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Abstract

Background

The brain is a dynamic organ that develops and involutes in volume. The process of volume loss known as brain atrophy commonly occurs in elderly. However, some conditions have been implicated to provoke this paradoxical process in childhood and making it important to have methods and techniques of quantifying brain volume. Automated quantitative methods are very important in brain atrophy assessment but these tools have limited availability in developing countries. The simplified linear radiological methods are poorly reproducible and hence there is a need to develop an alternative formula that is reproducible and applicable at all healthcare levels.

Methods

The multi-linear diagonal brain fraction formula (DBF) was designed from dimensions of brain relative to skull. To test a developed formula, a total of 347 subjects aged between 0 and 18 years who had brain CT scans performed at the health facilities in Northern Tanzania were recruited and subjected to a systematic measurement of their brains in a diagonal brain fashion.

Results

Out of 347 patients evaluated, 62 subjects (17.8%) were found to be cases of brain atrophy. The three radiological measurements which included sulcal width (SW), ventricular width (VW) and Evans Index (EI) were concurrently performed. SW and VW showed good age correlation while EI showed no significant correlation with age. Similar tests were extended to diagonal brain fraction (DBF) and skull vertical horizontal ratio (VHR) in which DBF showed significant correlation.

Conclusions

The DBF formula shows significant ability of differentiating changes of brain volume suggesting that it can be utilized as an alternative brain fraction quantification method bearing technical simplicity in assessing gross brain volume with the ability to classify degrees of brain atrophy into mild, moderate, severe and very severe stages.

Background

The brain is said to be atrophied when it has its volume deviated from the relative intracranial volume of an individual. The understanding of brain volume dynamics is important in the course of studying various central nervous system pathologies in childhood and even in senile age(1). Brain atrophy has been reported to occur in both extremes of age even though it is commonly found in old age as part of

degenerative changes of elderly(2). This suggests that, young age is not exclusion for radiological occurrence of brain atrophy.

Various techniques including conventional and automated methods have been designed and invented to establish quantification of brain volume in terms of liters, mass or percentage fraction in reference to the skull volume(3). In most methods, the skull is taken as a standard reference for individualized brain volume quantification as there is broad diversity of skull shapes and sizes based on age, gender and ethnicities(4). On account of this diversity, individualization of brain values in reference to case based skull size forms the best practice of assessing brain volume and depiction of atrophic cases.

The key role of different techniques is to differentiate between normal brain volume and atrophic brain cases at certain ages. These methods include the simple linear methods such as mid lateral ventricular body width (VW)(5), Evans Index (EI)(6), cortical sulcal width (SW)(7) and sella media index (SMI). The other methods are more advanced and automated. These methods include Voxel Based Morphometry (VBM)(8), Brain Intensity Abnormality Classification Algorithm (BIANCA)(9) and Brain Parenchymal Fraction (BPF)(10). Most of the automated methods which utilize segmentation volumetric techniques can be affected by artifacts and partial volume effect(11). Among various automated methods, SIENA (structural image evaluation using normalization of atrophy) is reported to have the best performance in the measure of brain volume changes(12). Although most of these automated methods define brain atrophy or brain volume in a three-dimensional way, the techniques are highly computerized and therefore require high hands-on technical skills which may limits their use is most health care systems. The method of choice in all health levels therefore, should consider technical simplicity, accessibility and reasonable level of accuracy among other criteria.

In the most developing countries, the existing methods of brain volume quantification have limited application and accessibility in remote areas(13). The radiological images are distributed in printed films as 2-dimenstional achieved images making it very difficult for distant clinicians to execute quantitative evaluation of brain volume status for their patients(14). Compact disc(CD) and digital versatile disc (DVD) image achieving is another emerging modality of disseminating post processed radiological images(15). In addition, the volume automated software are very expensive and rarely known to most radiologists, hence there is less information generated about quantitative evaluation of patients' brains in these parts of the world(16). Moreover, the automated segmentation techniques may need real time procedures and supervision as mostly they were rooted and developed from artificial intelligence(17). Consequently, diverse types of quantitative tools are needed to meet specific requirements like onsite expertise and machinery upgrading while manual methods remain to be the strong backup methods whose utility is far reaching to the lowermost healthcare level.

The linear methods appear to be the easiest ways of performing brain volume evaluation(18). However, these methods lack the power of reproducibility as what is measured on the Computerized Tomography (CT) or Magnetic resonance imaging (MRI) console cannot be reproduced in the same measures through various disseminating tools such as printed films due to issues related to magnification and

minimization of image sizes(19). These methods can be accurately performed using source image or raw image data. The measurements can only be reproduced when a pre-defined scale is provided. However, this provision is not always in practice hence this makes the qualitative observational evaluation of brain status becoming the most common practice among radiologists and neurologists in developing countries(20). In some conditions such as focal loss of brain volume in case of medial temporal lobe atrophy (MTA), visual qualitative assessment of brain atrophy using the Schelten's five points scale has shown significant degree of accuracy than the time demanding quantitative methods(21). Hence, when qualitative and quantitative assessment of brain is utilized in combination a comprehensive and better patient' pathological details can be obtained.

The current study was conducted in response to the emerging trends of increased rates of brain atrophy cases among(22). The goal was to design a multi linear semi-quantitative formula for brain volume evaluation whose application can be far reaching and manageable by all clinicians in different parts of the worlds irrespective of their varying levels of technology. In this research we are presenting an alternative method of brain volume estimation in terms of ratios which were measured in a diagonal fashion. The measurements involves the widest part of the lateral ventricle just at the level between the corpus callosum and inter-commissural line or (the equator of the brain) in axial planes(23). This area of interest is marked by the first appearance of the upper pole of the choroid plexus but more precisely, the widest continuous part of the lateral ventricle above the fornix and below the corpus callosum. The assumption is that the skull volume is the normal standard reference of each individual and the deviation of brain volume from its edges is the measure of atrophic change since the ratio between brain volume and cranial cavity is constant in early age(24). This simple reproducible formula is a linear synthesis of the popularly known Brain Parenchymal Fraction (BPF) which is automated quantitative method(25). Inasmuch as the manual evaluation methods remain to be alternative techniques when automated methods cannot be accessed, this study was done to be part of the solution to such limitations.

Methods

2.1 Subjects

We studied 456 patients between the age of 0 and 18 years old who presented to the radiology department of health facilities in the Northern Tanzania. We scrutinized the performed brain CT scan examinations between 2013 to 2019 years. All the images were reviewed by the radiologists. Only the images that were free of artifacts were selected for the study.

