

Exploring the Determinants of Childhood Brain Atrophy: A Study in Northern Tanzania

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Abstract

The reduction of brain parenchymal volume than expected per age is the hallmark of brain atrophy. While the condition is most prevalent in elderly, it is currently increasingly observed in pediatric ages.

Despite the scattered lists of the determinants of brain atrophy worldwide; their Preferential magnitude of influence in causing childhood atrophy has not been elicited in local and global literature.

It was the goal of this research to investigate the influence and percentage contribution of various risk factors thought to be common in Northern Tanzania that may provoke premature reduction in brain volume of the growing children less than 18 years of age.

The study was a cross sectional hospital based focusing on the use of Neuro-imaging tools in which 209 children were examined by Brain CT scanners from the year 2013 to 2019. The Brain findings were reviewed by four linear radiological measurements involving sulcal width, Evans index, lateral ventricular body width and diagonal brain fraction. Medical records were retrieved and mothers were interviewed for birth and medical histories of their children.

Additional tests such as HIV serological tests were complemented.

Results showed a significant number of brain atrophy with male children preponderance. Varied percentages of risk factors influences were showed in which infections of the central nervous system influenced the study population by 29.72% while head and neck radiotherapy influenced the least among ten categories of the considered determinants.

In conclusion; Infections of the central nervous system, space occupying lesions, birth injury and head trauma are the four cardinal and influential determinants of childhood brain atrophy in the Northern Tanzania.

Keywords: Brain Atrophy; Brain Volume; Prevalence; Neuroimaging

Introduction

The brain as many other organs in human body is known to respond by losing its normal volume when subjected to unfavorable conditions for tissue growth and maintenance. The common atrophic process is that which related to age degenerative changes and this process occurs in advanced age otherwise known as senile brain atrophy [1].

The senile brain atrophy is known to occur from the age of 50s and above after the plateau stage of brain development which happens after 40 years of age [2]. Both age and Body Mass Index (BMI) are known to be associated with the decrease in brain volume [3]. When this pattern of normal brain development and involution is considered in timeline, it is unusual for atrophic process to occur in childhood or at any time below 40 years since this is the plateau phase of human brain development [4]. Therefore, when such manifestations occur, they should always be considered pathological and an intensive search for offending cause is vital.

In Tanzania just as many other Sub-Saharan African countries, there have been many cases of brain atrophy among children whose causes have not been exhaustively scrutinized and reported in order to lay down plans of interventions and mitigation [5]. Scattered information about brain atrophy is reported. The findings of pediatric brain atrophy cases in Ibadan, Nigeria have been reported to about 10.6% among children [5]. Therefore, as much as development and prevalence of head injuries are increasing, brain atrophy is ceasing to be rare in children and this press for further investigations on the causes and prevention of this pre-mature brain volume loss.

Among others, various causes for brain atrophy have been reported in different global regions include prematurity [6], central nervous system infections such as meningitis, HIV encephalopathy [7] and cerebral malaria [8]. Other causes include head trauma especially in incidences associated with loss of consciousness [9], metabolic disorders such as Cushing syndrome [10], drug related causes such as antiepileptics usage, chemotherapy for cancers [11], maternal alcoholism especially more than 300ml/day during pregnancy [12], convulsive disorders especially status epilepticus [13], radiation induced brain injury [14], perinatal hypoxic ischemic encephalopathy or birth asphyxia and birth injury by instrumental delivery [15]. Others includes, malnutrition both protein energy malnutrition and avi-

taminosis-B is associated with reversible causes of brain atrophy [16]; however vitamin B1 and B12 levels in blood are too dynamic with unstable state in continual evaluation of non-vegetarian population [17]. Therefore, the determinants of brain atrophy are so diverse depending on the location. They can hence forth be studied in categories. It was therefore the aim of this study to scrutinize and quantify the burden of the trending causes of brain atrophy among children in Northern Tanzania ranging between the ages of 0 to 18 years of age.

This study was so significant and timely so that mitigation plans may be developed according to the causes of brain atrophy which were not formerly investigated and measured in the study area. The results of this study are important in enabling the stakeholders in medical fields in countries with similar problems to pro-actively formulate and optimize their standard operating procedures in safeguarding the mental health of the growing children.

Methods

Study health facilities

A total of four health facilities namely Agakhan health center, Arusha Lutheran Medical Center, Afyamax diagnostic center and Kilimanjaro Christian Medical Center were included in the study. The centers were purposively selected based on availability and accessibility to CT scan imaging services for people residing within the Northern Tanzania. The two regions namely Tanga and Manyara did not have CT scan facilities during this study period. However, their patients were captured within the named facilities through referral system.

Recruitment of subjects

A total of 209 children who were presented in radiology departments of the four health facilities in the Northern Tanzania and performed brain CT scan examinations between the years 2013 and 2019 were recruited. The images were reviewed and passed by a radiologist and ensured to be of diagnostic qualities.

The inclusion criteria involved a consideration of all children with age ranged between 0- 18 years, children born and raised within Northern Tanzania, accessibility of mothers for birth and early childhood history provision and availability of quality CT scan images of the patients.

Children whose mothers were not accessible, children born and raised outside the Northern part of Tanzania and those whose CT scan images were not of diagnostic quality were excluded in the study.

Image acquisition

All patients underwent CT scan brain using the standard axial scans whose protocol included slice thickness of 5mm and increment of 2mm. All the images were taken along the standard radiological baseline.

CT Scan Image Analysis

The Brain CT scan images were scrutinized by a radiologist where by the three known radiological linear methods namely sulcal width, lateral ventricular body width and Evans index were measured in order to determine presence or absence of brain atrophy. Thereafter, along with visual qualitative analysis the subtypes of brain atrophy were differentiated as global atrophy, central atrophy, cortical atrophy, focal atrophy and hemi-atrophy.

The diagonal multi linear technique also known as Diagonal Brain Fraction (DBF) was as well calculated to the subjects who were eligible for the utility of this method (Figure 1).

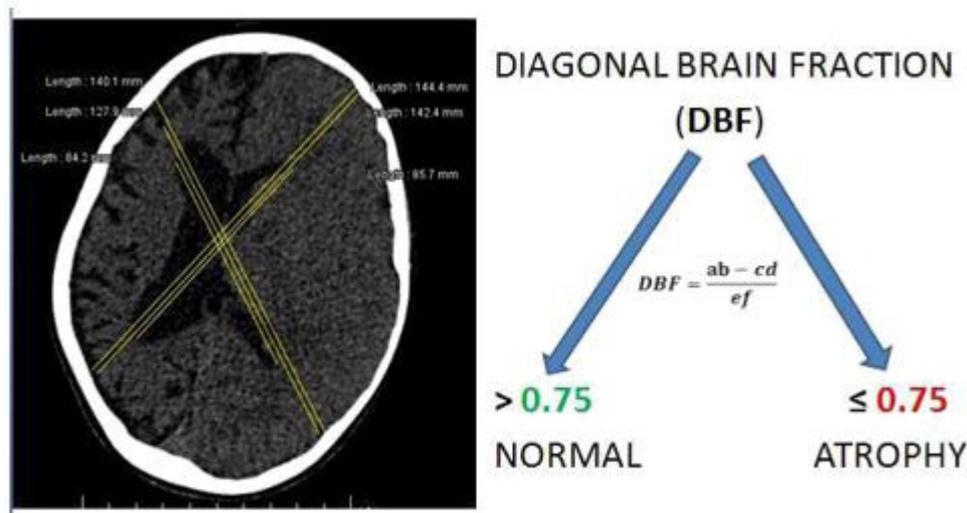


Figure 1: Application of the Diagonal Brain Fraction formula to classify brain status

The DBF multi linear radiological method by Sungura, *et al.*, 2020 (article in press) differentiates between normal brain fraction and atrophied brain. The atrophied brains can further be classified basing on severity as the DBF becomes lower.

