Comparative Stereological Analysis of Intracranial Volume fractions among Patients with Brain Atrophy and Normal Pressure Hydrocephalus from a Nigerian Population

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ABSTRACT

Background: Differentiation between symptoms of normal pressure hydrocephalus (NPH) and other neurodegenerative disorders such as Brain Atrophy (BA) are usually confusing. Available diagnostic methods are invasive while the few non-invasive methods did not take care of potential factors known to influence intracranial volumes. We, therefore, aim to determine and compare the intracranial volume fractions among patients with NPH and BA.

Methods: This was a prospective, cross-sectional age-matched control study among consenting patients that were diagnosed with NPH, BA and healthy control in Aminu Kano Teaching Hospital from March 2018 to November 2020. Each patient was routinely examined with CT-Scan; However, control participants were from other reasons. Participants with a medical history known to influence the intracranial volume were excluded. Volume estimation was based on a stereological Cavalieri method and three volume fractions were determined mathematically for each of the group. Test-point computing was facilitated through a locally developed software (voXas_2018). Ethical approval was sort prior to the study.

Results: Patients with NPH have higher total CSF: brain ratio, intraventricular volume: brain ratio and extra-ventricular: brain ratio. Similar pattern was exhibited according to age grouping, except in the older age category where BA volume fractions were higher.

Conclusion: Age, gender and stature are known to influence intracranial volumes. We controlled their potential effects through age-matched control of participants between groups and the use of intracranial volume ratios for objective diagnosis of NPH and BA. However, TcSF:Br and InV:Br volume fraction ratios were found to be reliable indices for distinguishing patients with NPH and BA.

Keywords: Brain atrophy, Normal pressure hydrocephalus, Stereology, Volumetric Diagnosis.

I. INTRODUCTION

Normal Pressure Hydrocephalus (NPH) is a form of communicating hydrocephalus and also a form of dementia that is potentially reversible [1]. The term was first coined by Adams, Fisher, Hakim, Ojemann and Sweet in 1965 to describe hydrocephalus with enlargement of ventricles, normal CSF pressure and a triad of symptoms: gait disturbance, dementia, and urinary incontinence [1]. The diagnosis of idiopathic -NPH (I-NPH) without a known cause is more difficult [1], [2] while that of secondary NPH is easily diagnosed with evidence of previous history of subarachnoid hemorrhage, meningitis, head injury or numerous other conditions [1], [3]. The differentiation between symptoms of Normal Pressure Hydrocephalus (NPH) and other neurodegenerative disorders such as Brain Atrophy (BA) presents significant difficulties [4]. This is possibly due to the similarities that exists between NPH and BA since both conditions were associated with changes in cerebral and intracranial cerebrospinal fluid (CSF) distribution [4]. Correlation exists between volume of any particular organ of interest and particular medical condition [5]. In neurological sciences, the volume of cortical structures devoted to a function influences the quality of a person’s ability to perform that function [6]. A number of studies have reported wide and inconsistent result regarding the volumetric dimension of the cerebral and ventricular systems [7]-[9]. These studies only considered the volume of target structure as an entity without capturing the potential influence of whole reference structure [10]. Comparing solely the intracranial tissue volume between two groups (i.e., control and experimental groups) may not provide reliable data. For scientific and medical purposes, it seems crucial that any evaluation of intracranial structure should take body composition into consideration [10]. The volume fraction (CSF deployment indicator) approach of stereological methods is an alternative way of...
evaluating intracranial structures, that allows for volume assessment relative to the components of intracranial structures (i.e., cerebral tissue, cerebrospinal fluid) and independent from the body size of subject [8], [10]. Volume fraction estimates the ratio of structural components to each other and is independent of the body size of the individuals [10]. It explains the volumetric relationship of a target structure relative to a reference structure.

In recent years, diagnosis of central nervous disorders is related to a greater degree with radiological assessments using Computed Tomography (CT) scans and Magnetic Resonance Imaging (MRI) [4]. The easy manipulation of radiological images and non-invasiveness in assessing intracranial structures allows for precise, reliable, and reproducible volumetric estimations of specific intracranial compartments [4], [11]. The Cavalieri stereological principle has been modern volumetric method that is widely applied on radiological images [11]. Results from this method are highly objective, statistical, and reproducible. Therefore, volume fraction comparisons among patients with NPH and BA will clearly proffer a cheaper method of objectively diagnosing and differentiating these medical conditions particularly coming from a resource limited locality.

