration on the common problem of acute brain swelling in the human.

Historical Approaches to the Problem

In 1905 Reichardt [1] related the most common method for measuring relative brain size (that is, relative to skull cavity size) to be used during this century. The main purposes of his study were to determine how acurate the method was (since it had been used by predecessors with the accumulation of much somewhat uncertain data) and what likely sources of error there were. The report contains many fascinating and accurate insights on brain swelling and its importance not "seen" by all present-day pathologists. He outlined common fatal causes of sudden acute swelling including convulsions, heat stroke, head trauma, and idiopathy (sudden death in apparently healthy individuals). He was aware that brain swelling or atrophy may not be grossly recognized and emphasized that quantitation of brain swelling would be very useful to forensic pathologists. The method measured the volume of the intracranial space after removal of the brain. The accuracy of the method depended on the removal of the calvarium by a circular saw cut having a flat plane such that when the calvarium and skull base were filled with water (to measure the intracranial volume) the level of the water would closely match that of the saw cut. He plugged the foramina before the filling with water and after removal of most of the dura mater. He made ten measurements in many cases and found that only after the fourth were they internally consistent, or matched. There was often water absorption during the first four. He did not measure the brain volume but instead used the brain weight only. He reported not direct data but generalizations stemming from his study. He stated that if the brain weight was only 5% (or less) smaller than the skull cavity volume, swelling was present, and if it was 20% (or more), atrophy was present (that is, he compared the dissimilar units of grams of brain with cubic centimetres of skull cavity volume). Normal relative brain sizes fell between 5 and 20. There are a number of problems with this method:

1. It is very impractical.
2. Although multiple skull cavity measurements probably provide a reasonably accurate result in most cases, if the calvarium is not removed in a flat plane the skull cavity volume will be falsely low.
3. Filling a container such as the semi-bisected skull with water gives a large area at the surface of the water, which is problematic because water tends to form a reverse meniscus that may exceed the true volume by 50 cm^3. One must be careful that the water level also has a flat plane, but this is not easy in the given autopsy situation because it is difficult to flex the neck so that the surface of the base is truly horizontal and motionless (it is even more impractical to use the isolated skull, as Reichardt did in some cases).
4. The relationship between the brain weight and volume is too variable to be used routinely to determine skull cavity volume because the brain density BD normally has a maximum range from 1.0203 to 1.0464 [27]. For instance, given a BW of 1300 g, the extrapolated volumes corresponding to BD values of 1.0203 and 1.0464 would be 1242 and 1274 cm^3, respectively, a spread of 32 cm^3 ($\pm 2.5\%$ of mean). On the other hand, in most cases the BD only varies by $\pm 0.33\%$, so usually one would be reasonably accurate by assuming a BD of 1.037.

Brandes [28] used a similar method for measuring the skull cavity volume. He did not directly measure the brain volume, although he states that he should have, but apparently

derived a "brain capacity" or volume from a density measurement that he did not clearly define. He also measured the total cerebrospinal fluid *CSF*, including that surrounding the spinal cord, in each case. He attempted to relate postmortem intervals with brain swelling and decreased *CSF*. There was some indication of more brain swelling and less *CSF* in "acute" cases with longer postmortem intervals, but the data are not good. Indeed, recent work [27] indicates brains do not swell as a function of the postmortem interval (up to five days). The main problems with his methods are as follows:

1. The same problems previously mentioned concerning cutting the calvarium in a flat plane and the meniscus error still exist.
2. Deriving a *BV* from a *BD* may be inaccurate unless the *BD* is very accurately measured.
3. Measuring the total *CSF* surrounding the brain and cord without differentiating between spinal and cerebral components is not helpful. All his data showed was that with brain swelling there is a decrease in the total *CSF*. He did not appreciate that the important measurement is *SACF* or peri-brain fluid *PBF*, the amount being inversely related to the severity of brain swelling. He incorrectly thought that the decreased *CSF* in swollen brains was due to postmortem absorption of the *CSF* by the brain (also see Refs *24* and *29*).