2.2 Inclusion/ exclusion criteria

Children with brain CT scans at the age between 0–18 years and children without anatomical malformations were included in this study. The children with space occupying lesions bearing deformation of native brain anatomy were excluded. A total of 347 subjects who met inclusion criteria were recruited and 109 subjects who did not meet inclusion criteria were excluded due to co-existing pathologies which distorted natural architecture of the brain anatomy. This involved tumor or space

occupying lesion and children whose images showed severe artifacts or did not follow radiological baseline were excluded from the study.

2.3 Image acquisition

All patients' brains were scanned using 6, 16 and 128 slices, Siemens Somatom Emotion, Sensation and Definition machines respectively, with slice thickness of 5 mm and increment of 2 mm as designed by the manufacturer. All the images were taken along the standard radiological baseline.

2.4 CT scan image analysis and the designing of new brain volume formula.

Brain CT scan images were examined by a radiologist. Three known radiological linear methods were measured in order to determine presence or absence of brain atrophy (Fig. 1). The brain atrophy was considered when sulcal width(SW) > 2.5 mm, lateral ventricular body width(VW) > 30 mm(5) or Evans index(EI) of > 0.3(26) was demonstrated.

Furthermore, the similar patients CT scans were extended for further evaluation using the newly designed method namely the Diagonal Brain Fraction (DBF) whose points land marks' of measurements are described in (Fig. 1) were performed in either category of patients.

DBF) formula was applied by measuring the difference between the product of diagonal inter-gyri and inter-sulci distance through the lateral ventricle minus the product diagonal distances of lateral ventricles and finally divided by product diagonal skull distances through the lateral ventricle of the same individual. The obtained results were in form of ratio or fraction and could also be presented in percentage manner. In this exercise the pre-defined normal subjects were acting as control group against the cases of brain atrophy.

2.6 The assumptions behind diagonal brain fractional (DBF) formula design.

The following were the considered assumptions and facts to the designing of multi linear formula for manual estimation of brain fraction.

(i) Brain develops by increasing volume concurrently with head circumference (skull volume)(27)

(ii) Brain has its volume intimately related to the inner table of calvarium during childhood(28).

(iii) When loss of volume (atrophy) occurs there is no vacuum left instead the lost volume is compensated by cerebrospinal fluid as evidenced by enlargement of ventricles and extra-axial CSF spaces.

(iv) During atrophy the gyri (elevated convolutions) and sulci (depressions) become prominent.

(v) In a typical global atrophy ventricles and CSF spaces becomes prominent uniformly and in all directions.

(vi) While brain volume, ventricular size and sulci make significant change during brain atrophy, the calvarial volume or circumference remains constant(29). From this basis a mathematical deviation of brain volume in terms of ratio or fraction and percentage can be deduced.

(vii) Measurements were designed and taken at the widest section of the lateral ventricle at the first appearance of the choroid plexus by subtracting linear products of CSF from linear brain dimensions and divided by intracranial space dimensions.

2.7 Additional procedure

Following incidental observation of skull shape variations, we therefore measured skull vertical size along the radiological baseline and divided by horizontal size to get ratios designated as vertical-horizontal ratio (VHR) (Fig. 2) in order to test them and see if these would associate with the other variables pre-determined in the study objectives.

2.8 Statistical analysis

Analysis of data was done by R-statistical tool where mean and p-values for age and gender correlation of the ventricular size, sulcal width and VHR were obtained.

Non-parametric data were tested using Wilcoxon-Mann-Whitney test as the DBF data were found to be not normally distributed.

Results

Out of 347 patients evaluated, 285 subjects were found to have normal brain volume and 62 subjects were found to be cases of brain atrophy. The following were findings obtained in this study as presented in the following figures and tables.

Table 1
Demographic characteristics of participants in cross section survey with DBF

Variable	Category	Frequency (n)	Percent (%)
Age	< 2 years	28	8.1
	3–7 years	87	25.1
	8–12 years	92	26.5
	13–17 years	140	40.3
Sex	Female	137	39.5
	Male	210	60.5

The demographic characteristics of the children participated in this study had a mean age of **10.3324 (± 4.9965)** years. Male children were significantly more than female amounting to a total of 210 (60.5%) and 137 (39.5%) male and female respectively.

Results shows that the brain atrophy condition trends in 1:1 male to female ratio (data not shown). Furthermore, results show that irrespective of this equal ratio of disease propensity most severe forms of brain atrophy were mostly found in female children while male children predominated with moderate form of brain atrophy. Furthermore, brain dimensions have shown varying relations with age in a general study population (Fig. 3) and a different picture in specific group with normal volume of brain (Fig. 4).

Table 2
Brain dimensional measurements for all children, and correlations of dimensions with age

Quantification method	n	Mean(± SD)	Age and dimension correlation	P value
Sulcal width	347	1.94(± 0.70)	-0.19	0.0004
Ventricular width	347	24.99(± 6.98)	-0.23	< 0.001
Evans index	347	0.34(± 1.38)	0.04	0.431
DBF	347	0.74(± 0.10)	0.21	0.0001
VHR	160	0.73(± 0.05)	-0.13	0.0899

The three radiological measurements which were used included sulcal width (SW), ventricular width (VW) and Evans Index (EI). SW values were measured in 357 children to examine for peripheral or cortical atrophy while VW and EI were measured in 346 children to ascertain the central type of brain atrophy. Both SW and VW correlated well with age at p-value of < 0.05 while EI showed insignificant correlation with age at p-value of 0.431. Similar correlation tests were extended to DBF and VHR in which DBF showed significant correlation with p-value equal to 0.0001 while VHR was insignificant and was measured among 160 subjects as it was an incidental observation in the course of the study.

Table 3
Association between gender and brain dimension measurements

Quantifying method	Male	Female	
	Mean(± SD)	Mean(± SD)	P-value
Sulcal width	1.90(± 0.67)	2.01(± 0.73)	0.122
Ventricular width	24.49(± 4.54)	25.75(± 9.58)	0.152
Evans index	0.26(± 0.04)	0.46(± 2.21)	0.308
DBF	0.75(± 0.08)	0.73(± 0.12)	0.117
VHR (of skull)	0.73(± 0.05)	0.73(± 0.05)	0.398

The association between gender and brain dimensions was insignificant in all of the radiological parameters measured.

Post hoc analysis

Wilcoxon-Mann-Whitney Test was done in both unpaired groups of 285 children with normal brain and 62 children with atrophic brain. The test had the out of z-value of 11.563 and the cut-off probability value of 0.000 which was less than 0.05.