II. METHODOLOGY

This was a prospective cross-sectional study involving consenting patients who reported to the neurology and neurosurgical clinics of Aminu Kano Teaching Hospital (AKTH) and were clinically diagnosed with NPH and BA from March 2018 to November 2020. Clinical diagnosis was strictly limited to a qualified neurosurgeon and neurologist and based on hospital protocol. Detailed clinical and patient history was taken, and any medical condition known to influence intracranial volume were excluded from the study [7]. Ethical approval was sort from the human research and ethics committee of the hospital. Patients routine CT images were recruited into the study provided images were acquired under standard protocol and consisting of all intracranial tissue sections. Age matched (control) normal reported CT images were further recruited having ruled out any medical condition known to affect intracranial volume fraction/ CSF deployment indicator was determined using Kruskal-Wallis test. Data analysis was achieved using SPSS v20 (IBM corp. 2015). A p value of ≤0.05 was regarded as statistically different.

III. RESULTS

A total of twenty-nine CT series were recruited into the study. This comprised 7(24.1%), 8(27.6%) and 14(48.3%) clinically established cases of BA, NPH and age-matched control groups, respectively. Majority of the CT series were males (59%). Their age ranged from 0.33 years – 40 years with overall mean age of 13.62±14.29 years. Following age grouping, majority of the CT series were from individuals within the ages of 1-5 years (27.6%) followed by those between 36-40 years (20.7%). Age group < 1 year accounted for the CT series with the least number (Table I).

The descriptive statistics (mean ± SD) for the volume fractions (without group) indicated total intracranial CSF to brain volume having the highest mean value (Table II).
TABLE I: DISTRIBUTION OF PARTICIPANTS ACCORDING TO AGE CATEGORIES

| Age Group (years) | BA  | NPH | Control | Frequency (%) | Mean Age ± SD | Min  | Max |
|-------------------|-----|-----|---------|--------------|--------------|------|-----|
| <1                | 3(10.3) | 1(3.8) | 1(3.8) | 0.42±0.09 | 0.33 | 0.5 |
| 1-5               | 4(14.8) | 2(8.3) | 2(8.3) | 2.50±1.31 | 1 | 4 |
| 6-10              | 3(10.3) | 1(4.1) | 3(10.3) | 7.43±1.5 | 6 | 9 |
| 16-20             | 1(3.8) | 1(4.1) | 2(6.1) | 18.20±1.1 | 17 | 20 |
| 36-40             | 1(3.8) | 4(14.8) | 1(3.8) | 38.67±0.82 | 38 | 40 |
| TOTAL             | 7(24.1%) | 8(27.6%) | 14(48.3%) | 29(100) | 13.62±14.29 | 0.33 | 40 |

Key: BA: Brain Atrophy, NPH: Normal Pressure Hydrocephalus, Freq: Frequency, Min: Minimum, Max: Maximum.

IV. DISCUSSION

This study revealed the ratio of total CSF to Brain volume of 12.52±9.21% among patients with BA. A related work by De-Vis et al., [12] in the Netherlands carried out a study on CSF volumetric MRI mapping to quantitatively evaluate patients with BA. They reported higher relative value of Tcfs:ICrV among clinically diagnosed patients with BA as 17.4±4.3%. This indicated a difference of about 4.88% compared to values of the present study. A number of variations exist in the cranium as a result of various factors already reported by researchers [6], [13]. For instance, age, physical stature, and gender are reported to influence the size of intracranial structures [6], [13]. The effect of age and body size may have been addressed by the research design and volume fraction in the current study, further sources of variations could be attributed due to genetic, nutritional, geographic, and racial differences between the two studies. Another factor that may influence the variation may perhaps be methodology differences as equipment used in image acquisition between the two studies differ. A 3-Tesla MRI machine was used for image acquisition and analysis which was exclusively automated using a coded segmentation software by De-Vis et al. [12]. They had a programmed protocol which provides higher resolution MRI sequences with exact sub-voxel localization of the border between CSF and tissue interface. Conversely, the equipment used in the present study was a 160 slice CT equipment. To the best of researcher’s knowledge, this is the highest rated CT scanner in the entire North-west Nigeria. The superior soft tissue resolution of MRI added with its strength may have aided better delineation of adjacent structures. Similarly, the relative non-availability of MRI and attendant high cost of maintenance and service may be the reason of its non-availability in the study area.