Additional pathologies such as space occupying lesions including tumors, abscesses and hemorrhages were reported and considered in this scrutiny of brain atrophy causation.

Data collection method for the determinants of brain atrophy

The collection of data involved questionnaires that were set to check for the presence of 10 categories of risk factors using primary information from mothers of children spanning from antenatal to adolescence medical history, examination of obvious risk factors through image analysis such as tumor and sec-

ondary data were also considered in hospitals with computerized archives where history of laboratory tests for conditions such as HIV, Meningitis and cerebral malaria were extracted and used. Children, whose results for HIV tests not found, were subjected to these tests after consent from their parents.

All data were collected with informed consent after the study had obtained ethical clearance from KNCHREC on behalf of the National Institute of Medical Research (NIMR) with reference no:KNCHREC 0010.

Statistical analysis

Data were collected in Excel and analysis was done using R-Statistical tool version -3.6.1 where descriptive statistics were extracted. The Risk model development was done by Logis-

tic Regression Analysis. Magnitude of influence of each determinant was estimated. Relationships of variances among variables were tested by Principal Component Analysis (PCA).

Results

A total of 209 children who underwent Brain CT scan examinations for various reasons were recruited in this study. The findings obtained from this study are presented in texts, figures and tables.

Social Demographic Characteristics

The overall gender distribution in the studied population, males was predominant (58.9%) (Table 1). Both gender and age distribution of the study population was significant ($P < 0.05$). Arusha region contrary to Tanga and Manyara had the highest proportion of individuals included in the study (Table 1).

Table 1: The proportion of individuals by age and gender from the four regions

Variable	Regions				Totals	P-value
	Arusha	Kilimanjaro	Manyara	Tanga		
Gender						
Males (%)	58.7	69.0	30.0	66.7	58.9	
Frequency (n)	98	20	3	2	123	0.010 ^c
Females (%)	41.3	31.0	70.0	33.3	41.1	
Frequency (n)	69	9	7	1	86	
Age (mean±sd)	11.899±5.115	10.910±5.059	10.588±4.955	8.333±4.725	11.648±5.093	<0.0001 ^b

Note: Statistical tests: Chi-square (c); t-test (b) at 5% confidence level

High proportion of children availed for CT scan examination came from Arusha (80%) with majority (55%) of children at the age between 13-18 years availed for CT scan examination compared to early and middle childhood and the difference was statistically significant ($p=0.000$) (Table 2).

Table 2: Distribution of cases by age groups and locations

Variable	Arusha	Kilimanjaro	Manyara	Tanga	Totals	P-value
Age (years)						0.00 ^c
0 – 6 (n, %)	34, 20.4	7, 24.1	3, 33.3	1, 33.3	45, 21.5	
7 – 12 (n, %)	38, 22.8	8, 27.6	1, 10.0	2, 66.7	49, 23.4	
13 – 18 (n, %)	95, 56.9	14, 48.3	6, 60.0	-	115, 55.0	

Descriptive statistics are produced (frequency, percentage), Chi-square test used to compare the group difference at 5% confidence level.

The distribution of children in the study population during analysis was further amplified to show percentage distribution of children and their brain status by gender and location. Majority of children with brain atrophy were males (59.9%)

compared to females (41.1%). Brain atrophy was significantly associated with males ($P = 0.027$) compared to females (Table 3). However, majority of cases came from Arusha and Kilimanjaro regions.

Table 3: Percentage distribution of brain status by gender and regions

Regions						
Variable	Arusha	Kilimanjaro	Manyara	Tanga	Totals	P-value
DBF Status (Atrophy)						
Males (%)	60.4	75.0	30.0	100.0	58.9	
Frequency (n)	55	12	3	1	123	0.027 ^c
Females (%)	39.6	25.0	70.0	-	41.1	
Frequency (n)	36	4	7	-	86	
DBF Status (Normal)						
Males (%)	56.0	61.5	-	50.0	55.83	
Frequency (n)	42	8	-	1	51	0.173 ^c
Females (%)	44.0	38.5	-	50.0	44.17	
Frequency (n)	33	5	-	1	39	
Age (mean±sd)	11.899±5.115	10.910±5.059	10.588±4.955	8.333±4.725	11.648±5.093	<0.0001 ^b

Note: Statistical tests: Chi-square (c); t-test (b) at 5% confidence level

The descriptive statistics such as proportions in regions wise and means across the regions were calculated. The analysis of variance on the determinants regional-wise, none was predominant and thus statistical significance was not observed (P>0.05) (Table 4).

Table 4: The distribution of the Brain Atrophy determinants across the regions

Regions								
Variable	Arusha	Kilimanjaro	Manyara	Tanga	Mean	Total	Fisher's test	P-value
Birth outside								
No	67.3	13.5	4.8	1.9	21.875	87.5	1.755	0.157
Yes	12	0.5	0	0	3.125	12.5		
Malnutrition								
No	73.1	13.9	4.8	1.4	23.3	93.3	1.028	0.381
Yes	6.2	0	0	0.5	1.675	6.7		
CNS infection								
No	57.2	10.6	3.4	1.4	19.825	79.3	0.145	0.933
Yes	22.1	3.4	1.4	0.5	5.15	20.7		
Trauma								
No	63.5	11.1	3.4	1.9	19.975	79.8	0.533	0.660
Yes	15.9	2.9	1.4	0	5.05	20.2		
Metabolic								
No	74	12.5	4.3	1.9	23.175	92.8	0.304	0.660
Yes	5.3	1.4	0.5	0	1.8	7.2		
Drug Convulsions								
No	66.3	10.6	2.9	1.4	20.3	81.2	1.414	0.240
Yes	13	3.4	1.9	0.5	4.7	18.8		
SOL & ICP								
No	69.2	13.5	4.8	1.9	22.35	89.45	1.340	0.262
Yes	10.1	0.5	0	0	2.65	10.6		
Birth injury								
No	71.6	13	3.4	1.9	22.475	89.9	1.733	0.161
Yes	7.7	1	1.4	0	2.525	10.1		

Risk Model Development and Analysis

The risk model was developed using ten risk factors thought to be associated with brain atrophy development represented by DBF. The factors include birth outside health facility, premature delivery before term, central nervous system infections such as meningitis, cerebral malaria and HIV encephalitis. Others included malnutrition related conditions such as kwashiorkor and marasmus, head trauma with associated loss of consciousness, metabolic conditions such as maternal alcoholism

and smoking in pregnancy, convulsive disorders and drugs like antiepileptic and anti-cancers. Also, radiation injury from head and neck radiotherapy, space occupying lesions such as brain tumors, abscesses and hydrocephalus were factored. Birth injury including birth asphyxia and instrumental deliveries was another category of considered in the model.