Varying scores of DBF were found in this study (Fig. 5) and (Fig. 6). The severity score of brain atrophy by DBF increases inversely with DBF values (Fig. 7). Results showed that the lower the DBF value the severe the stage of brain atrophy. Brain atrophy below 0.15 was unfound in this study but at any time is considered to be the very severe form of brain atrophy. The DBF values above 0.75 were considered to represent normal brain status in children. At the level of > 0.75 of the DBF scale, there was no event of overlapping values indicative of any confounding mild form of brain atrophy by any of the linear radiological methods namely sulcal width, ventricular width and Evans index when were measured independently.

An alternative mathematical deduction presentation of the measurements to be taken for DBF calculation is hereby presented by in a stepwise manner (Fig. 6). This can show even the small changes for the mild atrophic cases which are nearly normal and discriminate them from the normal brain case. Knowing that a slight variation of skull and brain size exists between two genders, the mathematical deductions can help also evaluation of brain volumes and distribution of brain atrophy among male and female children with age consideration (Fig. 8).

MODEL DEVELOPMENT AND TESTING OF THE DBF FORMULA FOR BRAIN ATROPHY

A linear regression model was formulated with continuous dependent variable DBF and independent variables sulcal width, ventricle width, Evans width and age. Further, the most influencing factors towards the development of DBF are presented in (table 4).

Table 4: Variables influencing DBF.

Four independent variables with negative effect are responsible for lowering DBF due to reduction in brain volume also known as Brain Atrophy.

Variable	Estimate (β)	Std. Error	p-value
Age	-0.0005448	0.0005583	0.33004^{ns}
Evans index	-0.5768042	0.1139583	0.000000756^{***}
Sulcal width	-0.0084889	0.0057079	0.13809^{ns}
Ventricle width	-0.0022760	0.0008497	0.00783^{**}
Multiple R-squared: 0.1254			
Adjusted R-squared: 0.1128			
F-statistic: 9.997 on 4 and 279 DF			0.0000001421^{***}

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 (Means within each factor are compared with t-test at a significance level of 5%)

The developed multiple linear regression looked for the relation that exists between the DBF and the brain dimensional measurements such as sulcal width, Evans index, age and ventricular width. All variables are continuous that deemed us to use the simple multiple linear regression. The model shows that, the unit increase of Evan's index makes the DBF to decrease by factor of 0.5768042 followed by sulcal, ventricle widths and finally, age. The Evans index and ventricular width have statistically significant influence towards decreasing of DBF; hence they are very important factor to consider.

The f-test justified that the model has well fitted the data and it can be used since the p-value is far away less than the confidence level of 0.05, though the R-squared is small. Therefore, the model is statistically significant at confidence level of 5%.

Further, the impact of each predictor can be visualized as shown in (Fig. 9):

Discussion

The purpose of this study was to design the diagonal formula for brain volume estimation using cross sectional study data. The volume of brain was formulated and presented in the form of ratio from the assumption that the diagonal linear span of brain parenchyma over the diagonal span of the skull at the equatorial region of the brain may give a reproducible multi linear ratio to represent percentage amount of brain in relation to the skull volume. For this reason, these ratios are presented in the form of Diagonal Brain Fraction (DBF).

Before DBF were measured, all subjects were subjected to three known simple linear radiological quantifying methods in order to decide the presence or absence of brain atrophy among individuals. While DBF, SW and VW had significant age correlation in the general pediatric population, the incidental skull shape variation represented by VHR was statistically slightly less significant for age correlation at

confidence level of 5%, but definitely becomes significant at 10% confidence level. The EI was very insignificant statistically for age correlation. This phenomenon can be explained by the fact that, Evans index is a ratio obtained by its nominator measured at the anterior horns of the lateral ventricle and divided by the widest skull diameter. Since the white matter myelination of pediatric brain starts in occipital part of the brain and progressively matures toward frontal region(30), there is high likelihood that the volume of white matter has trivial change in the frontal or anterior brain region(31) in association with increase in age. A different picture was shown in a specific pediatric sub-population with normal brain volume. The analysis of children with normal brain volume shows a significant negative correlation of VW, VHR and DBF to age while SW shows significant positive age correlation. The possible explanation of this phenomenon is due to the fact that human brain does not increase in volume at 4th (32) as presented by Courchesne et al., 2000 study, but also the more rapid growth in early childhood in the first two years of life a process that favors small ventricular size(33). The VHR negative correlation with age implies that the skull has dynamic nature of morphology with age and this in turn affects the resultant brain volume as there is strong positive correlation between VHR and DBF(data not shown). Further, the value of VHR in diagnostic radiology may predict the expected trend of DBF or normal brain volume in children. The VHR values had the mean of 0.73(± 0.05). Therefore, the use of multi-parametric evaluation of brain is important consideration when manual evaluation of brain atrophy is attempted.

The SW, VW and EI measurements in the studied population showed insignificant association with gender. Similar observation was noted on DBF and VHR. This insignificant gender association is thought to be due to high likelihood that the studied population was at pre-pubertal stage of life in which gonadal hormone levels for secondary sexual characteristics were too low to show their effects on central nervous system. Low state hormonal receptors' concentration for age is another consideration for the lack of hormonal mediated sex differentiation in brain volume of the studied population. Studies have shown that estrogen has neuro-protective effect and that its withdrawal during menopause may accelerate brain atrophy in old females(34) and contribute to gender difference in brain volume. The influence of estrogen to brain changes is logically too minimal in pre-pubertal age which was the majority in the current study. Therefore age and gender should never be undermined when evaluation of human brain is made for meaningful results to be obtained.

The DBF offers a range of brain percentage as measured just below the bulk of brain mass (centrum semiovale). These ranges represent fractional amount of brain in the skull after excluding cerebro-spinal fluid (CSF). Further information from other studies suggests that an adult human skull volume is estimated to have average of 88.6% brain tissues(35) and 7–12% occupied by CSF(32). Even though these findings were derived from very advanced automated volume segmentation techniques, they did not factor in the presence of major blood vessels such as dural venous sinuses and cortical veins as part of the contents of the intracranial space(36). Studies have shown dynamics in brain volume of similar subjects in different times of a day on volume morphometric techniques(37) When these facts are considered the actual brain volume is likely to be lower than the presented. From the above light it seems that most brain volume methods remains to be mathematical estimation of the actual volume due to

inseparable accompanying small anatomical structures such as dural folds and vessels whose shapes and volume may vary according to state of intravascular pressure and level of hydration.