TABLE II: DESCRIPTIVE STATISTICS OF AGE, BODY WEIGHT AND CSF DEPLOYMENT INDICATORS

| Variable | Mean ± SD | Minimum | Maximum |
|----------|-----------|---------|---------|
| Age (years) | 3.64±10.03 | 5.84 | 17.4±4.3 |

Similarly, based on groups (BA, NPH and Age-matched control) and independent of age grouping, the CSF deployment indicators were further presented in Table III. Patients with NPH CT-series showed consistent higher mean values of CSF deployment indicators than other groups. Following a normality test using Shapiro-Wilk test, the explanatory variables were found not normally distributed (p<0.05). Therefore, Kruskal Wallis statistics was used in assessing the differences in intracranial volume fractions across the three groups (BA, NPH, Control). Total CSF to brain volume ratio (Tcfs:Br) and intraventricular CSF to Brain volume ratios (InV:Br) were found significantly different across groups (p ≤ 0.05) (Table IV). Similarly, a one-way non-parametric (pairwise comparison) post hoc analysis was conducted on Tcfs:Br and InV:Br. Result indicates three group comparisons were significantly different (p ≤ 0.05) (Table V). The source of difference was consistent in Control- NPH comparisons in the two variables, while Control - BA comparison was evident in Tcfs:Br only (p ≤ 0.05).

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TABLE III: DESCRIPTIVE STATISTICS OF CSF DEPLOYMENT INDICATORS BASED ON GROUP

| Variables | BA (n=7) | NPH (n=8) | CONTROL (n=14) |
|-----------|---------|---------|----------------|
| Age       | 11.90±14.49 | 10.80±12.64 | 16.18±15.52 |
| Tcfs:Br % | 12.52±9.21 | 26.83±34.87 | 5.62±1.74 |
| InV:Br%   | 3.06±1.24 | 5.15±12.63 | 1.98±0.87 |
| ExV:Br%   | 9.46±8.25 | 11.81±19.99 | 3.65±1.43 |

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Key: Tcfs:Br %: total cerebrospinal fluid volume to brain volume, InV:Br: intraventricular CSF volume to brain volume, ExV:Br: Extraventricular CSF volume to brain volume.
An overall comparison between the TcSF:Br in BA, NPH and control in the present study indicated statistical significant difference between control-BA and the control-NPH comparisons. This may presumably be due to CSF and brain tissue involvements in BA and NPH conditions. Volume of CSF is significantly higher in the extra-ventricular spaces among patients with NPH [4] while peripheral subarachnoid CSF volume is established to be significantly higher among patients with BA [4], [12]. This explains that cerebral volume and ventricular volume distribution varies among patients with NPH and BA as against their age-matched controls. Similarly, the strength of the volume fraction approach presented by the present study accounts for the simultaneous changes occurring between the cerebral tissue and CSF by expressing CSF as a ratio to the brain as highlighted by Sahin & Elfaki [6], Akdogan et al. [7], De-Vis et al. [12]. However, difference between BA-NPH comparison was not statistically established in the present study. This may presumably be due to the smaller sample size between the two conditions and also across the age groupings.

The present study estimated InV:Br as 1.98±0.87% among healthy controls. Akdogan et al. [7] in Turkey conducted a CT-stereological study using similar volumetric method and reported total ventricular to brain volume ratio of 2.00±1.6% among normal age and gender matched subjects. This perfectly agrees with the age-matched control subject obtained in the present study. The agreement between the two studies could be on account of methodology similarities employed between the two studies. Both studies utilized CT images, using stereological methods of volume estimation and age-matched normal subjects and further highlights the sensitivity and reliability of stereological methods.

The present study estimated InV:Br as 3.06±1.24% and 15.02±16.30% among patients with BA and NPH, respectively. A higher value of InV:Br was observed among patients with NPH than those with BA in the present study.

This is in agreement with the pattern reported by a relevant study by Tsunoda et al. [2] who carried out a study on intracranial CSF fluid measurement studies among suspected patient with iNPH due to NPH and BA in Japan. The authors obtained a marked increase in intraventricular: intracranial CSF ratio among patients with NPH (37.8%) when compared with the healthy control (15.6%) subjects.