Alexander and Looney [30] used the same method of measuring the skull cavity and measured the *BV* by placing the brain in a bucket brim-full of water. The volume of displaced water should equal the brain volume. They also derived *BD* from *BV* and *BW*. Their cases showed a range of relative brain size including normal values, swelling, and atrophy, but, as will be explained, their data cannot be used because of inaccuracies. They introduced the differential ratio *DR*:

$$\frac{ICV - BV}{ICV}$$

where *ICV* is intracranial volume, and when this value is multiplied by 100 it equals the percentage of the skull cavity or *ICV* occupied by the *SACF* or *PBF*. Normal values were between four and nine, and less than four indicates swelling while greater than nine, atrophy. These values are approximate. Problems with their methods are as follows:

1. As with the other methods, the calvarium must be cut in a flat plane.
2. Their method of measuring the *BV* is inaccurate because of the problems with the reverse water meniscus and the splashing that occurs when a brain is put into a brim-full bucket of water. Proof of this is evident not only through manipulation of these methods, but also by the large variation of *BD* values in their data (1.004–1.097). How can a brain have a *BD* (1.004) less than that of *CSF* (1.007)? Their *BD* data could have such a falsely high variation if there were inaccurate brain volume measurements (weight measurements are routinely fairly accurate). An abnormally heavy *BD* could also be explained by extensive mineral deposits.

Davis and Wright [27] used entirely different methods. They filled the empty skull with a balloon and pumped it full of water to a pressure of 150 mm Hg, with the calvarium clamped to the skull base, and the amount of water should have equalled the skull cavity volume. They placed the brain in a glass desiccator of known internal volume and tare weight and, after filling the spare internal volume with saline to the level of the meniscus with a very small area, determined the *BD*. The *BV* was derived from the *BD*.

Their useful data contain several facts on 100 patients. Their values of *BD* are reliable, but the relative brain size indexes (in their study expressed as *BV/ICV* as a percentage) are all low by about 3% (because of balloon herniation). Problems with their methods are as follows:

1. They did not plug the foramen magnum prior to the measurement and consequently the balloon herniated an unknown volume down the spinal canal in every case. This probably amounts to 3% of *ICV* as their two grossly swollen brains were both close to 97% of *ICV* and should have values of 100% (or slightly more with tonsillar herniation).

2. There may have been air pockets in the skull base outside of the balloon,[2] which would render the *ICV* a bit low.

3. Their methods are not practical as routine autopsy procedures and require a special apparatus.

Other methods of measuring *ICV* that depend on filling it with materials other than water, such as peas, BBs, and so on, are fraught with many of the same problems as filling it with water. Indirect methods of deriving brain or skull cavity volumes by the use of various diameters [*31*] are grossly inaccurate.

Harvey et al have evaluated measuring *ICV* by filling the skull cavity with dental plaster (Alginate, Codesco, Inc.). This method is fairly accurate but must be done in one rapid step. It is not practical, is relatively expensive, and is rather difficult.

The main problem with all the reported methods of measuring relative brain size is conceptual. All ask the question, What is the volume that fills an empty skull? Answering that question is too impractical and inaccurate in the standard autopsy situation. Measuring the volume of the brain is much easier to do accurately, but in some cases it is not even necessary.

These methods are generally inadequate and have produced largely unreliable data, with one exception [*27*].

Redefinition of the Problem

The historic approach to measuring relative brain size has been comparing the size of the brain with that of the skull cavity. The difference between these two volumes is the amount of intracranial (subdural) space surrounding the brain. This space is usually occupied by *PBF*, including *SACF* and abnormally subdural blood,[3] and can be directly measured. It must be related to the total *ICV*.

How can we know *ICV* a priori?

The whole equals the sum of its parts. Thus when the calvarium is removed one must measure all that comes out! What comes out is the brain and *PBF*. The *BV* plus the volume of *PBF* must equal the *ICV*. This stands as an a-priori fact unless there is air in the subarachnoid space or there is a tear in the dura allowing leakage of *PBF*. The value (*PBF/ICV*) × 100 gives the percentage of skull cavity occupied by *PBF*, which is the same as the differential ratio already defined. It is no longer necessary to ponder how to measure the volume contained within an empty skull.

We thus have a different solution to the problem of measuring the space (volume of *PBF*) surrounding the brain. This solution does not require an unusual saw cut (of skull) or complicated volumetric determinations. All we might want is a simple method for measuring *BV*.

Methods

Volume of Peri-Brain Fluids

Before the saw cut is made in the skull a tray is placed beneath the cadaver head. As the saw cut is made, and calvarium and brain are removed, all fluids and the brain are caught in

[2]F. H. Harvey, B. Archeleta, E. Finney, and K. Pershall, unpublished observations, 1979.
[3]Subarachnoid hemorrhage of a significant amount contributes to brain swelling and is measured as part of the *BV* since it does not leave the subarachnoid space during removal of the brain.

the tray. Additional fluid pooled in the cranial fossae is aspirated with a volumetric syringe. The brain is lifted up after removal of the dura from its attachments to the brain. When it ceases dripping (10 to 20 s) BV is measured and the fluids in the tray are aspirated into the syringe, resulting in a total volume measurement of PBF (the volume of a partially clotted subdural hematoma is also part of the PBF but must obviously be measured in some other way).