The interval between 0.75 and 0.67 (data not shown) of the diagnonal brain fraction (DBF) scale has overlapping values or outliers between the seemingly normal and atrophic brain according to the three linear radiological methods. The phenomenon can be explained by mild morphological variations of sulci and gyri at the level where the measurements are supposed to be taken, but also more importantly is the hydration status of children at the time of scanning since both over hydration and dehydration cause alteration in brain volume and hence may confound brain atrophy quantification(38). Timing of the day has also been recently reported to be another confounder of significant variation in brain volume measurements(37). However, this phenomenon occurs in an early segment of the mild form or grade-1 stage of brain atrophy in the DBF scale. Compared to the study by Vagberg et al(39), their normal brain parenchymal fraction (BPF) value of adults was 0.890+/_0.004 using Automated BPF method. The value is not far from our maximum DBF value of 0.88, but CSF and BLOOD are also components of intracranial volume that need technical consideration to delineate. DBF values also are in close alignment with the recently published new automated method of brain volume estimation using CT scan by comparing total brain volume (TBV) from total intracranial volume (TIV) whereas the binarized estimate between automated and manual method had perfect agreement of 0.94 and 0.97 while the probabilistic estimate had lower agreement of 0.74 and 0.71 respectively(40). In the DBF scale, it was found that the value above 0.75 represents the threshold score of the normal brain volume. Consequently, individuals with DBF $\leq$ 0.75 are considered to have reduced brain volume relative to their own intracranial volume.

In our study females had higher DBF values of 0.73(± 0.12) than males who had 0.75(± 0.08). The varied results of fractional brain volume has been reported, while some studies suggest that BPF which is a prototype of DBF is generally higher in female, other studies suggest that this difference is negligible(41). However, this and other studies still demonstrate that females have higher brain fractional values than males and among other reasons is the smaller intracranial volumes they have (42). In addition, the DBF values in this study were measured in African subjects, probably minor difference can be found in other ethnic groups. Gender variation is therefore a common finding in quantitative evaluation of brain parameters.

According to the scale of values shown in this study, there is reciprocal relationship between the DBF values and the increase in severity of brain atrophy. Furthermore, when the absolute atrophic cases are analyzed mathematically and categorized by an interval factor of 0.15 subtractions which was obtained through the difference between the uppermost atrophic value (0.75) minus the minimum value (0.15) and divided by 4 to obtain four scale intervals of severity, the following classification of DBF ranges were obtained;

Above 0.75 is Normal Brain DBF (Grade-0)

1. 0.75 to 0.61 is Relative or Mild Brain Atrophy (Grade-1)
2. 0.60 to 0.46 is Moderate Brain Atrophy (Grade-2)

3. 0.45 to 0.31 is Severe Brain Atrophy (Grade-3)
4. 0.30 to 0.15 is Very Severe Brain Atrophy (Grade-4)

Further scrutiny of the study data shows that, most female children with severe and very severe forms of brain atrophy were under the age of 10 years while male children with very severe form of brain atrophy were under the age of 5 years. The female population with very severe form of brain atrophy is almost twice the male children with the same. The difference in severity scale of brain atrophy between male and female is attributed by variation in the determinants of brain atrophy in both genders in which the main players are infective causes and traumatic causes which a distributed differently in age and gender groups. Additionally, these determinants have varying influence in the degree of brain atrophy causation as described in a study by Sungura et al (article in the media). The results therefore indicate that, the newly designed formula can be used to diagnose and grade brain atrophy in various stages as DBF has statistical significance in the ability to show variation in brain volume.

The model for DBF formula was tested using F-test and shows that there is a significant difference between the DBF and dimensional measurements (groups) namely age, sulcal width, ventricular width, and Evans Index and hence the model is good in explaining the data of the given variables as the p-value of 0.0000001421 is less than the error value. The significance is tested at a confidence level of 5%. Therefore, DBF method when accurately utilized may show extensive scope of application in various levels of health facilities without the need of special software. The DBF can however not be used when the native brain anatomy is deformed by any space occupying lesion, therefore other linear methods may always be used to complement the optimal evaluation of brain atrophy.

Conclusions

The multi linear diagonal brain fraction (DBF) is an alternative method for estimation of brain volume using raw axial data of CT imaging at the mid-level of lateral ventricle with potential utility in diverse health care levels.

The spans of multi linear diagonal brain fractions whose DBF values range above 0.75 represent absolute normal brain fraction. The DBF below 0.75 represent reduced brain fractional volume in keeping with Cerebral Atrophy. The DBF equal and below 0.75 can be further subdivided to define (i) Mild (ii) Moderate, (iii) Severe and (iv) Very severe forms of brain atrophy.

The vertical and horizontal ratio (VHR) of the skull has weak age correlation though it correlates well with trends of expected brain volume ratios (DBF) of normal children. VHR can be obtained through scanogram or lateral view of skull radiograph.

In the scale of brain atrophy, the female children lead the male children by presenting with severe forms of brain atrophy twice as much that of male children even though generally brain atrophy trends more among male children. Strategic determinants based interventions are crucial in mitigation of brain atrophy and its progression to severe forms.

What is already known?

Brain atrophy assessment can be done by visual qualitative methods. However, there are different manual and automated qualitative radiological techniques to evaluate brain volume. While most automated methods such as segmentation are time consuming, the simple linear methods have challenge in reproducibility or repeatability in images which have been provided in different scales. Among the automated methods, there are some which measures absolute volume of brain and others such as BPF which measures percentage or fractional quantity of brain in intracranial space.

What was added from this research?

Brain volume at any given cross sectional imaging scale can be estimated by an alternative method using multi-linear diagonal distances. The measurements are along the equatorial region of the brain through the lateral ventricle between the corpus callosum and the fornix. Mathematically, the linear product of the CSF span is subtracted from the linear product of the brain parenchyma and divided by linear product of the skull diagonal distance through the lateral ventricle.

The values obtained represent normal brain volume when DBF > 0.75. The values equal and below 0.75 are ranges of brain atrophy in stages spanning from mild, moderate, severe and very severe forms of brain atrophy.

Female children have double severe forms of brain atrophy than male children with the similar problem.

Future directions

A comparative study using automated brain volume quantifying methods need to be conducted in order to establish equivalence in severity scale of brain atrophy by DBF versus that of BPF. Additional DBF study need to be conducted using different ethnic groups as the primary study was done using the Tanzania population from the Northern part of the country.

Further studies are needed to harmonize and improve protocols for revised brain volume quantitative evaluation by factoring hydration status and timing in the day to resolve confounding effects with mild forms of brain atrophy.