The higher values obtained by Tsunoda et al. [2], may presumably be due to slight differences in the volume fractions between the two studies. The present study used the cerebral tissue as the denominator whereas Tsunoda et al. used volume of CSF within the intracranial spaces. This perhaps may explain why they reported higher values. Nonetheless, there was consistency in pattern and volumetric relationships between patients with NPH and control among the two studies. The findings further agree with the work of Szczepak et al. [4] where they highlighted marked increase in intraventricular CSF volume among patients with NPH when compared with patients with BA or control. Similarly, the InV:Br for patients with NPH in the present study was 15.02±16.3% while 3.06±1.24% was for patients with BA. Szczepak et al. [4] obtained 13.9±1.3% for NPH patients and 9.9±1.3 for patients with BA. These indicates variation from the values of normal subjects reported in the present study and other studies [7], [12], [13]. Both the present study and Szczepak et al. [4] reported a significantly higher InV:Br ratio among patients with NPH than those with BA. Therefore, since InV:Br values in BA and NPH differ from the normal control subject reported in literature and also varies among BA and NPH, InV:Br can be reliable index in differentiating the conditions. Additionally, with respect with InV:Br, statistically significant differences were established between control-BA and control-NPH comparisons. This is because CSF distribution within the intracranial compartments is different between the two groups [4]. Larger CSF is observed in the extra-ventricular, subarachnoid space and associated cisterns among patients with BA than with NPH and controls. This is further emphasized when evaluating patients with BA. Brain tissue loss is assumed when peripheral CSF spaces are enlarged in relation to intracranial volume due to global cortical and medial temporal lobe atrophy [12], [14]. Similarly, CSF is observed larger in the intra-ventricular spaces among patients with NPH than BA and control subjects. Therefore, in comparison with normal subjects, marked differences will be expected. However, differences between NPH and BA could not be established even after controlling for age effects. A possible reason may be due to the small proportion of participants between the 2 conditions (BA/NPH) in the present study.

The present study further revealed the extra-ventricular CSF to brain (ExV:Br) ratio as 9.46±8.25%, 11.81±9.99 and 3.65±1.43 among patients with BA, NPH and age matched control, respectively. A relevant study in Poland by Szczepak et al. [4] used the similar indicator and reported a different ExV:Br values for patients with BA and NPH as 12.4±2% and 4.2±0.7%, respectively. This indicated patients with BA having significantly higher subarachnoid space and basal cisterns -to-brain ratio than patients with NPH. The contradictory finding may as well be ascribed to differences in mean ages between the two studies. The mean ages for patients with NPH and BA in the study reported by Szczepak et al. [4] were 56.9±6.1 and 70.6±5 years, respectively. Mean ages for patients with NPH and BA in the present study were 10.80±12.64 and 11.90±14.49 years, respectively. Therefore, the lower value obtained in the present study could be on account of the age differences. It is already established that BA is a continuous process that progresses with age [4], [12]-[15]. The sub-arachnoid, peripheral, cortical area, and medial temporal lobes are the intracranial compartments where CSF accumulation is pronounced in BA [4]. Participants with

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**TABLE V: POST-HOC KRUSKAL-WALLIS (PAIRWISE COMPARISON) ANALYSIS**

| Statistic | Median (IQR) | Group Comparison | Chi Square | Std. Error | Std. Test Statistic | p value |
|-----------|--------------|-----------------|------------|------------|---------------------|---------|
| TcSF:Br   | 7(7)         | Control-BA      | 9.89       | 3.91       | 2.53                | 0.034   |
|           |              | Control-NPH     | 11.67      | 3.74       | 3.12                | 0.005   |
|           |              | BA-NPH          | -1.77      | 4.37       | -0.41               | 1.00    |
|           |              | Control-BA      | 5.71       | 3.86       | 1.48                | 0.42    |
|           |              | BA-NPH          | 13.64      | 3.69       | 3.69                | 0.001   |
| InV:Br    | 3(2)         | Control-BA      | -7.93      | 4.31       | -1.84               | 0.20    |

Key: (TcSF:Br%: Total cerebrospinal fluid volume to brain volume, InV:Br: Intraventricular CSF volume to brain volume). BA: Brain Atrophy, NPH: Normal Pressure Hydrocephalus, Std. Error: Standard Error; p-value: Level of significance (p≤0.05).
lower age will have lower values when compared to elderly adults due to the normal inverse relationship between cerebral tissue and CSF with age [4], [7]. Thus, highlighting the variation of our result from that of Szczepak et al. [4]. Nonetheless, numerical differences exist between BA and NPH when compared with control in the present study. However, these differences were not statistically significant and may be presumably due to the smaller samples between the groups.

There are some potential limitations to this study that needs to be considered when interpreting the data. The low number of participants witnessed across all the three conditions limit this study. This is largely due to the study design to control the effect of age. This action grossly excluded a significant number of available potential participants from the groups of BA and normal healthy control.

In conclusion, volume fractions are objective and reliable indices which can be used in differentiating patients with NPH and BA while at the same time taking care of potential influence of other compounding factors such as body stature.

DECLARATION OF INTEREST
The authors declare there was no conflict of interest in the entirety of this work.

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