This measurement is not applicable if the dura mater is lacerated but is if there are skull fractures without dural laceration.

There is no leakage of fluids surrounding the spinal cord into the cranial cavity as this is physically impossible in the usual supine position with elevation of the base of the neck of the cadaver by a support.

Volume of the Brain

1. On a standard autopsy organ scale place a six-litre brain bucket two thirds full of water. Note the total weight, designated x g.

2. After inserting string between the basilar artery and pons (as is usually done to suspend the brain in formalin), put the brain in water and suspend the brain motionless above the bottom, completely immersed in water, by attaching the string to an independent suspension point (for example, a loop of another string attached to the chain suspending the scale from the ceiling). The total weight is y g, and $y - x =$ grams water displaced $=$ volume of water displaced.[4]

3. Remove the string from the independent suspension point, or completely remove the string, so that the brain falls to the bottom of the bucket. The total weight is z g, and $z - x = BW$.

This method avoids the reverse meniscus problem; is rapid, inexpensive, and accurate within the given weight ranges;[5] and allows for simultaneous density measurement (which is not a true brain tissue density and is thus of uncertain value).

During removal of the brain most of the $SACF$ leaks out into the skull cavity and the tray or pan, an additional small amount leaks out when the brain is placed in the tray, and the brain ceases dripping soon after being lifted up. It is not necessary to let the brain sit upside down for 30 min to let all the $SACF$ drain out as some investigators [27] advise. Also, there is often reddish discoloration of normal $SACF$ by a very small amount of blood leaking from veins and sinuses.

With the relatively rapid handling of the brain prior to volumetric measurement very little ventricular fluid leaks out [27] and this is appropriate as the brain volume should include "full" ventricles. In some cases where there is ventricular enlargement and laceration into the ventricle(s), the CF leak prevents a BV measurement. In most forensic science cases the ventricles are small (younger age group) and it actually matters little whether there is this leakage.

Discussion

This method of measuring individual relative brain size has not been previously reported, to our knowledge, in the world literature. Its accuracy depends on the scale and syringe

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[4]Temperature-determined alterations in weight versus volume units of water are not significant in the context of this method.

[5]The brain does not absorb a significant amount of water in the 30 s or so that this measurement of BV and BW takes. When the brain is removed from the water the subarachnoid space may fill with up to 25 cm^3 of water, and this drains if it is allowed to. It is not necessary to suspend the brain in more concentrated ("isosmolar") liquids, such as saline, in this method.

used: the BW and BV are probably accurate to ± 5 to 10 g and PBF to 1 cm^3. The DR is thus accurate to two decimal places. That is quite adequate. The value of the method largely stems from directly measuring the volume of the PBF. The complete method is adequate for routine determination of relative brain size, or it can be abbreviated.

The abbreviated method simply requires that the PBF be collected and measured as described above (this should become a routine measurement in almost all forensic science and hospital autopsies). The BV need not be measured but the brain is weighed as usual. An approximate BV ($B\overline{V}$) can be derived from the BW by assuming a BD of 1.036. Thus, $BW/1.036 = B\overline{V}$, and

$$\frac{PBF}{(B\overline{V} + PBF)} \times 100 = DR$$

which represents the percentage of the skull cavity occupied by PBF. This calculation allows one to relate the PBF to variations in brain size owing to height, as the normal volume of PBF is proportional to the total BW or BV. For instance, 20 cm^3 of PBF from an individual two weeks old with a BW of 500 g should be normal:

$$B\overline{V} = 500/1.036 = 482.6 \quad (\pm 2.5\%)$$

and

$$\frac{20}{486.2 + 20} \times 100 = DR \text{ of } 3.95$$

On the other hand, a PBF of 20 cm^3 in an individual with a brain weighing 1300 g is abnormal:

$$1300/1.036 = 1254.8 \quad (\pm 2.5\%)$$

$$\frac{20}{1254.8 + 20} \times 100 = DR \text{ of } 1.57$$

Normal values of DR range from approximately from 3 to 9, so a DR of 1.57 is definite evidence of brain swelling.

Rather commonly at the forensic science autopsy the pathologist will find a relatively small amount of PBF. The value of $(PBF/BW)100$ nearly (smaller by 2 to 4% of DR) equals the DR,[6] and in cases of severe swelling the DR will be in the range of 1 or less. In such cases the BV need not be measured because quantitative swelling is already established. In other words, a 1300-g brain with 13 cm^3 of PBF has a DR of 1 and is swollen, as is a 400-g brain with 4 cm^3 of PBF. As the DR rises, normal variation in BD, and therefore in $B\overline{V}$, will lead to inaccuracies in some cases, and the BV must be measured to assure an accurate DR. Thus the abbreviated method is useful in rapidly recognizing severe brain swelling (or atrophy). In such cases signs of swelling may be absent, or very subtle, and this additional reference point is most helpful. It is less reliable than the full method for diagnoses of mild swelling or atrophy and normal values of DR.