Abbreviations

1. BIANCA- Brain Intensity Abnormality Classification Algorithm
2. BPF-Brain parenchymal fraction
3. CD-Compact disc.
4. DVD- Digital versatile disc.
5. CSF-Cerebral spina; fluid.
6. CT- Computerized tomography.
7. DBF-Diagonal brain fraction

8. EI- Evans index
9. KNCHREC-Kibong'oto, Nelson Mandela and Cedha Research and Ethical Committee.
10. MTA-medial temporal atrophy.
11. MRI- Magnetic resonance imaging.
12. VBM-Volume based morphometry.
13. VHR- Vertical-horizontal ratio.
14. VW- Ventricular width.
15. SW- Sulcal width.

Declarations

Ethical approval

The study was done after obtaining the ethical clearance from KNCHREC ethical review authority on behalf of National Institute of Medical Research with reference number KNCHREC 0010. Permissions to use patients data were institutionally granted since it this stage the study did not seek to have direct patients interviews. Names of patients were not disclosed in this part of the study. Radiological images used in the article have maintained high level of anonymity hence did not need written consent from owners of images

Competing interests

None of the other authors or institutions has a conflict of interest in relation to publication of this article.

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Author's contribution

The corresponding author 'SR' was the principal investigator who presented the idea, formulated the study plan and conducted most of the field work. The 2nd author 'ME' contributed in early structuring of the methodological part of the study including formula design and sample size calculation. Further, he did statistical design and cross checking of the data accuracy. The 3rd author 'SJM' contributed for the overall look of the research output. The 4th author 'OC' did most the evaluation of the radiological significance of the study. The 5th author 'SE'contributed in the study feasibility, proposal review and proof reading of the research output. The 6th author 'VJM' was the main supervisor of the whole project and

participated in the earliest study design, formulation, proposal review, ethical clearance, field visit and pre-submission review of the research output.

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Figures

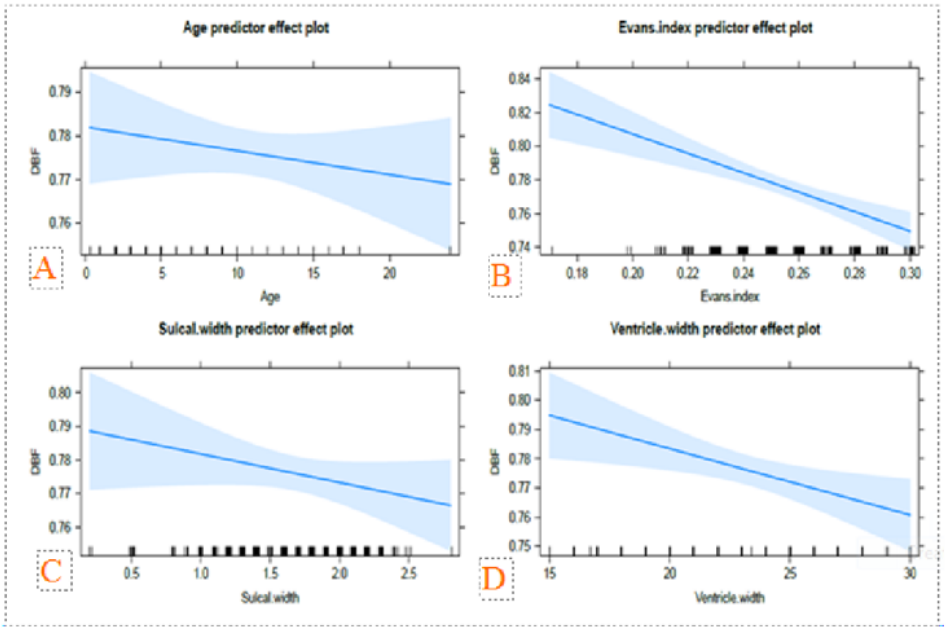

Figure 1

Impact of predictor variables on DBF A: DBF has negative correlation with age. B: Evans index shows negative correlation with DBF development. C: Sulcal width correlates negatively with DBF. D: Ventricular width also increases with decrease in DBF value.

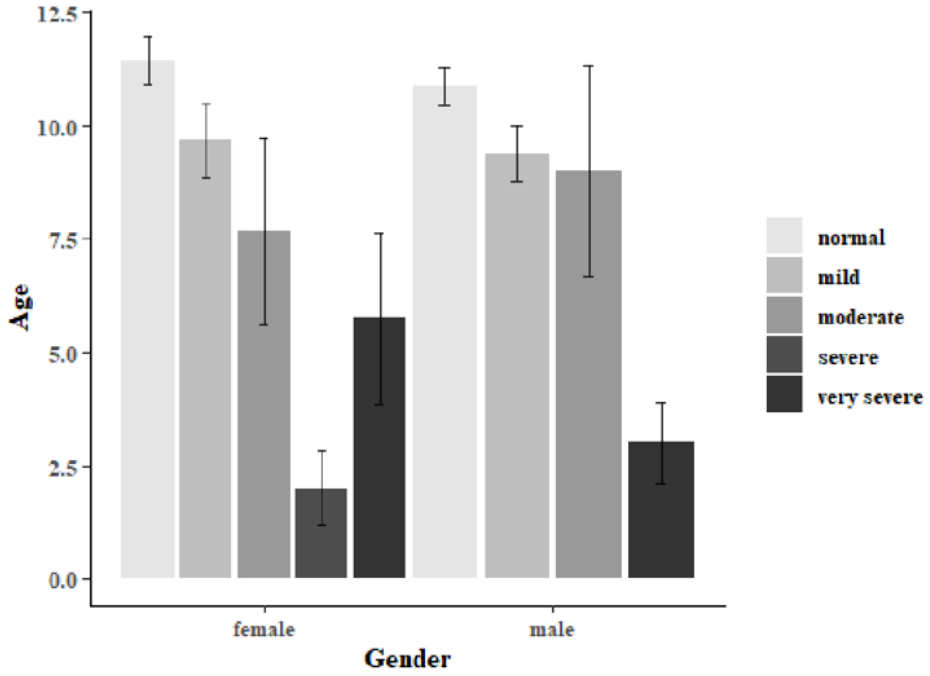

Figure 2

Distribution of Brain Atrophy severity by Age and Gender. A polymorphic results pattern was shown when both age and gender were considered in further analysis of brain atrophy cases. While male children dominated the category of moderate brain atrophy, female children dominated in mild, severe and very severe cases of brain atrophy. The severe or grade-3 form of atrophy was unfound in male children. Also female children who dominated the severe and very severe forms of brain atrophy were under the age of

10 years while male children with very severe form of brain atrophy were under the age of 5 years. The female population with very severe form of brain atrophy is almost doubled the male children.