The univariate analysis of the brain atrophy determinants found that immaturity, CNS infection, trauma, drug related and SOL&ICP were statistically significant associated with the occurrence of brain atrophy ($P < 0.05$) (Table 5).

Table 5: Univariate analysis for the determinants of brain atrophy

Variable	Coefficient (β)	P-value	Odds ratio (CI-95%)
Birth Outside facility	0.612	0.174	1.845(0.763-4.459)
Immaturity	-1.535	0.00	0.215(0.103-0.451)
CNS infection	1.488	0.000	4.427(2.129-9.205)
Malnutrition	1.092	0.102	2.981 (0.806-11.02)
Trauma	0.796	0.034	2.216 (1.062-4.624)
Metabolic	0.454	0.423	1.574 (0.518-4.779)
Drug& Convulsions	0.804	0.038	2.234 (1.045-4.778)
Radiation injury	-0.274	0.847	0.761(0.047-12.329)
Birth injury	0.981	0.066	2.667 (0.938-7.580)
SOL &ICP	1.353	0.018	3.870 (1.261-11.874)

Univariate regression analysis was done at 5% confidence level

From the univariate analysis, it is found that, determinants such as CNS infection, trauma, drugs & convulsions and SOL&ICP are statistically significant at the confidence level of 0.05. But for the sake of keeping important determinants we increased the confidence level to 0.1 and found that, birth injury

is statistically significant. Therefore, the significant factors at the later confidence interval were used for multivariate analysis.

The final model for brain atrophy included the birth injury, CNS infection, immaturity, trauma, drugs and SOL&IP.

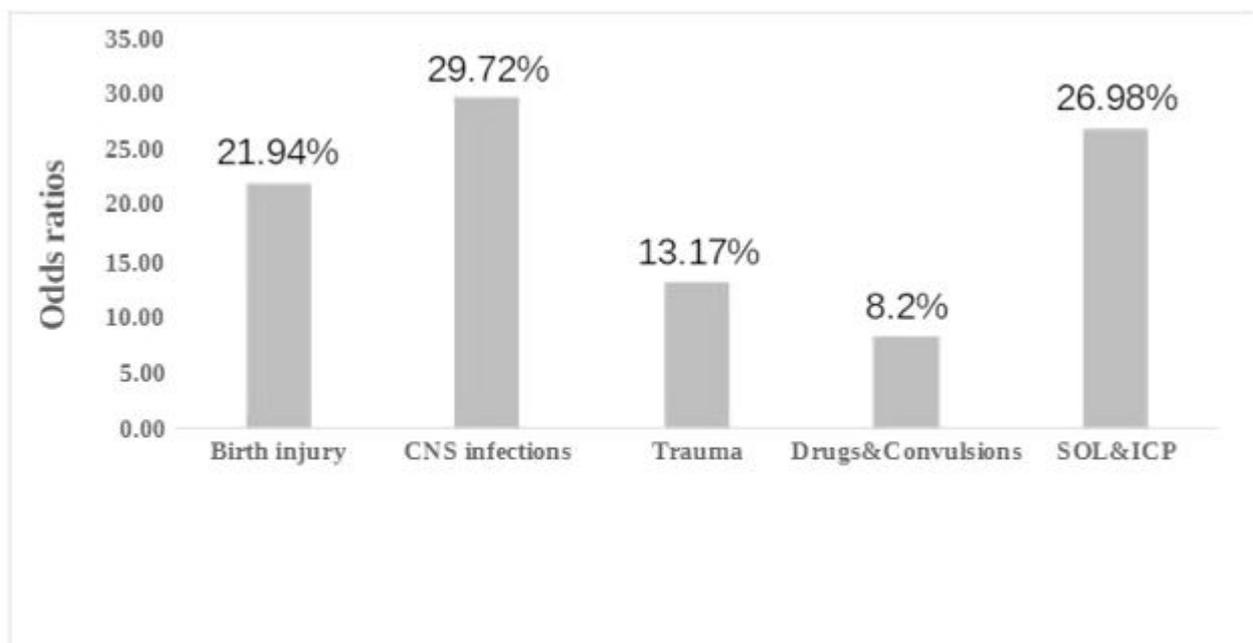
Table 6: A multivariate logistic regression

Variable	Coefficient (β)	P-value	Odds ratio (CI-95%)
Birth injury	1.248	0.029	3.483(1.135-10.692)
CNS infection	1.551	0.000	4.717(2.202-10.107)
Trauma	0.737	0.071	2.090(0.939-4.652)
Drug &Convulsions	0.264	0.542	1.302(0.558-3.039)
SOL& ICP	1.454	0.016	4.282(1.306-14.046)

Multivariate regression analysis was done at 5% confidence level

From the multivariate analysis, it is observed that, DBF determinants such as birth injury, CNS infection and SOL&ICP were statistically significant at the confidence level of 0.05. It seems also that trauma factor is very close to be significant at the confidence level of 5% but it is statistically significant at 10% confidence level (Data not shown). Rather, drugs& convulsions factor is not significant at the confidence level of 5% to the DBF development. Furthermore, it also observed that, factors such as CNS infection and SOL&ICP have great positive effect towards DBF followed by trauma and drug & convulsions factors. But the immaturity determinant has the negative impacts towards DBF occurrence (Table 5).

There are various risk factors associated with brain atrophy in children. In the current study top five determinants of brain atrophy in children were found and their influences are hereby presented according to percentage of contribution in this neurological disorder for growing children in Northern Tanzania. These factors include birth injury, CNS infections, head trauma, drugs and convulsive disorders and also intracranial space occupying lesions (Figure 2). From the records, the major CNS infections included meningitis, HIV encephalitis and cerebral malaria (data not shown).

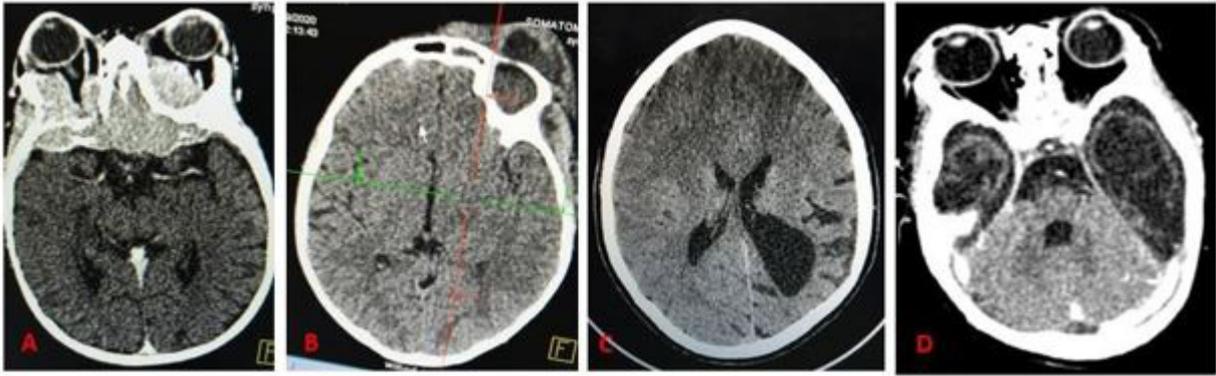


CNS infections mark the peak among determinants of brain atrophy. Other conditions that lead to brain atrophy include, space occupying lesions, birth injury, trauma and trivial contribution from drugs and convulsive disorders.