The reader may note some similarities between the abbreviated method and other methods cited. Reichardt [1] related the ICV to the BW. Such a relationship depends on the

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[6]Assuming $BD = 1.036$, $PBF/(B\overline{V} + PBF)100 = DR$ manipulates to $PBF = DR(B\overline{V})/(100 - DR)$. Thus, for a 1500-g brain $B\overline{V} = 1448$ cm^3; with $DR = 1$, PBF is 14.6 cm^3; with $DR = 2$, PBF is 29.5 cm^3; with $DR = 3$, PBF is 44.8, and so on, and $(PBF/BW)100 = 0.97$ (DR 1), 1.96 (DR 2), 2.98 (DR 3), and so on. The PBF/BW ratios hold for all brain weights.

actual *BD*. Any errors encountered because an actual *BD* differs from the assumed *BD* are further compounded by the previously discussed primary error of *ICV* determination. In the abbreviated method just described the most critical measurement, that of *PBF*, is made directly at the outset.

Brandes [*28*] also measured fluids, but always total CSF without specifically determining *CF* or *PBF*. At that time it was not appreciated [*32*] that in brain swelling with occlusion of the tentorial aperture by hippocampal herniation not only may the spinal fluid pressure remain normal, but its volume also remains relatively unchanged. It is not driven into the venous system as the *CF* is. Thus his data record a reduction in total *CSF* associated with brain swelling, but the percentage of reduction $(CF \times 100)/CSF$ is rather meaningless unless one knows the normal spinal fluid volume $(CSF - CF)$ in the individual prior to swelling (which is generally impossible). Again, the critical measurement is that of *PBF*, and Brandes did not appreciate this.

One of the very important applications of our method is to pediatric neuropathology. The cited methods cannot be applied to infants because the sutures are not fused. Our method is just as easily applied to infants as to adults. We are presently establishing normal data during infancy, which has not heretofore been possible.

Another application of such routine brain swelling measurements is to "normal" brain weight data. Such data continue [*33*] to be related to multiple parameters such as height, weight, race, and age. These data are to some unknown extent inaccurate, depending on the unrecognized incidence of brain swelling without signs. It is evident that in the early phase of decompensation the brain swells to fill the *ICV*. Signs generally do not develop until the *BV* nearly equals the *ICV*, as only at that point is the brain forced against skull, tentorium, and foramen magnum.

It does appear [*9,28*] that in the case of a relatively gradual death of hospitalized patients the incidence of brain swelling is lower than in acute natural and traumatic deaths; however, this has not been well established. Thus existing normal brain weight data may need to be reevaluated to take into account the incidence and amount of brain swelling or atrophy present in so-called normal brains.

Summary

A new method of measuring relative brain size (relative to the skull cavity) at autopsy is presented. It is convenient and accurate and may be applied almost routinely. It consists of measuring *PBF* at the time of brain removal. The *BV* is also measured. These $(PBF + BV)$ must add to equal *ICV*. This is self-evident and does not require scientific demonstration. In fact, $(PBF + BV)$ stands as the measure of *ICV* to which all other methods must be compared.

The differential ratio is defined as

$$\frac{PBF}{PBF + BV} \times 100 = DR$$

Normal values of *DR* range from approximately 3 to 10. Less than 3 means brain swelling, and greater than 10, brain atrophy (or hypoplasia).

An abbreviated method consists of relating the *PBF* volume to *BW*. Its accuracy depends on the assumption that the individual brain has a density of 1.0367, but this assumption may occasionally be substantially incorrect because of a normal *BD* range from 1.0203 to 1.0464. For the abbreviated method,

$$\frac{PBF}{PBF + (BW/1.037)} \times 100 = DR$$

The abbreviated method is probably satisfactory if $(PBF/BW)100 =$ either less than 1 or 2 or more than approximately 15, but it should not be relied on routinely in less severe departures from normal.

The pertinent literature is reviewed, and it is seen that all other existing methods of determining relative brain size are impractical. It is also noted that the significance of measuring the peri-brain fluids at the time of brain removal has not been appreciated prior to this report.

Acknowledgments

Addendum

For purposes of historical accuracy it is noted here that appreciation for concepts in this paper is apparent in the article by F. Apelt, "Der Wert Schädelkapazitätsmessungen und Vergleichen Hirngewichtsbestimmungen für die innere Medizin und die Neurologie," *Deutsche Zeitschrift für Nervenheilkunde*, Vol. 35, 1908, pp. 306–333.

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