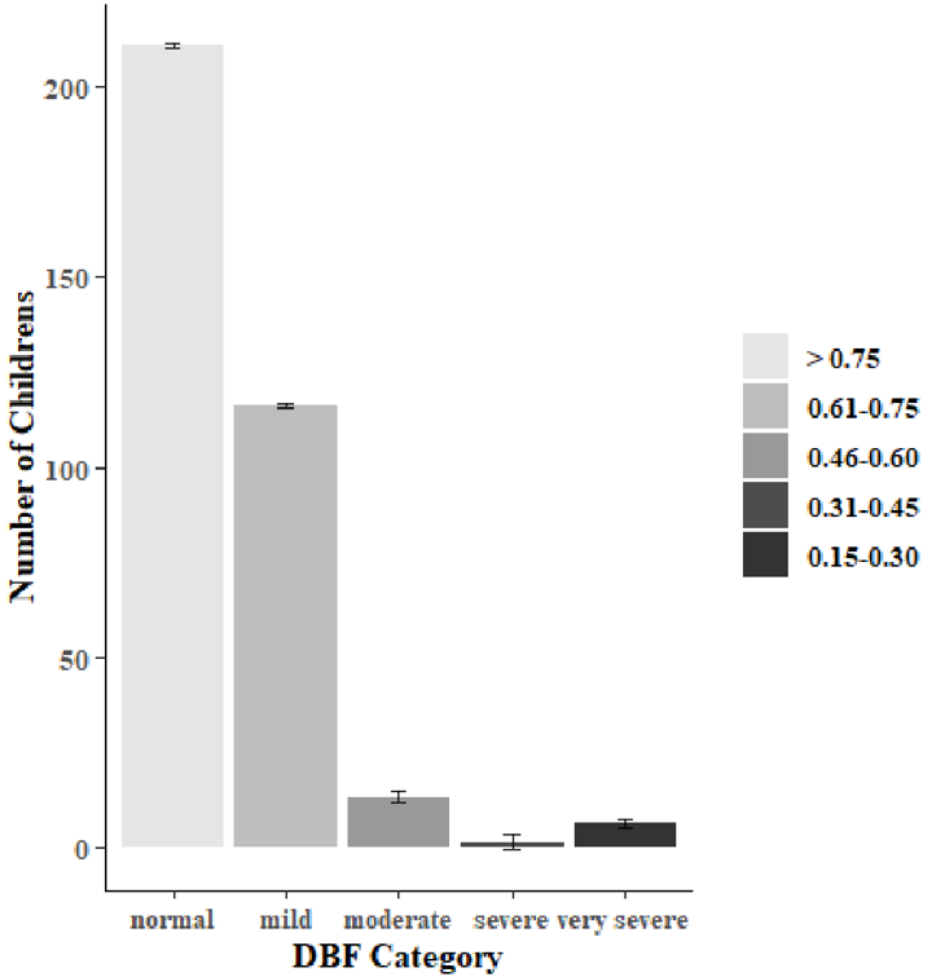

Figure 3

Distribution of grades of Brain atrophy severity by DBF. Analysis of brain volume status is shown in ranges of DBF intervals in which among cases of brain atrophy a chronological pattern of results is observed as the majority of children fell under mild form of brain atrophy followed by moderate and very

severe form of brain atrophy. The minority had severe form of brain atrophy otherwise known as grade-III brain atrophy. All data values are reported as mean±the standard error of the mean (SEM), p-value ≤ 0.05.

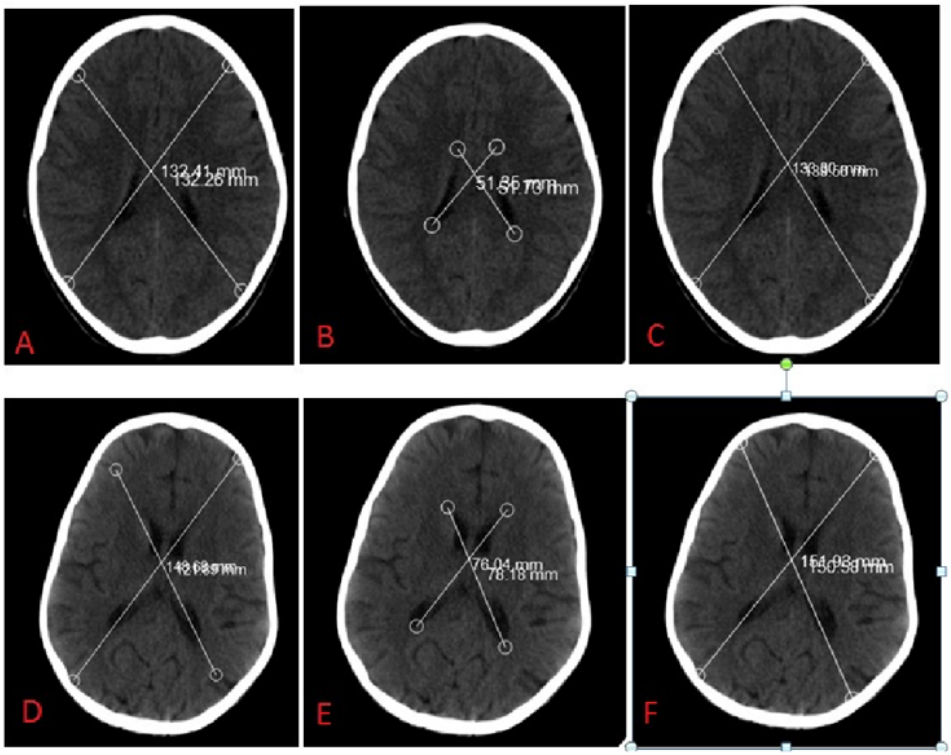

Figure 4

Diagonal Brain fraction measurements taken at mid lateral ventricular level. A: showing a and b linear diagonal distances of brain parenchyma. B: Showing c and d diagonal distances covering fluid of the

lateral ventricle at body level. C: showing e and f diagonal distances of the calvarium through the lateral ventricle. D, E and F show similar measurements. A, B, and C represent measures of a normal brain case with DBF of 0.79 also known as 79% while D,E and F measures of moderately atrophied brain case with DBF of 0.52 (52%) at the lateral ventricular body level. The diagonal lines of A and C have almost no difference because of the fullness of brain mantle with intimate relation to the inner side of the skull outline suggesting normalcy for age brain volume.