Figure 2: Determinants of Brain Atrophy and their influence

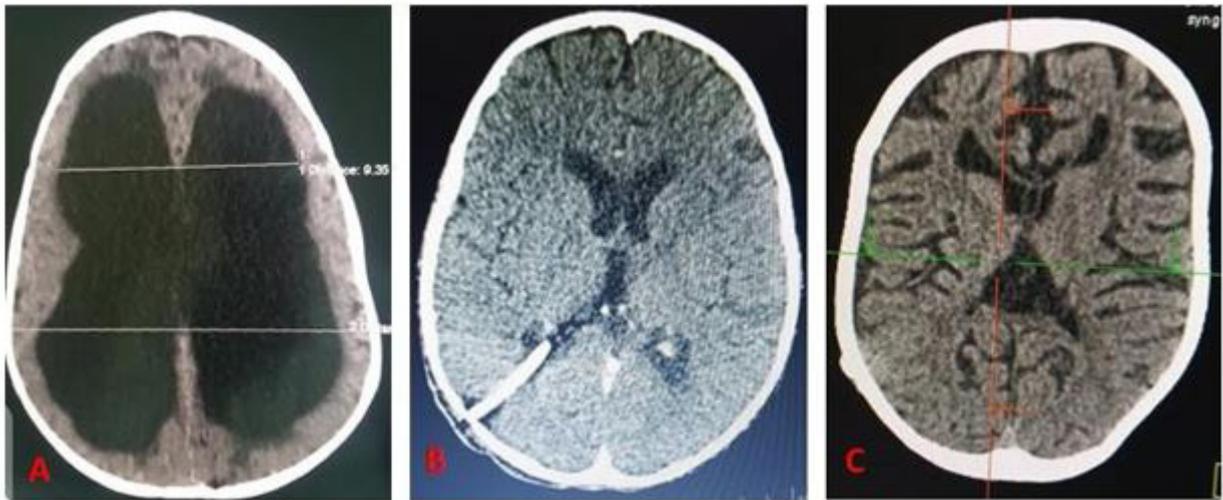
Most determinants of brain atrophy are not visible radiologically. Past medical, social history and laboratory investigations help clinicians to build knowledge on the trending causes of brain atrophy in children. Nevertheless, some determinants and their corresponding effects may be clearly visualized in neuroimaging. Among other things are space occupying lesions,

congenital malformations that may in addition associate with convulsions (Figure 3) and increased intracranial pressure such as hydrocephalus (Figure 4) can be well demonstrated through cross section imaging modalities including CT scan and Magnetic Resonance Imaging.



A: Bi-lateral planum sphenoidale meningioma in 16 years boy with extracranial extension through the optic tract resulting into mild cerebral cortical atrophy. B: left frontal scalp abscess with frontal sinusitis with mild cerebral cortical atrophy. C: Left parietal focal brain atrophy in connection with history of trauma. D: White cerebella sign with bitemporal hypoattenuation due to birth asphyxia.

Figure 3: Varying additional determinants of Brain atrophy effects



A: Enlarged lateral ventricles due to severe hydrocephalus with failed shunt. High reading of Evans index >0.3 is evident. B: Brain re-expansion to normal volume or mild atrophy after successful shunt. Borderline sulcal width and ventricular width is shown. C: Severe brain volume loss despite

Figure 4: Hydrocephalus and possible outcomes after interventions ventriculo-peritoneal shunt (VPS) due to delayed intervention. More enlarged cortical sulcal width is shown indicating severe cortical brain atrophy

The Risks Distribution Within the Northern Tanzania

The risk distribution was visualized using principal component analysis to examine dimensionality and directionality of data distribution among determinants of brain atrophy (Figure 5)

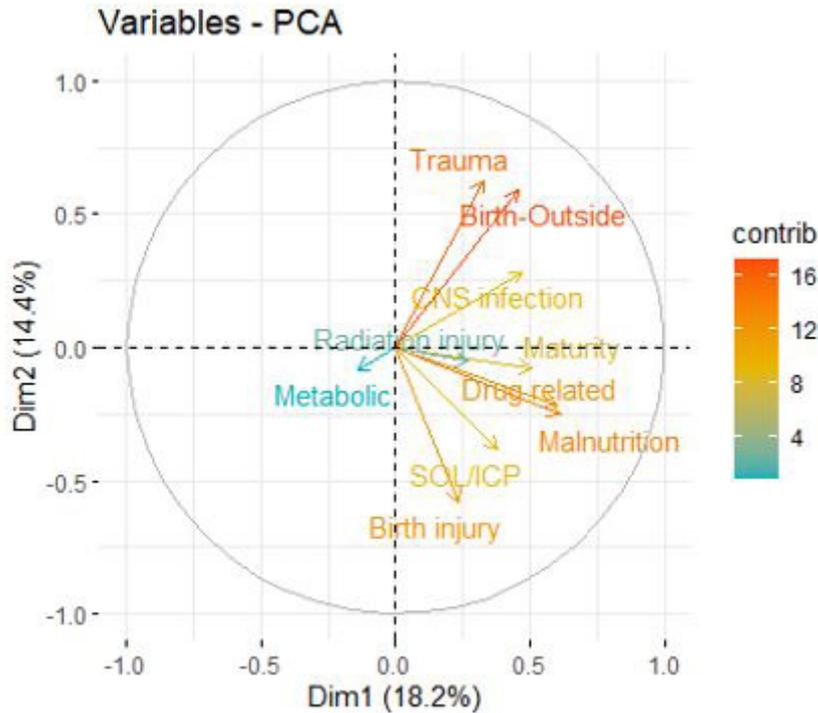


Figure 5: Principal component analysis of the determinants of brain atrophy and DBF

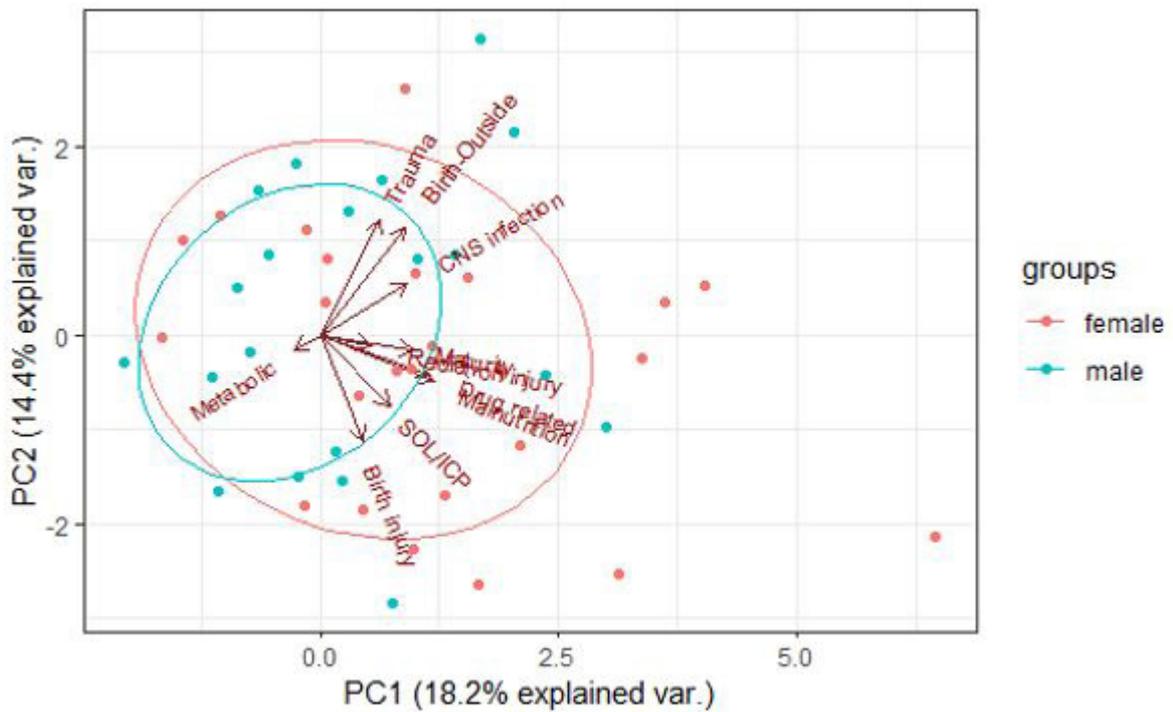
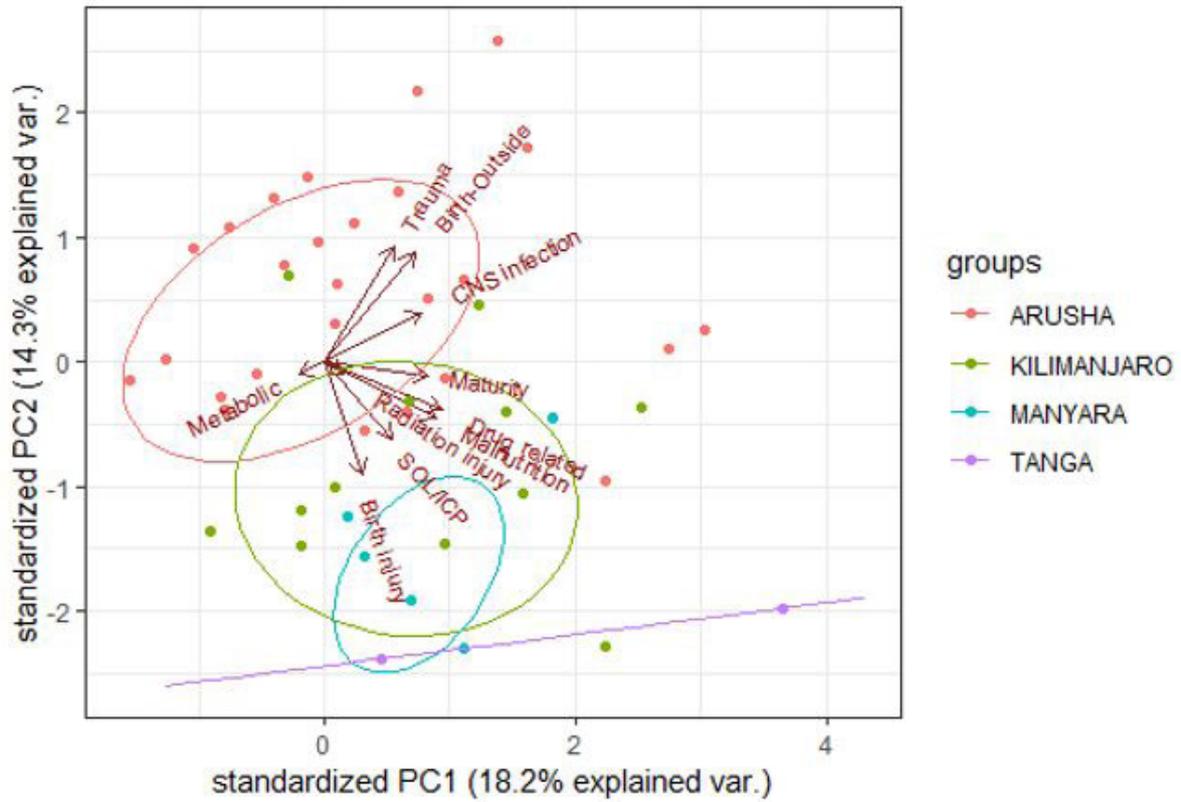
The figure above (PCA) shows the variances contributed by each variable. The total variance explained by PCA1(18.2%) and PCA2(14.4%) is 32.6%. The most contributors are Birth outside and Trauma followed by malnutrition, drug related, birth injury CNS infection, SOL/ICP maturity and less contributed by radiation injury and metabolic.

Further scrutiny of the principal component data distribution by regions and gender was made and transpired interesting results in the overall disease trend within the four regions of Tanzania with their male to female risk distribution in the study population (Figure 6).

In the over view of risk factors distribution by region, the central nervous system infections, space occupying lesions, head trauma and birth asphyxia were predominantly distributed in Arusha region. Additional determinants found to dominate this region were malnutrition, events of birth outside health facilities, drug effects and convulsive disorders (Figure 6A)

Kilimanjaro region had wider distribution of cases with metabolic related conditions and specifically maternal alcoholism. Maternal cigarette smoking was not found in the sampled population. Manyara region of Tanzania had more distribution of cases related premature deliveries while Tanga region presented with one case of brain atrophy in relation to head and neck radiotherapy (Figure 6A).

When gender analysis was made; the infections of the central nervous system, head trauma associated with loss of consciousness, birth injury, and metabolic conditions with the focus to maternal alcoholism, radiation injury, premature deliveries, drugs and convulsive disorders were widely distributed among male children. Furthermore, this category showed more risk of space occupying lesions, malnutrition and birth outside health facilities were profoundly distributed among female children of the studied population (6B).



A: The PCA figure above shows that, Arusha region is affected by all the factors followed by Kilimanjaro region and Manyara. Tanga region is less affected despite its exposure to trivial radiation injury. **B:** PCA shows that female are exposed more by most contributing factors of brain atrophy compared to male individuals.

Figure 6: Regional and gender distribution of the determinants of brain atrophy

When the brain volume were considered categorically, its was noted that the distriction of the risk factors had significant difference among cases of brain atrophy from those of normal brain volume in that the individuals with brain atrophy were overwhelmed by the risk factors exposure among them

(Figure 7). The brain volume was determined by diagonal brain fraction (DBF) in which the cases of brain atrophy had the the DBF (Mean ± Sd) of 0.69 ± 0.04 while the normal individuals had the mean score of 0.79 ± 0.03 (Table 7).