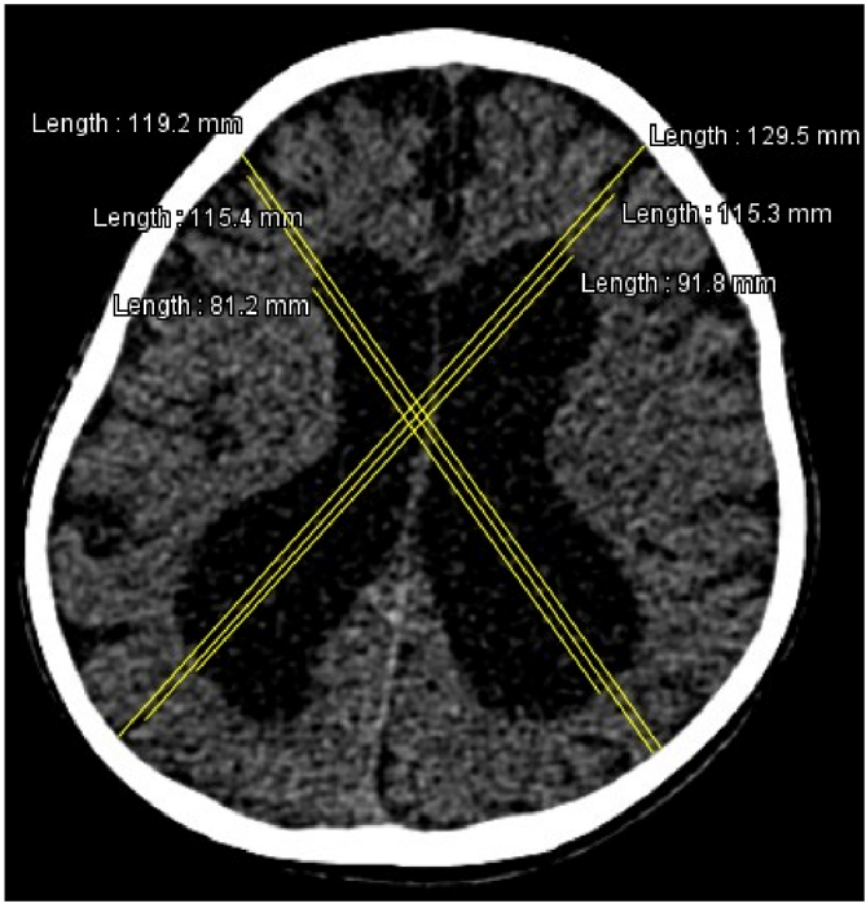

Figure 5

Brain image with calculated DBF. DBF = (115.4x115.3 - 01.8x81.2) / 119.2x129.5 A child from the studied population with calculated DBF of 0.38. Since there is evidence of gross dilatation of lateral ventricle and widening of sulci the child represents global type of brain volume loss and classified as severe or Grade-3 brain atrophy for age. DBF is the fractional measure of the residual brain volume after a part volume loss relative to the calvarium volume measured in the equatorial region of the brain.

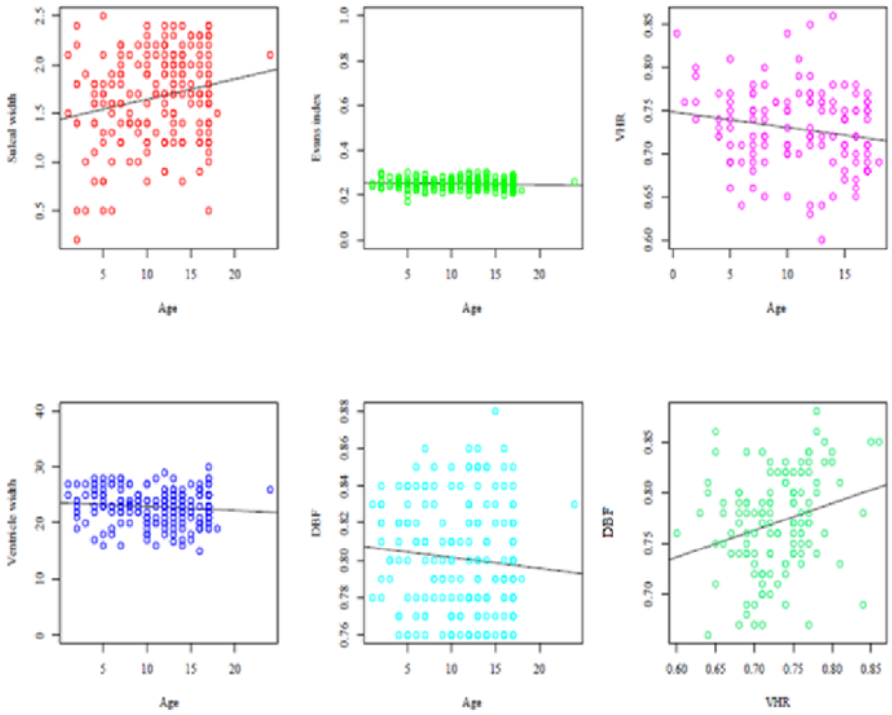

Figure 6

Relationship between Age and Brain Dimensional measurements in specific subgroup with normal ranges of brain volume. Only Sulcal width shows a positive correlation with age among children subgroup with normal brain volume while Ventricular width, DBF and VHR show negative correlation with age. Evans index has negative but very weak correlation with age in children less than 18 years.

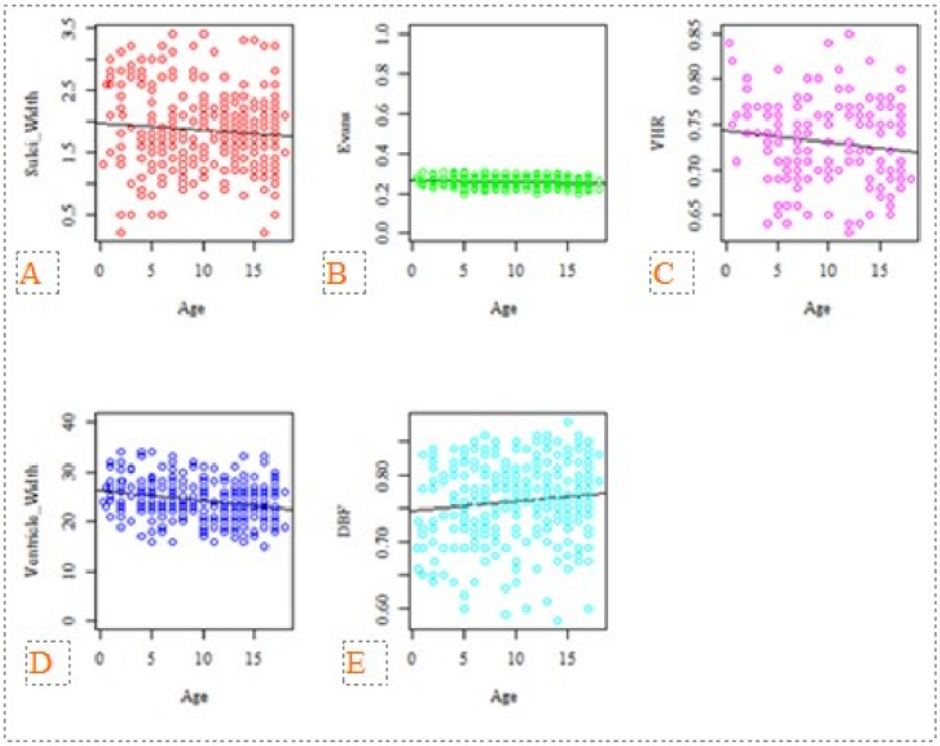

Figure 7

Relationship between Age and Brain Dimensional measurements among the general childhood population of the Northern Tanzania. Four variables including sulcal width, Evans index, VHR and Ventricular width show negative age correlation while DBF shows positive age correlation within the overall childhood population entailing normal and atrophied brains.

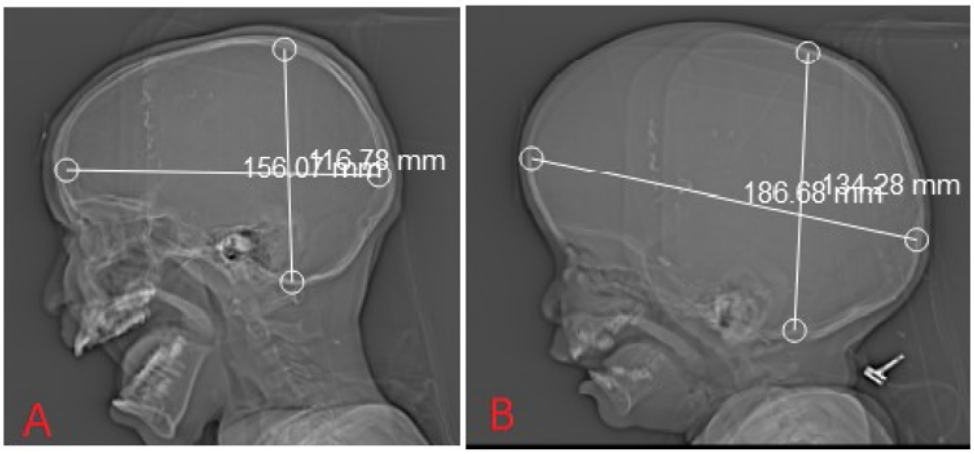

Figure 8

Scanograms of children from the study population. The primary CT images as road maps toward axial cross-sectional scanning. The Vertical and Horizontal distances give VHR of 0.74 and 0.71 A and B respectively. The CT scanogram for head is similar to the conventional radiograph (xray) taken in a lateral view. VHR can be measured in either modality as at this stage CT scan produces a 2 dimensional image as a preliminary roadmap to the final cross sectional or 3 dimensional images.

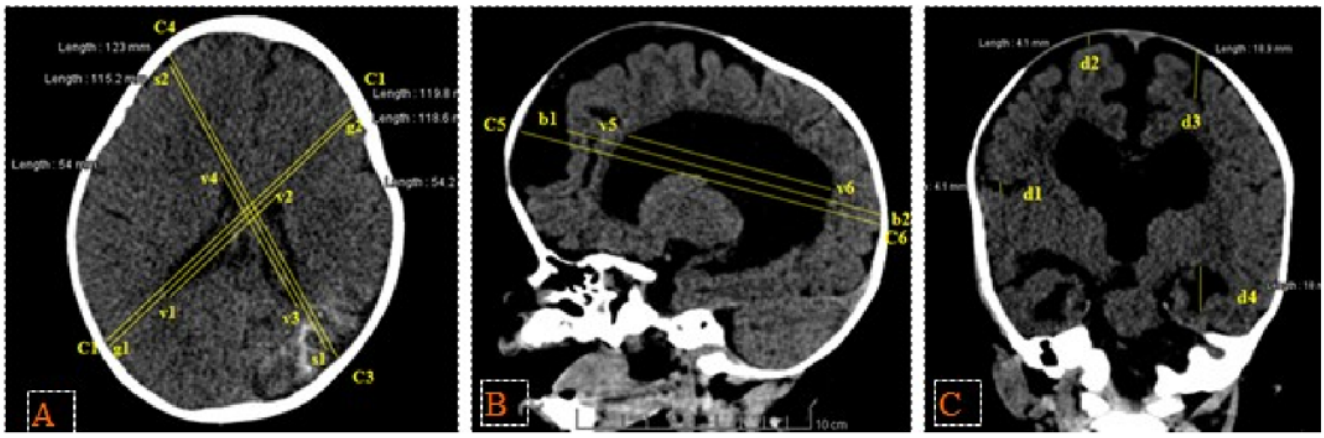

Figure 9

Views and levels for mapping the DBF measurements points. A: Brain axial view at the level of widest part of the lateral ventricle below the corpus callosum and above the fornix. B: Brain at sagittal view showing the largest continuous fluid filled space of the lateral ventricle between the inferior margin of the corpus callosum and the fornix; a structure that represents an arch of major hypocampal fiber tracts. In this view v5v6 is lateral ventricular span at widest part, b1b2 is maximum brain span and c5c6 is longest skull span at the level of mathematical deductions for DBF calculations.. C: Brain coronal view showing the mid part of the body of lateral ventricle, widened CSF spaces in which d1-is sulcal width, d2-gyral deviation from calvarium, d3-sulcal deviation from calvarium and d4-temporal horn of the left lateral

ventricle. DBF = [(g1g2)(s1s2) - (v1v2)(v3v4)] / (c1c2)(c3c4). From the above primary formula when it is assumed that a represents line g1g2, b for s1s2, c for v1v2, d for v3v4, e for c1c2 and f representing the line c3c4. Hence, the formular can be simplified into DBF = (ab-cd) / ef Likewise from the above simplified formular; ab- diagonal product of gyrus to gyrus and sulcus to sulcus distances/ (g1g2)(s1s2). cd- product of the measure of diagonal lateral ventricle distances/ (v1v2)(v3v4). ef-product of the measures of diagonal calvarial distances through the lateral ventricle/ (c1c2)(c3c4).