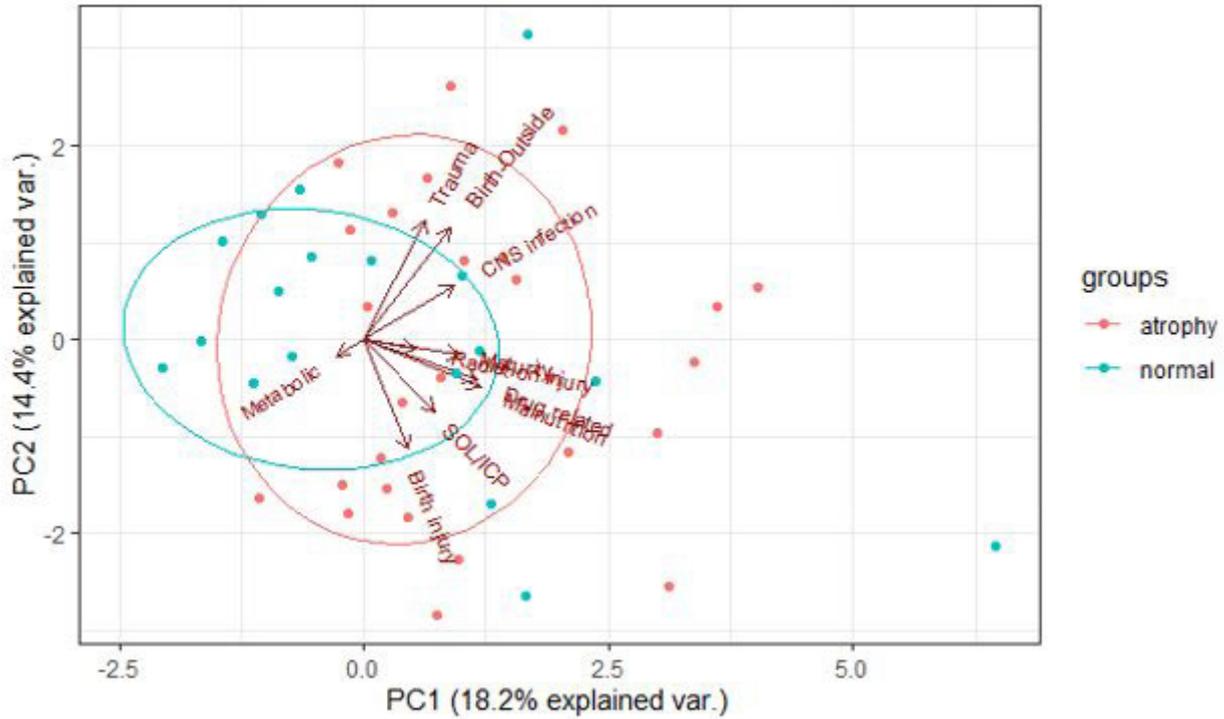


Figure 7: PCA showing distribution of the determinants of brain atrophy among cases and controls
The figure above shows exposure distribution of risk factors among the normal and atrophied brain. Most factors point toward the atrophied brain compared to normal brain

A significant difference in mean brain volume is shown among cases of brain atrophy and their normal counterpart in which individuals with atrophied brains are overwhelmed by risk factors.

Table 7: comparison of brain volume score among cases of brain atrophy and normal controls

Table: Comparison between Normal and effected brain

Variable	Normal	Atrophy	t-value	P-value
DBF-value (Mean ± Sd)	0.79 ± 0.03	0.69 ± 0.04	19.81	0.0001***

Descriptive statistics (mean±sd) is computed, the DBF mean differences between normal and effected brain (atrophy) is compared using t-test at 5% confidence level and found that they are mostly significant different.

Discussion

Socio-Demographic Characteristics

In this study Arusha region contrary to Tanga and Manyara had the highest contribution of the participants due to the high availability and accessibility to CT scan imaging facilities. The dominant population is represented by male children compared to female children such that male children are 58.9% while females are 41.1%. These results reconcile very well with the trends and pattern of the use of computerized tomography among children in Catalonia as seen in the year 1991 to 2013 in which male children again dominated the study population at the rate of 56.9% for male children while 43.3% were female children [18]. Similarly another study in Italy showed a higher male children attendance in CT scan services to about 68% in connection with trauma [19]. Apart from trauma related conditions, another study likewise showed higher number of male children who attended facilities in connection with long standing headache in which 53% were male children [20]. Therefore, the magnitude of male children hospitalization with the pressing need for radiological imaging overrides the female children for the similar conditions.

Risk Model Development and Analysis

Even though there are many other determinants of brain atrophy such as congenital neuro- developmental malformations such as Sturge-Weber syndrome [21] and blood dyscrasias such as sickle cell haemoglobinopathy [22], this study addresses ten categories of highly possible trending causes of brain atrophy in children in Northern Tanzania.

The central nervous system infections including meningitis, cerebral malaria and HIV encephalopathy are the leading infective causes of brain atrophy in children. This category collectively represents 29.72% of the studied determinants of brain atrophy in Northern Tanzania. Even though, there is no statistical equivalent of this category but many studies have shown increasing contribution of brain atrophy in children with these conditions. A study by Han, *et al.* 1985, revealed brain atrophy as a subsequent result of bacterial meningitis in infants [23]. Further studies suggests that the mechanism resulting into brain atrophy is the onset of cerebral infarction caused by bacterial meningitis that may later lead to loss of volume [24]. Cerebral malaria is another cause of brain atrophy in this category, the study done in

Malawi using MRI revealed presence of brain atrophy in children who survived cerebral malaria due to induced necrotic changes in brain parenchyma [8]. HIV encephalopathy is another trending cause of brain atrophy among children in which studies suggests that along with the central type of brain atrophy, there is different pattern of brain finding when compared to adults with similar condition (Safriel, *et al.*, 2000). The findings presented by Safriel, *et al.*, 2000, is in alignment with the findings of this study (Data not shown) in which among children we observed presenting with HIV encephalopathy there was no child presented with white matter demyelination changes which commonly present as progressive multifocal leukoencephalopathy (PML) in adults with CNS manifestations of HIV [25]. This condition has as well being described to be the uncommon pathology in children [26]. This observation could be attributed by the fact that there is high rate of white matter development in children evidenced by progressive myelination and hence overriding the demyelination process induced by the JC viruses responsible for progressive white matter demyelination [27]. Therefore, the extraordinary rate of myelination process in childhood is what possibly accounts for why PML is not common white matter degenerative condition in young children with HIV.

In the category of space occupying lesion and increased intracranial pressure (SOL&ICP) 26.97% of brain atrophy cases were represented. These conditions included brain tumors such as meningioma, glioma, medulloblastoma and retinoblastoma. Others include abscesses. Further studies have shown strong association between malignant glioma and brain atrophy among survivors of this SOL [28]. The SOL mechanism of action in causing brain atrophy is thought to be related to pressure effect and competing nutritional demand with the native brain tissues as most malignant tumors have high mitotic activities necessitating high demand of nutritional and energy supply [29]. Also tumor may induce Wallerian degeneration of the axons leading to unilateral brain atrophy [30]. Hydrocephalus is another determinant of brain atrophy. It presents as intraventricular or extraventricular type [31]. This condition may be congenital or acquired but it has its mechanism of brain tissue injury through pressure effect which causes ischemia of brain tissues and thereafter tissue necrosis and phagocytosis [32]. While timely intervention by ventriculo-peritoneal shunting (VPS) of CSF and ventriculostomy have been known to relieve the brain from pressure necrosis and cause brain re-expansion to normal volume, patients without this interventions undergo brain atrophy with corresponding thickening of the bony calvarium as a compensatory mechanism

[33]. Many other cases of hydrocephalus end up with brain atrophy due to tissue ischemia even after VP shunting due incorrect timing for intervention [34]. Head trauma has also been associated with acquired forms of hydrocephalus when mechanism of injury involves intraventricular hemorrhage. The collected blood within the ventricle causes CSF obstruction through inflammation and fibrosis [35]. The right timings for intervention of hydrocephalic brain need to be ascertained in order to formulate strategic interventions and mitigation of brain atrophy.

Birth asphyxia and birth injury has appeared as one of the common determinants of brain atrophy in the under 5 children in the current study with influence of 21.94%. Other studies have shown as well a close association between birth asphyxia and resultant brain atrophy [45]. In the study by Windle, (1970), it was shown that, apart from cerebral hemorrhage which is an immediate finding of birth-asphyxia, brain atrophy was a subsequent finding [46]. In general, studies have shown different forms of injuries happening in birth asphyxia. A study by Swarte, *et al.*, (2009) suggests six different patterns of brain injuries that include deep grey-matter injury with limited cortical injury, deep grey matter with associated cortical watershed injury, isolated injury of white matter, and cortical necrosis [47]. In neonates, hypoxic ischemic injury of birth asphyxia is not only limited to cerebral part of the brain but also involves the cerebellum especially the vermis part and most imaging modalities may demonstrate atrophic change in this part of brain as in the study by Sargent, *et al.*, (2004) [48]. A 5 years follow up study for neonates who encountered neonatal hypoxic ischemic injury revealed motor and cognitive dysfunction as depicted by EEG continuous recording [49]. Some children in this study have cross over to the age above 10 years with brain atrophy resulted from birth asphyxia suggesting that this condition is largely irreversible, although some studies have suggested that the use of citicoline injection have shown neuroprotective effect on brain tissues that have been subjected to ischemia. This future potential treatment has been proven in animal models when 300mg/kg dose of citicoline was administered two weeks after ischemic insult [41]. Despite this and other future treatment possibilities, more efforts are called to improve antenatal and intrapartum care of pregnant mothers in order to strengthen primary prevention of brain atrophy resulting from anoxic brain changes due to prolonged labor, obstructed labor and instrumental deliveries.

Head trauma is an outstanding cause of brain atrophy scoring 13.17% of the influence of brain atrophy among children with high propensity to male children than it is in females. This

observation can be attributed by behavioral component of the risk factors for brain injury and then atrophy. Many studies have shown that in both accidental and non-accidental head trauma, male children were overwhelmingly more involved than female children. A study by Iranmesh, 2009, showed the male: female ratio of 3:1 in Iran [36]. Almost a similar trend is shown in non-accidental injury where male children predominance remained highly observed at 2:1 male: female ratio [37]. Remarkable findings by MacKenzie, *et al.*, (2002), showed closer association of brain atrophy and severe form of brain injury and that it takes about eleven months for brain atrophy to manifest after traumatic brain injury that was associated with loss of consciousness [38]. Ventricular enlargement measured using Evan's index is another way of assessing brain atrophy post trauma. In the study by Poca, *et al.*, (2005) showed significant ventriculomegaly related to low Glasgow Coma Scale post head injury as early as 2 weeks post trauma [38]. Irrespective of the importance of ventricular size in studying brain atrophy, the finding can as well be confounded by trivial intraventricular hemorrhage that may result in blockage of CSF flow through the ventricular system leading to post hemorrhagic hydrocephalus (ventriculomegaly) which may be confused with brain atrophy [39]. The brain atrophy that is related to trauma can be well studied by considering a comprehensive evaluation of intracranial structures involving brain parenchyma and CSF spaces including ventricles using methods such as brain parenchymal fraction (BPF) [40]. Head injury accelerates brain atrophy such that the effects of age and injury acts synergistically in causing neurocognitive dysfunction [41]. There are various mechanisms of neuronal injuries of brain post trauma and among others, activation of oxygen-dependent free radical is a known mechanism at molecular level in which through mitogen-activated protein kinase cascades at the cell membrane, unleashes neuronal damage through apoptotic like cell death [42]. Further studies have shown that unselective reaction of the macrophages whose goal is to engulf the injured neurons tend to affect the innocent brain cells leading to further reduction in brain volume [32]. This observation can be complemented by the rareness of focal subtype of brain atrophy as well as presence of hemiatrophy since most atrophic brains presents as symmetrical diffuse pattern than asymmetrical brain atrophy as presented in cases of brain hemiatrophy [43]. It is therefore, thought that the interference of phagocytic activities of these macrophages may be vital in the future therapeutic mitigation of brain atrophy. In addition, studies have shown different other possibilities of protecting neuronal cells from further damage by activating amyloid precursor protein through the use of minocycline. This endogenous protein is said to have neuroprotective role from the effects

of trauma [44]. Therefore, multi model approach is likely to be the future of neural protection against traumatic triggered brain atrophy.

Convulsive disorders and antiepileptic drugs have been implicated in causing brain atrophy [50]. In this study drugs and convulsive disorders as one category have influenced the population by 8.2% in causing brain atrophy. While statistical significance is shown in both conditions, it is still not clear which one causes the other between brain atrophy and convulsions since anti-epileptic or anticonvulsive drugs therapeutic goal is to stabilize neuronal conductivity and stop convulsions [51]. Their use as anticonvulsant therapies are still controversial to be implicated in causing brain atrophy as a convulsive state like status epilepticus is said to cause high consumption of energy [52] at the epileptic epicenter of the brain leading depletion of energy in the form of Adenosine Triphosphate (ATP) which thereafter leads to focal brain tissues necrosis and hence loss of volume [53]. The process of controlling convulsions using anti-epileptic therapy such as carbamazepine and phenobarbitone would be expected to salvage the brain from the necrotic effects induced by the convulsions and therefore become neuroprotective just as reported in the animal study using levetiracetam [54].

Malnutrition appears to have surprisingly contributed to low influence in brain atrophy development within the scope of this study with statistical insignificance in univariate analysis at p-value of 0.102. This category of brain atrophy determinants is highly dynamic and known to be reversible. Many studies have shown evidence brain re-expansion after a course of food supplements in malnourished children who were found to have brain atrophy. A study by Gupta, *et al.*, (2016) showed gross recovery of brain volume in children with brain atrophy who presented with infantile tremor syndrome [55]. A similar result was experienced in a case of vitamin B12 deficiency in patient with dementia [56]. The therapeutic reversal of brain atrophy goes as deeper as to cases of inborn errors of metabolism sighting an example of the study by Bousounis, *et al.*, (1993), who demonstrated reversal of brain volume to a patient with biotinidase deficiency after supplementing with Biotin [57]. There is however, a challenge in associating vitamin levels with brain atrophy since most neurotrophic vitamins including Vitamin B1 and B12 are water soluble and lack stable state in human body. In this study, protein energy malnutrition was therefore, the main focus. Nevertheless, from the light of literature, protein energy malnutrition rarely occurs alone rather it almost always accompanies avitaminosis [58]. An-

other challenge that needs attention is that the results can possibly be presenting an iceberg phenomenon due to the challenges of determining the presence and quantification of levels of malnutrition as physical features of general body weight in relation to the imaging changes of the brain volume. Many studies including Gunstad, *et al.*, (2008), have shown that there is independent relation between body mass index (BMI) and brain volume on imaging [59]. The observed results can also be supported by the high likelihood of the difference in tissues tolerance levels in nutritional deficiencies between the brain and other body tissues like muscles. Taking example of oxygen deficiency; the brain can tolerate up to maximum of 3 minutes of anoxic state before serious tissues damage while muscles can withstand anaerobic respiration for longer time [60]. In addition, the brain is made to almost exclusively depend on glucose as nutrition for metabolism while other body parts can depend on alternative pathways [61]. Therefore, the instability of serum vitamins levels, the mismatching between BMI and brain volume together with the national nutrition support programs have possibly contributed to a relatively low contribution of brain atrophy from this category.

The pediatric brain atrophy related to antenatal maternal alcoholism has just a trend in inducing brain atrophy among newborns but without statistical significance. The results are not well reconciled with some studies. In the study by Guio, *et al.*, (2014), the group with antenatal exposure to maternal alcoholism had 16% of their brain volume reduced [62]. Compared to the results of this study, the number is far from our study and the most possible explanation is the possibility that ethnicity, maternal weight, age and duration of alcohol intake during pregnancy needed to be factored. In addition, the former study used automatic MRI based image analysis with possible variation with the CT scan technology used in this study. Nevertheless, a number of mothers with alcoholic life style during pregnancy presented with children with normal brain volume. From these results the most plausible explanation is that the effects of alcohol can be individualized depending on individual metabolism and genetic makeup [63]. Alcohol is metabolized by first pass effect in the liver; depending on individual's metabolic rate, the fetal toxic values of alcohol can be disintegrated faster by the cytochrome P450 rendering suboptimal concentration of alcohol to cross through the placenta to the fetus [64]. Hence, the diverse pattern of alcohol metabolism is the result of unpredictable effect on alcoholic and non-alcoholic mothers in causation of newborn brain atrophy.

The Risks Distribution Within Northern Tanzania

In the distribution of the determinants of brain atrophy among children in Northern Tanzania, it is observed that overwhelming risks are trending within the Arusha region. In which risk factors such as central nervous system, trauma, space occupying lesions, birth asphyxia, malnutrition and birth outside facilities are leading in this region. This observation can be due to higher general population level together with increased accessibility to the cross-sectional imaging centers such as CT scan and MRI in comparison to other regions in this zone of the country.

The Kilimanjaro region is leading in cases of metabolic related brain atrophy in connection to antenatal maternal alcoholism. Studies have shown that alcoholism reduces brain growth, and that parental alcoholism may induce similar behavior to offspring by genetics or environmental conditions [65]. In comparison to socio-cultural issues studied in other regions, alcoholism is connected to overall higher economic status of the people in this region with gender equality while in most other regions alcoholism is most restricted to middle aged and old adults with preference to men [66]. The outcomes of this study is supported by the study by Saffitz, (2010), that reported high alcoholism rate in Kilimanjaro region which also is associated with gender violence [67]. Furthermore, alcoholism starts from among young individuals at the level of secondary school age. In the study done among breast feeding mothers 39% were consuming alcohol during pregnancy and lactating period [68]. Apart from brain atrophy presented by most studies, other consequence of alcoholism among pregnant women in Kilimanjaro region included cases of neonatal low birth weight [69]. Therefore, this together with other studies discourages alcoholism during pregnancy and lactation periods.

Even though Manyara and Tanga regions were trending more in distribution of brain atrophy associated to premature deliveries and radiation therapy respectively which have overall statistical insignificance, these regions had limited accessibility to CT scan services and henceforth their contributions in this study population were also low. A close scrutiny of data show that, some determinants including central nervous system infections, trauma, birth asphyxia, drugs and convulsive disorders have shown predilection to male gender while space occupying lesions, immaturity (premature delivery), and malnutrition have

widely been distributed in female children more than male of the study population. From the light of other studies, male children have been closely associated with infections and head trauma due to behavioral and socio-cultural activities. The study in Germany and many other developed countries have shown increased trend of head injuries in male children up to 58% (70). A study by Luo, *et al.*, (2014) suggested that the central nervous system infections among hospitalized children was 2:1 male to female ratio due to increased exposure to risks in this group [71]. Both trauma and central nervous system infections have synergistic effects to each other and the study by Boque, *et al.*, (2000) suggests that head trauma has 4% risks to the central nervous system infections but this risk increases to 50% when there is leakage of cerebro-spinal fluid [72]. Therefore, male preponderance in principal component analysis of the availed data of this study leans more toward behavioral mediated risks.

A different picture is observed in the distribution of brain atrophy determinants among female children in which malnutrition and premature deliveries were the most spread risks within this gender. When socio-cultural behavior is considered, female children in the study population have the tendency to be confined within domestic areas in close intimacy with their mothers hence they are less vulnerable to trauma and other mechanical injuries. Nevertheless, in pastoralist communities like Maasai, female children remaining at home may be deprived of certain nutrition like meat and milk in dry seasons as male children are involved in social mobility with adults migrating far for grazing cattle rendering female children and their mothers in nutritional decline as per study done in Kajiado, Kenya [73]. A study done in Maasai pastoral community in Simanjiro district of Manyara region showed that men and boys were served with meals in priority during times of food insecurity [74]. The intra-household decision and bargaining power on nutrition habits conflicts significantly the maternal and child health programs [75]. On the other hand, the social intimacy between mothers and daughters has resulted to be of protective advantage to female children against events of head trauma. Studies have shown that most mothers were concerned more on prevention of risk behavior to trauma among their female children than male counterparts [76]. Therefore, gender difference dictates a certain distribution pattern of the determinants of brain atrophy among children.

Conclusions

Infections of the central nervous system, space occupying lesions, birth injury and head trauma are the cardinal determinants of childhood brain atrophy in the Northern Tanzania. Brain atrophy resulting from the most profound determinants in Northern Tanzania, is almost irreversible, hence prevention and early detection is key in long term intervention against childhood brain Atrophy.

Neonatal Pre-maturity and Radiotherapy related brain injury are rare causes of pediatric brain atrophy in the studied population.

The white matter demyelination changes such as Progressive Multifocal Leukoencephalopathy (PML), is unlikely presentation of childhood HIV encephalopathy despite brain atrophy.

Recommendations

The study recommends plans to improve accessibility to neuro-imaging facilities as a vital step to ensure mental health of children as timely intervention of some determinants of brain atrophy may salvage the brain from cascade of atrophic process. The study recommends sustainable development and dispensation of improved antenatal and intrapartum care as the pro-active way of preventing early neonatal brain atrophy.

What Is Already Known

Brain atrophy is rare in childhood and it is a common condition in elderly. There are many determinants of brain atrophy including malnutrition, head trauma, central nervous system infection and birth asphyxia.

What Is Added From This Study

Brain atrophy is increasingly becoming common in childhood depending on the trending causes of premature volume loss. There are five most influential determinants of childhood brain atrophy that include infections of the central nervous system, space occupying lesions, birth asphyxia and head trauma when Northern Tanzania is considered at sighted example.

Conflict of Interest

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 was the principal researcher who presented the idea, formulated the study plan and conducted most of the field work. The 2nd author contributed for the overall look of the research output and language presentation. The 3rd author cross checked the methodological part of the study and data accuracy. The 4th author contributed in the study feasibility, proposal review and proof reading of the research output. The 5th author 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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